Considerations of Pharmacotherapy in Hospice End-of-Life Care

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Anniek Dorien Masman

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The pictures on the cover illustrate 'the life of people'. In end-of-life care I experienced that near death people often looked back on their life and told me stories about going on holiday, having fun with grandchildren, gardening, swimming in the sea, enjoying the sunshine etcetera. The people on the pictures are all members of my family. Most of them died a long time ago and could be alike the participants in the studies described in this thesis: all with their own stories of life; the pictures remain as dear memories.

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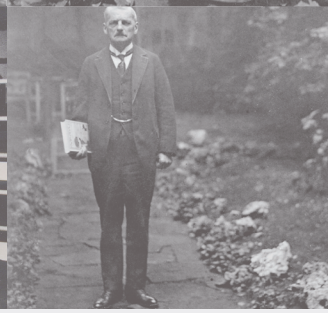

PART I
GENERAL INTRODUCTION









CHAPTER 1

GENERAL INTRODUCTION




CONTEXT

Palliative care was defined by the World Health Organisation (WHO) in 2002[1] and by the European Association for Palliative Care (EAPC) in 1998[2]. Although those definitions mainly overlap, some differences can be addressed. For one thing, the WHO definition includes patients at an earlier stage in their illness trajectory. Second, the EAPC definition adds two important implications: palliative care has an explicit interdisciplinary approach and it is provided wherever the patient is cared for, either at home or in the hospital. It should be noted, however, that other terms are also used in literature to define the care for patients at the end of life, such as *hospice care*, *terminal care*, *end-of-life care* and *supportive care*.

Definition of palliative care proposed by the WHO (2002)
Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Definition of palliative care proposed by the EAPC (1998)
Palliative care is the active, total care of the patient whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of social, psychological and spiritual problems is paramount. Palliative care is interdisciplinary in its approach and encompasses the patient, the family and the community in its scope. In a sense, palliative care is to offer the most basic concept of care – that of providing for the needs of the patient wherever he or she is cared for, either at home or in the hospital. Palliative care affirms life and regards dying as a normal process; it neither hastens nor postpones death. It sets out to preserve the best possible quality of life until death.

In 2013 approximately 141,000 persons died in the Netherlands, at a mean age of 75 years for males and 80 years for females. Almost one third of them died from the consequences of cancer, mainly cancer of the digestive organs or the respiratory organs[3]. Moreover, advanced cancer is the main diagnosis for the majority of patients in a hospice[4]. However, of all palliative patients, only a relatively small number, estimated on less than 25%[5], is admitted to a hospice,

and reasons for admission include the complexity of their problems, lack of family caregivers or giving family caregivers some respite, or the patient's preference.

ASSESSMENT OF PAIN

Pain is highly prevalent in palliative patients; 45 to 70% of patients with incurable cancer, either admitted to a hospice or staying elsewhere, suffer from moderate to severe pain[6-9]. The prevalence of pain even increases as death approaches[10]. To control pain, 45 to 59% of patients need the highest-step drugs of the WHO pain ladder, i.e. opioids[7, 9, 11]. However, even when opioids are administered, pain is still prevalent or not relieved adequately in 43 to 50% of patients[9, 11]. These three aspects of pain in end-of-life patients - high prevalence, frequent use of opioids and a considerable portion of patients with unrelieved pain - indicate the need for accurate pain assessment to recognize pain and to guide pain treatment as death comes near.

Self-report of pain is typically considered the 'gold standard' for assessment[12]. However, terminally ill patients may not be able to self-report pain or to express it in another way due to their advanced illness state or cognitive failure, which is often seen prior to death[13-15]. It would seem obvious that assessment with observational scales is needed for non-communicative end-of-life patients. The EAPC reported about pain assessment in palliative care in 2002 and stated that, at that time, no valid assessment of pain in cognitively impaired was applicable[16]. Even today the number of validated observational scales for pain to use in palliative care facilities is still very limited[17]. To our knowledge, only one pain assessment tool for palliative patients whom are unable to self-report pain has been developed and tested: the Multidimensional Objective Pain Assessment Tool (MOPAT)[17]. It showed good internal consistency and sensitivity to change after a pain-reducing intervention, but has a major disadvantage in that blood pressure and heart rate measurements are included, which seem not sensitive for pain alone[18-21]. Further, these measurements are often stopped at the end of life, as recommended in the Liverpool Care Pathway for the dying patients[22].

Over the years our research group has developed and validated pain observations scales for three different patient groups who are unable to express their pain; very young children (the COMFORT-behavior scale)[23-25], patients with intellectual disabilities (Child Behavior Checklist)[26] and non-communicative elderly (Rotterdam Elderly Pain Observation Scale; REPOS)[27]. The REPOS was developed and validated in a nursing home[27].

PALLIATIVE SEDATION

The national guideline developed by the Royal Dutch Medical Association (KNMG, 2009) defines *palliative sedation* as follows: 'the deliberate lowering of a patient's level of consciousness in the last stages of life'[28]. It may be administered in two distinct ways: either continuous sedation until the moment of death or intermittent, which is temporary sedation. Continuous sedation is administered to patients who are expected to die within 1 to 2 weeks and who suffer unbearably from one or more intractable or refractory symptoms. A symptom is considered refractory if the conventional treatment is ineffective or if unacceptable side effects are present while symptoms remain uncontrolled.

The prevalence of palliative sedation until death varies widely in literature; the highest prevalences mentioned are 64% and 69% of patients[29, 30]. In the Netherlands, the prevalence ranges from 8.2% of all deaths in 2005[31] to 43% of patients in a specialized palliative care unit in a cancer hospital over the period 2001 to 2005[32]. The three most common refractory symptoms that determined the indication to start palliative sedation are delirium, dyspnoea and pain[32, 33]. Midazolam is the most often administered drug to achieve palliative sedation, both national and international[32, 33].

The Dutch national guideline proposes that palliative sedation should be applied proportionately; to the extent that it alleviates the patient's suffering[28]. So, it is the degree of symptom control rather than the depth of sedation that determines the adequacy of palliative sedation. According to this description, the effect of palliative sedation should be assessed by symptom control. However, in literature there is no consensus on how the effect of palliative sedation should be assessed; either by symptom control or by sedation depth or maybe both simultaneously[34, 35]. In addition, there is no validated observational assessment scale or device available for this purpose in sedated end-of-life patients.

Sedation can be guided by either an observational scale or a device that measures a form of brain activity. The bispectral index (BIS) monitor, an electrophysiological device derived from non-invasive EEG monitoring, is being used in clinical practice in anaesthesia and on intensive care units[36-38]. The use of BIS monitoring in palliative care has been reported in only two studies; one case study and one pilot study with 12 patients[39, 40]. These studies concluded that BIS monitoring is acceptable for patients, family and care-givers, but validation of BIS monitoring in palliative care was beyond the scope of these studies.

PHARMACOLOGY

Two main areas of pharmacology are pharmacokinetics and pharmacodynamics. *Pharmacokinetics (PK)* describes how the body handles the drug through the mechanisms of absorption, distribution, metabolism and elimination and determines the time course of drug action. *Pharmacodynamics (PD)* is described in terms of how the drug affects the body and determines the pharmacological responses, including both desired and adverse effects[41, 42]. Only few pharmacological PK/PD studies concerned palliative care[43-45]. The topic reported mostly on within the context of pharmacology in palliative care is drug interactions[44, 46-49]. Moreover, these papers are mainly theoretically based and the actual description of the palliative clinical practice is lacking.

Pharmacokinetic properties of drugs may be affected by factors such as the route of administration, drug dose and frequency of dosing. The actual prescription of drugs in palliative care is described in a few studies performed in palliative care units[50-52] and outpatient palliative facilities[53-56]. However, these studies do not describe the most prescribed drugs with their doses and route of administration.

In addition, the pharmacokinetics of drugs may be affected by factors such as body composition (cachexia or obesity), liver and kidney function. These factors are likely to change if death approaches, since then a gradual decline in physical health and functional status is seen[57, 58]. This decline includes, among other clinical manifestations, dehydration, weight loss and cachexia, liver impairment and kidney failure[59-61]. The clinical signs of the decline towards death may be reflected in laboratory results and this might have consequences for the pharmacokinetics and consequently for the effect of drugs in the end-of-life patient.

RESEARCH SETTING

The work presented in this thesis was performed in Regional Palliative Care Centre, Laurens Cadenza, in Rotterdam, the Netherlands. This is the largest 'hospice' in the Netherlands, with 20 beds for end-of-life care and symptom management. Annually 200 to 250 patients are admitted, of whom most suffer from advanced cancer. A multidisciplinary team of health care professionals, including specialised nurses and elderly care physicians specialised in palliative care, is available 24 hours per day. Also, many volunteers perform supporting tasks.

RESEARCH QUESTIONS OF THIS THESIS

The following research questions were addressed:

1. Is the Rotterdam Elderly Pain Observation Scale (REPOS) a reliable and valid tool for pain assessment in non-communicative or unresponsive end-of-life patients?
2. Is Bispectral Index (BIS) monitoring a feasible and valid tool for assessing the depth of sedation in terminally ill patients?
3. What drugs are administered, and at what dose and route of administration, from admission to day of death in patients admitted to a palliative care centre?
4. Are laboratory parameters of patients at the end of life disturbed such that it may have consequences for the pharmacokinetics of drugs often used in those patients?
5. What are the pharmacokinetics of morphine and its two major metabolites in terminally ill patients and what are the clinically relevant parameters for individualized dosing based on a population PK model approach?

OUTLINE OF THIS THESIS

Chapter 2 concerns a validation study of the REPOS for pain assessment in non-communicative or unresponsive end-of-life patients.
Chapter 3 determines the feasibility and validity of BIS monitoring to assess the depth of sedation in terminally ill patients in a hospice setting.
Chapter 4 describes doses and routes of administration of the most frequently used drugs at admission and at day of death in patients admitted to a palliative care centre.
Chapter 5 evaluates laboratory parameters of hospice patients in the week before death and discusses the changes in laboratory results, and their potential relevance for the pharmacokinetics of drugs.
Chapter 6 describes a population pharmacokinetic analysis of morphine and its two major metabolites (morphine-3-glucuronide and morphine-6-glucuoride) in terminally ill patients and presents clinically relevant parameters for individualized dosing.
Chapter 7 provides a general discussion of the results of the studies presented in this thesis as well as directives for future research.
Chapter 8 summarizes the results of the studies described in this thesis, both in English and in Dutch.

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PART II
ASSESSMENT OF PAIN AND THE DEPTH OF SEDATION

CHAPTER 2

THE ROTTERDAM ELDERLY PAIN OBSERVATION SCALE (REPOS) IS RELIABLE AND VALID FOR NON-COMMUNICATIVE END-OF-LIFE PATIENTS




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ABSTRACT

Background: In palliative care, administration of opioids is often indispensable for pain treatment. Pain assessment may help recognize pain and guide treatment in non-communicative palliative patients. In the Netherlands the Rotterdam Elderly Pain Observation Scale (REPOS) is recommended to this aim, but not yet validated. Therefore the objective of this study was to validate the REPOS in non-communicative or unconscious end-of-life patients.

Methods: In this observational study, the primary researcher applied the REPOS, both the researcher and a nurse applied the Numeric Rating Scale (NRS). If possible, the patient in question applied the NRS as well. The NRS scores were compared with the REPOS scores to determine concurrent validity. REPOS scores obtained before and after a pain-reducing intervention were analysed to establish the scale's sensitivity to change.

Results: A total of 183 REPOS observations in 100 patients were analysed. Almost 90% of patients had an advanced malignancy; observations were done a median of 3 days (IQR 1 to 13) before death. Internal consistency of the REPOS was 0.73. The Pearson product moment correlation coefficient ranged from 0.64 to 0.73 between REPOS and NRS scores. REPOS scores declined with median 2 points (IQR 1 to 4) after a pain-reducing intervention ($p<0.001$). Optimal sensitivity (0.81) and specificity (0.62) were found at cut-off score 3.

Conclusions: This study demonstrates that the REPOS is reliable and valid for pain assessment in non-communicative end-of-life patients. This scale may be of additional value to relieve suffering, including pain, in palliative care.

BACKGROUND

Several studies reported that 45% to 70% of patients with incurable cancer, either admitted to a hospice or staying elsewhere, suffer moderate to severe pain[1-3]. Forty-five per cent of them need the highest-step drugs of the WHOs pain ladder, i.e. opioids, to relieve their pain[2, 4]. The high prevalence of pain and the frequent use of opioids make clear that accurate pain assessment in palliative care is needed to recognize pain and to guide pain treatment.

Patients' self-report of pain is considered the 'gold standard' for pain assessment[5]. However, in the terminal phase of life, patients may not be able to self-report pain. To illustrate this, 68% to 83% of patients had cognitive failure prior to death[6, 7] and 90% to 98% of patients were drowsy or unresponsive in those last days[8-10]. Proxy pain assessment by a nurse was needed, therefore, in 90% of patients in a palliative care unit at the day of death[9]. Assessment of suffering, including pain, is challenging anyway in the terminal phase, especially when sedation is needed[11].

Proxy assessment often results in underestimation of the patient's pain and subsequent risk of under treatment[12, 13]. Application of a validated observation scale could be more effective in non-communicative patients as the observer is required to pay attention to well-defined behaviour that could indicate pain.

We, therefore, previously developed the Rotterdam Elderly Pain Observation Scale (REPOS), published in 2008[14]. In Dutch national palliative guidelines it is recommended for specific non-communicative patient groups[15], such as persons with dementia and intellectual disability. It proved a valid tool to measure pain in the nursing home population, including those who could not communicate[14].

The Multidimensional Objective Pain Assessment Tool (MOPAT) published in 2011 was developed for hospice patients who are unable to self-report pain. It was tested in a small sample of 28 alert patients and 30 non-communicative patients and showed good internal consistency and sensitivity to change after a pain-reducing intervention[16]. A disadvantage of the MOPAT, however, is that blood pressure and heart rate measurements are needed, and these measurements are often stopped at the end of life, as recommended in the Liverpool Care Pathway for the dying patients[17]. Also these measurements are not valid to assess chronic pain conditions.

In the Netherlands, the REPOS is increasingly adopted in nursing homes and institutions for intellectually disabled or non-communicative patients [18]. Hospice patients may have other characteristics, however. They often suffer from advanced cancer and are mostly bedridden. Self-report is not possible due to their illness state (comatose, delirium or adverse effects of medication), in contrast to

nursing home patients who more often have dementia. In addition, end-of-life patients are in another emotional state and may be extremely anxious, facing death. All these aspects may influence experiences or expressions of pain[19].

METHODS

Aim

The aim of this study was to establish whether the REPOS is a reliable and valid tool for pain assessment in non-communicative or unresponsive end-of-life patients.

Design, participants and setting

This observational study was performed in Laurens Cadenza in Rotterdam, the Netherlands. This is the largest palliative care centre in the Netherlands, with 20 beds for end-of-life care and symptom management; 200 to 250 patients are admitted annually. A multidisciplinary team of health care professionals, including specialised nurses and elderly care physicians specialised in palliative care, is available 24 hours per day. In addition, many volunteers perform supporting tasks.

This study was approved by the Medical Ethics Review Board of the Erasmus University Medical Center and the institution's local board of directors, and was performed in accordance with the principles of the Declaration of Helsinki and its later amendments. Pain assessment is standard care, and therefore informed consent was not required.

Assessment tools

The Rotterdam Elderly Pain Observations Scale (REPOS) consists of 10 behavioural items (see Supplement), which the observer scores as present or absent, after having observed the patient for two minutes[14]. To optimize inter-observer reliability, a definition chart and an intervention decision tree are provided as well. To ascertain sufficient interrater reliability of a REPOS observation, nurses receive training including at least 10 bedside paired observations with an experienced REPOS observer[20, 21]. A previous validation study in nursing home residents revealed a significant difference between painful and rest situations and a large correlation with the PAINAD (r= .75) indicating good construct validity. For nursing home residents both the sensitivity (.85) and the specificity (.83) were optimal at a cut-off score of 3[14]. However, as behaviour might be the result of other emotions than pain, the observer in addition estimates the pain intensity on

a Numeric Rating Scale (NRS) from 0 (no pain) to 10 (worst possible pain). Thus, assigning an 'NRS-observer' score is a standard part of the REPOS observation and assigning a NRS-observer is part of the training[18]. A REPOS score of 3 or higher and a NRS-observer score of 4 or higher suggests moderate to severe pain and requires an intervention[14, 22]. The NRS is considered a valid tool to assess cancer pain intensity[23, 24].

Procedure

Data were collected during three phases. First, from March to October 2010, the first researcher (A.M.) trained nurses in Laurens Cadenza to assess pain with the REPOS, since at that time symptom measurement was not standard of care. To ascertain sufficient interrater reliability, the primary researcher performed at least 10 bedside observations simultaneously with an experienced REPOS observer. Sufficient interrater reliability is defined as Cohen's kappa>0.65. As Cohen's kappa for the primary researcher was established as 0.76, she could serve as a REPOS observer in this study. November-December 2010, NRS and REPOS assessments were implemented in daily practice for all non-communicative or unresponsive patients.

During the second phase, from January 2011 to May 2012, the first researcher or a trained nurse assigned a REPOS score and an NRS-observer score in daily practice as standard of care.

In the third phase, from February to June 2013, the second researcher (A.B.) was called in when a patient received a pain-reducing intervention and assigned a REPOS score just before and at least one hour after this intervention. These pre- and post-intervention data were used for the sensitivity-to-change analysis.

To determine internal consistency, concurrent validity and the optimal cut-off score, only REPOS observations made by the experienced REPOS observer (first researcher) in phase one are selected; REPOS observations by the first researcher or trained ward nurses in phase two; and observations by the second researcher in phase three. For the sensitivity-to-change analysis only the pre- and post-intervention data form phase three were used.

The caregiving nurse assigned a NRS score (NRS-proxy) in non-communicative or unresponsive patients, and communicative patients rated their pain themselves (NRS-patient).

Other variables

Demographic characteristics (age, gender, diagnoses, and duration of admission) were extracted from the electronic medical records; the primary diagnoses and the number of comorbidities were evaluated. The primary diagnoses refer to the

WHO's International Classification of Diseases (ICD-10 classification) coding for the patient's terminal illness.

Analgesics prescribed at the time observation were recorded and classified according to the WHO three-step pain ladder as non-opioids, NSAIDs and opioids[25, 26]. The highest WHO step prescribed for a patient over all the observations is given in the patient characteristics.

Data analysis

Only the end-of-life assessments were included for analysis; data from patients who had been discharged and data obtained earlier than three months before death were excluded.

Data are presented as mean (standard deviation; SD) in case of normally distributed variables and as median (interquartile range = IQR or minimum-maximum range = range) in case of non-normally distributed variables.

To determine interrater reliability, for the first and second researcher and for all trained nurses who assigned REPOS scores, Cohen's kappa was applied and defined as good if ≥ 0.65[27].

Cronbach's alpha coefficient served to examine the internal consistency of the REPOS items. Pearson product moment correlation coefficient was applied to determine concurrent validity of the REPOS with the NRS scores. This validity coefficient should exceed 0.30[28]. The Wilcoxon signed rank test served to estimate sensitivity to change after a pain intervention. The optimal cut-off value for REPOS score was determined as the best combination of sensitivity and specificity comparing the REPOS total scores with NRS proxy as reference.

Data analyses were performed using IBM SPSS Statistics 20. A p-value of < 0.05 (two-sided) was deemed statistically significant.

RESULTS

Patient characteristics

Over the three study phases, REPOS scores were assigned to 103 patients. Data from three patients were not considered end-of-life assessments; only data of the remaining 100 patients were included in the analysis. For those included patients, the first (or only) observation was done a median of 3 days (IQR 1 to 13) before death. The median age was 77 years (IQR 67 to 85), 65% were female, and the median duration of admission was 28 days (IQR 9 to 51). Advanced malignancy, mainly of digestive and respiratory organs, was the main reason for admission (89% of patients). Most patients (73%) were receiving the highest WHO-step:

opioids around the clock. Opioids were prescribed on an as needed basis in 6% of patients (rescue medication when breakthrough pain was present) and 11% received no analgesics. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Characteristics	**N=100**
Gender in %	
Male / female	35 / 65
Age in years; Median (IQR)	77 (67 to 85)
Duration of admission in days; Median (IQR)	28 (9 to 51)
Assessment days before death; Median (IQR)	3 (1 to 13)
Primary diagnosis in N (%)	
Neoplasms	89
Digestive organs	*26 (29)*
Respiratory and intra-thoracic organs	*17 (19)*
Female genital organs	*9 (10)*
Breast	*7 (8)*
Eye, brain and other parts of central nervous system	*7 (8)*
Lymphoid, hematopoietic and related tissue	*7 (8)*
Ill –defined, secondary and unspecified sites	*7 (8)*
Other	*9 (10)*
Disease of nervous system	4 (acquired brain injury; Parkinson's disease; systemic atrophy)
Infectious and parasitic disease	3 (pneumonia and frailty)
Other	4 (CVA; lung disease, kidney failure, invalidity)
Analgesics in %	
Opioids around the clock	73
None	11
Non-opioids around the clock	8
Opioids as needed	6
Non-opioids as need	1
NSAID around the clock	1

IQR, interquartile range

REPOS scores and NRS scores

All trained nurses achieved good interrater reliability with the researcher after 6 to 10 paired observations (Cohen's kappa values ranged from 0.70 to 0.78). A total of 183 REPOS observations in the 100 included patients were done.

In 46% of patients, two or more pain observations were done. 34% of observations were made in the situation of washing and dressing in, 30% in posture change, 21% in rest, 9% during a transfer, and in 6% in other situations.

The median REPOS score was 2 (IQR 1 to 5); the median NRS scores (NRS-observer, NRS-proxy and NRS-patient) ranged from 2 to 6. REPOS scores indicative of pain (3 to 10) were assigned in 55% (101/183) of observations. Pain was rated moderate to severe (NRS 4 to 10) in 30% to 67% of NRS scores (Table 2). All 10 REPOS items were scored more frequently when NRS was 4 to 10, when comparing them to no pain and mild pain cases. The items tense face, raising upper lip and closing eyes scored most frequently in the presence of moderate to severe pain, while the items fearful look and panicky were scored least (Figure 1).

Table 2. Pain assessments results

	Median score (IQR)	Moderate to severe pain (NRS 4 to 10) Number of observations (%)
REPOS score (N=183)	3 (1 to 5)	101 (55)
NRS-observer (N=182)	2 (0 to 4)	54 (30)
NRS-proxy (N=107)	3 (1 to 6)	47 (44)
NRS-patient (N=24)	6 (2 to 7)	16 (67)

REPOS, Rotterdam Elderly Pain Observation Scale; NRS, Numeric Rating Scale; IQR, interquartile range

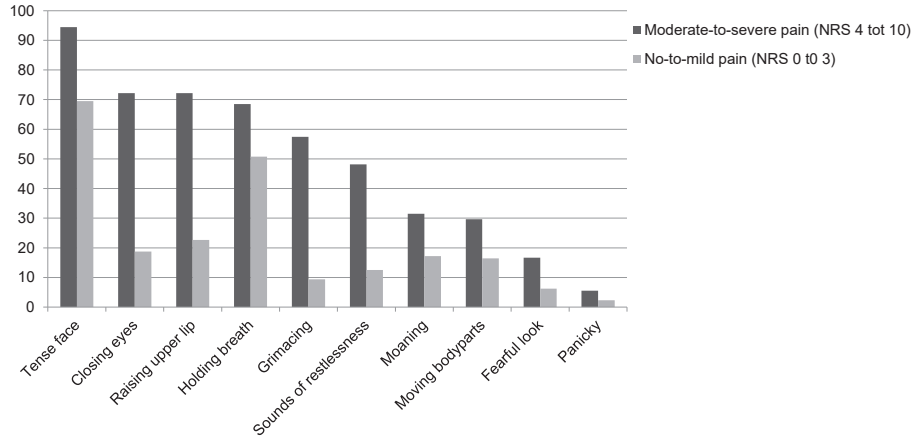

Figure 1. Percentage of scored REPOS items for no-mild pain and for moderate-to-severe pain

Internal consistency

The Cronbach's alpha coefficient for internal consistency of the REPOS was 0.73. The item-total correlations ranged from 0.18 to 0.69, and were below 0.30 for 4 items (panicky, fearful look, moaning and moving body parts).

Concurrent validity

The REPOS score was correlated to the NRS-observer, NRS-proxy and NRS-patient separately. The Pearson product moment correlation coefficient ranged from 0.64 (95% CI 0.51 to 0.74) to 0.80 (95% CI 0.72 to 0.86) (Table 3).

Deleting the 4 items with low correlations for internal consistency had hardly any effect on the Pearson coefficients, which then ranged from 0.62 (95% CI 0.49 to 0.73) to 0.80 (95% CI 0.72 to 0.86).

Table 3. Correlation between REPOS score and the various NRS scores

		REPOS score	NRS-observer	NRS-proxy	NRS-patient
REPOS score	*Number of observations*	*183*	*182*	*107*	*24*
	R	-	0.73	0.64	0.66
	95% CI	-	0.65 to 0.79	0.51 to 0.74	0.35 to 0.84
NRS-observer	*Number of observations*		*182*	*107*	*24*
	R		-	0.80	0.77
	95% CI		-	0.72 to 0.86	0.53 to 0.90
NRS-proxy	*Number of observations*			*107*	*24*
	R			-	0.72
	95% CI			-	0.45 to 0.87
NRS-patient	*Number of observations*				*24*
	R				-
	95% CI				-

REPOS, Rotterdam Elderly Pain Observation Scale; NRS, Numeric Rating Scale; R, Pearson correlation; CI, Confidence Interval

Sensitivity to change

Twenty-three pairs of before-and-after scores were included for the sensitivity-to-change analysis. Twenty-one concerned a pharmacological pain-reducing intervention; in 17 cases (81%) administration of an opioid. The other 2 pairs concerned non-pharmacological interventions, namely taking a rest when moving is painful and changing posture to relieve pressure sores

The median REPOS score declined significantly from 4 (IQR 3 to 6) to 1 (IQR 1 to 3) with a median reduction of 2 points (IQR 1 to 4) after a pain-reducing

intervention, both pharmacological and non-pharmacological. This change was statistically significant ($p<0.001$). The percentage of REPOS scores indicating no pain (score 0 to 2) increased from 9% (2/23) to 70% (16/23).

Cut-off score

In 107 observations, both a REPOS score and a NRS-proxy score were available. At the cut-off REPOS score of 3, sensitivity was 0.81 and specificity was 0.62. The ROC curve, with an AUC of 0.80 (95% CI 0.71 to 0.88), is displayed in Figure 2.

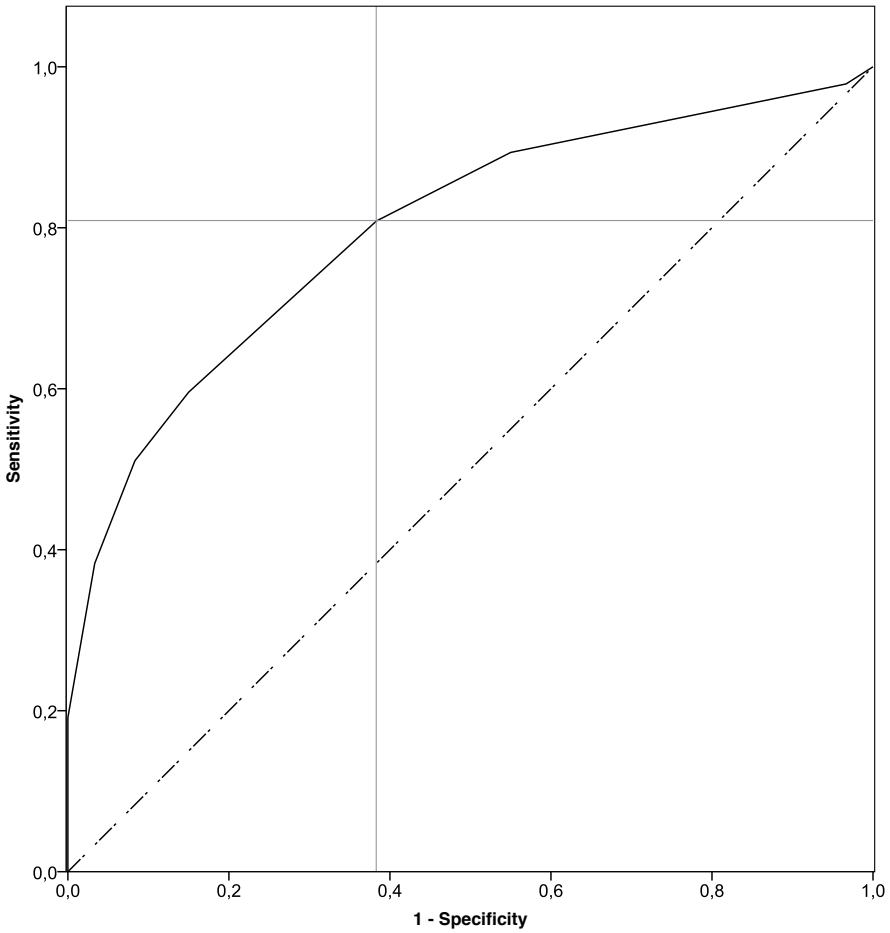

Figure 2. ROC curve of the optimal sensitivity and specificity for the REPOS score

The full line represents sensitivity and specificity of de REPOS score. The dotted line represents the line for which sensitivity and specificity are equal. A horizontal and a vertical grey line are added to show the optimal cut-off value of the REPOS score

The positive predictive value was 0.62 and the negative predictive value was 0.80.

In 21% (23/107) of observations the REPOS score was indicative for pain (score 3-10) whereas the NRS-proxy score was below 4; suggesting false-positive outcomes of the REPOS. In contrast, in 8% (9/107) of observations the REPOS score did not indicate pain (score 0-2) whereas the NRS-proxy score did (score 4-10), suggesting false-negative outcomes.

DISCUSSION

The findings from this study show that the REPOS is a reliable and valid tool to assess pain in non-communicative end-of-life patients. In addition, good sensitivity to change was demonstrated.

A variety of observational pain scales have been developed for other settings where non-communicative patients are treated, including intensive care units[29] and nursing homes[30]. Only one, the MOPAT[16], has been validated for non-communicative end-of-life patients, albeit preliminary and without establishing a cut-off score. The MOPAT was published (2011) after start of our study (2010). We therefore could not use it, although it would have been interesting to compare the two scales. One disadvantage of the MOPAT, however, is that changes in heart rate and blood pressure are included. We question the usefulness of these items, as a person's physiology may change at the end of life, regardless of the presence of pain. Also, these measurements are often stopped at the end of life, as recommended in the Liverpool Care Pathway for the dying patients[17]. In addition, the behavioural items are scored on a 4-points scale (none, mild, moderate or severe), which might be subject to individual interpretation. In contrast, the well-defined items of the REPOS are scored for presence or absence. This may result in a more objective assessment.

The overall internal consistency of the REPOS in the present study was adequate as judged from the Cronbach's alpha coefficient of 0.73[31]. Although the item-total correlations of 4 items (panicky, fearful look, moaning and moving body parts) were below 0.30, we chose to retain those items. These low values could be related to the less frequent occurrence of those behaviours. For example, the ability to fully react with all body parts is often diminished in the end-of-life stage. In terms of concurrent validation, a 6-items REPOS from which those 4 items were removed did not perform better than the original 10-items REPOS. A major reason for retaining these items is that the scale would be applicable in other settings with non-communicative patients as well.

With respect to concurrent validity, a high correlation (0.73) was found – not surprisingly – between REPOS and NRS scores assigned by the same person. The correlation between REPOS and the gold standard (NRS-patient) was only moderate[31], as is seen in other pain scale studies too[32, 33]. This moderate correlation is perhaps explained by patient characteristics. Patients who are unable to report pain with the NRS seem to be more nonverbally responsive[32, 34]. For these patients a behavioural score would be a better reflection of their pain than a proxy NRS only.

It is not unlikely that the REPOS score and the NRS-proxy score differ to some extent. A high REPOS score combined with a lower NRS-proxy score, or a so-called false positive score, is typically seen in patients who show 'emotional' behaviour not related to pain, but based on anger, fear or agitation[35, 36]. The opposite, a false-negative score, may occur when the attending nurse has observed behaviour not included in the REPOS score, such as muscle tension. Alternatively, the nurse's NRS score reflects knowledge of relevant characteristics, such as history or medication use, illness and other patient specific characteristics[12, 13, 37].

This study showed that the cutoff score of 3 or higher is applicable for non-communicative end of life patients. Application of a 'one-fits-all' cutoff score is debated, however[38, 39]. A reason suggested by Chan et al is that different underlying conditions cause different types of damage to the brain, and consequently different responsiveness to pain[39]. Based on these arguments one could plead for an individualized cutoff score, which has been recommended for other vulnerable patients groups, i.e. young children[40]. However, this approach asks more from the caregivers: a dynamic approach with evaluation and adjustment at regular times and when indicated. As daily pain assessment itself was shown to be problematic[41], one can wonder if an individualized approach is feasible in a daily care situation[42, 43].

A strength of the present study is that most observations were done within the last two weeks of life and therefore including even those patients near the time of death. In the previous validation study of the REPOS[14], only a small proportion of the population was at the end of life. In addition, communicative patients rated their pain themselves, which enabled comparison between the REPOS and the gold standard of self-report. Also, the sample size in the present study was 100 patients, which far exceeds the minimal number of 50 patients[44, 45].

Some limitations of this study have to be addressed, however. First, this is a single-centre study and therefore extrapolating the findings to other settings, like palliative home care or community based palliative care, should be done carefully. Nevertheless, it seems unlikely that pain behaviour would be different in a different palliative environment. Second, the sensitivity-to-change analysis con-

cerned only a relatively small sample. However, this limitation is encountered in many other psychometric studies, seeing that researchers often are not available when patients receive additional analgesia and also because nurses may tend to forego reassessment after a pain-reducing intervention[46]. The comparable MOPAT study[16] overall also included fewer patients than planned, also in part for logistical reasons. The fact that the observer knew whether the patient received pain medication or not, could be considered a weakness of the sensitivity-to-change analysis. In the ideal situation, observers blinded for this condition apply the REPOS when watching video recordings made before and after an intervention. However, it was felt undesirable to ask relatives' approval for video recordings of their loved ones in the dying phase for research purposes. Still, knowing that the REPOS is sensitive enough to measure small changes after an intervention means that it is suitable for pharmacodynamic studies, which are urgently needed in this palliative patient group[11]. Lastly, in the present study the REPOS was compared with NRS scores, however a comparison with another behaviour pain scale would have strengthened the reliability and validity testing[47]. At the time this study with the REPOS score was started (2010), the MOPAT score or another behaviour pain scale were not validated for the palliative population. In future studies different observational scales could be compared and should than preferably be assigned by different observers.

CONCLUSIONS

In conclusion, the REPOS seems to meet the criteria for the use of pain measurement tools in palliative care of the Expert Working Group of the European Association of Palliative Care (EAPC)[48]. That is, ease of administration, validity, sensitivity to treatment effect, validation study in palliative care, and multilingual validity (it is available in Dutch and English). In addition, next to the Dutch national palliative guidelines[15], the use of the REPOS for pain assessment in non-communicative patients is recommended in a report on quality indicators in palliative care, published by the Netherlands Institute for Health Services Research[49]. We have demonstrated that the REPOS is a valid tool for the assessment of pain in non-communicative end-of-life patients. We recommend its use on a daily basis for every non-communicative palliative patient. After a brief training course every professional palliative caregiver will be able to use it in daily practice. A REPOS instruction sheet and an educational CD-ROM and e-module (both in Dutch or English) are available to guide implementation and training[18].

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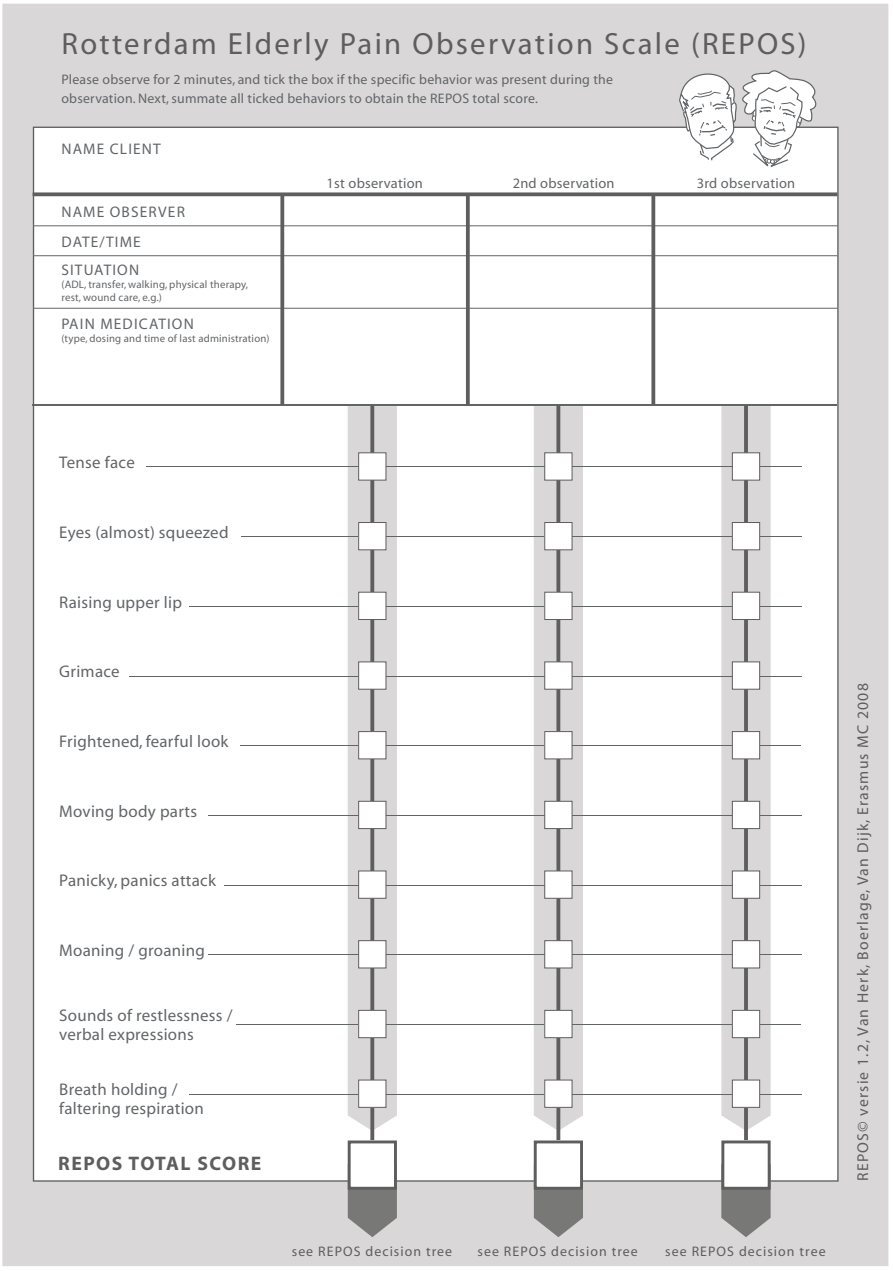
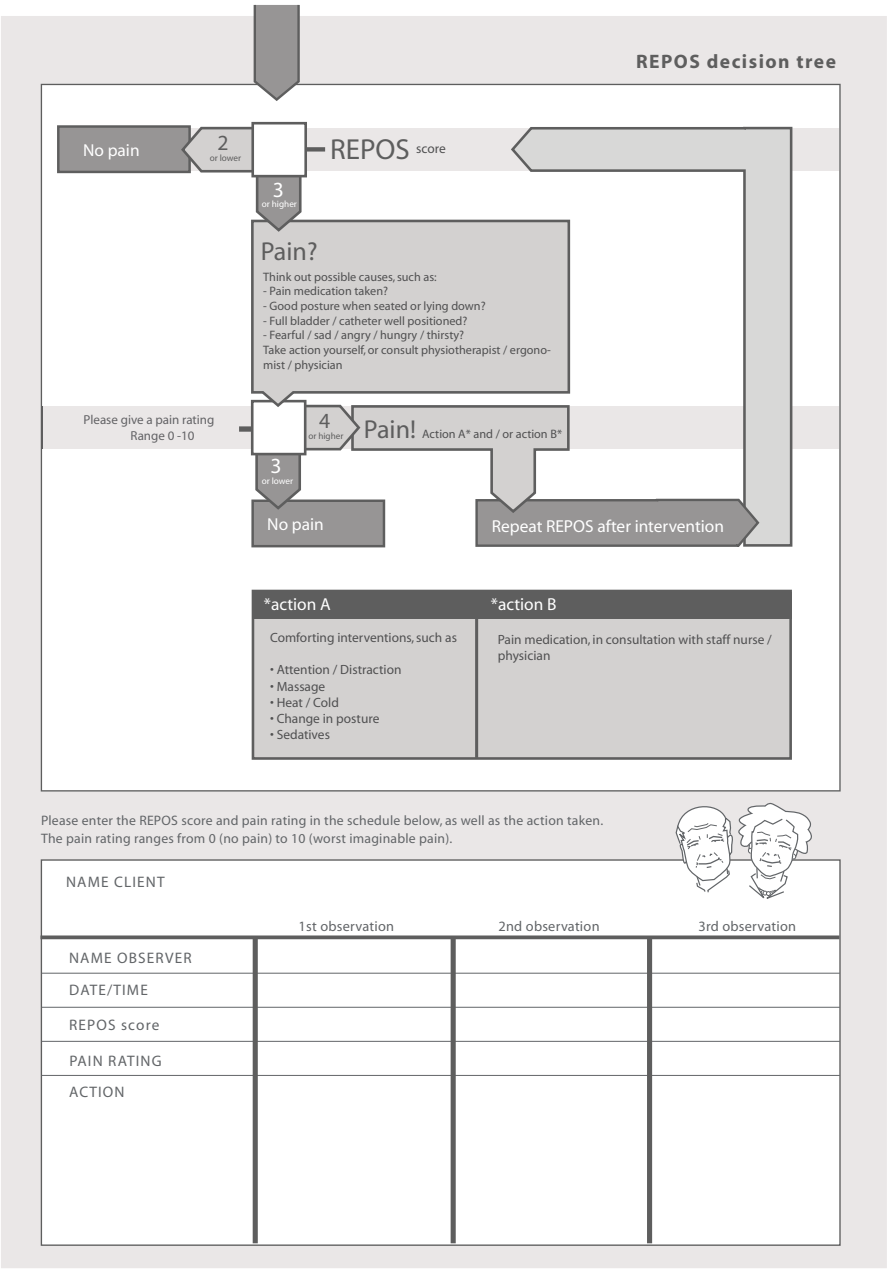
SUPPLEMENTARY FILES



Supplement 1. Rotterdam Elderly Pain Observation Scale (REPOS) score form



Supplement 2. Rotterdam Elderly Pain Observation Scale (REPOS) decision tree

Rotterdam Elderly Pain Observation Scale (REPOS)

Instruction chart

Definitions of the behaviors

Each item in the REPOS represents specific behavior or a certain reaction. The REPOS does not score intensity of behavior, but rather occurrence, yes or no. An item is only scored as present if the behavior in question was clearly visible. Scoring is not useful if the client is in relaxed sleep.

Tense face
One or more facial muscles are being tightened (are not relaxed).
This is NOT scored when client is talking.

Eyes (almost) squeezed
Eyes tightly shut or squeezed.
Do NOT score if client shows blinking eyes or eyes shut without squeezing.

Raising upper lip
The upper lip is being pulled up, shortening the distance between upper lip and nose; nasio-labal furrows deepened, nostrils raised and enlarged.

Grimace
Scored as present only when the following three facial expressions occur together:
1) Eyebrows drawn together and downward, with the skin fold between the eyebrows bulged out.
2) Eyes tightly shut or squeezed.
3) Nasio-labal furrows deeper than normal and drawn up sideways.

Frightened, fearful look
Large, widely opened eyes, and inner sides of eyebrows slightly raised and drawn together.

Moving body parts
Each movement indicative of resistance or protecting a (painful) body part. Included are movements such as changing one's position in a chair so as to relieve one's bottom, and grasping the head.
Do NOT score when the movement or action is functional, e.g. pushing one's hair out of one's face, or raising arms to take off clothes.

Panicky, panics attack
An extreme manifestation of anxiety showing in random nervous body movements or fierce resistance. This may co-occur with:
- *Frightened expression characterized by large, widely opened eyes, and inner sides of eyebrows slightly raised and drawn together; and/or*
- *Intense screams or verbal expressions of pain, such as 'ouch' or "you're hurting me'.*

Moaning/groaning
Monotonous and whining sound.

Sounds of restlessness/verbal expressions
Sudden or persisting intense screams or verbal expressions of pain, such as 'ouch' or "you're hurting me'.

Breath holding/faltering respiration
Briefly interrupted breathing, gasping.

Supplement 3. Rotterdam Elderly Pain Observation Scale (REPOS) instruction chart

CHAPTER 3

BISPECTRAL INDEX (BIS) MONITORING IN TERMINALLY ILL PATIENTS – A VALIDATION STUDY

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ABSTRACT

Context: If regular therapies cannot relieve symptoms sufficiently in the last days of life, continuous palliative sedation may serve to reduce consciousness. Sedation level can be measured with EEG monitoring with the bispectral index (BIS) monitor.

Objective: To determine the feasibility and validity of BIS monitoring in terminally ill patients.

Methods: In this prospective study, BIS registrations were performed in unconscious end-of-life patients admitted to a palliative care centre. Validated scores were used to measure level of sedation (Ramsay score), pain (NRS or REPOS), delirium (DOS score) and overall comfort (NRS). Validity and sensitivity to change of BIS values were considered and the effects of medication and the time till death on BIS values were evaluated in a linear mixed model analysis.

Results: Fifty-eight patients were included for analysis. BIS monitoring was acceptable to patients, relatives and medical staff. BIS values were moderately correlated with Ramsay scores (0.46), but were highly variable for deeply sedated patients. BIS values changed significantly before and after a midazolam dose ($p<0.001$). Midazolam treatment resulted on average in a statistically significant reduction of the BIS values (-4.5, 95% CI -7.0 to -2.0) whereas morphine and haloperidol did not.

Conclusion: This is one of the first validation study in which BIS monitoring in end-of-life patients is described. BIS monitoring is feasible in unconscious terminally ill patients. However, based on our results, the wide range of BIS values in deeply sedated and comfortable patients seems to hamper its use in daily clinical practice.

INTRODUCTION

In some patients in the terminal phase of life, regular medication may fail to provide adequate symptom relief. Then, continuous palliative sedation may be an option of last resort. However, it cannot be excluded that patients suddenly awaken[1]; this occurred in 39% and 49%, respectively, of patients in two separate studies[2, 3]. During palliative sedation, it is important to monitor the patient's comfort[4-6]. However, a valid assessment tool within this context is not available[7].

Patients' self-report of comfort is typically considered the 'gold standard'[8, 9]. However, in the terminal phase of life, patients may not be able to self-report their symptoms, due to cognitive failure prior to death[10, 11] or due to being unresponsive in those last days[12-14]. It would seem obvious that assessment with observational scales or physiological devices is needed for non-communicative end-of-life patients[15]. Most observational sedation scales (e.g. Ramsay score), however, have not been validated for palliative care facilities[15, 16]. Moreover, there is no general consensus on how the effect of palliative sedation should be assessed; either by symptom control or by sedation depth, neither which observational assessment should be used[15, 16].

Monitoring palliative sedation is still based on observational scales only. A main problem with these scales is that they consider unresponsiveness equal to unawareness, the correctness of which has been questioned[15, 17]. We aimed to explore whether an electrophysiological device, the bispectral index (BIS) monitor, would prove a clinically relevant parameter that measures unawareness and may help improve the care for end-of-life patients.

During general anaesthesia, the level of sedation can be continuously monitored using the BIS monitor: a continuous electrophysiological measure, derived from non-invasive EEG monitoring. The values displayed on the BIS monitor serve to guide sedation therapy[18-20]. BIS monitoring during palliative sedation may be valuable, since distressed behaviour is often diminished in the end-of-life stage. Therefore patients could mistakenly be considered to be comfortable when using only behavioural assessment[15, 21].

So far, the use of BIS monitoring in palliative care has been reported in only two studies with small sample sizes (respectively, one and 12 patients)[22, 23]. These studies concluded that BIS monitoring is acceptable for patients, family and care-givers and can be used to monitor sedation level as well as the effect of medication. However, these descriptive studies were not aimed at validation of BIS monitoring in the palliative care setting. Therefore, in this study we applied BIS monitoring in combination with validated pain, sedation and delirium assess-

ments, and aimed to determine whether BIS monitoring is feasible and valid for use in a hospice setting.

METHODS

Design and setting

This prospective observational pilot study was performed during various periods over the years 2008 to 2012, for almost 3 years in total, in Laurens Cadenza, the largest palliative care centre in the Netherlands, with 20 beds for terminal care and symptom management. Annually 200 to 250 patients are admitted.

Participants

Patients admitted for palliative care during the study period were eligible to participate, except those who were unable to provide consent and those admitted for a short period, for instance to find the most effective pain medication. The timing of information provision about the study was decided in consultation with the responsible health professionals. If possible, the patient was informed in the presence of a relative. They were given at least 24 hours to consider their decision. Written consent was obtained from participants. Later, the patient and/or the family were asked renewed consent for BIS monitoring.

This study was approved by the Medical Ethics Review Board of the Erasmus University Medical Centre and the institution's local board of directors of Laurens Cadenza.

Assessment tools

Level of sedation

Level of sedation was assessed both with the Ramsay score and with BIS monitoring. The Ramsay score consists of 6 sedation levels, ranging from 1 (agitated and restless) to 6 (no response to stimulus)[24]. This score is easy to use also in palliative care[25], and has been validated for intensive care and surgical patients[26, 27]. BIS monitoring measures the level of sedation based on a 4-points EEG. Level of sedation is expressed as the bispectral index, which is a dimensionless parameter ranging from 0 (flat line EEG) to 100 (fully awake). We used the BIS Vista monitor (Covidien, Mansfield, U.K.) with the commercially available adult BIS quartosensor placed on the patient's forehead. During a BIS registration a single BIS value was saved every minute. In this study, the minimum duration of a single registration was 30 minutes.

Pain

Pain was assessed in one of two ways, based on the patient's capacity to communicate. Communicative patients self-reported a Numeric Rating Scale (NRS) score for pain, from 0 (no pain) to 10 (worst possible pain). A NRS pain score of 4 or higher is considered to reflect moderate to severe pain[28]. The NRS is considered a valid tool to assess cancer pain intensity[29, 30]. For non-communicative patients, nurses applied the NRS to provide a proxy-score and in addition applied the Rotterdam Elderly Pain Observations Scale (REPOS)[31]. The REPOS is recommended in Dutch national palliative guidelines for specific non-communicative patient groups[4]. The REPOS consists of 10 behaviours, which the observer scores as either present or absent after having observed the patient for two minutes[31]. Thus, the score range is 0-10; a score of 3 of higher is indicative for pain.

Delirium

The Delirium Observation Screening (DOS) scale consists of 13 verbal and non-verbal behaviours which are scored for their presence three times a day, resulting in a total score ranging from 0 to 39. This total score is divided by 3 and a resulting mean of 3 or higher for those three observations over 24 hours is indicative for delirium. The DOS scale has been validated for use in patients with a high risk for delirium[32].

Comfort

The degree of comfort was measured with an NRS-comfort score from 0 (no comfort at all) to 10 (optimal comfort)[33]. Communicative patients self-reported the NRS-comfort score, and for non-communicative patients nurses assigned a score based on the following reasoning: 'what total comfort score would you give for the patient's present situation, imagining a score of 10 as the most comfortable situation the patient can be in?'[34]. An NRS-comfort score of 5 or less was defined as reflecting insufficient comfort.

Procedures

The above-mentioned scales for pain, delirium and comfort were applied daily by the responsible nurse or the first author (AM). In patients receiving sedatives, level of sedation was assessed with the Ramsay score at least once a day and if possible more often during BIS monitoring.

In newly included patients, BIS monitoring was first tested, if possible during a regular sleep without the need for a sedative. This test measurement was started just before the patient went to sleep, either during the day or at night, and stopped after the patient woke up. It served to familiarize the patient and

family with the procedure and to identify potential problems. Next, more registrations were made, provided that the patient's condition permitted this, and especially when sedative drugs were administered, including a single dose. If the test measurement proved valid, the data obtained were also included in the analysis. BIS monitoring was applied for research purposes only, and medical treatment was not based on BIS values. The monitor was not covered and values were visible to caregivers and relatives.

Next to validity, feasibility and clinical utility of BIS monitoring were considered. Feasibility was defined on the basis of aspects such as ease of use, the need and time for training of caregivers, and the acceptability for patients and their family [35]. Clinical utility was defined on the basis of aspects such as the relation of the BIS values with norm values for sedation and the fact whether BIS monitoring adds information to the already available measurement tools for symptoms [35].

Medication

A record was kept of all drugs administered, and notably the consumption of morphine, midazolam and haloperidol was analysed. Drugs were prescribed according to the Dutch national palliative guidelines [4]. In our practice, for continuous palliative sedation midazolam is usually given in subcutaneous boluses 6 times a day via a subcutaneous-access device (insulfon™) and titrated individually to a level of sedation in which the patient is sufficiently asleep (detailed in appendix 1). 'A single midazolam dose' was defined as one administration not preceded, within 4 hours, by another dose.

We assumed that the BIS might be influenced by a subcutaneous bolus morphine or midazolam over a period of 4 hours after administering and for haloperidol a period of 24 hours was set. These timeframes were chosen based on the dosage frequency of 6 times daily for morphine and midazolam or once daily for haloperidol[4].

Other variables

Demographic characteristics (age, gender, diagnoses, and duration of admission), the primary diagnosis and the number of comorbidities were extracted from the electronic medical records. The primary diagnosis refers to the WHO's International Classification of Diseases (ICD-10 classification) coding for the patient's terminal illness. Reasons for exclusion and refusal were recorded.

Statistics

Two aspects of validity were considered, namely concurrent validity and sensitivity to change. For the concurrent validity, Spearman's rank correlation coefficient

was calculated between BIS values and Ramsay scores and between mean BIS values and dichotomized pain, comfort and delirium scores. For validity of the BIS values, the correlation coefficient should exceed 0.30 [36]. At the times when a Ramsay score, pain (REPOS) or comfort (NRS-comfort) score was/were assigned, mean BIS values during 10 minutes (5 minutes before and 5 minutes after the assessment) were calculated and included in this analysis. Since delirium was scored with the DOS over a period of 24 hours, mean BIS values within the same 24 hours were used to correlate BIS with the DOS. Dichotomization was based on the cut-off values for the respective measurement scales, as described above.

For the sensitivity to change analysis, paired mean BIS values before and after a single midazolam dose were selected. Mean BIS-before values were calculated based on the 30 minutes before a midazolam administration. Midazolam administered via the subcutaneous route reaches a maximum plasma level at 20 to 30 minutes after administration[37, 38]. To account for this maximal effect of midazolam, a mean BIS-after value was calculated over a 30-minute period, i.e. from 30 to 60 minutes after administration. The Wilcoxon signed-rank test was applied to compare BIS-before and BIS-after values of single midazolam doses.

A linear mixed model was used to evaluate both the effect of medication (midazolam, morphine and haloperidol) and the time till death on BIS values. The dependent variable in this model was the longitudinal BIS values, and the independent variables were midazolam use during the last 4 hours (yes/no), morphine use during the last 4 hours (yes/no), haloperidol use during the last 24 hours (yes/no), and natural cubic splines of the time till death. This cubic spline function was required to model the complex nonlinear effects of time till death on BIS values. A B-spline basis matrix was used to parameterize the spline variables. The number of knots in the spline function was selected using the Bayesian information criterion, based on which 4 knots and thus 5 spline variables were included for the effect of time till death. A random intercept and an ARMA(1,1) error covariance matrix were used to account for the within-subject correlations. Only BIS registrations of the last week (7 days) before death were selected for this analysis. Mean values per 60 minutes for BIS values and the medication variables were calculated to reduce the strength of the within-subject correlations, to ensure that modelling these within-subject correlations would not lead to an overly complicated model. For this linear mixed model, only data of patients for whom the exact time of medication administration was recorded could be analysed.

Differences in background characteristics between included patients and refusals were checked with the Pearson's chi-square test, Mann-Witney test and Fisher's exact test as appropriate. A two-sided p-value <0.05 was considered

statistically significant. The statistical software programs IBM SPSS Statistics 21 and R (version 3.1.2)[39] with the packages nlme and splines were used to analyse the data.

RESULTS

Participants

During the study period a total of 516 patients were assessed for eligibility. One hundred sixty-five (32%) patients were informed of the study, of whom 65 (39%) gave consent. Figure 1 shows the flow chart of patient inclusion. Four (7%) patients and/or family withdrew from the study after initially giving consent; in

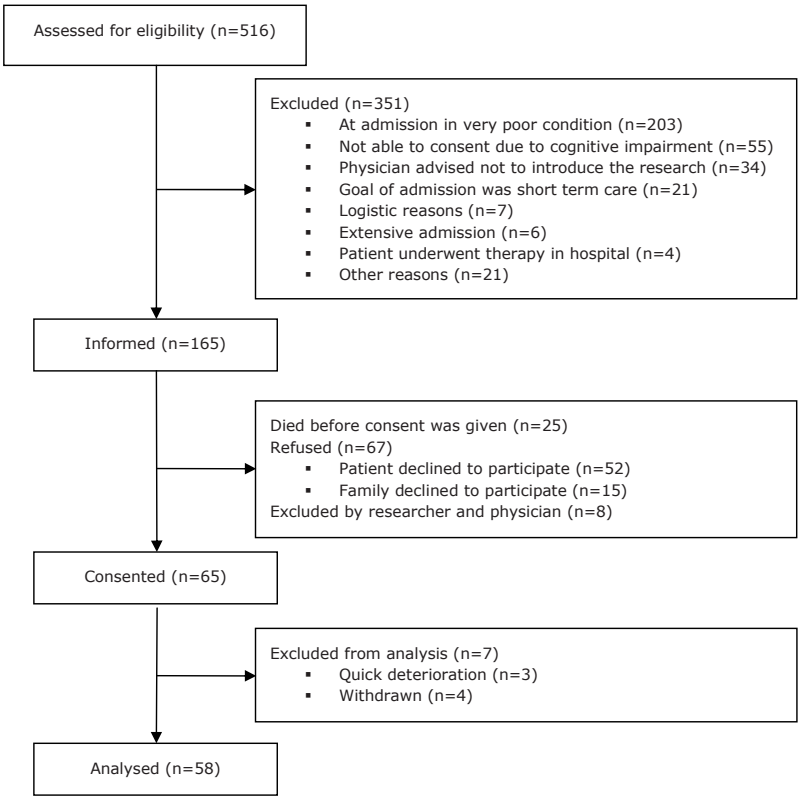

Figure 1. Flow chart patients

3 (5%) patients a BIS registration was not performed because of a very quick deterioration; and thus 58 patients were included in the final analysis. Their median age was 75 years (IQR 63 to 82), 55% were female, and the median duration of admission was 36 days (IQR 17 to 54). Advanced malignancy, mainly of respiratory and digestive organs, was the main reason for admission (97% of patients). None of the background characteristics considered differed significantly between participants and refusals (n=67). Table 1 provides the characteristics of the included patients (N=58).

Thirty-three participants (57%) were continuously sedated during admission. Their median daily midazolam dose during sedation days was 30 mg (IQR 15 to 70).

Table 1. Characteristics of included patients

Characteristic	**N =58**
Gender in N (%)	
Male : female	26 (45) : 32 (55)
Age in years; Median (IQR)	75 (63 to 82)
Duration of admission in days; Median (IQR)	36 (17 to 54)
Primary diagnosis in N (%)	
Neoplasms	56 (97)
Respiratory and intra-thoracic organs	*17 (30)*
Digestive organs	*15 (27)*
Lymphoid and hematopoietic tissue	*5 (9)*
Female genital organs	*4 (7)*
Urinary tract	*4 (7)*
Ill-defined, secondary and unspecified sites	*4 (7)*
Male genital organs	*3 (5)*
Eye, brain and other parts of central nervous system	*3 (5)*
Other	*1 (2)*
Disease of nervous system	1 (Parkinson's disease)
Disease of circulatory system	1 (Heart failure)
Co-morbidities	
Median (IQR) number of diagnoses	2 (1 to 3)

IQR, interquartile range

Feasibility

In total 167 BIS registrations (in 58 patients) were made, 18 (11%) of which were excluded from analysis because of poor quality or too short duration (<30 minutes). Too short duration was mostly the result of the patient removing the sensor in a confused state of mind.

Nurses needed no more than approximately 10 minutes' instruction to ensure an adequate BIS registration, since the use of the monitor and the application of BIS sensor on the patient's forehead were fairly easy.

BIS monitoring was acceptable to patients and their relatives. Participants felt they were carefully looked after, even if they would become unable to communicate symptoms. Relatives felt supported by the measurement. Even the medical appearance of the sensor on the patients' forehead did not bother relatives. Patients and their relatives explicitly told us that they were very thankful for participation in this study.

Validity

For the analyses, 149 BIS registrations of 58 individual patients were used, with a median of 2 (IQR 1 to 3) BIS registrations per patient and a median duration of 520 minutes (IQR 249 to 844 minutes) per registration. Thirty-one patients (53%) were studied till death.

For 26 patients Ramsay scores were available during a BIS registration, with a median of 4 (IQR 2 to 7) Ramsay scores per patient. The Spearman's rank correlation coefficient between BIS and Ramsay scores was 0.47, which indicates a moderate correlation. Figure 2 shows a boxplot relating BIS values and Ramsay scores. Notably, BIS values varied from below 30 to above 90, even when the Ramsay score indicated that the patient did not respond to a stimulus.

Median (IQR) BIS values during symptom assessments (pain, comfort and/or delirium) and the accompanying Spearman's rank correlations coefficients are given in Table 2. Spearman's rho varied from 0.03 for delirium to 0.30 for comfort, which indicates weak correlations.

Regarding sensitivity to change, figure 3 shows a boxplot of 42 paired mean BIS values before and after the administration of a single dose of midazolam during 34 registrations of 24 patients. The median BIS-before value of 76 (IQR 65 to 82) was reduced to a median BIS-after value of 60 (IQR 54 to 76). This change was statistically significant ($p<0.001$).

The exact times of medication administration were recorded for 40 patients, and in 33 of those BIS registrations had been made in their last week before death. Data of these 33 patients were included in the linear mixed model analysis. Figure 4 shows a plot of the predicted BIS values, with the 95% confidence interval, in the last week before death, for patients who had not received morphine, midazolam or haloperidol. On the last day before death, a steep decline in BIS values is seen, with a remarkable spike just before death. In this model, midazolam treatment resulted on average in a statistically significant reduction of the BIS values of -4.5 (95% CI -7.0 to -2.0, $p<0.001$). Morphine and haloperidol

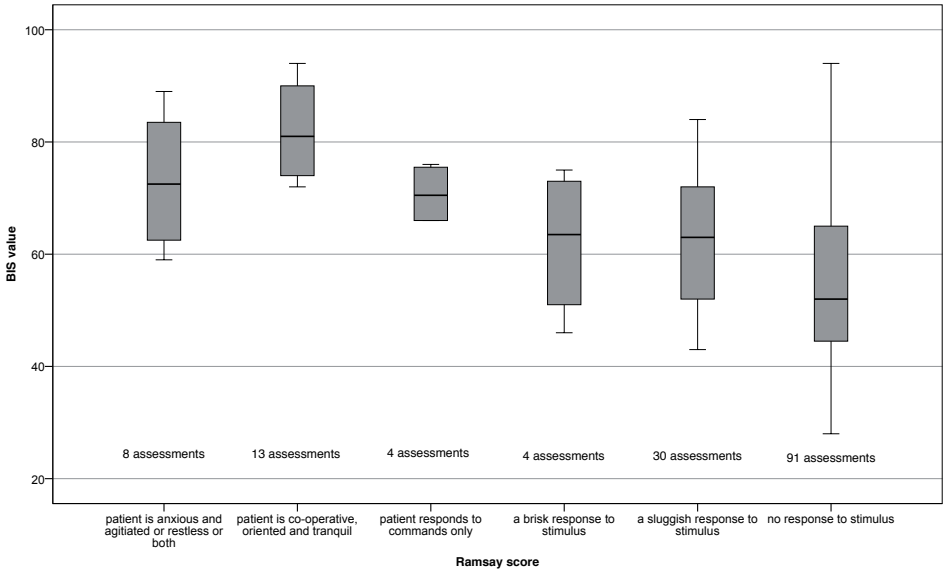

Figure 2. Boxplot for BIS values at different levels of Ramsay scores

This figure shows median and 25th and 75th percentiles [box top and bottom] and 5th and 95th percentiles [whiskers]

Table 2. BIS values during symptom assessments

Symptoms assessment	Number of assessments (number of patients)	BIS value Median (IQR)	Spearman's rho
Pain			
Yes (NRS score 4 to 10)	10 (8)	68 (59 to 76)	0.11
No (NRS score 0 to 3)	124 (22)	58 (48 to 75)	
Comfort			
Yes (NRS score 6 to 10)	115 (21)	54 (46 to 69)	0.30
No (NRs score 0 to 5)	23 (11)	66 (60 to 80)	
Delirium			
Yes (DOSscore >3/24hrs)	12 (9)	71 (62 to 75)	0.03
No (DOSscore <3/24hrs)	37 (27)	71 (65 to 79)	

NRS, Numeric Rating Scale; DOS, Delirium Observation Screening; IQR, interquartile range

had no statistically significant effect, p=0.85 and 0.35 respectively; with an average reduction of BIS values of -0.8 (95% CI -6.1 to 4.4) for morphine and -2.5 (95% CI -7.8 tot 2.7) for haloperidol. In addition, patients who received either midazolam, morphine or haloperidol would have had a similar pattern of predicted BIS values in their last days as displayed in figure 4, with the only difference a reduction of 0.8 to 4.5 in BIS values depending on the medication administered.

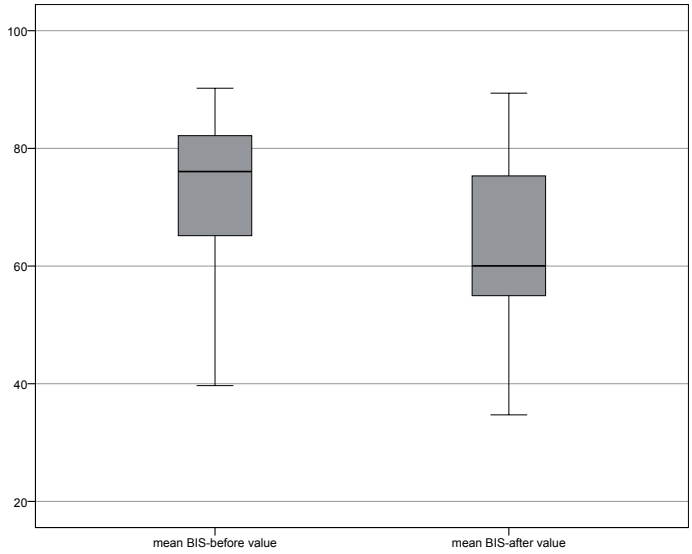

Figure 3. Boxplot for BIS values before and after a single administration of midazolam (42 doses)

This figure shows median and 25th and 75th percentiles [box top and bottom] and 5th and 95th percentiles [whiskers]. The change in BIS value before and after was statistically significant ($p<0.001$)

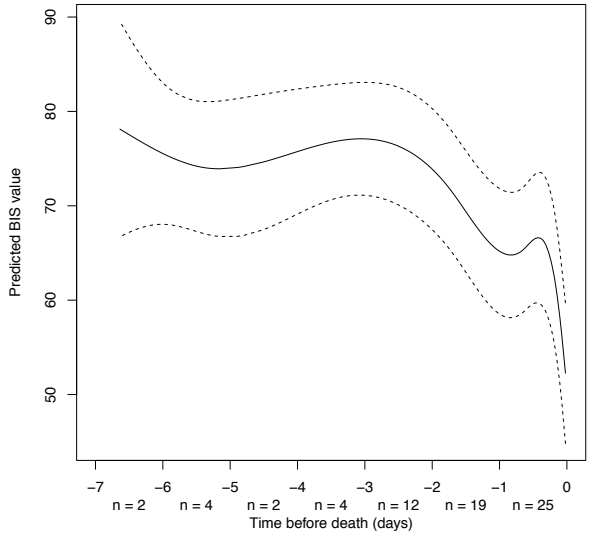

Figure 4. Plot of predicted BIS values, including the 95% confidence interval, in last week before death, for patients who have not received morphine, midazolam or haloperidol

DISCUSSION

This study considered the concurrent validity, sensitivity to change and feasibility of BIS monitoring in end-of-life patients. We found only a moderate correlation between BIS and Ramsay scores (concurrent validity) due to varying BIS levels (between 30 and 90) in patients with a Ramsay score indicating deep sleep, as was reported for midazolam sedation in intensive care and surgical patients[40-42]. This suggests that BIS might be of added value in these cases as suggested by another recent paper as well[43]. Next, BIS values were significantly lower after midazolam treatment but the difference was too small to be clinically relevant. We found some anecdotal arguments that BIS monitoring may be of relevance for family and nurses, like found in other studies on BIS monitoring in palliative patients[22, 23].

Another aspect of concurrent validity we studied was the correlation of BIS and pain scores, which was weak. Another variable measured during BIS monitoring - electromyography of the forehead (EMG) - may be of value for pain assessment[44]. Future research may incorporate EMG as an additional and probably relevant parameter for both sedation and pain assessment.

Regarding the clinical utility, norm BIS values for adequate anaesthesia range from 40 to 60[45]. However, norm values for continuous palliative sedation with midazolam are not available and cannot be established on the basis of our data. Moreover, in our population only 50% of patients reached BIS values below 60 after a single midazolam dose. Since norm values are lacking and BIS values for comfortable and adequately sedated patients are variable (illustrated in 2 cases in appendix 2), further research is needed to use BIS values for individual drug titration of palliative sedation. In addition, palliative patients differ in several aspects from other patients groups (e.g. intensive care patients) for which sedative monitoring by BIS is used; differences in administered sedatives drugs and their route of administration[41, 46], disease status and/or emotional burden for patient and family, and possible changes in brain processes during end-of-life could affect BIS values.

Worth mentioning is the remarkable peak in BIS values in more than half of the registrations just before death, which is also reflected in the predicted effect curve for time till death in the linear mixed model (figure 4 and appendix figure 2). This typical phenomenon was also seen in a case series of intensive care patients[47] and in the other two previous studies on BIS monitoring in dying patients[22, 23]. Chawla and co-workers[47] propose several explanations for this phenomenon: 1. External artefacts causing unreliable BIS values, 2. Muscular activity interfering with BIS values and 3. Cerebral ischemia resulting in a loss of electrical potential

and a cascade of electrical activity. In addition, this peak effect and other fluctuations were found to be comforting for families in those studies, like in our study.

Some limitations of this study have to be addressed. The main limitation of this study is the use of non-validated scales for terminally ill patients. Validated scales were not available at the time of the data collection for the current study. A non-validated sedation scale (not otherwise named), which resembles the Ramsay scale, is described in the Dutch guideline for palliative sedation[48]. Therefore, the use of the Ramsay score for our study was, at that time, an obvious choice. In addition, validated pain and delirium scales were lacking for terminally ill patients at the time we prepared for this study and in later years, publications became available[7, 16, 49]. Regarding the delirium score, DOS, we found its use in palliative patients sometimes inappropriate, since some items could not be scored in unresponsive patients, like Detroyer et al published recently[50]. The accuracy of observational scales in palliative patients may be questioned for another reason, since the ability to react with facial expressions or body movements may be diminished in the end-of-life stage. With monitoring palliative sedation we aim for a comfortable patient with a relaxed posture and a calm facial expression, but what if unresponsiveness is not equal to unawareness[17]? We consider the Ramsay scale as a measure to distinguish between unresponsiveness and responsiveness, and that BIS might be of valuable in the unresponsive patient but future studies should use the more recently validated instruments for sedation, delirium and pain. Another limitation is that pain and comfort were assessed only once daily.

In conclusion, based on our results we were not able to support the statement that BIS would differentiate between the various levels of sedation during midazolam treatment. Further research is needed to consider BIS as a tool for monitoring the level of sedation in palliative patients in daily practice.

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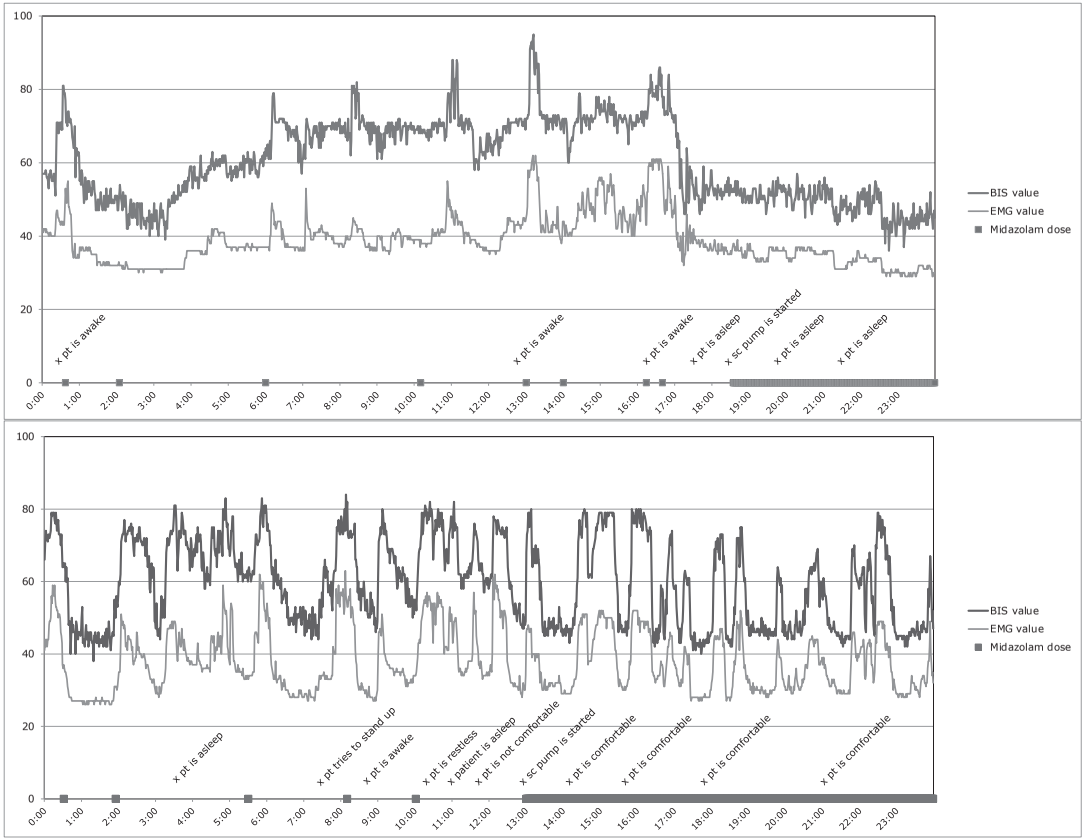
APPENDIX

Dosing regimen of midazolam for continuous palliative sedation

Based on the Dutch national palliative guidelines[4], continuous palliative sedation is started with a loading dose of midazolam 10 mg subcutaneously, followed by subcutaneous bolus injections of 5 mg midazolam six times daily. In case of insufficient effect, an additional bolus dose of 5 mg midazolam may be administered after 2 hours and after minimal 4 hours the midazolam maintenance therapy may be increased with 50% (to 7.5 mg) subcutaneously six times daily. A subcutaneous pump for continuous administration of midazolam was used when high dosages (a volume of at least 3 millilitres per time) were needed.

Two illustrative cases

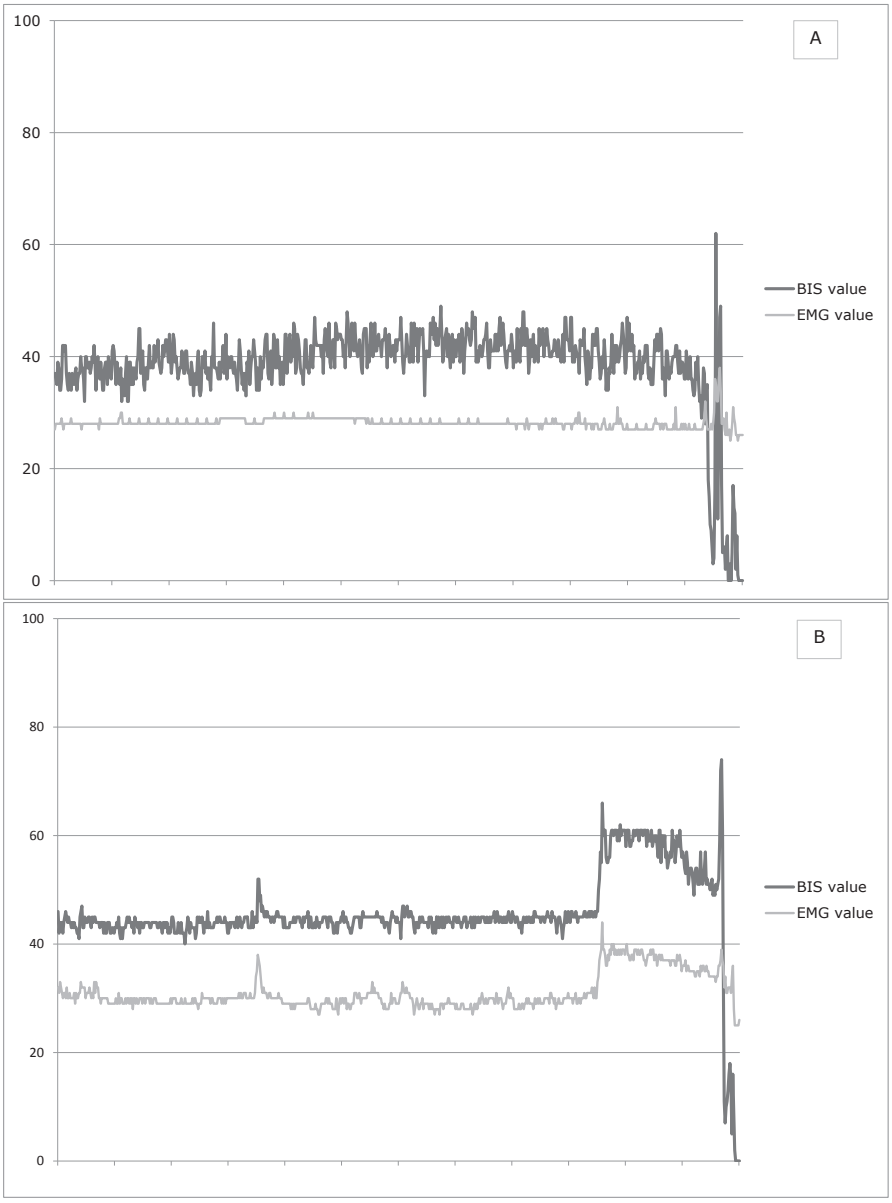
Appendix Figure 1 illustrates BIS graphs over a 24-hour period of two patients who needed very large doses of midazolam that day (260 to 295mg/day). For both patients a subcutaneous pump had to be started, since bolus injections were no longer appropriate due to large volumes of the injection fluid (over 3ml per bolus) needed. These two registrations show different patterns toward a comfortable and asleep status; one with a somewhat abrupt decline in BIS values at the time a subcutaneous midazolam pump is started (graph A) and the other with great variability in BIS values even during continuous midazolam administration (graph B). In both registrations the influence of the muscle activity of the forehead (EMG) can be seen; BIS values increase and decrease synchronous with EMG. Later, both registrations became more stable, with BIS values between 30 and 50 till death 2 to 3 days later (Appendix Figure 2, A and B correspond to the same patients as in Appendix Figure 1). Notably, both registrations show an abrupt decline in BIS values with a remarkable peak shortly before death. In all registrations till death we found decreasing BIS values during the last hours or minutes of life; this could be either a slow decrease or an abrupt steep decline. This peak in values was seen in 17 (55%) of the 31 registrations till death.



Appendix Figure 1. Two BIS graphs of patients who needed high amounts of midazolam (24 hours)

A and B shows different patterns towards a comfortable and asleep state

BIS, bispectral index; EMG, electromyography; sc, subcutaneous; pt, patient



Appendix Figure 2. Two BIS registrations of the last 12 hours till death
BIS, bispectral index; EMG, electromyography

PART III
PHARMACOTHERAPY IN PALLIATIVE PATIENTS

CHAPTER 4

MEDICATION USE DURING END-OF-LIFE CARE IN A PALLIATIVE CARE CENTRE

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ABSTRACT

Background: In end-of-life care, symptoms of discomfort are mainly managed by drug therapy, the guidelines for which are mainly based on expert opinions. A few papers have inventoried drug prescriptions in palliative care settings, but none has reported the frequency of use in combination with doses and route of administration.

Objective: To describe doses and routes of administration of the most frequently used drugs at admission and at day of death.

Setting: Palliative care centre in the Netherlands.

Method: In this retrospective cohort study, prescription data of deceased patients were extracted from the electronic medical records.

Main outcome measure: Doses, frequency and route of administration of prescribed drugs.

Results: All regular medication prescriptions of 208 patients, 89% of whom had advanced cancer, were reviewed. The three most prescribed drugs were morphine, midazolam and haloperidol, to 21%, 11% and 23% of patients at admission, respectively. At the day of death these percentages had increased to 87%, 58% and 50%, respectively. Doses of these three drugs at the day of death were statistically significantly higher than at admission. The oral route of administration was used in 89% of patients at admission versus subcutaneous in 94% at the day of death.

Conclusions: Nearing the end of life, patients in this palliative care centre receive discomfort-relieving drugs mainly via the subcutaneous route. However, most of these drugs are unlicensed and guidelines are based on low level of evidence. Thus, there is every reason for more clinical research on drug use in palliative care.

INTRODUCTION

In 2011 approximately 136,000 persons died in the Netherlands, almost one third of them from the consequences of cancer[1]. A systematic review on symptom prevalence in patients with incurable cancer found that the most reported symptoms were: fatigue (88%), appetite loss (56%), pain (45%), dyspnoea (39%), drowsiness (38%), dry mouth (34%), constipation (29%), confusion (24%), nausea (17%), and insomnia (14%)[2].

The goal of palliative care is symptom control by a combination of non-pharmacological measures and drugs. Palliative experts have reached consensus on the essential drugs to treat specific symptoms. These have been compiled in two different but largely overlapping lists: one published by the International Association for Hospice and Palliative Care (IAHPC)[3] and one based on a survey of Australian palliative care physicians[4]. Regrettably, both lack recommendations on optimal dose or route of administration.

Existing recommendations[5, 6] on dose and route of administration are mainly based on level 3 and 4 evidence from case studies or from expert panels. Level 1 evidence from a systematic review or randomized controlled trials is available only for NSAIDs administered to relieve nociceptive pain[7] and morphine to alleviate dyspnoea[8]. Level 3 evidence is available for the treatment of cancer pain with oral morphine[9]. Haloperidol treatment of a delirium in hospitalised patients is based on level 2 evidence from well designed, non-randomized trials[10]. Recent updates of systematic reviews for morphine and haloperidol found no new significant information[11, 12].

The choice of drug and dose tailored to the individual patient is thus hardly supported by evidence from prospective clinical trials. Likewise, there is little evidence for the optimal route of administration, although the subcutaneous route is often preferred in palliative care. Dose adjustment may be needed because liver and kidney function undergo changes at the end of life[13, 14]. It follows that a number of drugs used in palliative care are unlicensed or off-label[15, 16].

Only a few studies in palliative care units[17-19] and services for mainly outpatient groups[20-23] have described medication use in palliative care. To our knowledge, there are no published studies describing the most used drugs with their doses and administration routes, on admission and at the day of death in a large group of patients receiving palliative care.

AIM OF THE STUDY

The aim of this study was to evaluate what drugs were administered, and at what dose and route of administration, from admission to day of death in patients admitted to a single palliative care centre.

ETHICAL APPROVAL

Ethical approval from a review board was not required, since this is a descriptive retrospective study. For retrospective analysis of patient files ethical approval is waived according to Dutch law. All patient data were handled and processed in accordance with the recommendations of Good Clinical Practice.

METHODS

Design and setting

This retrospective cohort study was performed in Laurens Cadenza in Rotterdam, the Netherlands. This is the largest palliative care centre in the Netherlands, with 20 beds for terminal care and symptom management; from 200 to 250 patients are admitted annually. A multidisciplinary team of health care professionals is available 24 hours per day.

Measurements and technical information

Age, gender, primary diagnosis, comorbidities, and duration of admission were extracted from the electronic medical records. The primary diagnosis was assigned according to the WHO's International Classification of Diseases (ICD-10 classification) coding for the patient's terminal illness.

Medication data of all deceased patients in 2010 were extracted: name, dose, frequency, and route of administration, and dates of start and discontinuation of the prescription. Only the regular prescriptions for maintenance therapy were included, because the electronic prescription system does not detail how much as needed medication was given.

Drugs were prescribed according to the symptom-specific Dutch national palliative guidelines [5]. The presence of symptoms was daily checked by the nurses and reported to the physicians, but validated assessment instruments were not standard of care.

Two top-10s of individual drugs prescribed were constructed: One covering the day of admission (Ta), the other the day of death (Td).

Medication was categorized by the anatomical therapeutic chemical (ATC) classification system [24]. The ATC system groups the drugs into 5 different levels according to the organ or system on which they act and according to their chemical, pharmacological and therapeutic properties. For this study we used the main therapeutic-group level. Furthermore, the WHO classification of analgesic drugs was applied: non-opioids, NSAIDs and opioids.

Morphine and haloperidol doses per 24 hours were calculated taking into account route of administration. Oral bioavailability of morphine and haloperidol is 30% and 50%, respectively, versus almost 100% after subcutaneous, intravenous and intramuscular administration. Equivalent subcutaneous doses of oral drugs were calculated by dividing oral morphine doses by 3 and oral haloperidol doses by 2[5, 25, 26]. An oral morphine dose of less than 300 mg/24hours is considered a low-to-moderate dose[27-29]. Consequently, a daily subcutaneous morphine dose of less than 100 mg/24hours was considered a low-to-moderate dose.

Fentanyl is mainly given via transdermal patches, which are replaced every 2-3 days. The daily dose was calculated as the dose of the prescribed patch divided by the number of days the patch was in place. Midazolam for continuous palliative sedation was administered either by subcutaneous boluses six times every 24 hours or by constant subcutaneous infusion. Insomnia was mainly treated by a single subcutaneous bolus of midazolam or by intermittent boluses.

Statistics

Data were analysed using descriptive statistics. Data are presented as mean (standard deviation; SD) in case of normally distributed variables and as median (interquartile range = IQR or minimum-maximum range = range) in case of non-normally distributed variables. IBM SPSS Statistics 20 was used for data analysis.

McNemar test served to detect differences in numbers of patients receiving the 3 most frequently used drugs both at Ta and Td. We limited ourselves to these 3 drugs to prevent repeated testing with too small samples. Differences in the daily doses of these drugs for patients receiving these both at Ta and Td were evaluated with the Wilcoxon signed rank test. A p-value of < 0.05 (two-sided) was deemed statistically significant.

RESULTS

Participants

In the study year 2010, 234 patients had been admitted. Ten had been discharged in the course of 2010 and 16 were still alive at 1st January 2011. All other 208 patients died in the palliative care centre and were included for analysis. Their median age was 76 years (IQR 63 to 83 years), 50.5% were female, and the median duration of admission was 11 days (IQR 5 to 29 days). Advanced malignancy, mainly of the digestive or respiratory organs, was the main reason for admission (88.9% of patients). A median of two comorbidities (IQR 1 to 4) had been documented. Patient characteristics are given in Table 1.

Table 1. Background characteristics of the included patients

Characteristics	N=208
Gender, in number (%)	
Male / female	103 (49.5) / 105 (50.5)
Age, in years; Median (IQR)	76 (63 to 83)
Duration of admission, in days; Median (IQR)	11 (5 to 29)
Primary diagnosis, in number (%)	
Neoplasm	185 (88.9)
Digestive organs	*50 (27.0)*
Respiratory and intra-thoracic organs	*47 (25.4)*
Breast	*13 (7.0)*
Urinary tract	*12 (6.5)*
Unspecified or unknown sites	*12 (6.5)*
Lymphoid, hematopoietic and related tissue	*10 (5.4)*
Eye, brain and other parts of central nervous system	*9 (4.9)*
Male genital organs	*8 (4.3)*
Other	*24 (13.0)*
Disease of circulatory system	11 (5.3)
Other	12 (5.8)
Co-morbid conditions, in number; Median (IQR)	2 (1 to 4)

IQR, interquartile range

Prescriptions

Drug prescriptions had not been issued for two patients; one died quickly after admission and stayed for a few hours only, all medications for the other patient had already been discontinued shortly before admission. A total of 4890 prescriptions for 206 patients has been extracted, of which 3032 were regular prescrip-

tions (62.0%) for 203 patients. Regular prescriptions were issued for 194/198 (98.0%) patients at Ta and for 202/206 (98.0%) patients at Td.

The median number of drugs per patient at Ta was six (IQR 3 to 8) and this number had decreased to four (IQR 3 to 5) at Td.

Top-10 individual regular drugs

The top-10 individual drugs prescribed at Ta and Td are given in Table 2. Figure 1 shows percentages of patients with a prescription of these top-10 drugs at Ta and Td. Morphine, midazolam, haloperidol, butyl scopolamine and fentanyl were prescribed more frequently at Td than at Ta. Numbers of patients with a prescription of morphine, midazolam or haloperidol increased statistically significantly from Ta to Td (all p-values <0.001). This increase was most notable during the last week before Td as shown in Figure 2. Prescriptions of lactoluse-senna mix, rabeprazole, acetaminophen, metoclopramide, temazepam, dexamethasone, macrogol/salts and metoprolol had been discontinued before Td.

Morphine, midazolam and haloperidol were often prescribed concomitantly (Table 3). Thirty-one per cent of the patients received all three at Td, but 11% had neither a prescription of morphine, midazolam nor haloperidol at Td.

Table 2. Top-10 individual regular drugs (in bold) at the day of admission (Ta) and the day of death (Td); given in descending order for the day of death

Individual drug Top 10	Ta (N=194)		Td (N=202)	
	N (%)	Dose/24hours Median (IQR)	N (%)	Dose/24hours Median (IQR)
Morphine*	**41 (21.1)**	30 (17.5 to 60) mg	**175 (86.6)**	60 (30 to 65) mg
Midazolam	22 (11.3)	10 (5 to 10) mg	**118 (58.4)**	60 (20 to 90) mg
Haloperidol*	**45 (23.2)**	2 (range 0.25 to 4) mg	**101 (50.0)**	2 (range 0.5 to 5) mg
Butyl scopolamine	4 (2.1)	80 mg	**68 (33.7)**	80 (range 40 to 80) mg
Fentanyl	**29 (14.9)**	16.7 (8.3 to 25) mcg/hr	**61 (30.2)**	16.7 (8.3 to 25) mcg/hr
Lactulose-senna mix	**65 (33.5)**	15 (range 10 to 60) ml	**30 (14.9)**	15 (range 7.5 to 60) ml
Rabeprazole	**99 (51.0)**	20 (range 10 to 80) mg	**21 (10.4)**	20 (range 20 to 40) mg
Acetaminophen	**65 (33.5)**	4000 (range 1000 to 4000) mg	**20 (9.9)**	4000 (range 3000 to 4000) mg
Metoclopramide	24 (12.4)	40 (30 to 40) mg	**16 (7.9)**	40 (30 to 40) mg
Temazepam	**31 (16.0)**	10 (10 to 20) mg	**13 (6.4)**	10 (10 to 20) mg
Dexamethasone	**34 (17.5)**	8 (4 to 12) mg	9 (4.5)	8 (5.5 to 16) mg
Macrogol/salts	**28 (14.4)**	1 (1 to 2) sachets	7 (3.5)	1 (1 to 2) sachets
Metoprolol	**30 (15.5)**	50 (50 to 100) mg	4 (2.0)	50 (31.25 to 87.5) mg

Ta, day of admission; Td, day of death; IQR, interquartile range

*The route of administration is taken into account; the subcutaneous dose equivalent is given

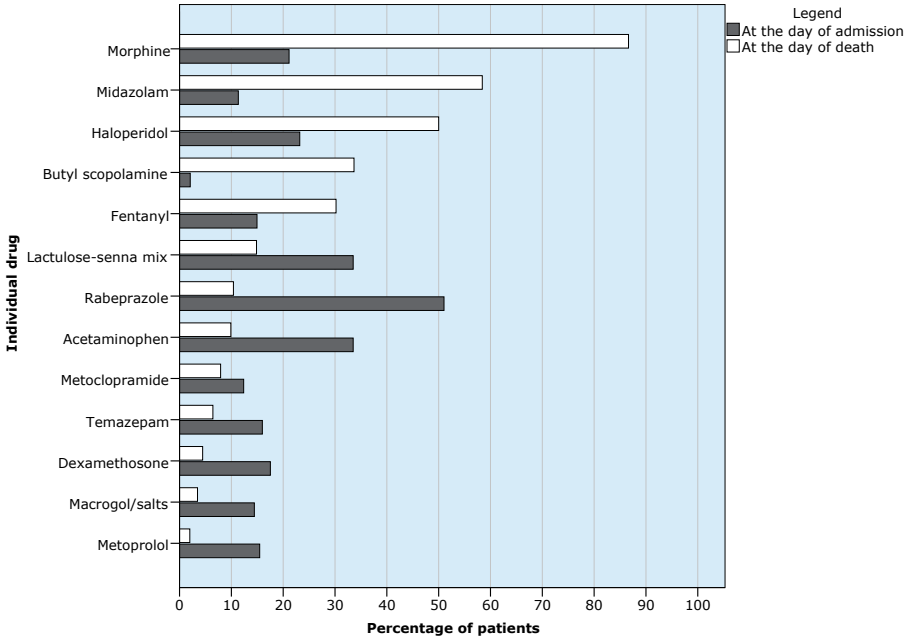

Figure 1. Differences in top-10 individual drugs at admission (dark grey bars) and at day of death (white bars); shown in descending order for the day of death

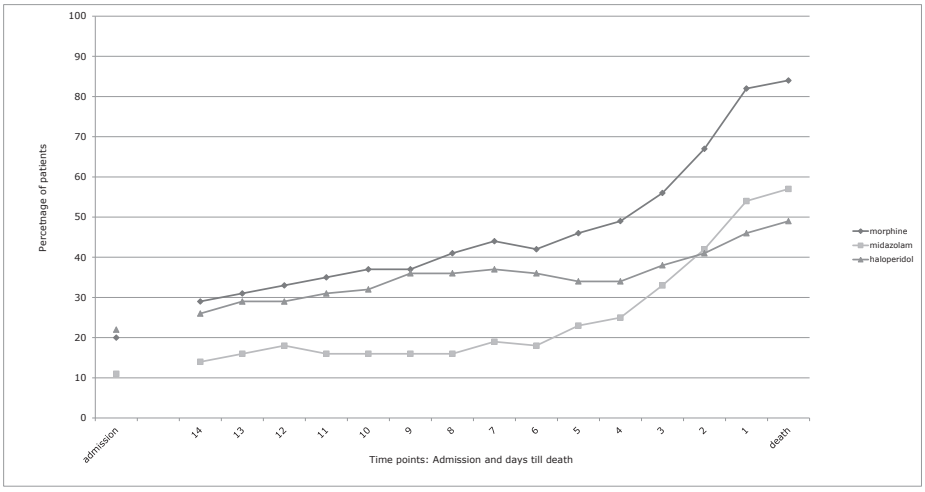

Figure 2. Prescriptions of top-3 drugs; morphine (diamond), midazolam (square) and/or haloperidol (triangle), at several time points during admission

Table 3. Combination of prescription for top-3 drugs; morphine, midazolam and haloperidol (N=202)

Single or combination of regular prescriptions at day of death	N (%)
Morphine, midazolam and haloperidol	63 (31.2)
Morphine and midazolam	46 (22.8)
Morphine	36 (17.8)
Morphine and haloperidol	30 (14.9)
No morphine, midazolam or haloperidol	22 (10.9)
Midazolam and haloperidol	6 (3.0)
Midazolam	3 (1.5)
Haloperidol	2 (1.0)

Top-10 regular drug classes

Top-10s of ATC drug classes prescribed at Ta and Td are given in supplementary Table S1. Three classes were prescribed more frequently at Td than at Ta: analgesics, psycholeptics and drugs for functional gastrointestinal disorders. While the top-10 at Ta included beta blocking agents, psycho-analeptics and anti-thrombotic agents, those drug classes were not included in the top-10 at Td. (Table S1, see supplement). Percentages of patients with a prescription of the top-10 drug classes at Ta and Td are shown in supplementary Figure S1.

Numbers of patients with analgesics classified by the different grouping systems are given in supplementary Table S2. The two most frequently prescribed opioids, i.e. morphine and fentanyl, are included in the top-10 of individual drugs in Table 2. The frequencies of combinations of prescriptions of non-opioids, NSAIDs and opioids are given in supplementary Table S3.

Drug doses

The median daily doses for each individual drug prescribed at Ta and Td are displayed in Table 2. The median daily doses of the top-3 drugs at Td were: morphine 60 mg, midazolam 60 mg, and haloperidol 2 mg. Patients receiving these drugs both at Ta end Td were prescribed statistically significantly higher doses at Td than at Ta (morphine (n=40) $p<0.001$, midazolam (n=18) $p=0.003$ and haloperidol (n=37) $p=0.028$).

At Td, 83% of the patients receiving morphine had a low-to-moderate subcutaneous equivalent morphine dose of less than 100mg/24hours.

Routes of administration

The three most common routes of administration were: oral (solid and liquids), subcutaneous, and transdermal. Percentages of patients with prescriptions of

solid oral drugs declined from 89.2% (n=173) at Ta to 21.3% (n=43) at Td. Use of the subcutaneous route increased from Ta (47.9%; n=93) to Td (93.6%; n=189). Prescriptions of a transdermal drug almost doubled from Ta to Td, from 16.0% (n=31) to 31.7% (n=64) of patients (Table 4).

Morphine, midazolam and haloperidol were almost exclusively given via the subcutaneous route. At Ta morphine was given subcutaneously to 95.1% (39/41) of the patients, midazolam to 90.0% (20/22) and haloperidol to 66.7% (30/45). At Td these percentages had even increased to 98.9% (173/175), 100% (118) and 99% (100/101) respectively.

Table 4. Prescriptions via the various routes of administration at the day of admission (Ta) and the day of death (Td); given in descending order for the day of death

Routes of administration	Ta (N=194)		Td (N=202)	
	N (%)	Number of drugs per patient (median; IQR)	N (%)	Number of drugs per patient (median; IQR)
Subcutaneous	93 (47.9)	1 (1 to 2)	189 (93.6)	3 (2 to 3)
Transdermal	31 (16.0)	1	64 (31.7)	1
Oral, liquid	115 (59.3)	1	47 (23.3)	1
Oral, solid	173 (89.2)	4 (3 to 6)	43 (21.3)	3 (2 to 5)
Intramuscular	5 (2.6)		28 (13.9)	
Cutaneous*	15 (7.7)		16 (7.9)	
Inhalation	29 (14.9)		12 (5.9)	
Rectal	20 (10.3)		11 (5.4)	
Intravenous	4 (2.1)		3 (1.5)	
Ocular	4 (2.1)		2 (1.0)	
Intravesical	-		2 (1.0)	
Intrathecal	-		1 (0.5)	
Nasal	1 (0.5)		1 (0.5)	

Ta, day of admission; Td, day of death; IQR, interquartile range

*The cutaneous route is used for local skin treatment

DISCUSSION

This study found that morphine, midazolam and haloperidol were the most frequently prescribed drugs at the day of death for patients in the largest palliative care centre in the Netherlands. Doses of these drugs were statistically significantly higher than those at the day of admission. Upon admission almost 90% of patients received oral medication but over the admission period a shift

occurred to the effect that at the day of death more than 90% of patients received subcutaneous medication.

Other studies, too, found that morphine, midazolam and haloperidol were the most prescribed drugs in the palliative setting[30-33]. These drugs are given to relieve symptoms such as pain, restlessness and agitation, which are frequently seen in advanced cancer[2]. Nauck and co-workers[17] in a similar study found that 26% of patients received morphine at admission (versus 21% in the present study), but corresponding figures at the end of treatment were 42% versus 87%. The latter difference is probably explained by the fact that Nauck and co-workers also included patients who were discharged from the centre, whereas we solely considered patients who died in the palliative centre. Nevertheless, other studies reported opioid use in 82% to 97%[28, 30, 32], and morphine use in 66% to 93%[27, 28, 30, 32] of patients at the end of life, which percentages correspond well with our results.

We found that midazolam was prescribed for 58% of patients at the day of death, while in other studies this was the case for 23% of patients in the last 48 hours of life[30] or 82% of patients in their last week[31]. An explanation for this wide range could be the studied time frame. Midazolam is often stopped in the last days before death, to avoid that patients become comatose. On the other hand, midazolam may be started for palliative sedation, notably in the last 24 hours before death.

Many more patients in the present study were prescribed haloperidol than in the study by Nauck et al[17]; at admission 23% versus 3%, respectively, and at end of treatment 50% versus 13%, respectively. Our higher figures may be explained by the difference in the studied patient population; we only included patients who died in the palliative centre. Other studies, however, found percentages (21-43%) comparable to the present study[30-33]. Haloperidol is the drug of first choice to treat delirium. In other studies, delirium was suspected in approximately 50% of cancer patients admitted to a palliative care centre and in up to almost 90% of all cancer patients in the last day or hours before death[34, 35]. We suspect, however, that haloperidol is also prescribed in agitated or restless patients who have not been clearly diagnosed with a delirium. Therefore, assessing delirium with a validated scale, such as the Confusion Assessment Method, should become standard of care[36, 37].

In the present study the median number of drugs decreased from 6 to 4 as death approached, probably because in our centre oral drugs are stopped when a patient enters a recognizable dying phase[38]. Other studies, however, have

reported increasing numbers of drugs towards death[20, 22, 23], possibly to control a new or advancing symptom.

The doses of the top-10 drugs compared well to the titration schemes given in the national symptom specific guidelines[5]. Eighty-three percent of patients in the present study received a subcutaneous morphine dose of less than 100 mg/24hrs at the day of death, which is considered a low-to-moderate dose[27-29]. In two other studies more than 90% of the patients received low-to-moderate morphine doses either upon admission[27] or in the last 24 hours before death[28].

The median subcutaneous midazolam dose (60 mg/24hrs) at the day of death in the present study fits within the range found in other studies; mean midazolam doses of 26 to 70 mg/24hrs during the last days of life[30, 31, 39]. Moreover, these doses (IQR 30-65mg/24hrs, in present study) are recommended in the Dutch national guideline for palliative sedation[5]. However, midazolam dose titration should be guided by regular assessment of level of sedation.

The median haloperidol dose was 2 mg/day, both at admission and the day of death. Other studies found median haloperidol doses of 2.5 to 3.8 mg/day during the last days of life[30, 32]. The Dutch national guideline for delirium treatment, however, recommends a maximum parenteral maintenance dose of 10 mg/day[5]. In practice the recommended starting dose of 0.5 to 2 mg/day seems sufficient to treat delirium in most patients. Moreover, in elderly patients a low starting dose is recommended to prevent neurological and cardiovascular effects[25].

Over the admission period a shift occurred from the oral route to mainly the subcutaneous route, in line with recommendations from both guidelines[5, 6] and the Liverpool Care Pathway for the dying[38]. The subcutaneous route is preferred in palliative care because most patients are unable to take oral medication at the end of life and the intravenous route is often complicated by infection or discomfort. Absorption via the subcutaneous route may be suboptimal, however, especially in cachectic cancer patients with very little or no subcutaneous fat.

Although the subcutaneous route is preferred in palliative care, this route has not been fully studied. In addition, midazolam and haloperidol are unlicensed or off-label in this patient group[15, 16, 40, 41]. Regarding opioids, only small and mostly non-randomized controlled clinical trials have compared the subcutaneous route with another route of administration[12, 42]. In those studies similar feasibility, efficacy and opioid doses were found for the subcutaneous route and the intravenous route. Moreover, in some studies the subcutaneous route was preferred because of lower complication risks. Only small and outdated prospective studies are available for midazolam, which all found subcutaneous administration

of midazolam to be feasible and effective[39, 43, 44]. Regarding haloperidol, only retrospective descriptive studies or overview articles are available, even without addressing the administration route[45-48]. In conclusion, strict monitoring of the efficacy of subcutaneous morphine, midazolam and haloperidol is essential and more pharmacokinetic and pharmacodynamics studies are needed.

Strengths and limitations

A strength of the present study is that actually administered regular medication in the palliative care setting was evaluated at two significant time points, detailing drug doses and routes of administration. In addition, electronically recorded prescriptions were available, preventing the errors of written medication orders when extracting data.

Several limitations should be addressed however. First, this was a single-centre study of which the results cannot be extrapolated to other palliative care settings or other countries as prescription practices may differ. Second, as needed prescriptions were excluded from analysis, since our electronic prescription system did not detail how much as needed medication was actually given. In our centre, 'as needed' prescriptions mainly serve to increase the already prescribed doses of the medications, for example when worsening of symptoms is expected. When a patient is given the 'as needed' medication on a regular basis, the maintenance prescription dose is adapted accordingly. Unfortunately, also indications for drugs could not be analysed, since this information was not electronically recorded. In future research, both the as needed medication and the indications should be included, so as to provide a complete overview of administered symptom-specific drugs. Lastly, outcomes of validated assessment instruments for pain, sedation and delirium were not available. In future research these assessments should be included to add information on the efficacy of drugs.

From the above it follows that pharmacotherapy in palliative care offers room for improvement. Therefore, we would recommend to strictly monitor the efficacy of the subcutaneously administered drugs with the use of validated pain, sedation and delirium assessment instruments. This will help recognize worsening of symptoms and enable to taper treatment to a patient's needs.

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SUPPLEMENTARY TABLES

Supplement Table S1. Top-10 ATC drugs classes (in bold) at admission (Ta) and the day of death (Td); given in descending order for the day of death

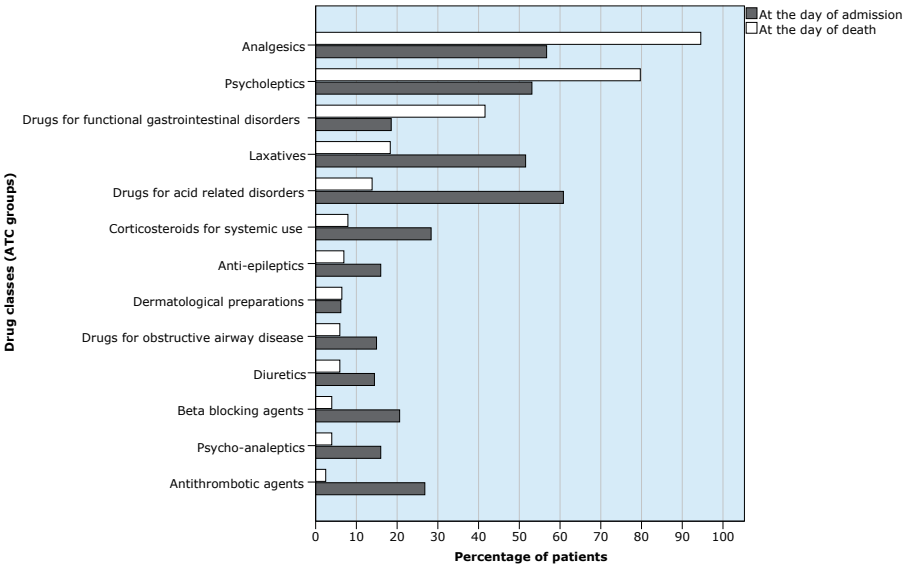
Drug classes Top 10	Ta (N=194)	Td (N=202)
	N (%)	N (%)
Analgesics	**110 (56.7)**	**191 (94.6)**
Psycholeptics	**103 (53.1)**	**161 (79.7)**
Drugs for functional gastrointestinal disorders	**36 (18.6)**	**84 (41.6)**
Laxatives	**100 (51.5)**	**37 (18.3)**
Drugs for acid related disorders	**118 (60.8)**	**28 (13.9)**
Corticosteroids for systemic use	**55 (28.4)**	**16 (7.9)**
Anti-epileptics	**31 (16.0)**	**14 (6.9)**
Dermatological preparations	12 (6.2)	**13 (6.4)**
Drugs for obstructive airway disease	29 (14.9)	**12 (5.9)**
Diuretics	28 (14.4)	**12 (5.9)**
Beta blocking agents	**40 (20.6)**	8 (4.0)
Psycho-analeptics	**31 (16.0)**	8 (4.0)
Antithrombotic agents	**52 (26.8)**	5 (2.5)

Supplement Table S2. Analgesics at admission (Ta; N=194) and at the day of death (Td; N=202); given in descending order for the individual drugs per drug class at the day of death

ATC therapeutic subgroup	WHO groups	Ta	Td	Individual drugs	Ta	Td
		N (%)	N (%)		N (%)	N (%)
Analgesics	Opioids	82 (42.3)	187 (92.6)	Morphine	41 (21.1)	175 (86.6)
				Fentanyl	29 (14.9)	61 (30.2)
				Oxycodone	16 (8.2)	4 (2.0)
				Hydromorphone	1 (0.5)	2 (1.0)
				Tramadol	5 (2.6)	1 (0.5)
	Non-opioids	66 (34.0)	20 (9.9)	Acetaminophen	65 (33.5)	20 (9.9)
				+codeine	1 (0.5)	-
Anti-inflammatory and anti-rheumatic drugs	NSAIDs	19 (9.8)	5 (2.5)	Diclofenac	11 (5.7)	3 (1.5)
				Ibuprofen or naproxen	4 (2.1)	2 (1.0)
				Celecoxib or etoricoxib	4 (2.1)	-

Supplement Table S3. Combinations of analgesics according to the WHO grouping at admission (Ta) and the day of death (Td); given in descending order for the day of death

Single or combination of regular analgesics	Ta (N=194)	Td (N=202)
	N (%)	N (%)
Single opioid	36 (18.6)	119 (58.9)
Combination of opioids	3 (1.5)	49 (24.3)
Non-opioid and opioid(s)	33 (17.0)	15 (7.4)
Single non-opioid	24 (12.4)	3 (1.5)
NSAID and opioid(s)	5 (2.6)	3 (1.5)
Non-opioid, NSAID and opioid(s)	5 (2.6)	1 (0.5)
Non-opioid and NSAID	4 (2.1)	1 (0.5)
Single NSAID	5 (2.6)	-



Supplement Figure S1. Differences in top-10 ATC drugs classes at admission (dark grey bars) and at the day of death (white bars); shown in descending order for the day of death

CHAPTER 5

PREVALENCE AND IMPLICATIONS OF ABNORMAL LABORATORY RESULTS IN PATIENTS IN THE TERMINAL PHASE OF LIFE

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ABSTRACT

Background: Pathophysiological changes at the end of life may affect pharmacokinetics of drugs. However, caregivers typically do not extensively monitor patients' laboratory parameters at the end of life.

Objective: To describe laboratory parameters of hospice patients in the week before death.

Methods: A cohort study on available laboratory results in the week before death, including clinical chemistry and haematology tests.

Setting/Subjects: Patients in a palliative care centre.

Results: Laboratory data of 125 patients were included, assessed at a median of 3 days before death. Eighty percent of patients had anaemia and almost all had hypoalbuminemia (97%). Elevated levels of gamma-glutamyltransferase were found in 75%, of alkaline phosphatase in 60%, of aspartate aminotransferase in 60% and of calcium in 68%. Alanine aminotransferase, bilirubin, sodium and potassium were abnormal in from 8.8% to 36.0% of patients. A previous unknown poor kidney function was found in 60% of patients. Thirteen patients (22%) with a regular morphine prescription and one patient treated with an NSAID had severe kidney failure.

Conclusions: Abnormal laboratory results were expected due to the pathophysiological changes that occur during the last phase of life. Remarkably, however, electrolytes (sodium and potassium) were balanced even shortly before death. eGFR, reflecting the kidney function, seems the most clinically relevant laboratory parameter, since it may guide drug choice and dosing.

BACKGROUND

In Europe most patients (>90%) who are cared for in a hospice suffer from an advanced malignancy[1]. In contrast, the proportion of cancer patients is notably smaller (40%) in hospices in the United States[2]. These patients often show a gradual decline in physical health and functional status, like in chronic illness[3, 4]. This, combined with a lower oral intake may result in weight loss and cachexia, liver impairment and kidney failure[5, 6], eventually leading to end-stage organ failure, affecting the heart, kidneys, lung and gastro-intestinal tract[7, 8]. The most marked deterioration is clinically seen in the last few days. Several aspects of pharmacokinetics, including the absorption, distribution, metabolism and elimination of drugs, may then change as well (table 1). As these pharmacokinetic changes have hardly been systematically described in palliative patients[7, 9, 10], they are extrapolated from other patient populations, such as cancer patients[11, 12], elderly patients[13-19] and intensive care patients[20-23].

The pharmacokinetic changes can result in a prolonged drug effect and accumulation of drugs. To prevent side effects it may be necessary to reduce the doses of sedatives and analgesics, which are often prescribed at the end of life[24], or to choose another drug. The latter is recommended by European Association of Palliatieve Care (EAPC)[25] and the Dutch palliative pain guideline[26] for the use of opioids in palliative patients with renal failure; both recommend prescribing another opioid, such as fentanyl, buprenorphine or hydromorphone, instead of

Table 1. Potential pharmacokinetic changes at the end of life

Pharmacokinetic parameter	Pathophysiological change or relevant disease state	Effect
Absorption	Malignancy of digestive organs Intestinal complications (vomiting or ileus) Subcutaneous route of administration	Diminished absorption of drugs
Distribution	Change in body composition Lowered serum albumin (both due to cachexia in advanced malignancies or chronic disease state)	Lowered volume of distribution of lipophilic drugs Greater portion unbound drug in serum
Metabolism	Hepatic disease (primary malignancy or secondary disease, like metastasis)	Reduced hepatic function Increase in half-life of drugs metabolized by the liver Increased risk for drug-drug interactions
Elimination	Kidney disease (primary or secondary disease)	Decrease of GFR Increase in half-life of renally eliminated drugs

GFR, glomerular filtration rate

morphine in patients with renal failure. The latter guideline proposes to adjust drug doses in the case of liver of kidney failure[26] to avoid a negative impact on the quality of dying.

Only a few studies describe actual laboratory results during the last month[27, 28] or last week[29-31] of life. However, the primary aim of these studies was not to describe laboratory results in relation to pharmacokinetics, and in most cases only few parameters were assessed, such as sodium, potassium and albumin. Therefore we aimed to describe the results of a more complete panel of laboratory results of hospice patients in the week before death. Furthermore, we evaluated the relevance of the laboratory parameters for the pharmacokinetics of drugs often used in patients at the end of life. As pronounced pathophysiological changes occur prior to death, we hypothesised, that laboratory results of patients shortly before death may be quite abnormal with consequences for the choice of drugs and the dosing of sedatives and analgesics.

METHODS

Design and setting

This observational cohort study was performed in Laurens Cadenza in Rotterdam, the Netherlands. This is the largest palliative care centre in the Netherlands, with 20 beds for end-of-life care and symptom management; 200 to 250 patients are admitted annually. A multidisciplinary team of health care professionals, including specialised nurses and elderly care physicians specialised in palliative care, is available 24 hours per day. Dutch palliative guidelines form the core for clinical practice, including the abstinence, in principle, of artificial fluids or nutrition in the last few days of life[26].

Data collection

All available laboratory results, including clinical chemistry and haematology tests, from April 2009 till September 2013, were extracted from the electronic medical records. Subsequently, only the last results of patients in their last week before death were selected. All patients died in the palliative care centre. There is no policy for routine testing at admission or during the admission. In practice, laboratory testing, including clinical chemistry and haematology tests, is often done in the first one or two weeks after admission and as follow-up testing if needed. In a number of patients (48/125, 38.4%) laboratory tests were requested in the context of a drug study, and in the other patients laboratory testing was done at the physician's discretion and for clinical purposes only. Common indica-

tions for laboratory testing were monitoring a patient's health status, guiding medication use, finding causes of symptoms or guiding symptom management, such as weighing the need for a blood transfusion in the case of severe anaemia.

Laboratory parameters

The following serum parameters were available for the majority of patients in their final week: haemoglobin (Hb), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyltransferase (gGT), alkaline phosphatase (ALP), total bilirubin (Bili), albumin, sodium (Na), potassium (K), calcium (Ca) and creatinine (from which the glomerular filtration rate was calculated). The reference values of the hospital laboratory are given in Table 2.

Table 2. Laboratory results of palliative patients in the final week before death (N=125), including the corresponding laboratory reference values

Parameter	N	Laboratory result Median; IQR		Abnormal results N (%)		Laboratory reference values	
		male	female	low	high	male	female
Hb in mmol/l (in g/dl)	86	6.3; 5.3 to 7.5 (10.1; 8.5 to 12.1)	6.4; 4.8 to 7.6 (10.3; 7.7 to 12.2)	69 (80.2)	-	8.5 to 11.0 (13.7 to 17.7)	7.5 to 10.0 (12.1 to 16.1)
ALAT in U/l	106	18; 10 to 34	18; 8 to 47	-	27 (25.4)	0 to 41	0 to 31
ASAT in U/l	104	39; 23 to 83	36; 28 to 65	-	62 (59.6)	0 to 37	0 to 31
gGT in U/l	108	61; 44 to 145	95; 45 to 343	-	81 (75.0)	0 to 50	0 to 35
ALP in U/l	108	139; 89 to 301		-	65 (60.2)	0 to 120	
Bili in umol/l (in mg/dl)	100	11; 7 to 20 (0.6; 0.4 to 1.2)		-	27 (27.0)	0 to 17 (0 to 1.0)	
Albumin in g/l	115	23; 20 to 27		112 (97.4)	-	35 to 50	
Na in mmol/l	114	137; 133 to 140		41 (36.0)	10 (8.8)	135 to 145	
K in mmol/l	113	4.2; 3.7 to 4.7		13 (11.5)	18 (15.9)	3.5 to 5.0	
Ca_{corr} in mmol/l (in mg/dl)	94	2.76; 2.63 to 2.95 (11.0; 10.5 to 11.8)		-	64 (68.1)	2.20 to 2.65 (8.8 to 10.6)	
eGFR	115	63; 33 to 94		Displayed in table 4			

For Hb, Bili, and Ca also, the values in US units are given between parentheses.

ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ASAT, aspartate aminotransferase; Bili, total bilirubin; Ca, calcium; Ca_{corr}, calcium level corrected for albumin level; eGFR, estimated glomerular filtration rate; gGT, gamma-glutamyl transferase; Hb, haemoglobin; IQR, interquartile range; K, potassium; Na, sodium

The calcium levels were corrected for albumin levels according to the following equation: Ca+0.025(40-albumin)[32]. The corrected calcium levels are presented (Ca_{corr}).

The glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula[33]. This MDRD formula includes four variables: serum creatinine, age, ethnicity and gender and is accurate for estimating eGFR across a wide range of subgroups for eGFR <60ml/min/1.72m^2. An eGFR of less than 30ml/min is considered to reflect a poor kidney function.

Other variables

Age, gender, diagnoses, and duration of admission were extracted from the electronic medical records; the primary diagnoses and the number of comorbidities were evaluated. The primary diagnoses refer to the WHO's International Classification of Diseases (ICD-10 classification) coding for the patient's terminal illness. For each patient pre-existing liver diseases, (including primary or secondary liver malignancies, cirrhosis and hepatitis) and pre-existing kidney diseases (including primary or secondary kidney malignancies) were recorded.

The prescriptions of regular medication were extracted from the pharmacy database, including drug name, dose, frequency, route of administration, and dates of start and discontinuation of the prescription. Drugs were prescribed according to the symptom-specific Dutch national palliative guidelines[26]. For this study data of morphine (administered orally or subcutaneously) and non-steroidal anti-inflammatory drugs (NSAIDs, administered orally or rectally) were analysed.

Daily morphine doses were calculated taking into account the route of administration, so a subcutaneous equivalent was used for analysis[26, 34]. A daily subcutaneous morphine dose of less than 100 mg/24hours was considered a low-to-moderate dose[35-37].

Statistical analysis

Data were analysed using descriptive statistics. Data are presented as mean (standard deviation; SD) in case of normally distributed variables and as median (interquartile range = IQR or minimum-maximum range = range) in case of non-normally distributed variables. Data analyses were performed using IBM SPSS Statistics 20 (IBM Corp., Armonk, NY). A p-value of < 0.05 (two-sided) was deemed statistically significant.

Ethics

Given the retrospective nature of the study ethical approval was waived according to Dutch law. All patient data were handled and processed in accordance with the

recommendations of Good Clinical Practice. For patients participating in a drug study (48/125) permission from the Medical Ethics Review Board of the Erasmus University Medical Centre was granted and written informed consent had been obtained from them for study purposes, including laboratory testing.

RESULTS

Participants

Laboratory results from in total 285 patients were available over the given time period. Final week results were available of 125 patients, of which the last (or only) ones had been assessed at a median of three days (IQR 1 to 4) before death. These 125 patients' median age was 75 years (IQR 64 to 81 years), 52% were female, and the median length of stay was 13 days (IQR 7 to 34 days). An advanced malignancy, mainly of the respiratory or digestive organs, was the reason for admission in 116 patients (93.6%). A pre-existing liver disease was recorded in 38 patients (30.4%), and a pre-existing kidney disease in 18 patients (14.4%). See further Table 3.

Laboratory results

In 80.2% of 86 patients the Hb levels were below the reference values. Median Hb levels were 6.3mmol/l (10.1g/dl) for men and 6.4mmol/l (10.3g/dl) for women. Albumin levels were markedly below the reference values in 97.4% of 115 patients, with a median level of 23g/l (IQR 20 to 27). The median levels of several liver enzymes were too high for a major proportion of patients: gGT in 75.0% of 108 patients, ALP in 60.2% of 108 patients and ASAT in 59.6% of 104 patients. The median Ca_{corr} levels were above the normal range for 68.1% of 94 patients. ALAT, Bili, Na and K were abnormal in smaller proportions (8.8% to 36.0%) of patients. The median eGFR was 63 mL/min (IQR 33 to 94). See further table 2.

In 25/115 patients (21.7%) the eGFR was <30ml/min, indicating a poor kidney function. Only 10 of the patients (40.0%) were known with a pre-existing kidney disease (table 4). In 12 of the patients (48.0%) an eGFR <30ml/min was accompanied with an increased Ca_{corr} (>2.65mmol/l).

Levels of the liver enzymes (table 5) were within the normal range in fewer patients with a documented pre-existing liver disease (10.5 to 47.4% of 38 patients) than in patients without that disease (26.4 to 71.3% in 87 patients). Moreover, the median levels of ASAT, ALP and gGT were distinctly higher in the patients with a pre-existing liver disease.

Table 3. Patient characteristics

Characteristics	**N=125**
Gender in %	
Male / female	48 / 52
Age in years; Median (IQR)	75 (64 to 81)
Duration of admission in days; Median (IQR)	13 (7 to 34)
Assessment days before death; Median (IQR)	3 (1 to 4)
Primary diagnosis in N (%)	
Neoplasms	117 (93.6)
Respiratory and intra-thoracic organs	*32 (27.4)*
Digestive organs	*29 (24.8)*
Lymphoid, hematopoietic and related tissue	*13 (11.1)*
Breast	*9 (7.7)*
Female genital organs	*7 (6.0)*
Male genital organs	*6 (5.1)*
Urinary tract	*5 (4.3)*
Eye, brain and other parts of central nervous system	*4 (3.4)*
Ill –defined, secondary and unspecified sites	*4 (3.4)*
Other	*8 (6.8)*
Disease of circulatory system	4 (3.2)
Disease of digestive system	2 (1.6)
Other	2 (1.6)
Pre-existing liver disease in N (%)	
Yes	38 (30.4)
Secondary malignancy in liver	*33 (86.8)*
Primary malignancy in liver	*3 (7.9)*
Other	*2 (5.3)*
No or not documented clearly	87 (69.6)
Pre-existing kidney disease in N (%)	
Yes	18 (14.4)
Not otherwise specified	*8 (44.5)*
Primary malignancy in kidney	*4 (22.2)*
Secondary malignancy in kidney	*2 (11.1)*
Drug induced kidney disease	*2 (11.1)*
Other	*2 (11.1)*
No or not documented clearly	107 (85.6)
Co-morbidities	
Median (IQR) number of diagnoses	3 (1 to 4)

IQR, interquartile range

Table 4. Renal function in patients with and without a pre-existing kidney disease

eGFR categories in ml/min/1.73m^2	**Total N=125**	**Pre-existing kidney disease N=18**	**No known pre-existing kidney disease N=107**
	Number (%) of patients	Number (%) of patients	Number (%) of patients
0-14 (kidney failure)	6 (4.8)	3 (16.7)	3 (2.8)
15-29 (severe kidney disease)	19 (15.2)	7 (38.9)	12 (11.2)
30-59 (moderate kidney disease)	31 (24.8)	6 (33.3)	25 (23.4)
60-89 (mild kidney disease)	27 (21.6)	1 (5.6)	26 (24.3)
≥90 (very mild or no kidney disease)	32 (25.6)	1 (5.6)	31 (29.0)
eGFR was not assessed in the final week	10 (8.0)	--	10 (9.3)

eGFR, estimated glomerular filtration rate

Table 5. Results of liver test for patients with and without pre-existing liver disease

Liver tests	**Total N=125**	**Pre-existing liver disease N=38**		**No known pre-existing liver disease N=87**	
	Number (%) of patients within normal range	Number (%) of patients within normal range	Laboratory result Median (IQR)	Number (%) of patients within normal range	Laboratory result Median (IQR)
Bili	73/100 (73.0)	18 (47.4)	14 (7 to 53)	55 (63.2)	10 (7 to 15)
ALAT	79/106 (74.5)	17 (44.7)	34 (17 to 79)	62 (71.3)	14 (9 to 27)
ASAT	42/106 (39.6)	6 (15.8)	85 (36 to 273)	36 (41.4)	34 (23 to 45)
ALP	43/108 (39.8)	6 (15.8)	312 (158 to 766)	37 (42.5)	117 (81 to 153)
gGT	27/108 (25.0)	4 (10.5)	315 (95 to 897)	23 (26.4)	56 (32 to 103)

ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ASAT, aspartate aminotransferase; Bili, total bilirubin; gGT, gamma-glutamyl transferase; IQR, interquartile range

Prescriptions of NSAIDs and morphine

Medication data during the last week of life in combination with an eGFR value were available for 102/125 patients (81.6%); for 22/25 (88.0%) patients with a poor kidney function and for 80/90 (88.9%) with an eGFR ≥30ml/min.

Twelve patients were on regular treatment with oral or rectal NSAIDs in the last week of life. One of six of these patients whose kidney function was checked in the last week had severe renal failure (eGFR 20ml/min).

Morphine was prescribed on a regular basis via the oral or subcutaneous route for 94/102 patients (92.2%). Kidney function was checked in 60 of them (63.8%) and in 13 of those (21.7%) had severe renal failure: median eGFR of 21ml/min (range 5 to 28). A low to moderate subcutaneous equivalent morphine dose (<100mg/day) was administered to 12/13 patients (92.3%) with poor kidney function versus 39/47 (83.0%) patients with an eGFR ≥30ml/min. The median morphine daily dose in patients with severe kidney failure was 30mg (IQR 15 to 60) and not different from the 30mg (IQR 15 to 75) morphine dose in patients with eGFR ≥30ml/min.

DISCUSSION

This study found that most patients had anaemia (80%) or hypoalbuminemia (97%) in their last week of life and that many (60 to 75%) had elevated levels of gamma-glutamyltransferase (gGT), alkaline phosphatase (ALP), aspartate aminotransferase (ASAT) or corrected calcium (Ca_{corr}) levels. Notably, levels of alanine aminotransferase (ALAT), bilirubin, sodium and potassium were within the normal range for most patients (abnormal in 8.8% to 36.0%). In 60% of patients whose kidney function proved to be poor (eGFR <30ml/min) this was not documented in the medical history. Some patients with severe kidney failure were on treatment with a NSAID and morphine (1 and 13 patients respectively), which is not recommended in palliative treatment guidelines[25, 26].

Both lowered albumin and haemoglobin levels are related to chronic disease and are therefore not surprising in this population of mainly oncology patients. Severe anaemia (Hb < 5.0mmol/l, 8.0g/dl)[38] was found in 20% of patients. The prevalence of anaemia in the present study (80%) is comparable to that in other studies in palliative care patients (72% to 82%)[27, 28, 39]. Differences in case mix or patient population and in timing of laboratory testing (table 6) will influence the prevalence of anaemia. To illustrate this, one study excluded the very ill patients and found anaemia in 77% of men and 68% of women[39].

The prevalence of hypoalbuminemia (albumin <35g/l) differs between studies. In the present study almost all patients had hypoalbuminemia (97%) compared to only two thirds in the referred studies[27, 28]. This discrepancy might be explained by a difference in the median time till death (table 6); 3 days in the present study versus about 1 month in the other studies[27, 28]. Moreover, hypoalbuminemia is

Table 6. Overview of literature about laboratory parameters in palliative patients, displaying differences in case mix

Reference	Design	Primary aim	Patients				Prognosis	
			N	*Setting*	*Type*	*Deceased*	*Duration of admission*	*Survival after assessment*
Present study	Cohort study	To describe laboratory parameters	125	Palliative care centre	94% advanced cancer	125/125	Median 13 days (IQR 7 to 34)	Median 3 days (IQR 1 to 4)
Jiménez-Gordo 2009[27]	Cohort study	To describe clinical and laboratory parameters	406	Hospital	All advanced cancer	368/406	Median 27 days (range 0 to 547)	--
Morita 2006[29]	Observational study	To relate hydration volume and laboratory parameters	125	Various (oncology units, palliative care units, home based programs)	All advanced lung or abdominal cancer Note: patients with liver cirrhosis or liver cancer, renal failure, hypercalcemia were excluded	125/125	--	All assessments were done in the last week of life
Sarhill 2003[28]	Cohort study	To evaluate nutritional status assessments	352	Various (inpatient units and outpatients clinic)	All advanced cancer Note: actively dying patients were excluded	-- Note: Survival was recorded for 53% of patients	--	Median about 1 month (range 1 day to 7 months)
Dunn 2003[39]	Cohort study	To determine the prevalence and causes of anaemia	105	Hospice inpatient unit	91% advanced cancer Note: patients recognized to be near death were excluded	--	13% of patients deceased within 10 days of admission	--
Ellershaw 1995[30]	Cohort study	To relate symptoms and dehydration	82	Hospice	All advanced cancer	82/82	--	Median 2 days (range 1 to 5 days)
Oliver 1984[31]	Secondary analysis	To study hypercalcemia upon admission	22	Hospice	All advanced cancer	22/22	--	12 patients within 1 day, 10 patients between 1 and 2 days

IQR, interquartile range

expected in end-of-life patients since these patients often suffer from oedema, ascites, carcinomatous pleural effusion and are in a cachectic state[28]. Some studies suggest that albumin level may help predict the time till death in oncology or palliative patients; the lower the level, the nearer to death[40-42]. However, this prognostic value of albumin levels was not confirmed in all studies; especially in studies testing multiple factors different outcomes are described[43-45].

Albumin is an important protein for the transport of various drugs in plasma[46, 47]. Therefore, hypoalbuminemia may lead to a significant decrease of protein binding capacity of drugs and an increase in the unbound drug fraction, which could strengthen the pharmacological effect. The extent of this phenomenon is debated; the theory and clinical relevance may be contradictory. Benet and co-workers concluded that, clinically, for changes in plasma protein binding adjustment of a drug dose is not necessary, except for drugs with a high extraction ratio and a narrow therapeutic index that are given parenterally[48]. Midazolam and haloperidol are often prescribed in palliative care[24] and both are listed in the referred paper as drugs in which protein binding may influence clinical drug exposure[48]. However, the actual consequences for in clinical practice remain unknown.

The abnormal liver enzyme test results in the present study do not all tally with those in previous studies[27]. Laboratory tests of liver enzymes are notoriously bad indicators for liver function. Unfortunately, the levels of liver enzymes, even if severely elevated, do not predict a change in hepatic function, including drug metabolism[49, 50]. Moreover, liver enzymes may be elevated for other reasons than liver disease only, such as polypharmacy, alcohol consumption, metastatic disease or other organ diseases[51]. Bilirubin levels may reflect bile duct related problems (obstruction), while metabolic liver capacity is normal.

Hypercalcemia was found in 68% of patients in the present study versus 7% in another study[27]. This discrepancy might be explained by the median time till death (table 6), i.e. 3 days versus 26.5 days. In 48.0% of patients hypercalcemia was accompanied with kidney failure, possibly due to severe dehydration.

The median eGFR in our study population was 63ml/min. Seeing that the median age of this population was 75 years, this value reflects the physiological changes in renal function associated with advanced age[52]. Severe kidney failure, however, was found in 19% of patients. Kidney function impairment may be the result of a variety of underlying causes in cancer patients, including dehydration and extra-renal obstruction[11]. While an altered kidney function may be caused by drug treatment, poor renal function in its turn can have pharmacological consequences. This is illustrated by the finding of higher metabolite concentrations in patients with a worse kidney function[7, 53]. Those patients with kidney failure might be at risk for opioid-induced side effects, since metabolites will accumulate. In

our study most patients with poor kidney function were on treatment with a low-to-moderate morphine daily dose (92%), perhaps because the accumulation had resulted in stronger effects, and the dose needed to be reduced.

Remarkably, most of our patients had normal levels of sodium and potassium. This is also described in other studies during the last month[27] and the last week of life[29-31], indicating that these electrolytes even shortly before death are balanced.

To the best of our knowledge, this is the first overview of laboratory results in the week before death in hospice patients. We were also able to include data on actual morphine and NSAID use. An additional strength of our study is that we related the laboratory results to probable pharmacokinetic effects. Generally, in such a vulnerable patient population, the possibly negative impact of blood taking should be weighed against the benefits of the laboratory results. However, even in end-of-life patients, laboratory testing may be used to monitor or guide pharmacological treatment, to assess the need for additional treatment like blood transfusion or to explain symptoms like fatigue, confusion or vomiting. This is illustrated by one study in a palliative care unit, which concluded that 96% of the cases of laboratory testing were clinically relevant to confirm or exclude a diagnosis and that 30% resulted in a change of drug therapy[54].

Several limitations of this study have to be addressed however. This was a single-centre study in patients with mainly oncologic disease, so that findings should be extrapolated with caution. Furthermore, clinical details on diagnoses, mainly liver and kidney disease, could be incomplete. In a palliative care setting the observation of impaired kidney function will not lead to an exhaustive diagnostic work-up to identify the cause. This might have consequences for the classification of patients having a pre-existing kidney or liver disease. In addition, the exact severity of the kidney or liver disease was not detailed and all diseases states were therefore grouped together. Unfortunately, symptoms had not been routinely recorded with validated objective scoring instruments. And then, not for all included patients medication data were available. It would be of added value to relate laboratory results to validated symptom scores and administered medication in future research, since this may give additional insights into the clinical relevance of the abnormal laboratory results.

CONCLUSION

In conclusion, although clinically relevant abnormal values were found for several laboratory parameters, five out of eleven parameters studied were within the normal range for most of patient in their last week of life. Anaemia and hypo-

albuminemia were not unexpected, due to the physiological changes that occur during the last phase of life. Remarkably, electrolytes were balanced even shortly before death. The most clinically relevant laboratory parameter seems to be eGFR, reflecting the kidney function, as for some drugs (including morphine and NSAIDs) adverse effects may negatively impact on quality of life and knowledge of eGFR may assist in deciding on drugs and their dosing.

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CHAPTER 6

PHARMACOKINETICS OF MORPHINE, MORPHINE-3-GLUCURONIDE AND MORPHINE-6-GLUCURONIDE IN TERMINALLY ILL ADULT PATIENTS

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ABSTRACT

Background and objective: Morphine dosing can be challenging in terminally ill adult patients due to the heterogeneous nature of the population and the difficulty of accurately assessing pain during sedation. To determine the pharmacokinetics of morphine (M), morphine-3-glucuronide (M3G) and morphine-6-glucuoride (M6G) in this population, and to find clinically relevant parameters for dose individualisation we performed a population pharmacokinetic analysis.

Methods: Blood samples were randomly collected from 47 terminally ill patients in both the pre-terminal and terminal phase. Non-linear mixed-effects modelling (NONMEM) was used to develop a population pharmacokinetic model and perform covariate analysis.

Results: The data were accurately described by a two-compartment model for morphine with two one-compartment models for both its metabolites. Typical morphine clearance (Cl) was 48L/h and fell exponentially by more than 10L/h in the last week before death. Decreased albumin levels and a decreased estimated glomerular filtration rate (eGFR) resulted in lower metabolite clearance. Between-subject variability in CL was 52% (morphine), 75% (M3G) and 79% (M6G) and changed to 53, 29 and 34%, respectively, after inclusion of the covariates.

Conclusion: Our results show that morphine clearance decreased up to time of death, falling by more than 10l/h (26%) in the last week before death, and that M3G and M6G accumulated due to decreased renal function. Further studies are warranted to determine whether dose adjustment of morphine is required in terminally ill patients.

INTRODUCTION

Morphine is widely used to treat pain and dyspnoea in terminally ill patients[1]. A recent study showed that at the time of death, 87% of the patients in palliative care were treated with morphine[2]. Morphine is metabolised mainly into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is pharmacologically active and contributes to the analgesic effect[3-5]. M3G does not have any analgesic properties yet it has been suggested that it may be responsible for the side effects of morphine[6, 7]. As the morphine dose is determined clinically according to the patients' need, accurate pain assessment is crucial. However, in terminally ill patients this can be difficult as pain assessment can be complicated by delirium or palliative sedation[8-11]. Another difficulty with morphine dosing in this population is that its pharmacokinetics are likely to be highly variable. To date, no studies have been conducted on the pharmacokinetics of morphine in this specific population, although variability between patients is to be expected due to the heterogeneous nature of this population, e.g. differences in age, diagnosis and comorbidities. This variability is further increased by changes within patients over time, which can be caused by the physiological changes that occur as death approaches, such as cachexia and a decrease in renal function[12-15].

Together with the difficulty of assessing pain in these patients, this significant interpatient and intrapatient variability indicates the need for a dosing algorithm. The first step in developing an individualised dosing regimen is to gain more insight in the pharmacokinetics in this specific patient population. There have been very few studies performed in hospice patients and to our knowledge no population pharmacokinetics of morphine have been performed in terminally ill patients. To determine the pharmacokinetics in this population and to find clinically relevant parameters for individualised dosing, we therefore performed a population pharmacokinetic analysis of morphine, M3G and M6G in terminally ill patients.

MATERIALS AND METHODS

Study design

This prospective observational study in terminally ill patients was approved by the Medical Ethics Committee of the Erasmus University Medical Centre, Rotterdam, the local directors' board of the Laurens organisation agreed to the practicability and this study was performed in accordance with the principles of the Declaration of Helsinki and its later amendments. The study was conducted in the palliative

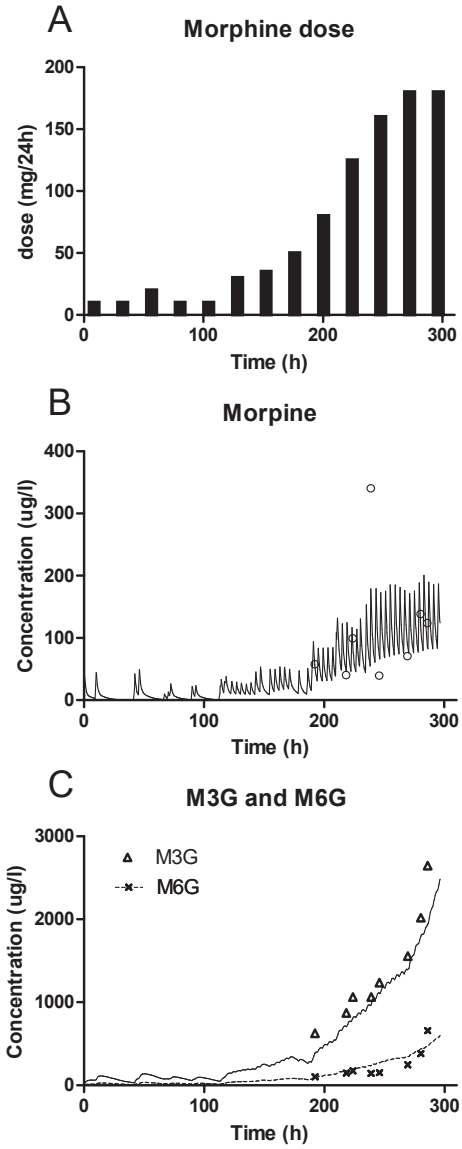

Figure 1. Dose and concentration data of a representative patient over time. This individual had a decrease in renal function with a drop in eGFR form 41.1 to 16.3 at T=283h.

A: Daily doses of subcutaneous morphine over time until the time of death B: Morphine concentrations over time. Post-hoc predictions (*solid line*) and measured morphine concentrations (*open circles*) C: Metabolite concentrations over time. Post-hoc predictions of M3G (*solid line*) and M6G (*dashed line*), as well as measured M3G (*triangles*) and M6G (*crosses*) concentrations. eGFR, estimated glomerular filtration rate; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide

care centre, Laurens Cadenza, Rotterdam, the Netherlands, over a 2-year period. Patients were included in the study upon admittance to the palliative care centre and were followed until the time of death. Inclusion criteria were terminal illness, prognosis survival of more than 2 days and less than 3 months, administration of morphine and patients had given informed consent.

Morphine was administered for pain and dyspnoea and was administered according to national palliative guidelines, daily doses ranging from 15mg to 540mg[16, 17]. Figure 1 A shows a representative patient receiving increasing daily morphine doses over time. Morphine was administered orally as controlled release tablets or immediate-release liquid, or administered subcutaneous as bolus injection or infusion. The exact times of administration were recorded in the patient record. Any concomitant use of codeine was also registered in the patient's record. Demographic characteristics (age, sex, weight, race, primary diagnosis, and time of death) were extracted from the electronic medical records. Primary diagnosis of the patient's terminal illness was classified using the International Statistical Classification of Diseases and Related Health Problems–10th Revision (ICD-10).

Blood samples were collected randomly at various time points in both the pre-terminal and terminal phases. The terminal phase was defined as the last hours to days before death in which a patient becomes bedbound, semi-comatose, is not able to take more than sips of fluid and is no longer able to take oral medication[18]. After collecting blood via either venipuncture or indwelling venous catheter samples were centrifuged, after which the plasma was collected and stored at -80°C until analysis. Blood sampling was preferably performed in combination with sampling for clinical chemistry (standard of care) for which serum levels of albumin, creatinine, urea, bilirubin, gamma-glytamyl transpeptidase (GGT), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), and C-reactive protein (CRP) were determined. With regard to these clinical chemical values, blood was collected in heparin tubes, centrifuged and analysed by the clinical chemistry laboratory as standard care for these patients.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) analysis

Morphine, M3G and M6G were analysed in the plasma samples using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) with electrospray ionization in the positive ionization mode on a Shimadzu LC-30 (Nishinokyo-Kuwabaracho, Japan) system coupled to a ABSciex (Framingham, MA, USA) 5500 Qtrap MS. To 10µl of patients' plasma, 75µl acetonitril/methanol 84:16 (v/v%) containing the internal standards morphine-d3, M3G-d3 and M6G-d3 was added

to precipitate proteins. Samples were vortexed, stored at -20°C for 30 minutes to optimise protein precipitation, vortexed again and centrifuged. A total of 3 µl was injected into a Thermo Scientific Hypersil Gold HILIC (50 x 2.1mm, 1.9µm) column. A stepwise chromatographic gradient was applied using 1% ammonium formate / 2% formic acid in water as mobile phase A and acetonitrile as mobile phase B. The flow rate was 0.6ml/min and the column was kept at 40°C. Using multiple reaction monitoring (MRM), morphine, M3G and M6G were measured as [M+H]+ using the mass transitions 286.1/165.1, 462.2/286.2 and 462.2/286.2, respectively. Retention times for morphine, M3G and M6G were 0.44, 2.77 and 2.58 respectively. For the internal standards morphine-d3, M3G-d3 and M6G-d3 were used with the same retention times and mass transitions of 289.1/165.1, 465.2/289.2 and 465.2/289.2, respectively.

The method was validated over a range of 2 – 500µg/L for all compounds with six calibration curves each containing seven concentrations. The accuracies ranged from 93.5% to 105.5%. Intraday and interday precision were calculated with six replicates of four concentrations (2, 6, 60 and 500µg/L) for all compounds and resulted in intraday and interday precisions below 9.6% and 12.9%, respectively. Three quality controls (low level 2µg/L, medium level 60 µg/L and high level 500µg/L) were validated and used for this method.

Population Pharmacokinetic modelling

Pharmacokinetic analysis was conducted by non-linear mixed-effects modelling using NONMEM® version 7.2 (ICON Development Solutions, Ellicott City, MD, USA) and PsN® version 3.7.6.

Base model development

The data were log-transformed and concentrations of M3G and M6G were adjusted to their morphine equivalents using the molecular weight. Bioavailability of subcutaneous morphine was assumed to be 100%[19, 20]. One- two- and three-compartment models were tested for morphine and its metabolites using the first-order conditional estimation method with interaction (FOCE+I) and the ADVAN5 subroutine. First, a structural model for morphine was developed. These parameters were then fixed to test the different structural models for M3G and M6G. In the final model all parameters were estimated, with the exception of the transformation ratios for M3G and M6G. Since there was no information on the mass balance, the fractions of morphine transformed into metabolites and fractions excreted could not be determined independently. These ratios were therefore set to previously described values, i.e. 0.55 for M3G and 0.10 for M6G[21-23].

Between-subject variability (BSV) was assessed on each parameter using an exponential and additive model, and residual variability was incorporated as an additive error on the log scale. Model selection was based on minimum objective function values (OFVs), parameter precision, error estimates, shrinkage values and visual inspection of the goodness-of-fit plots.

Covariate model development

Demographic and disease characteristics including age, sex, race, primary diagnosis, renal function (estimated glomerular filtration rate (eGFR), plasma creatinine, and plasma urea), hepatic function (plasma levels of bilirubin, GGT, ALP, ALT, and AST), CRP, albumin, and the concomitant use of codeine, were evaluated as potential model covariates. Time to death (TTD) was also evaluated as a covariate. This parameter cannot be used as a covariate parameter for a priori prediction of individual pharmacokinetic changes but it may give insight in quantitative changes at the end of life that are not predicted by standard blood chemistry tests. As heart and respiratory rates are not measured in a palliative care centre, standard disease severity scoring systems used in internal medicine (e.g. the simple clinical score or rapid emergency medicine score) cannot be used in this situation. The relationship between covariates and individual estimates was first investigated graphically and was further tested in a univariate analysis. Covariates that significantly improved the model, ($p \leq 0.05$) were added to the full model. A backward elimination process was then performed with statistical significance indicated by $p \leq 0.001$.

Continuous covariates were normalised to the population median values and incorporated as power model functions (Eq. 1). Categorical covariates were transformed to binary covariates and incorporated as shown in Eq. 2.

$$\theta_i = \theta_{pop} * \left(\frac{cov_i}{cov_m}\right)^{\theta cov} \quad (1)$$

$$\theta_i = \theta_{pop} * \theta_{cov}{}^{cov_i} \quad (2)$$

With θi being the individual model-predicted pharmacokinetic parameter (e.g. clearance) for an individual with covariate value cov_i, θpop being the population estimate for that parameter, cov_m representing the median covariate value and θcov representing the covariate effect. In the equation for categorical covariates, cov_i is either 1 or 0.

To evaluate the time to death (TTD) as a covariate, time-dependency of the parameters was modelled as a first-order process given to following equation (Eq. 3).

$$\theta_i = \theta_{pop} - \theta_{\Delta} * \exp(-\theta_{rate} * TTD) \quad (3)$$

In which θ_{Δ} is the change in parameter value from its initial value and θ_{rate} is a first-order rate constant determining the rate with which the parameter value changes over time.

Model evaluation

A bootstrap with 500 runs was performed on the final model to evaluate the validity of the parameter estimates and their corresponding 95% confidence intervals (CIs). Due to the study design, i.e. sparse sampling, different dosing regimens and both oral and subcutaneous administrations, a visual predictive check could not be performed to evaluate the model. We therefore evaluated the predictive performance of the final model using a normalised prediction distribution errors (NPDE) analysis. NPDE is a simulation-based diagnostics which can be used to evaluate models developed on datasets with variable dosing regimens. The analytical value of this method has been previously described by Comets et al[24].

RESULTS

A total of 47 terminally ill patients were included in the study. Their median age was 71 years (range 43 – 93), 55.3% were female and the median duration of admittance (from moment of admittance until time of death) was 33 days (range 7 – 457). Almost all patients (95.7%) had advanced malignancy as primary diagnosis. Patient characteristics are given in Table 1. From these patients, a total of 152 blood samples were collected and analysed for morphine, M3G and M6G concentrations. Figures 1B and 1C show the concentrations of morphine, M3G and M6G over time for a representative patient. As shown in these graphs, the morphine concentration increases as the dose increases, and near the end of life M3G and M6G concentrations increase significantly. Circa 12% of the plasma concentrations were below the quantification limit (BLQ), largely due to two patients who had had blood samples taken more than 10 days after the last morphine dose. BLQ data were therefore discarded using the M1 method discussed before by Ahn et al[25].

Table 1. Patient characteristics

Characteristics	**N = 47**
Age, years (median, range)	71 (43 - 93)
Male, *n* (%)	21 (44.7)
Female, *n* (%)	26 (55.3)
Ethnic origin, *n* (%)	
Caucasian	45 (95.7)
Afro-Caribbean	2 (4.3)
Primary diagnosis, *n* (%)	
Neoplasm	45 (95.7)
Disease of the circulatory system	1 (2.1)
Disease of the respiratory system	1 (2.1)
Blood chemistry, serum levels at admission (median, range)	
Albumin, g/l	26 (14-39)
Urea, mmol/l	7.2 (1.5-43.4)
Bilirubin, umol/l	8 (3-256)
Gamma-glytamyl transpeptidase, U/l	64 (7-3859)
Alkaline phosphatase, U/l	112 (20-2117)
Alanine transaminase, U/l	12 (7-406)
Aspartate transaminase, U/l	32 (14-255)
C-reactive protein, U/l	67 (1-188)
Creatinine, umol/l	72 (22-229)
eGFR by standard MDRD[a], ml/min/1.73 m^2	96 (27-239)
eGFR by original MDRD[b], ml/min/1.73 m^2	83 (22-202)
Patients using codeine[c], *n* (%)	2 (4.2)
Duration of stay, days (median, range)	33 (7 - 457)
Blood samples collected, *n* (median, range)	2 (1 – 10)

eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

[a] The abbreviated MDRD equation consists of four variables (age, sex, race and serum creatinine) as shown in Eq. 4

[b] The original MDRD formula consist of six variables (age, sex, race, serum creatinine, serum albumin and serum urea) as shown in Eq. 5

[c] During any moment while receiving morphine treatment

Structural model

The data were best described by a two-compartment model for morphine and two one-compartment models for both its glucuronidated metabolites (Figure 2). Since limited data was available in the absorption phase, the absorption constants (Ka) could not be estimated, and were therefore fixed to known literature values (10 h^{-1} for subcutaneous injection, 6 h^{-1} for immediate-release liquid and 0.8 h^{-1} for controlled release tablets)[26, 27]. The population mean estimates for volume of distribution were, 185 L (relative standard error [RSE] 28%) for the central morphine compartment (V1); 243 L (RSE 33%) for the peripheral morphine compartment (V2); 7.65 L (RSE 33%) for the M3G compartment; and 7.1L (RSE 30%) for the M6G compartment. The population mean estimates for clearance were 37.2L/h (RSE 9%) for morphine; 1.48L/h (RSE 8%) for M3G and 1.87L/h (RSE 8%) for M6G. An overview of all parameter estimates is given in Table 2.

Including BSV on morphine clearance and bioavailability (F) of oral morphine both significantly improved the model fit with a change in OFV (ΔOFV) of -43.3 and -7.05 respectively. The correlation between BSV of M3G and M6G clearance was high and fixed to unity. A similar approach was used for BSV on the volumes

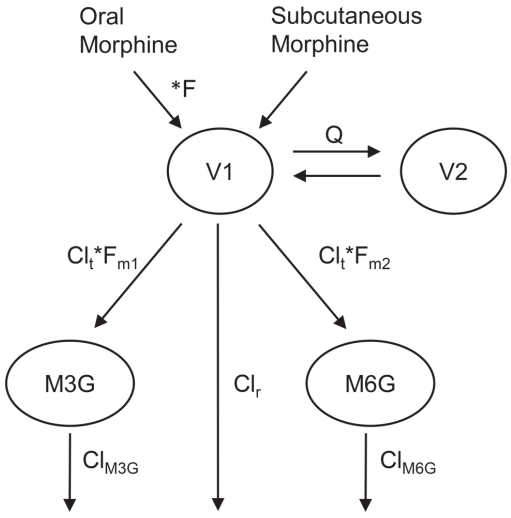

Figure 2. Schematic representation of the two-compartment model for morphine and its two main metabolites.

F, bioavailability of oral morphine; V1, central compartment for morphine; V2, peripheral compartment for morphine; Q, intercompartmental clearance of morphine; Cl_t, total morphine clearance, F_{m1}, fraction of morphine clearance responsible for M3G formation; F_{m2}, fraction of morphine clearance responsible for M6G formation; Cl_r, remaining morphine clearance (Cl_t*1-(F_{m1}+F_{m2})); Cl_{M3G}, clearance of M3G; Cl_{M6G}, clearance of M6G, M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide

Table 2. Parameter estimates of the base model, final model and bootstrap analysis

Parameter	Structural model	Final model	RSE %	Shrinkage %	Bootstrap of the final model		
					Estimate	95% CI (lower)	95% CI (upper)
OFV	-323.7	-351.6					
Morphine							
F	0.28	0.30	13.6	-	0.31	0.18	0.53
Cl (L/h)	37.2	47.5	11	-	49.9	39.1	75.6
V1 (L)	185	190	28	-	190	116	369
Q (L/h)	75	76.1	35.7	-	65.1	9.95	146
V2 (L)	246	243	19	-	248	121	377
M3G							
F_{m1}	0.55[a]	0.55[a]	N/A	-	0.55[a]	0.55[a]	0.55[a]
Cl (L/h)	1.48	1.44	4.8	-	1.44	1.30	1.59
V1 (L)	7.65	8.02	33.2	-	7.75	3.62	14.9
M6G							
F_{m2}	0.1[a]	0.1[a]	N/A	-	0.1[a]	0.1[a]	0.1[a]
Cl (L/h)	1.87	1.78	6.8	-	1.79	1.56	2.05
V1 (L)	7.1	8.24	30.7	-	7.97	3.77	14.0
Covariate effect on M3G and M6G clearance							
eGFR[b]	0.83	0.673	16.8	-	0.67	0.50	1.03
Albumin	-	1.1	23.3	-	1.06	0.332	1.56
Covariate effect on M3G and M6G clearance							
TTD[c] (Δ), days	-	17.6	24.7	-	19.2	9.48	46.6
TTD[c] (rate), days	-	0.13	32	-	0.12	0.05	0.31
Between subject variability (%)							
F	48.2	37.8	38.3	9.5	38.7	1.7	58.0
morphine Cl	54.0	53.4	30.1	13.3	50.0	31.7	71.8
M3G Cl	39.7	29.3	29.2	5.5	29.3	20.4	41.7
M6G Cl	43.5	34.3	29.2	5.5	34.1	23.8	48.4
M3G V1	135.5	151.7	31.4	6.1	147.9	80.3	203.1
M6G V1	130.4	143.0	31.4	6.1	141.5	76.8	194.4
Residual variability							
Morphine	0.448	0.432	10.4	10	0.425	0.335	0.510
M3G	0.250	0.246	9.3	10	0.239	0.194	0.282
M6G	0.261	0.265	6.6	10	0.254	0.218	0.294

RSE, relative standard error; CI, confidence interval; OFV, objective function value; F, bioavailability; Cl, clearance; V1, central compartment; Q, intercompartmental clearance; V2, peripheral compartment; M3G, morphine-3-glucuronide; F_{m1}, fraction of morphine clearance responsible for M3G formation; M6G, morphine-6-glucuronide; F_{m2}, fraction of morphine clearance responsible for M6G formation; eGFR, estimated glomerular filtration rate; TTD, time to death; MDRD, Modification of Diet in Renal Disease; GFR, glomerular filtration rate

[a] Transformation ratios for M3G and M6G were fixed to known literature values

[b] GFR was estimated using the standard four-variable MDRD equation

[c] TTD was incorporated as a first order process, with TTD_{Δ} (overall change in clearance) as the change in parameter value from its initial value and TTD_{rate} (change in clearance per day as described by the first order process) as the first order rate constant

of distribution of the M3G and M6G. Adding BSV on metabolite clearance and metabolite volume significantly improved the model fit with a change in objective function of 157.0 and 41.1, respectively. In all cases, an exponential model for BSV proved superior to an additive model.

Since M3G and M6G are renally cleared, and because there were patients who developed renal failure over time, a measure for renal failure was added to the structural model. This was done by evaluating the covariate effect of creatinine levels, urea levels, and eGFR on metabolite clearance. Glomerular filtration rate was estimated using the generally excepted four-variable, Modification of Diet in Renal Disease (MDRD) equation consisting of age, sex, ethnicity, and serum creatinine levels (Eq. 4)[28]. Estimated GFR gave the best results (ΔOFV -75.97 vs -73.58 for creatinine levels and -66.77 for urea levels) and was therefore included in the structural model.

$$eGFR = 186 \; x \; serum\ creatinine\ (mg/dl)^{-1.154} \; x\ age^{\ -0.203} \; x\ (1.210\ if\ black)\ x\ (0.742\ if\ female) \qquad (4)$$

Covariate analyse

The structural model including eGFR on metabolite clearance was used as a reference for the covariate analysis. The univariate analysis resulted in a further eight significant covariates, three of which were correlated with morphine clearance (i.e. TTD, bilirubin, and urea), two were correlated with metabolite clearance (i.e. albumin and CRP), two were correlated with the volume of distribution of the metabolites (i.e. creatinine and urea), and one was correlated with bioavailability (i.e. race). The results of the univariate analysis, in terms of decrease in OFV and covariate effect, are shown in Table 3. After backwards elimination of $p<0.001$, only albumin levels on metabolite clearance and TTD on morphine clearance remained in the final model.

Because the final model had both eGFR and albumin levels as covariates on metabolite clearance, we also tested if these two covariates could be replaced by the eGFR estimated using the original six-variable MDRD formula (Eq. 5)[28]. This formula calculates GFR using not only sex, weight, race and creatinine levels but also takes into account albumin and urea levels. However, this more elaborate version of the MDRD equation did not improve the model fit (OFV -342.9 versus -351.6 for the standard four-variable MDRD equation). Together, estimated GFR and serum albumin decreased the unexplained variability on M3G and M6G clearance from 75.4% and 79.1% to 29.3% and 34.3%, respectively. They hereby explain 61.1% of the BSV in M3G clearance and 56.6% of the BSV on M6G clearance. The covariate TTD did not decrease the unexplained variability on morphine

Table 3. Covariate effects in univariate analysis compared with the structural model

Covariate	ΔOFV	Covariate effect	Included after backward elimination
Structural model	-		
Covariates on bioavailability			
Afro-Caribbean Race[a]	6.36	0.52	No
Covariates on morphine Cl			
Time to Death	9.65	20.2 and 0.11[b]	Yes
Plasma Urea	7.04	-0.28	No
eGFR[c]	4.38	0.18	No
Plasma Bilirubin	4.06	-0.16	No
Covariates on metabolite Cl			
CRP	16.4	-0.21	No
Plasma albumin	15.4	1.10	Yes
Plasma GGT	6.10	-0.11	No
Covariates on metabolite Vd			
eGFR[c]	9.42	0.33	No
Plasma creatinine	8.16	-0.40	No
Time to death	7.92	-14.7 and 0.08[b]	No
Plasma urea	6.65	-0.26	No

OFV, objective function value; CL, clearance; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; GGT, gamma-glutamyl transpeptidase; Vd, volume of distribution; TTD, time to death; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

[a] Compared with subjects of Caucasian race

[b] 21.6 is the value for TTDΔ (overall change in clearance) and 0.10 is TTD_{rate} (change in clearance per day as described by the first order process)

[c] GFR was estimated using the abbreviated MDRD equation

clearance; however, it did decrease the RSE on the volumes of both metabolites (from 65.7% to 33.2% for M3G, and from 63.8% to 30.7% for M6G).

$$eGFR = 170 \; x \; serum\ creatinine \left(\frac{mg}{dl}\right)^{-0.999} x\ age^{-0.176} \; x \; (1.180 \; if \; black) \; x \; (0.762 \; if \; female) \; x \; serum\ urea\ nitrogen\ (mg/dl)^{-0.170} \; x \; albumin\ (g/dl)^{0.318} \quad (5)$$

Simulations

Based on the final model, the M3G clearance is reduced by approximately 30% (from 1.6L/h to 1.1L/h), while eGFR decreases form 90 to 50ml/min and albumin concentrations remain stable at 25g/L. A further reduction of eGFR to 30ml/min decreases M3G clearance to a value of 0.8L/h (Figure 3). The effect of a reduction

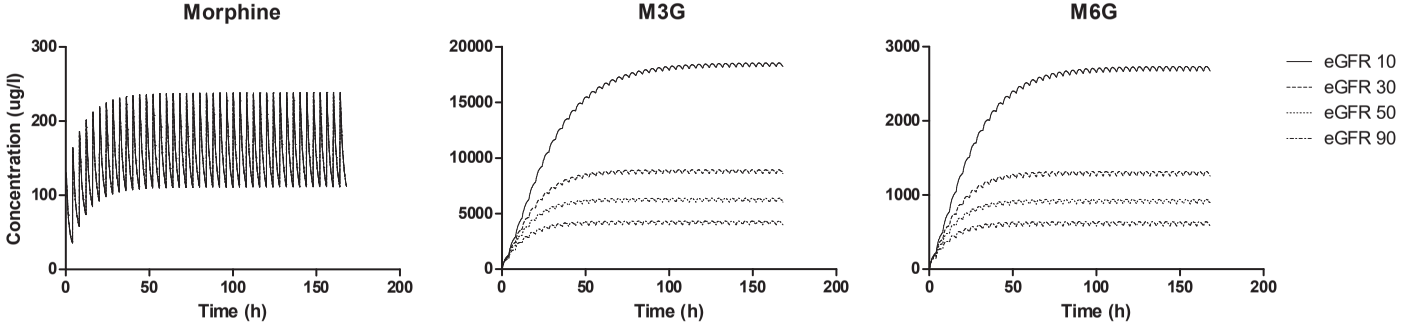

Figure 3. Simulated plasma profiles of morphine, M3G and M6G for patients with an eGFR of 10ml/min (*solid line*), 30ml/min (*dashed line*), 50ml/min (*dotted line*) and 90 ml/min (*dash-dotted line)* with a 30mg six-daily subcutaneous bolus injection dosing regimen and stable plasma albumin levels of 25g/l.

M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; eGFR, estimated glomerular filtration rate

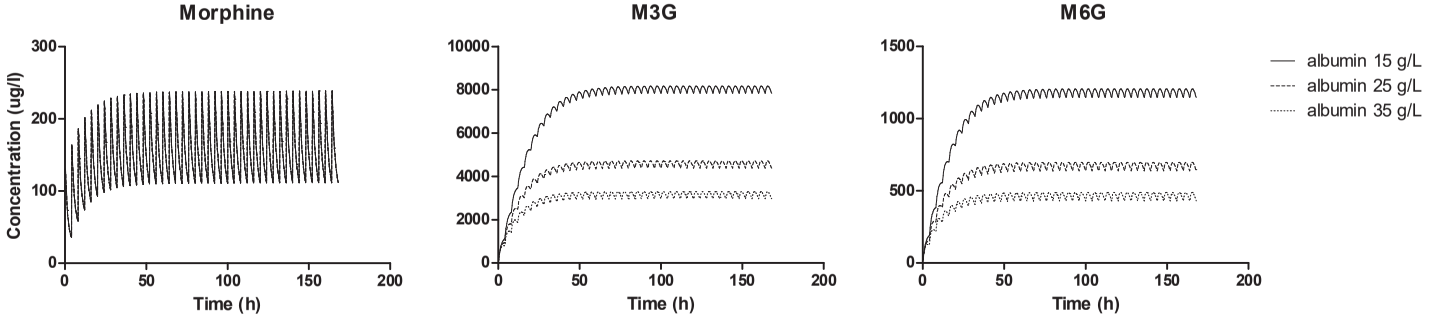

Figure 4. Simulated plasma profiles of morphine, M3G and M6G for patients with plasma albumin levels of 15g/l (*solid line*), 25g/l (*dashed line*), and 35g/l (*dotted line*) with a 30mg six-daily subcutaneous bolus injection dosing regimen and stable plasma albumin levels of 78.

M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide

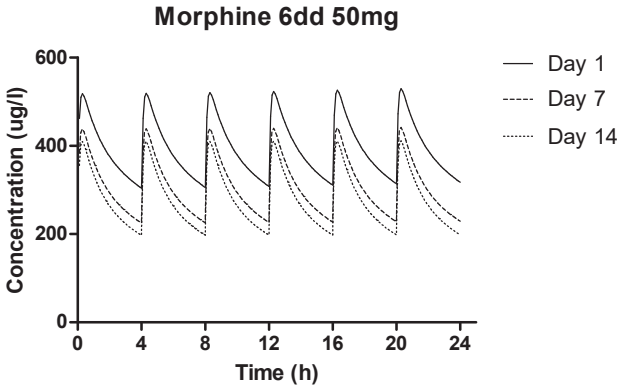

Figure 5. Simulated plasma profiles of morphine in the case of 50mg six times daily subcutaneous bolus infusion, 2 weeks (*dotted line*), 1 week (*dashed line*) and 1 day (*solid line*) before death

of eGFR on metabolite clearance is shown in Figure 1C, where the concentrations of M3G and M6G increase in the last few hours. Indeed, this individual had a decrease in renal function, with a drop of eGFR from 41.4 to 16.3 at T=283 hours. The final model also implies that with a stable eGFR of 78ml/min, a decrease in albumin from 35g/l to 25g/l produces a 31% decrease of M3G clearance (from 2.1L/h to 1.4L/h) (Figure 4). Respective changes in M6G clearance are also shown in Figures 3 and 4, and are similar to changes in M3G clearances.

Based on the covariate model, morphine clearance will decrease with 13%, from 46.4L/h 3 weeks before death to 40.6L/h 1 week before death. In the final week before death, morphine clearance would decrease by another 26% to 29.9L/h on the day of death. As a result, the area under the curve of morphine will be significantly increased in the final days of life, as can be seen in the simulations of morphine concentrations in Figure 5.

Evaluation of the final model

Goodness-of-fit plots of the final model showed the population predictions and individual predictions were evenly distributed around the line of unity. The conditional weighted residuals (CWRES) were normally distributed and did not show any correlation with the population predictions (Figure 6).

A bootstrap analysis was performed to obtain 95% CIs for all parameters. Results of the bootstrap are shown in Table 2. Evaluation of the predictive performance by NPDE analysis showed accurate predictive ability, with distribution of the NPDEs not significantly deviating from a normal distribution (global adjusted

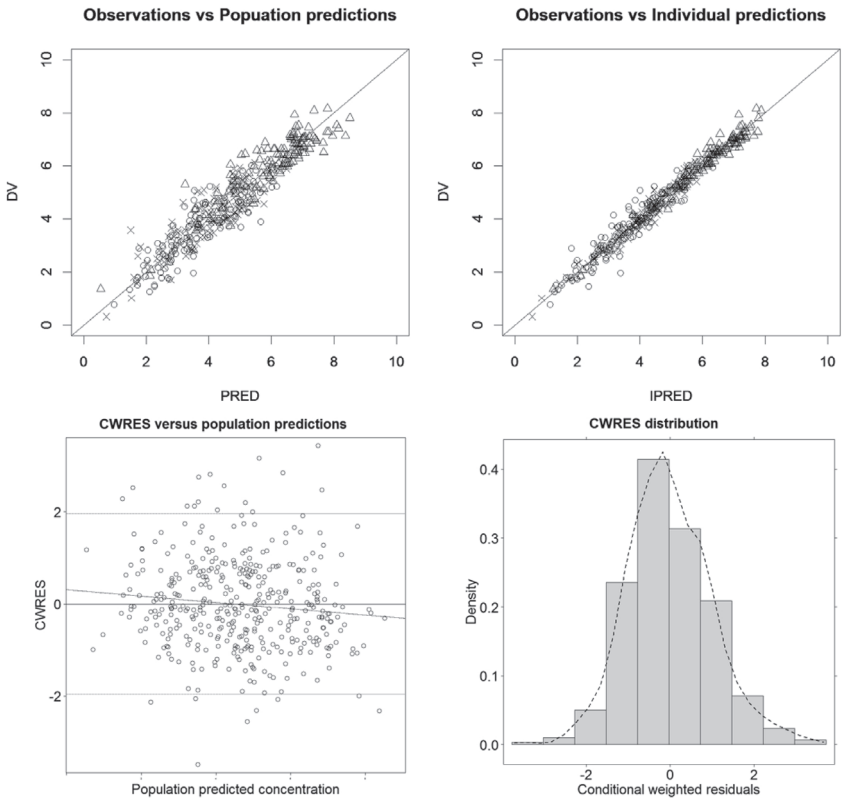

Figure 6. Goodness of fit plots of the final model

The top two panels show the PRED and IPRED concentrations versus the DV for morphine (*open circles*), M3G (*open triangles*), and M6G (*crosses*), with the *solid line* displaying the line of unity. The bottom two panels show the correlation of CWRES with the PRED concentrations , including the trend line and the distribution of the CWRES with the PRED concentrations, including the trend line and the distribution of the CWRES in *grey bars* and *dashed line.*

PRED, population predicted; IPRED, individual prediction; DV, observed concentrations; CWRES, conditional weighted residuals; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide

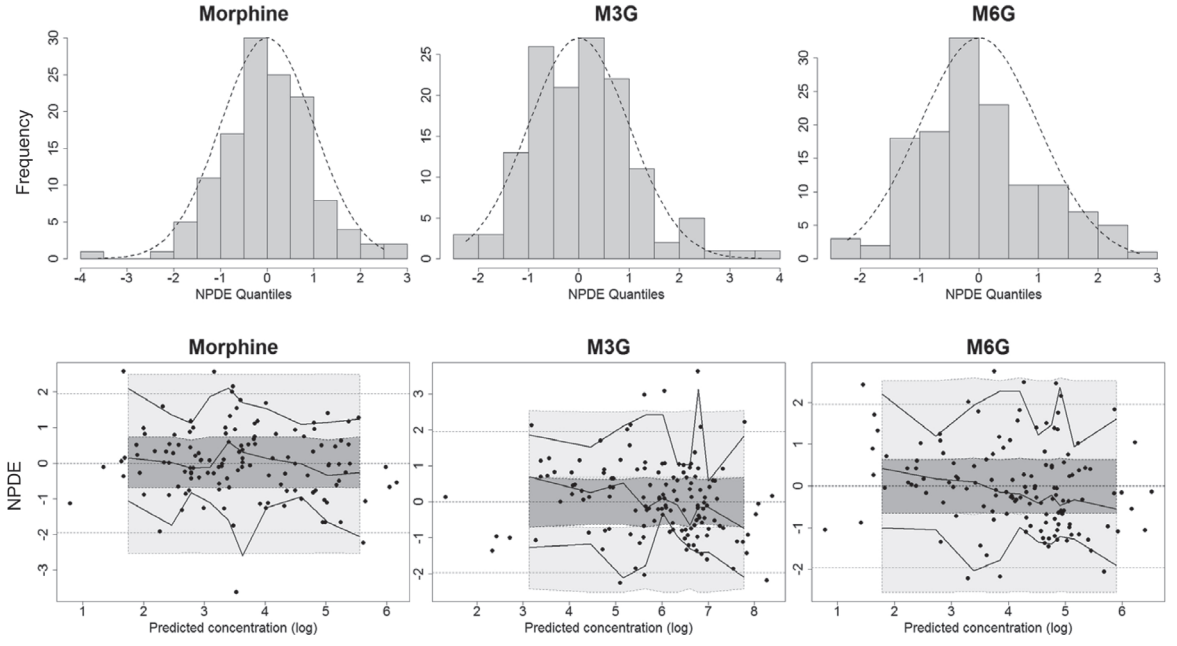

Figure 7. NPDE analysis of the final model for morphine, M3G, and M6G

The top panels show distribution of the NPDE quantiles (*grey bars),* with the shape of a normal distribution also shown (*dashed line)*. The bottom panels show the NPDEs versus the log of the predicted concentrations with individual NPDE values (*dots)* and 5th, 50th, and 95th percentile lines with their corresponding 90% confidence intervals (*grey shaded areas)*.

NPDE, normalised prediction distribution error; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide

p value, morphine 0.84, M3G 0.19, and M6G 0.09), and the majority of the NPDEs lay between the values -2 and 2 (Figure 7).

DISCUSSION

This is the first population pharmacokinetic study of morphine in end-of-life patients, performed in a nonacademic palliative care setting. We even included data of patients shortly before death, and were able to accurately describe the pharmacokinetics of morphine, M3G and M6G with a two-compartment model for morphine and with two one-compartment models for both its metabolites. As we followed patients until the time of death, we were able to show a decrease in morphine clearance as patients are nearer to time of death. We also showed that eGFR, together with albumin levels, were the best predictors for metabolite clearance, explaining approximately 60% of the unexplained variability between patients.

To the best of our knowledge, there have not been any population pharmacokinetic studies on morphine, M3G, and M6G in terminally ill patients. In the 1980's, Säwe et al. demonstrated that the bioavailability of oral morphine in cancer patients ranged between 15 and 64%[29], which is comparable with our results in which we found a variability on morphine bioavailability of 38%, with individual values for morphine bioavailability of between 16 and 52%. Because the bioavailability of morphine is dependent on first-pass metabolism, this variability is probably due to changes in liver blood flow as morphine has a high extraction ratio and glucuronidation is well-preserved, even in the case of sever liver disease[30-32].

In this same study, Säwe and co-workers found a morphine clearance ranging from 0.3 to 0.97L/h/kg, which would mean 21-67L/h for a 70kg individual. The latter compares favourably with our finding of 47.5L/h. Two other population pharmacokinetic studies on data from cancer patients and one study in intensive care patients reported similar values for morphine clearance of 63.8L/h and 35L/h respectively[27, 33, 34]. Interestingly, in studies of neurosurgical patients and healthy volunteers, higher clearances have been reported (110L/h and 75.3L/h respectively)[21, 23]. This indicates that morphine clearance is reduced in critically ill patients[23].

In the referred study in healthy volunteers, Lötsch et al. showed a delay between the rise of morphine concentrations and the formation of M6G; this delay was modelled using a transit compartment[23]. In our study, the addition of transit compartments did not improve the fit of the metabolite concentration to

the population model due to the sampling frequency in our study being too low in comparison with the reported transit time of 17 minutes for M6G[26].

In the previous studies in neurosurgical and cancer patients, a larger clearance for M3G and M6G was found than in our study (M3G clearance 2.67L/h in neurosurgical patients and 3.36L/h in cancer patients; M6G clearance 2.52L/h in neurosurgical patients and 3.36L/h in cancer patients)[21, 27, 34]. A possible explanation is that the patients in our study were closer to the time of death and had therefore had reduced renal clearance. Similarly, in the study of Ahlers and colleagues it was demonstrated that M3G clearance was significantly reduced in intensive care patients compared to healthy individuals due to decreased creatinine clearance[33].

Our results show large interpatient variability, especially in the volume of distribution of M3G and M6G, with values of 152% and 143%, respectively. A previous study in neurosurgical patients showed much less interpatient variability, which could be explained by this population being less heterogenic, and also that this study only included nine patients[21]. The high BSV in our study was mainly due to two patients with very high estimated volumes of distribution for M3G and M6G. A possible explanation for the large interpatient variability observed in our study might be a change in body weight, which we could not test as a covariate. Particularly during the last phases of life, patients can have decreased lean body weight or may have oedema, which could influence the volume of distribution of the metabolites[35].

The covariate analysis resulted in three significant covariates, with the first being time to death. Morphine clearance decreased exponentially as time to death decreased, falling by more than 10L/h (26%) in the last week before death. As none of the other covariates tested gave a similar significant effect on morphine clearance, this might association may be caused by a combination of factors. It may be the result of a physiological change (e.g. a decrease in hepatic blood flow) that is not detected with standard blood chemistry tests. This observed decrease in clearance implicates that morphine dose may have to be decreased according to life expectancy. Life expectancy is difficult to predict, as is, for instance, shown by the range of admittance in this study being significantly longer than the 3 months stated as an admittance criterion for the hospice. However, the terminal phase (where a patient will die within hours or days) is usually well-recognised based on several clinical signs (i.e. the patient becoming bedbound, semi-comatose, and that oral medication and fluid intake is no longer possible)[18, 36]. In this case, a clinical protocol, specific for the terminal phase, is started and specific domains will be registered in the patient record as standard of care[37]. Therefore, it might

be possible to re-evaluate the morphine dose when this phase is started as our model showed the biggest decrease in morphine clearance in the last week of life.

The two other covariates, eGFR and plasma albumin levels, were correlated with M3G and M6G clearance. The fact that eGFR is correlated with M3G and M6G clearance was expected as both metabolites are eliminated through the kidneys. Previous studies have indeed shown that M3G and M6G can accumulate in patients with impaired renal function[38, 39].

The effect of albumin on metabolite clearance has not been shown previously in other studies. As M3G and M6G are not highly bound to plasma albumin, it is unlikely that this effect will be due to changes in unbound fractions of the metabolites. A possible explanation for this effect of albumin may lie in the fact that some terminally ill patients will become cachectic, which also leads to hypoalbuminemia[14]. The MDRD equation is not appropriate for calculating GFR in cachectic patients due to severe muscle loss and thereby overestimation of GFR based on creatinine levels. Therefore, low albumin levels may be an indicator for patients in which GFR is overestimated. Another explanation why the combination of albumin and eGFR are a better predictor than eGFR alone may be that albumin can be an indication that a patient is closer to the time of death. Several studies have shown that low albumin levels can predict prognosis in palliative cancer patients[40-42]. If a patient is closer to the time of death, eGFR might be significantly decreased (for instance due to dehydration). As the MDRD formula also overestimates GFR when GFR is very low, in this case the addition of albumin levels in the model might partly compensate for this overestimation. Combining both eGFR and albumin levels will therefore result in better prediction of M3G and M6G clearance.

The main limitation of our study is the fact that we lacked data to evaluate associations between weight and the pharmacokinetic parameters. As mentioned above, this might affect the estimates of volume of distribution, and there is also a possible correlation with metabolite clearance since, as described before, renal function can be overestimated in patients with low body weight. Precise monitoring of weight is not common practice in palliative care because it does not contribute to the treatment and because patients might find it difficult to be confronted with their weight loss. However, as weight is possibly an important covariate, we recommend that it is monitored in future pharmacokinetic studies in terminally ill patients.

Another possible limitation of the study is that the absorption constant of all three dosing forms were fixed to known literature values. This was necessary as there were insufficient data points in the first 30 minutes after a dose administration due to the sparse sampling design. This could have biased the estimation of

volume of distribution for the central compartment as absorption rate and volume of distribution both affect the initial concentration. In the terminally ill population, patients receive morphine for extended periods of time; therefore, clearance (and BSV on clearance) instead of volume of distribution is the predominant parameter effecting total morphine exposure.

In addition, it was not possible to determine the transformation ratios of M3G and M6G. These ratios were set to previously described values, i.e. 0.55 for M3G and 0.10 for M6G[21-23]. This could have biased the results for the parameters of metabolite clearance and volume of distribution as these are both proportional to the transformation ratio (Cl/F and Vd/F). However, we consider the values of 0.55 and 0.10 to be valid as the liver's capacity for glucuronidation of drugs is reasonably stable, even in critically ill patients and in patients with mild to moderate cirrhosis[30, 31, 33]. The fact that there is between subject variability on morphine bioavailability (which is a result of first-pass metabolism) is most likely to be caused by a variation in liver blood flow instead of metabolic capacity as morphine is drug with a high extraction ratio[32]. In this case, the clearance of morphine will differ; however, the formation ratios should remain unchanged. Furthermore, setting the transformation ratios to 0.55 and 0.10 resulted in comparable estimates for clearance and volume of distribution for both metabolites (Table 2). This seems to be appropriate as both metabolites have an almost identical molecular structure and are therefore expected to have similar molecular properties. To establish whether the transformation ratios are not altered in these patients, information about the mass balance is required. This can be obtained by measuring the fractions of morphine, M3G, and M6G in urine samples.

In conclusion, our study again confirms that a reduction in eGFR resulted in a decreased clearance of M3G and M6G, which can have clinical consequences as M6G is a metabolite with analgesic activity, while M3G has been suggested to contribute to side effects. As a result, the morphine dose may be reduced in patients with renal failure, or analgesic therapy may be switched to an opioid with less or no active metabolites (e.g. oxycodone or fentanyl). We also found that eGFR combined with albumin levels was a better predictor for M3G and M6G clearance than eGFR alone. Therefore, dose adjustments should also take into account albumin levels besides eGFR. In addition, a positive correlation was found between time to death and morphine clearance. This important insight into the pharmacokinetics of morphine in terminally ill patients is a first step in developing an individualised dosing regimen for terminally ill patients. It suggests that morphine doses might be adjusted to a patient's creatinine and albumin levels and life expectancy. However, accurate prediction of the time of death can be

difficult and the need for morphine does not solely depend on pharmacokinetics. Therefore, further studies on the pharmacodynamics in this patient population are needed before any firm conclusions can be drawn on dose adjustments.

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ADDENDUM

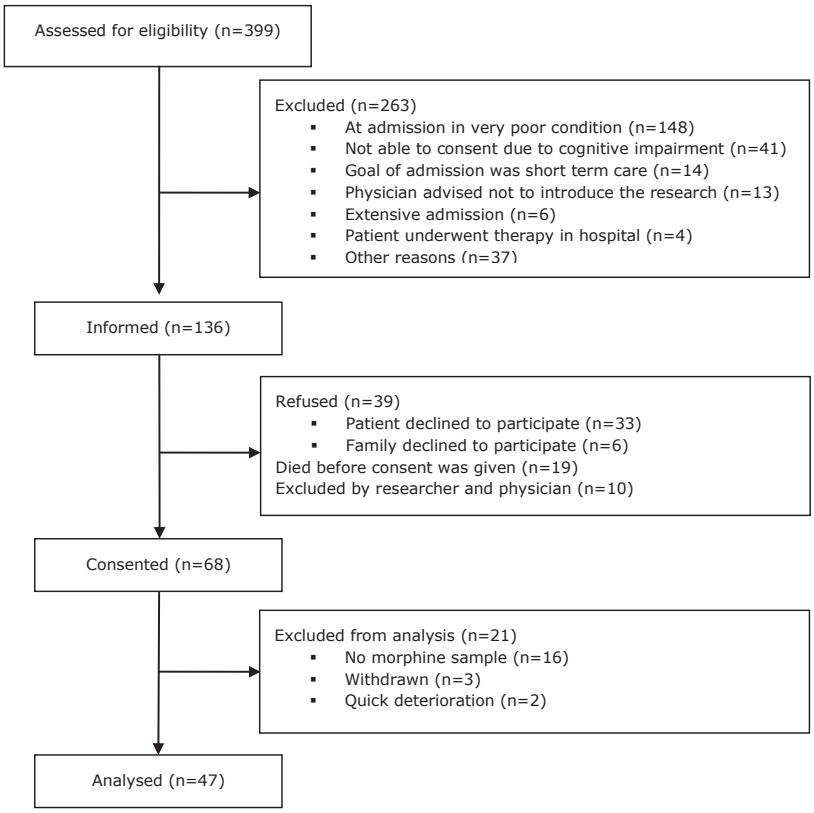
Study design and setting

This prospective observational study in terminally ill patients was conducted during two years in the palliative care centre, Laurens Cadenza, in Rotterdam, the Netherlands. This is the largest palliative care centre in the Netherlands, with 20 beds for end-of-life care and symptom management; 200 to 250 patients are admitted annually. A multidisciplinary team of health care professionals, including specialised nurses and elderly care physicians specialised in palliative care, is available 24 hours per day. In addition, many volunteers perform supporting tasks.

Participants

Patients were included in the study upon admittance to the palliative care centre and were followed until the time of death. Inclusion criteria were terminal illness, prognosis survival of more than 2 days and less than 3 months, administration of morphine and given informed consent. Patients admitted during the study period were asked to participate in this study, except those with a prognosis of survival of less than 2 days, those who could not consent themselves and those who were admitted temporally. The researcher (A.M.) informed the patients about this study after asking the responsible physicians and/or nurses for eligibility and appropriate timing. If possible, the patient was informed in the presence of a relative. They were given at least 24 hours to consider their decision before written permission was given. During participation and especially during the dying phase the patient and/or the family were asked renewed consent for participating in this study.

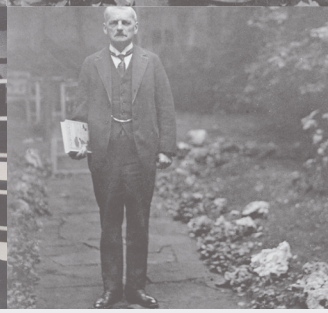
During the study period a total of 399 patients were assessed for eligibility. One hundred thirty-six (34%) patients were informed of the study, of whom 68 (50%) gave consent. Additional figure 1 shows the flow chart of patient inclusion. Of 16 (24%) patients no morphine sample was available, either morphine was not administered or no blood sample was taken after morphine administration; 3 (4%) patients and/or family withdrew from the study after initially giving consent; in 2 (3%) patients no blood sample was taken because of a very quick deterioration; and thus 47 patients were included in the final analysis of morphine's pharmacokinetics.



Additional Figure 1. Flow chart patients





PART IV
GENERAL DISCUSSION AND SUMMARY









CHAPTER 7

GENERAL DISCUSSION


The overall aim of this thesis was two-fold: 1. to evaluate the validity of assessment tools for pain and depth of sedation for unresponsive end-of-life patients; 2. to gain more knowledge on several aspects of pharmacotherapy in palliative care. This chapter first summarizes the main findings of the studies presented in this thesis in relation to the research questions. Several of these findings are interpreted in more detail and related to the available literature. Then, the strengths and limitation of the studies are discussed and implications for clinical practise as well as directives for future research are given.

MAIN FINDINGS

1. Is the Rotterdam Elderly Pain Observation Scale (REPOS) a reliable and valid tool for pain assessment in non-communicative or unresponsive end-of-life patients?

The REPOS showed adequate internal consistency, sufficient concurrent validity and was sensitive to change after a pain-reducing intervention. We concluded that the REPOS a reliable and valid tool for pain assessment in non-communicative or unresponsive end-of-life patients, even in their last days of life.

2. Is Bispectral Index (BIS) monitoring a feasible and valid tool for assessing the depth of sedation in terminally ill patients?

For the assessment of the depth of palliative sedation the BIS monitor (an electrophysiological device) seems feasible and some anecdotal arguments were found that BIS monitoring may be of relevance for family and nurses. However, we were not able to support the statement that BIS would differentiate between the various levels of sedation during midazolam treatment. Further research is needed to consider BIS as a tool for monitoring the level of palliative sedation in daily practice.

3. What drugs are administered, and at what dose and route of administration, from admission to day of death in patients admitted to a palliative care centre?

Morphine, midazolam and haloperidol were the most frequently prescribed drugs at the day of death. Doses of these drugs on the day of death were statistically significantly higher than those at the day of admission, with clinical relevance for morphine and midazolam. Median doses compared well to the titration schemes described in the national symptom-specific guidelines. Upon admission almost 90% of patients received oral medication but over the admission period

a shift occurred to the effect that at the day of death more than 90% of patients received subcutaneous medication.

4. Are laboratory parameters of patients at the end of life disturbed such that it may have consequences to the pharmacokinetics of drugs often used in those patients?

Abnormal laboratory results were expected to be found due to the physiological changes that occur during the last phase of life. Remarkably, levels of aspartate aminotransferase, alanine aminotransferase, bilirubin, sodium and potassium were within the normal range for most patients. Both the very high prevalence of hypoalbuminemia and the disturbed kidney function might have implications for the pharmacokinetics of drugs often used in end-of-life care.

5. What are the pharmacokinetics of morphine and its two major metabolites in terminally ill patients and what are the clinically relevant parameters for individualized dosing based on a population PK model approach?

The data were best described by a two-compartment model for morphine and two one-compartment models for both its glucuronidated metabolites (M3G and M6G). We found that the nearer to the time of death, the more morphine clearance decreases and that kidney function together with albumin levels are related to metabolite clearance. These findings suggest that morphine doses should be adjusted to a patient's kidney function and albumin levels and life expectancy.

INTERPRETATION OF THE FINDINGS

Assessment of pain and depth of sedation

Numerous pain assessment tools have been developed to recognize pain and prevent under- or overtreatment for several patients groups unable to self-report, including very young children, patients with intellectual disabilities and elderly with and without cognitive impairment[1-3]. However, to the best of our knowledge, only one validated observational tool for end-of-life patients is available, the Multidimensional Objective Pain Assessment Tool (MOPAT)[4]. This tool has a major disadvantage in that it includes blood pressure and heart rate measurements, which seem not sensitive for pain alone and not routinely assessed in end-of-life care[5-8] or stopped just before the end of life[9]. In contrast, the REPOS is based on pain-indicative behaviours only, including facial expression, body movements and vocalisation. In table 1 the items of the REPOS and MOPAT are displayed.

Table 1. An overview of items scored in two different observational pain tools: REPOS and MOPAT

Pain-indicative items	REPOS	MOPAT
Behavioural items	Tense face	Tense muscles
	Eyes (almost) squeezed	
	Raising upper lip	Frowning/Grimacing
	Grimace	
	Frightened/fearful look	
	Moving body parts	Restless
	Panicky, panics attack	
	Moaning/groaning	
	Sounds of restlessness/verbal expressions	Patient sounds
Physiological items	Breath holding/faltering respiration	Blood pressure
		Heart rate
		Respirations
		Diaphoresis (sweating)

All REPOS items are scored for presence of absence. MOPAT behavioural items are scored on a 4-points scale (none/normal, mild, moderate, severe) and MOPAT physiological items are scored based on change (usual/no change, change form usual)

The REPOS showed promising psychometric properties in nursing home residents[10]. We found that it is also valid to assess pain in palliative patients, even in their last days of life. It also meets the criteria of the European Association for Palliative Care (EAPC)[11]; being easy to use, valid, sensitive to treatment effect, validation studies performed in palliative care and multilingualism. Already before the validation in the palliative setting, the use of the REPOS was recommended in Dutch national palliative guidelines[12] and in a report on quality indicators in palliative care, published by the Netherlands Institute for Health Services Research in 2010[13].

In two small previous studies, BIS monitoring in palliative care was found to be acceptable for patients, family and professional caregivers[14, 15]. Although we also found BIS monitoring feasible in the palliative care setting, its validity may be insufficient and further research is needed.

The BIS monitor was initially developed to evaluate the effects of anaesthetics[16]; later also its ability to prevent awareness and overdosing was studied[17, 18]. Clear differences between anaesthesia and palliative sedation may contribute to the wide range of BIS values we found in palliative patients; the patient population (surgery versus end-of-life patients), the administered medication (inhala-

tion or intravenous anaesthetics versus subcutaneous sedatives) and primary aim of sedation (being unaware of surgery versus dying while being sedated). Moreover, the BIS monitor processes frontal EEG, which may not adequately represent an overall effect of sedative drugs, since it only reflects the degree of EEG suppression.

In our study on BIS monitoring, most patients were deeply sedated. The physicians frequently targeted at a status of deep sedation, ensuring that refractory symptoms are relieved. In practices, however, different approaches were seen: either start with mild sedation and deepen when necessary or initial deep sedation[19]. Those different approaches are related to the presenting symptoms, the wishes of the patient and relatives and the physicians' perceptions on communication, possible awakening or the dying process. For that matter, the Dutch national guideline for palliative sedation[12] states that sedation should be applied proportionally, but lacks recommendations on how to systematically guide or monitor this in practice.

The professional caregivers and even family of patients were very interested in the BIS registrations. The nurses hoped the BIS monitor would be an appropriate tool to assess the depth of sedation because at times they found it difficult to achieve adequate palliative sedation. Such impact of research on professional caregivers was also mentioned previously[20].

Against our expectations, relatives did not seem to mind placement of the BIS sensor on the patient's forehead. Some patients and their relatives even told us that they were thankful for participation in this study (See case description 1). Such positive reactions to palliative research are also described in literature[21-25] and might be a stimulus for researchers to study this vulnerable population.

> **Case description 1.** Thanks for using the BIS monitor for my mother, it helped me to say goodbye
> *I spoke with a woman whose mother had died the night before. Her mother participated in our study on BIS monitoring. I thanked the daughter for the participation, and she responded as follows:*
> *'Thank YOU for this research, since it helped me a lot!*
> *Last night my mother was not comfortable. She was restless and not well asleep with her sedative medication. Also she was in pain. The BIS monitor showed high values and the line was spiky. Also, the values representing her muscle activity of the forehead (EMG) were high. She was frowning. After my mother was given extra medication, she became calmer and could relax a bit and fall asleep. Then, I saw on the BIS monitor that the EMG values went lower and also the*

values for level of sleep were lower and more equal; about 45. Then I also went to sleep, because I was sure my mother was comfortable and well asleep.
Later that night I was woken by the nurse who cared for my mother. It seemed that my mother was 'taking the last track before death'. More and more she was sliding towards a deeper state. The BIS monitor also showed this, de values decreased to about 5. At that time, I started talking and singing to her and the BIS values increased to about 12. This meant a lot to me; I felt like she heard me. I even got a reaction of her!
At long last, my mother passed away peacefully. I and the nurse were there with her. When the nurse said, your mother has died, I found a confirmation on the BIS monitor; the values were 0.
Your research really helped me during this last phase. My mother, literally and figuratively, was sliding deeper and deeper.'

Pharmacotherapy in palliative care

We found that 94% of patients received subcutaneous medication at the day of death. Although the subcutaneous route is recommended in palliative guidelines[9, 12, 26] and considered as the preferred route of choice for patients unable to take oral medications[27], this route has not been studied in great detail.

The most often prescribed subcutaneous drugs at the end of life, morphine, midazolam and haloperidol, are used off-label. Still, small prospective or retrospective trials found subcutaneous administration of morphine[28, 29] and midazolam[30-32] feasible and effective. For haloperidol the optimal route of administration was not qualified[33-36]. Therefore strict monitoring of the efficacy of the off-label drugs with validated assessment tools is highly recommended. Furthermore, in future, pharmacokinetic based dosing needs to be an essential role in drug dosing in this vulnerable group of patients to prevent over and/or under dosing.

One important aspect of the subcutaneous route is the absorption of drugs. This might be suboptimal in end-of-life patients, who are often in a cachectic status or in contrast may have extensive oedema[37]. Furthermore, it is unknown which anatomical site is most optimal[38, 39] or what mode of subcutaneous administration is better; intermittent bolus injections[40, 41] versus continuous infusion[42, 43]. Therefore the subcutaneous route deserves to be further studied.

Theoretically seen, we expected to find abnormal laboratory results during the last week of life in view of the disease status of most patient, advanced malignancy in combination with a decreased nutritional intake. In practise, an overview of

laboratory results near death was lacking and only was described in the light of dehydration[44-46]. Although the timing of analysis differed in our two studies on this topic, in both, remarkably, we found most median laboratory results within the normal range values.

Some laboratory results are of greater relevance for pharmacotherapy in end-of-life care. A lowered albumin level is seen in the majority of end-of-life patients and showed to be an important determinant, together with kidney function, for the clearance of morphine metabolites. The lower the albumin level and the kidney function, the more the clearance of morphine metabolites will decrease. Theoretically, hypoalbuminemia may also have consequences for the pharmacokinetics of midazolam and haloperidol[47], in that lower doses of these drugs can be prescribed at the end of life. Furthermore, kidney function can help predict the clearance of morphine and its metabolites and consequently may guide morphine dosing. In a further study we will develop a dosing algorithm for morphine by pharmacokinetic and pharmacodynamic (PK-PD) modelling. Also the PK-PD of midazolam and haloperidol are being studied.

We were able to accurately describe the pharmacokinetics of morphine and its two major metabolites in end-of-life patients. This is, to our best knowledge, the first PK model of morphine in this patient population. Therefore, this model is a very important step towards an evidence based and tailor-made dosing regimen of morphine for these patients.

STRENGTHS AND LIMITATIONS

The data in this thesis is unique and adds importantly to existing literature, since all data was collected in a hospice setting and is representative for patients whose death is near. Much of the palliative literature either does not clearly define the patient group[48, 49], or excludes the very ill patients[50]. In contrast, we succeeded to include the very ill patients: REPOS observations done at a median of 3 days before death were presented; the laboratory results all concerned the last week before death. Such data near the very end of life was not published before, to the best of our knowledge.

In addition, our series of palliative studies is the first of its kind; the first study describing medication use on the day of admission and the day of death, including the dose and route of administration; the first study that gives an overview of laboratory results in the final week before death and the first pharmacokinetic study of morphine in end-of-life patients.

Another strength lies in the relatively large samples sizes. First, our BIS study included 58 patients versus only 1 to 12 patients in previous studies[14, 15]. Next, we studied the pharmacokinetics of morphine in 47 palliative patients until death. Previous studies on the pharmacokinetics of subcutaneous morphine concerned 8 or 10 patients with cancer pain[51, 52] and 22 elderly patients[53].

Several limitations have to be addressed, too. All our studies were performed in one hospice. Clinical practice in other palliative care settings and other countries may differ.

Because of the overall lack of validated assessment tools in palliative care[4, 54] at the time we started our studies, we used assessment tools validated only in other patient populations. The Ramsay score for depth of sedation has been validated in adult intensive care and surgical patients[55, 56] and has been found easy to use in palliative care[57]. However, it contains only one item scored from 0 'no response to test stimulus' to 6 'agitated'. One could question if this information is useful in the clinical setting, since the aim for end-of-life patients is overall comfort, including a relaxed posture, a calm facial expression and without being fidgety or restless. In our opinion the Ramsay score represents the level of consciousness, which may be helpful to evaluate the course of palliative sedation, but it might not be quite suited to evaluate the efficacy of the sedation.

The Delirium Observation Screening (DOS) scale has been validated for use in elderly patients with a high risk for delirium[58]. However, we found its use in palliative patients sometimes inappropriate, since some items could not be scored in unresponsive patients. Other delirium assessment tools could perhaps be recommended[59, 60], such as the Confusion Assessment Methods (CAM)[61]. This scale includes the criteria for the psychiatric diagnosis of delirium based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), including the acute onset and the fluctuating course of a delirium, which are lacking in the DOS score.

In addition, the used assessment tools were not standard of care and were initially implemented for research purposes only in the non-academic hospice setting. The nurses were sceptic about the extra workload and pointed at the risk of 'invasion' to the patients' and families' privacy. Therefore assessments were made only once a day; more frequent assessments were preferred, for both clinical practice and study purposes.

Lastly, the expected inclusion rates were too optimistic. For both the BIS study and the pharmacokinetics study we had to prolong the planned inclusion period because many more patients than foreseen were in a very poor condition upon admission and expected to die within 2 days, which was an exclusion criterion. No more than 11% (58/516) of admitted patients were included in the BIS study and

17% (68/399) in total for the pharmacokinetics studies (morphine, midazolam and haloperidol). Markedly, these figures seem representative for other clinical studies in palliative care, which succeeded to include 8% to 21% of screened patients[62-64]. Yet some other studies even failed to recruit a sufficient number of patients and had to discontinue their efforts[65-67].

IMPLICATIONS FOR CLINICAL PRACTICE

We have demonstrated that the REPOS can be considered a valid tool for the assessment of pain in non-communicative end-of-life patients. We think that after a brief training course every professional palliative caregiver will be able to use. A REPOS instruction sheet, an educational CD-ROM (in a Dutch and English version) and a website[68] are available to guide training and implementation. In the brief training course, correct interpretation of the items is explained and observations in practice together with an already trained professional are recommended.

However, pain assessment can only have clinical implications when the scores are documented in the patients' medical record, when assessed pain is treated effectively and when re-assessments after a change in treatment are performed. In other words: when a treatment decision-tree is available and used. However, in practice it appears that pain assessments and notes regarding pain medication are inadequately recorded[69-71], pain treatment is frequently not sufficient[72-74] and professional caregivers may tend to forego reassessment[73, 75, 76]. To overcome these barriers, various interventions are described[75-79], such as education, appointing nurse 'champions' and the implementation of pain protocols. These interventions may result in a better compliance to pain assessment and treatment algorithms[75, 76, 80] and may also be applicable for symptoms other than pain, such as delirium.

Assessing pain in non-communicative palliative patients can be difficult even when a validated tool such as the REPOS is used. Pain assessment tools will not only identify pain, but also other forms of distress[81-83], since there are no signs or behaviours exclusively for pain. This is also reflected in our REPOS study by the high number (23/107, 21%) of false-positive scores (REPOS score indicative for pain whereas the accompanying NRS score was low). Other assessment tools, such as a delirium scale or a combination of assessments, might help to recognize which form of distress—pain, delirium, fear or anger —is predominant[84, 85] (See case description 2). In addition, the experiences of relatives are more and more a topic of interest in palliative research[86, 87]. In family-centred care, relatives can be given an active role, including pain assessment and pain management.

Case description 2. Distress; distinguishing between pain or else?
A woman in a study was given palliative sedation but the family present had the impression that she was not comfortable. She moved her hands from time to time and the family was afraid she was in pain or suffered from confusion. The responsible nurse also observed the movements and asked me to have a look also, because she thought the patient was comfortable enough. To me the movements mimicked rolling a cigarette and taking puffs of a cigarette. I knew this patient had been an intense smoker. I did a REPOS observation during washing. The score was not indicative for pain. The DOS score was not adequately representative, since the patient was sedated. I told the family about the pain score and gave them my explanation for her movements, namely her former smoking habits. This fully satisfied the family. Pain observations were repeated at least once a day, to confirm that pain was not present. However, no medication was added to treat confusion.

Since we were now not able to recommend BIS monitoring as standard daily practice, further research is needed before it can be considered as the right device to monitor palliative sedation. Other electrophysiological devices[88, 89] may also be inappropriate to use in end-of-life patients. Then, the only method to assess the efficacy of palliative sedation would be an observational sedation scale. Most observational sedation scales (e.g. Ramsay score) have not been validated, however, for palliative care facilities[54, 90, 91]. Since the start of our study in 2008, the validity of only a few scales are limitary studied in palliative care, including the Richmond Agitation-Sedation Scale (RASS)[91, 92] and the Consciousness Scale for palliative care (CSPC)[93]. Moreover, there is no consensus on the preferred scale and on whether symptom control or sedation depth should be assessed used[54, 90]. Furthermore, distress behaviour may be subdued in the end-of-life stage and patients could therefore mistakenly be considered to be comfortable upon behavioural assessment only[90, 94]. Probably, a combination of validated symptom and sedation measures, together with the subjective assessment of experienced professional caregivers, will be the best strategy to monitor palliative sedation.

At the end of life, the most clinically relevant laboratory parameter seems to be kidney function, for a few reasons. First, poor kidney function has implications for drug choice and dosing (of renally cleared drugs), as shown in the morphine pharmacokinetics study. Second, we also found that poor kidney function was not

documented in up to 60% of cases. Several explanations may serve to explain this: the patient was actively dying and evaluation of kidney function was not seen as relevant anymore; kidney function could have declined rapidly as death approached; or the medical history might be incomplete. Still, kidney function is an important parameter as for some drugs (including morphine and NSAIDs) adverse effects may negatively impact the quality of dying and interfere with humane aspects. Therefore, both the European Association of Palliative Care (EAPC)[28] and the Dutch palliative pain guideline[12] for the use of opioids in palliative patients with kidney failure recommend prescribing another opioid, such as fentanyl, buprenorphine or hydromorphone, instead of morphine.

Based on our pharmacokinetics study, clinicians should be careful in escalating morphine doses in the last days of life. One paper proposed that for patients with a steady state concentration on regular oral opioids, only intermittent use of opioids may be sufficient in the last days before death[95]. Assuming that the medication is not cleared due to liver and kidney failure and excretion is delayed, the intermittent use suffices to maintain the effects of the prior steady state concentrations as drug half-life is significantly increased. Indeed, we showed that during the last week of life the clearance of morphine and its metabolites decreased most intensely.

In addition, this decreased clearance of morphine may result in accumulation and consequently in prolonged effects, including both the analgesic effect and adverse effects. Not only morphine itself is responsible for those effects, also the metabolites of morphine are of clinical importance; morphine-6-glucuoride (M6G) has analgesic activity[96-98], while morphine-3-glucuronide (M3G) has been suggested to contribute to side-effects, such as hyperalgesia, allodynia, myoclonus and the development of tolerance[99, 100]. In future, we hope that based on the pharmacokinetics of morphine, doses can be adjusted more rapidly and adequately after the initiation or during therapy. For instance, the interval between start of morphine administration and adequate symptom relief may be shortened by a higher starting dose; an impairment of renal function should result in a reduction of the administered dose or a switch to another opioid with less or no active metabolites (fentanyl).

However, more research is needed on the extent to which the morphine dose should be adapted to prevent accumulation or prolonged effects. In anticipation to the results of future studies, in practice is would be hard to convince clinicians to lower a morphine dose as the patients' death approaches. Perhaps a change of attitude towards more interest in non-pharmacological interventions

such as complementary and alternative medicines, including massage and music therapy[101-104], would be helpful therein.

DIRECTIVES FOR FUTURE RESEARCH

Since many practices in palliative care are based on experiences and consensus only[50, 105, 106], there is much room for further research. Below, some suggestions arising from the studies presented in this thesis.

- Validation of the REPOS in other languages, including English, is preferred. Now only the Dutch version of the REPOS has proven its validity in nursing home residents and end-of-life patients.
- Validation of assessment tools to monitor palliative sedation, including depth of sedation measures and tools for symptoms other than pain; such as a delirium scale like the Confusion Assessment Methods (CAM)[61], and a sedation scale like the Richmond Agitation-Sedation Scale (RASS)[91, 92] or the Consciousness scale for palliative care (CSPC)[93].
- Studies on the pharmacokinetics of subcutaneous administered drugs, including midazolam and haloperidol. Nowadays, subcutaneous drugs are often prescribed off-label and might have relevant individual variations, which are so far unknown.
- More detailed studies on subcutaneous administered drugs to determine the optimal anatomical site of administration and the most effective mode of administration, either intermittent bolus injections or continuous infusion.
- Studies on the pharmacodynamics of palliative drugs, including morphine, midazolam and haloperidol, to gain more knowledge on also the clinical effects of drugs.
- Pharmacogenetics is an emerging topic of interest also in palliative care[107-111] and also recommended to be incorporated in future research. Especially in cases of whom earlier in life abnormal responses were observed or very high doses were needed.
- Gaining more knowledge about the factors that may influence the complexity of palliative sedation and to define a risk profile. Sedation of palliative patients can be cumbersome; most striking is when a patient suddenly awakes after a period of effective palliative sedation. Also a 'long track' of titrating medication till an adequate level of sedation is found, is an undesirable situation. The reactions of surrounding persons can be different in such situations (See case descriptions 3 and 4). So far it is still unclear for which patients sedation will be difficult and consequently for whom an adapted starting dosing or another

choice of drugs is needed. Although some factors are suggested for this risk profile, such as a younger age, being underweight, having experienced a delirium previously, comorbidity and concomitant drug use[12, 112, 113], these have not been prospectively studied.

Case descriptions 3 and 4. Awake during palliative sedation; bothersome or relieved?

A 46-year-old female with a carcinoma of the rectum and multiple metastases in lungs and liver

Since the day of admission, her abdominal girth increased and she was progressively tired. She still wanted to do many things, which she could not accomplish. She experienced more and more bad days and became puffier. She was saying goodbye to many people around her.

One day she was very restless and tense and was afraid she would choke. She said: 'This is enough, I cannot handle this any longer and I want to sleep.' The clinician agreed and started palliative sedation. After a few hours she woke up and was moaning. Extra sedative medication was given, but after two hours she woke up again and could answer some questions. She did not have pain and had no shortness of breath. Again, extra medications were administered and a clinician was consulted and increased the dose of the sedative drug. The family present found it hard to see her awake again. She had been promised that she would go to sleep and never wake up. This had happened, nevertheless.

Before the following doses of sedative medication were scheduled, she woke up and was panicky. Extra sedative medication was administered and the dose was increased, but she was still restless. Other medication was added, but after one and a half hours she was still restless and more medication was administered. Finally, with three types of sedative medication and medication to treat pain and confusion, she was deeply asleep. She died calmly a few hours later, without family and only a nurse being present.

A 72-year-old female with a carcinoma of the rectum and multiple metastases in lungs, liver and abdomen

Since the day of admission she was confused from time to time and felt her own deterioration. The clinician assured her that she could ask for sedative medication to sleep during day or night. In the first

week she used this medication one evening and slept well for a few hours. In the following two weeks she asked again for the sedative medication.
She became progressively tired, had more pain and became less able and willing to communicate. After being cared for in the morning, she fell asleep. One day she woke up after a few hours and was not comfortable. A clinician was consulted and palliative sedation was started, in accordance with the wish of herself and her family. First she seemed adequately sedated, but after a few hours she woke up suddenly while her son was sitting next to her. At that moment she had pain and was restless. Extra sedative medication was administered and she fell asleep again. Her children were very sad and hoped that she would not suffer much longer. In the evening, she calmly died in the presence of her children.
The next day I spoke to her children and they were actually glad and relieved that their mother had been awake during sedation. They thought that she had received too much medication, was fully drugged and had deteriorated as a result of all those drugs. They now were more confident that the medication had been precisely titrated to her as an individual.

The ethics of research in palliative patients are addressed in many papers[50, 105, 114-119]; from the one extreme that research in these patients should not be conducted[115] to the other that this research is absolutely necessary to provide the best palliative care possible[105, 116]. In addition, numerous strategies are suggested to encounter the challenges of research in palliative care, both methodological and ethically[20, 25, 62-64, 67, 105, 120-126]. The following list is a selection of strategies that were crucial to our studies in these vulnerable end-of-life patients and may be essential for future palliative research as well.

- Having a full-time researcher on the floor for the inclusion process and the retention of patients into the study, to ensure an independent decision of the patient, without interference of the doctor-patient relationship[62, 64, 105].
- The researcher has to be sensitive for the context of palliative care, e.g. sensing the right time to contact patients and relatives[25, 121] and setting the right tone is essential for commitment to the study[25, 122].
- The informed consent process has to be adapted to the type of study and the setting. We therefore recommend seeking renewed consent should be standard in ongoing research. Such an evaluation of the patients' willingness to participate enhances the patients' autonomy[123] and opens the conversation

towards the potential burden of study participation. Next, seeking advanced consent from autonomous patients could help anticipate the problem that at a later stage they might be unable to give consent[67]. Lastly, we obtained consent from both the patients and a relative. In this way the relative served as a witness and could give renewed consent at the time the patient would be unable to do so, because the relative knew the patient's reasons for participation.

- The researcher has to be aware that patients may want to tell their life stories. Patients will often appreciate the opportunity to express and share their experiences of care with the researcher[21, 122, 123]. Time is needed for this aspect, before information, consent and adequate participation to the study can be accomplished.
- Intensive collaboration between the researcher and the professional team of caregivers is encouraged[20, 119, 122-124]. On the one hand this stimulates commitment of the caregivers' team, and on the other hand the researcher is informed about the actual status of patients, including physical or relevant psychosocial and spiritual aspects. This may also overcome the phenomenon of gatekeeping[25, 62, 105, 122, 123, 125], by which is understood the tendency of professional caregivers to overprotect the patients, thereby passing the opportunity for the patient to make an informed consent on participation (See case descriptions 5 and 6).
- Since end-of-life patients are often extremely tired and have to save their valuable time for important moments, the burden of data collection should be minimized. This can be done by incorporating several sub-studies in the main study[64]. Also, integrating validated symptoms scores into the daily clinical routine can help prevent overburdening.

Case descriptions 5 and 6. Gate keeping: opening or closing the gate

At the day of admission the responsible clinician told the patient of ongoing research. Sometimes I was present at this first conversation, or I met the patient within 2 days. The way in which the research was introduced could influence the potential participation; either the patient was encouraged to listen to my information about the ongoing study or was indirectly pushed towards refusal. The following quotes illustrate two different styles:

1. 'This hospice is actively involved in scientific studies; our researcher will visit you soon to give more information about the ongoing

studies'; a neutral way of presenting research that opens the gate for the researcher.
2. 'An ongoing study will be introduced to you by a young doctor, but you may decline to participate since studies will always have impact on you'; a somewhat negative implication that may close the gate for the researcher.

CONCLUSIONS

Although palliative research is challenging, this thesis proves that is doable. The following conclusions were reached.

- The REPOS is a promising pain assessment tool for end-of-life patients who cannot longer communicate verbally.
- BIS monitoring is feasible in a hospice setting and we found some anecdotal arguments that BIS monitoring may be of relevance for family and nurses. However, the wide range of BIS values in deeply sedated and comfortable patients seems to hamper its use in daily clinical practice now.
- The subcutaneous route is the general route for drug administration in palliative patients. Most drugs are prescribed off-label and without detailed knowledge about for instance the absorption rate via this route.
- Assessment of the kidney function should have a role at the end of life, because kidney function can have implications for the pharmacokinetics of drugs and may guide drug choice and their dosing, as illustrated by morphine pharmacokinetics.

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CHAPTER 8

SUMMARY


CONTEXT

In 2013 approximately 141,000 persons died in the Netherlands, almost one third of whom from the consequences of cancer, mainly localized in the digestive or respiratory organs. The most reported symptoms in patients with incurable cancer are: fatigue (88%), appetite loss (56%), pain (45%), dyspnoea (39%), drowsiness (38%), dry mouth (34%), constipation (29%), confusion (24%), nausea (17%), and insomnia (14%). The main goal of palliative care is to relieve and control these symptoms by a combination of non-pharmacological measures and a variety of drugs, such as analgesics and sedatives. This regimen may fail to provide adequate symptom relief, however. Then, continuous palliative sedation may be an option of last resort in the last days of life, as proposed by the Royal Dutch Medical Association (KNMG) in a national Guideline Palliative Sedation (2009).

Patients' self-report of pain or discomfort-symptoms is considered the 'gold standard'. However, terminally ill patients may not be able to do this due to various reasons, such as advanced illness state, cognitive failure or effects of multiple drugs such as sedatives often seen prior to death. Most observational scales for pain assessment have not been validated for the use in palliative care facilities.

Evaluation of the adequacy of sedation is equally important, but so far there is no general consensus on how the effect of palliative sedation should be assessed. In addition, there is a lack of validated methods to monitor palliative sedation.

The choice and dose of drugs for symptom relief should be preferably tailored to the individual patient, but evidence from prospective clinical trials is lacking. Likewise, there is little evidence for the optimal route of administration, although the subcutaneous route is often preferred in palliative care, according to the Dutch palliative guidelines (2010). Remarkably, to our knowledge, there are even no published studies describing the most prescribed drugs in palliative patients, let alone their doses and routes of administration.

Moreover, drug dose adjustment may be needed as death approaches due to changes in liver and kidney function, among other things, but this has not been studied in detail. Evidence from prospective studies on the pharmacological effects of often used palliative drugs is lacking.

The work presented in this thesis was performed in Regional Palliative Care Centre, Laurens Cadenza, in Rotterdam, the Netherlands. This is the largest 'hospice' in the Netherlands, with 20 beds for end-of-life care and symptom management.

VALIDATION OF REPOS FOR PAIN ASSESSMENT

In *chapter 2* we present a validation study for pain assessment in non-communicative or unresponsive end-of-life patients. The Rotterdam Elderly Pain Observation Scale (REPOS) was applied which tool that was originally developed and validated to assess pain in nursing home residents.

For this study we analysed 183 REPOS observations in 100 palliative patients. The observations were done at a median of 3 days (IQR 1 to 13) before death. Adequate internal consistency of the REPOS was shown with a Cronbach's alpha coefficient of 0.73. For concurrent validity a high Pearson product moment correlation coefficient was found; ranging from 0.64 to 0.80 between REPOS and numeric rating scale (NRS) scores. In addition, the REPOS was found sensitive to change for a pain-reducing intervention; REPOS scores declined with a median of 2 points (IQR 1 to 4) after a pain-reducing intervention ($p<0.001$). We concluded that the REPOS has promising psychometric properties to use for palliative patients, even in their last days of life.

VALIDATION OF BIS MONITOR FOR THE ASSESSMENT OF THE DEPTH OF SEDATION

In *chapter 3* we present a validation study for assessing the depth of sedation with an electrophysiological measuring device, the Bispectral Index (BIS) monitor, in unconscious end-of-life patients. Previous studies described that BIS monitoring was acceptable for patients, family and care-givers. We wanted to determine, whether BIS monitoring is feasible and also valid for use in a hospice setting.

For this study we analysed 149 BIS registrations in 58 palliative patients. BIS monitoring was acceptable to patients, relatives and medical staff. BIS values were moderately correlated with a validated observation score for sedation, the Ramsay scores ($r=0.46$), but BIS values were highly variable for deeply sedated patients. BIS was sensitive to change for the administration of the sedative drug midazolam; BIS values changed significantly before and after a midazolam dose ($p<0.001$). In addition, midazolam treatment resulted on average in a statistically significant reduction of the BIS values (-4.5, 95% CI -7.0 to -2.0). However, this reduction was not clinically relevant. Based on these findings we concluded that although BIS monitoring is feasible in the palliative care setting, its validity seems insufficient, mainly on the grounds of the wide range of BIS values in deeply sedated and comfortable patients. Therefore we were not able to support the statement that BIS would differentiate between the various levels of sedation

during midazolam treatment. Further research is needed to consider BIS as a tool for monitoring the level of sedation in palliative patients in daily practice.

MOST OFTEN ADMINISTERED PALLIATIVE DRUGS

In *chapter 4* we present a study describing doses and routes of administration of the most frequently used drugs at admission and at the day of death in patients admitted to a palliative care centre. For this study regular medication prescriptions of 208 patients were reviewed. The median length of stay of those patients in the palliative care centre was 11 days (IQR 5–29 days). Morphine, midazolam and haloperidol were the three most prescribed drugs at the day of death (87, 58 and 50% of patients, respectively). Doses of these drugs at the day of death were statistically significantly higher ($p<0.001$, $p=0.003$ and $p=0.028$, respectively) than those at the day of admission and compared well to the titration schemes described in the national symptom specific guidelines. The oral route of administration was used in almost 90% of patients at admission, but over the admission period a shift occurred to the subcutaneous route, so that at the day of death more than 90% of patients received subcutaneous medication. This shift in route of administration is in line with recommendations from both the national palliative guidelines and the Liverpool Care Pathway for the dying.

Most of these drugs are unlicensed for this specific application, optimal doses are unknown, and guidelines are based on low level of evidence. We would recommend to strictly monitor the efficacy of the subcutaneously administered drugs with the use of validated pain, sedation and delirium assessment instruments. In addition, prospective clinical trials are needed to formulate evidence base guidelines that can guide the choice and dose of drugs. Thus, there is every reason for more clinical research on drug use in palliative care.

LABORATORY PARAMETERS AT THE END OF LIFE

In *chapter 5* we present a study describing laboratory parameters of hospice patients in the week before death. Laboratory data of 125 patients, at a median of 3 days before death were analysed. Abnormal laboratory results were expected to be found due to the physiological changes that occur during the last phase of life. Eighty percent of patients had anaemia and almost all had hypoalbuminemia (97%). Elevated levels of gamma-glutamyltransferase were found in 75%, of alkaline phosphatase in 60%, of aspartate aminotransferase in 60% and of calcium

in 68%. Alanine aminotransferase, bilirubin, sodium and potassium were abnormal in from 8.8% to 36.0% of patients. Although, the median estimated glomerular filtration rate (eGFR), as a parameter of renal function, had a normal value for this population (63ml/min, IQR 33 to 94), a previous unknown poor kidney function was found in 60% of patients. Thirteen patients (22%) with a regular morphine prescription and one patients treated with an NSAID had severe kidney failure. Both the very high prevalence of hypoalbuminemia and possible disturbed laboratory liver and kidney tests might have implications for the pharmacokinetics of drugs often used in end-of-life patients. eGFR seems the most clinically relevant laboratory parameter, since it may guide drug choice and dosing.

THE PHARMACOKINETICS OF MORPHINE

In *chapter 6* we present a population pharmacokinetic analysis characterizing the pharmacokinetics of morphine and its two major metabolites (morphine-3-glucuronide and morphine-6-glucuoride) in terminally ill patients. Clinically relevant parameters for individualized dosing were also determined. For this study 152 blood samples of 47 palliative patients were analysed for the concentrations of morphine and its major metabolites. The data were best described by a two-compartment model for morphine and two one-compartment models for both its glucuronidated metabolites. The time till death and the renal function (based on the eGFR) combined with albumin levels were identified as relevant covariates; as patients are nearer to time of death the morphine clearance decreases and eGFR together with albumin levels were the best predictors for metabolite clearance, explaining approximately 60% of the unexplained variability between patients. These findings suggest that morphine doses should be adjusted to a patient's creatinine and albumin levels and life expectancy. However, more research is needed on the pharmacodynamics of morphine in this population before a dose algorithm can be implemented in daily clinical practice.

INTERPRETATION OF THE FINDINGS

In *chapter 7* the findings from the studies reported in this thesis are interpreted and discussed with a view on future directives. Among others, studies regarding the pharmacokinetics, pharmacodynamics and pharmacogenetic of palliative drugs, including morphine, midazolam and haloperidol are recommended. Also, some crucial strategies are listed to encounter the challenges of research in palliative care.

SAMENVATTING




ACHTERGROND

In 2013 overleden in Nederland ongeveer 141.000 personen. Van hen overleed bijna een derde aan de gevolgen van kanker, voornamelijk van het maag- en darmkanaal en de luchtwegen, waaronder de longen. Patiënten met ongeneeslijke kanker hebben het meeste last van: moeheid (88%), weinig eetlust (56%), pijn (45%), benauwdheid (39%), slaperigheid (38%), droge mond (34%), obstipatie (29%), verwardheid (24%), misselijkheid (17%), en slapeloosheid (14%). Het belangrijkste doel van palliatieve zorg is om deze symptomen te verlichten door een combinatie van niet-farmacologische interventies en geneesmiddelen zoals pijnstillers en rustgevende middelen. Mocht dit niet toereikend zijn, dan kan continue palliatieve sedatie een redmiddel zijn in de laatste dagen van het leven, zoals is voorgesteld door de KNMG in een nationale Richtlijn Palliatieve Sedatie (2009).

De zelfrapportage van een patiënt over pijn of symptomen van niet-welbevinden wordt gezien als de 'gouden standaard'. Maar terminaal zieke patiënten zijn, om diverse redenen, niet altijd meer in staat zelf te rapporteren. In plaats van zelfrapportage kan observatie door anderen worden gebruikt, maar de meeste instrumenten daarvoor zijn niet gevalideerd voor het gebruik in de palliatieve zorg.

Tot nu toe bestaat er geen algemene overeenstemming over hoe het effect van palliatieve sedatie het beste gemeten kan worden, en ontbreken gevalideerde methoden voor dit doel.

De keuze en dosering van geneesmiddelen zou bij voorkeur moeten worden afgestemd op de individuele patiënt. Maar er is zeer weinig bewijs vanuit prospectieve klinische studies daarvoor. Eveneens is er weinig bewijs over de optimale wijze van toediening van geneesmiddelen. Toch heeft in de palliatieve zorg de subcutane route vaak de voorkeur zoals ook is aangegeven in de Nederlandse Palliatieve Richtlijnen, te vinden op pallialine.nl (2010).

De dosering van geneesmiddelen moet wellicht worden aangepast als de dood dichterbij komt, omdat onder andere de lever- en nierfunctie zullen veranderen, maar daar is nog weinig over bekend.

De onderzoeken die in dit proefschrift worden beschreven, hebben plaatsgevonden in Laurens Cadenza, een regionaal palliatief centrum in Rotterdam. Dit is het grootste hospice van Nederland, met 20 bedden voor palliatieve en terminale zorg.

VALIDATIE VAN DE REPOS OM PIJN TE METEN

In *hoofdstuk 2* wordt een validatiestudie gepresenteerd van de Rotterdam Elderly Pain Observation Scale (REPOS) bij terminale patiënten die niet goed kunnen communiceren of reageren. De REPOS is een schaal die eigenlijk is ontwikkeld en gevalideerd om pijn te meten bij verpleeghuisbewoners.

Voor deze studie werden 183 REPOS-observaties van 100 palliatieve patiënten geanalyseerd. De observaties werden uitgevoerd gemiddeld 3 dagen (mediaan; IQR 1 tot 13) voor het overlijden . Uit de Cronbach's alfa coëfficiënt van 0,73 bleek een voldoende interne consistentie van de REPOS. Voor de concurrent validiteit werd een hoge Pearson product moment correlatie coëfficiënt gevonden; variërend van 0,64 tot 0,80 tussen de REPOS en de Numeric Rating Scale (NRS) scores. Bovendien bleek de REPOS gevoelig voor de verandering na een pijnverlichtende interventie; de score was gemiddeld 2 punten (mediaan; IQR 1 tot 4) lager na een dergelijke interventie ($p < 0{,}001$). Concluderend, de psychometrische eigenschappen van de REPOS zijn veelbelovend voor het gebruik bij palliatieve patiënten in de laatste dagen van hun leven.

VALIDATIE VAN DE BIS-MONITOR OM DE DIEPTE VAN SEDATIE TE METEN

In *hoofdstuk 3* wordt een validatiestudie gepresenteerd van de Bispectral Index (BIS) monitor bij patiënten met een verminderd bewustzijn aan het einde van hun leven. De BIS-monitor meet de diepte van de sedatie met een elektrofysiologisch apparaat, We wilden graag weten of het gebruik van de BIS monitor toepasbaar en valide zou zijn in de setting van een hospice en of dit acceptabel zou zijn voor alle betrokkenen.

Voor deze studie hebben we 149 BIS-registraties van 58 palliatieve patiënten geanalyseerd. Het gebruik van de BIS-monitor bleek acceptabel voor zowel de patiënten als hun naasten en de medische staf. De BIS-waarden correleerden redelijk met een gevalideerde observatiescore voor sedatie, de Ramsay score ($r=0{,}46$), maar waren zeer variabel bij diep gesedeerde patiënten. De BIS bleek gevoelig voor een verandering na het toedienen van het slaapmiddel midazolam. Dit bleek uit een statistisch significante verlaging van de BIS waarden (-4,5; 95% CI -7,0 tot -2,0). Toch was deze verlaging niet klinisch relevant. Ook vanwege de grote variatie in BIS-waarden bij diep gesedeerde patiënten kunnen we het gebruik van de BIS-monitor om de diepte van sedatie te meten niet aanbevelen in de dagelijks klinische praktijk van een hospice.

DE MEEST GEBRUIKTE GENEESMIDDELEN IN DE PALLIATIEVE ZORG

In *hoofdstuk 4* wordt een studie gepresenteerd naar de dosering en wijze van toediening van de meest gebruikte geneesmiddelen in een hospice. Voor deze studie werden de reguliere (vaste) voorschriften van geneesmiddelen van 208 patiënten nagegaan op de dag van opname én de dag van overlijden. De mediane opnameduur van deze patiënten was 11 dagen (IQR 5 tot 29). Morfine, midazolam en haloperidol waren de drie meest voorgeschreven geneesmiddelen op de dag van overlijden (87, 58 en 50% van de patienten, respectievelijk). De dosering van de geneesmiddelen was op de dag van overlijden statistisch significant hoger dan op de dag van opname. Deze doseringen komen overeen met de titratie-schema's in de nationale richtlijnen daarvoor. Op de dag van opname kreeg bijna 90% van de patiënten de geneesmiddelen via de mond (oraal) toegediend, maar gedurende de opname vond een verschuiving plaats maar de subcutane route (via het onderhuidse vet), die op de dag van overlijden bij meer dan 90% van de patiënten werd gebruikt. Dit is in overeenstemming met de aanbevelingen uit zowel de Nationale Palliatieve Richtlijnen (pallialine.nl) als het Zorgpad voor de Stervensfase.

De meeste van deze geneesmiddelen zijn echter niet gelicenseerd voor subcutane toediening, de optimale dosering is onbekend en de richtlijnen zijn gebaseerd op bewijs van laag niveau. We raden aan hun effectiviteit te beoordelen met gevalideerde meetinstrumenten voor pijn, sedatie en delirium. Ook zijn prospectieve klinische studies nodig om evidence-based richtlijnen op te stellen voor de keuze en dosering van geneesmiddelen.

LABORATORIUMUITSLAGEN AAN HET EINDE VAN HET LEVEN

In *hoofdstuk 5* wordt een studie gepresenteerd naar de laboratoriumuitslagen van 125 patiënten gedurende de laatste week voor het overlijden (mediaan 3 dagen voor het overlijden). Wij verwachtten abnormale uitslagen te vinden omdat er fysiologische veranderingen plaatsvinden gedurende de laatste fase van het leven. Tachtig procent van de patiënten bleek bloedarmoede te hebben en bijna alle patiënten (97%) hadden een verlaagd albuminegehalte. Te hoge waarden van gamma-glutamyltransferase , alkalische fosfatase, aspartaat aminotransferase en calcium werden gevonden bij 60-75% van de patiënten. Afwijkende waarden van alanine aminotransferase, bilirubine, natrium en kalium werden gevonden bij 8,8-36,0% van de patiënten. Bij 60% van de patiënten

werd een slechte nierfunctie gevonden, die voordien onbekend was. Dertien patiënten (22%) met een regulier (vast) voorschrift van morfine en 1 patiënt die behandeld werd met een NSAID hadden een ernstig nierfalen. Vooral het lage albuminegehalte en een slechte lever- en nierfunctie zouden implicaties kunnen hebben voor de werking van de geneesmiddelen die patiënten aan het einde van het leven vaak krijgen. De geschikte geneesmiddelen en de doseringen daarvan kunnen het beste worden bepaald aan de hand van de geschatte nierfunctie (glomerulaire filtratiesnelheid, eGFR).

DE FARMACOKINETIEK VAN MORFINE

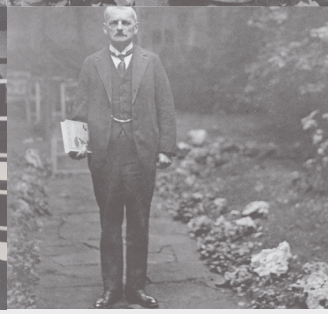
Hoofdstuk 6 betreft een studie naar de farmacokinetiek van morfine en de twee belangrijkste metabolieten (morfine-3-glucuronide en morfine-6-glucuoride) bij palliatieve patiënten. Voor deze studie werden 152 bloedmonsters van 47 patienten gebruikt. Uit de analyse bleek dat de werking van morfine het best wordt beschreven aan de hand van een twee-compartimenten model en van de beide metabolieten aan de hand van één-compartiment modellen. De tijd tot overlijden en de nierfunctie in combinatie met het albuminegehalte werden als belangrijkste covarianten gevonden; hoe dichter de patiënt bij het overlijden is, hoe minder de klaring van morfine wordt. Daarom verdient het aanbeveling de dosering van morfine aan te passen op basis van deze covarianten. Er is echter meer onderzoek nodig om dit in de vorm van een doseringsschema voor de dagelijkse klinische praktijk te kunnen gieten.

INTERPRETATIE VAN DE BEVINDINGEN

In *hoofdstuk 7* worden de bevindingen van de studies uit dit proefschrift geïnterpreteerd en bediscussieerd met ook aanbevelingen voor toekomstig onderzoek, zoals naar de farmacokinetiek, -dynamiek en -genetica van palliatieve geneesmiddelen, waaronder morfine, midazolam en haloperidol. Ook worden enkele cruciale strategieën genoemd om de uitdagingen die men tegenkomt bij het doen van onderzoek in de palliatieve zorg het hoofd te bieden.





PART V
APPENDICES









ABBREVIATIONS


ALAT/ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ASAT/AST	Aspartate aminotransferase
ATC system	Anatomical therapeutic chemical classification system; to categorize drugs
Bili	Total bilirubin
BIS	Bispectral index
BLQ	Below the quantification limit
BSV	Between-subject variability
Ca	Calcium
Ca_{corr}	Calcium, corrected for albumin levels
CAM	Confusion Assessment Methods
CI	Confidence interval
Cl	Clearance
CSPC	Consciousness Scale for palliative care
CRP	C-reactive protein
CWRES	Conditional weighted residuals
DOS scale	Delirium Observation Screening scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
DV	Observed concentrations
EAPC	European Association of Palliative Care
eGFR	Estimated glomerular filtration rate
EMG	Electromyography; a variable measured during BIS monitoring
F	Bioavailability
Fm1	Fraction of morphine clearance responsible for M3G formation
Fm2	Fraction of morphine clearance responsible for M6G formation
FOCE+I	First-order conditional estimation method with interaction
gGT/GGT	Gamma-glutamyltransferase
Hb	Haemoglobin
IPRED	Individual prediction
IQR	Interquartile range
K	Potassium
KNMG	Royal Dutch Medical Association
MDRD	Modification of Diet in Renal Disease formula; used to calculate eGFR
MOPAT	Multidimensional Objective Pain Assessment Tool
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
Na	Sodium
NRS	Numeric Rating Scale
NPDE	Normalised prediction distribution errors
NRS-observer	NRS score assigned by the same person who performed the observation for the REPOS score
NRS-patient	NRS score given by a patient himself

NRS-proxy	NRS score assigned by a caregiving nurse
NSAID	Non-steroidal anti-inflammatory drug
NPDE	Normalised prediction distribution errors
OFV	Objective function value
PAINAD	Pain Assessment in Advanced Dementia
PD	Pharmacodynamics
PK	Pharmacokinetics
PRED	Population prediction
Q	Intercompartmental clearance
RASS	Richmond Agitation-Sedation Scale
REPOS	Rotterdam Elderly Pain Observation Scale
RSE	Relative standard error
SD	Standard deviation
Ta	Day of admission
Td	Day of death
TTD	Time to death
V1	Central compartment
V2	Peripheral compartment
Vd	Volume of distribution
WHO	World Health Organisation

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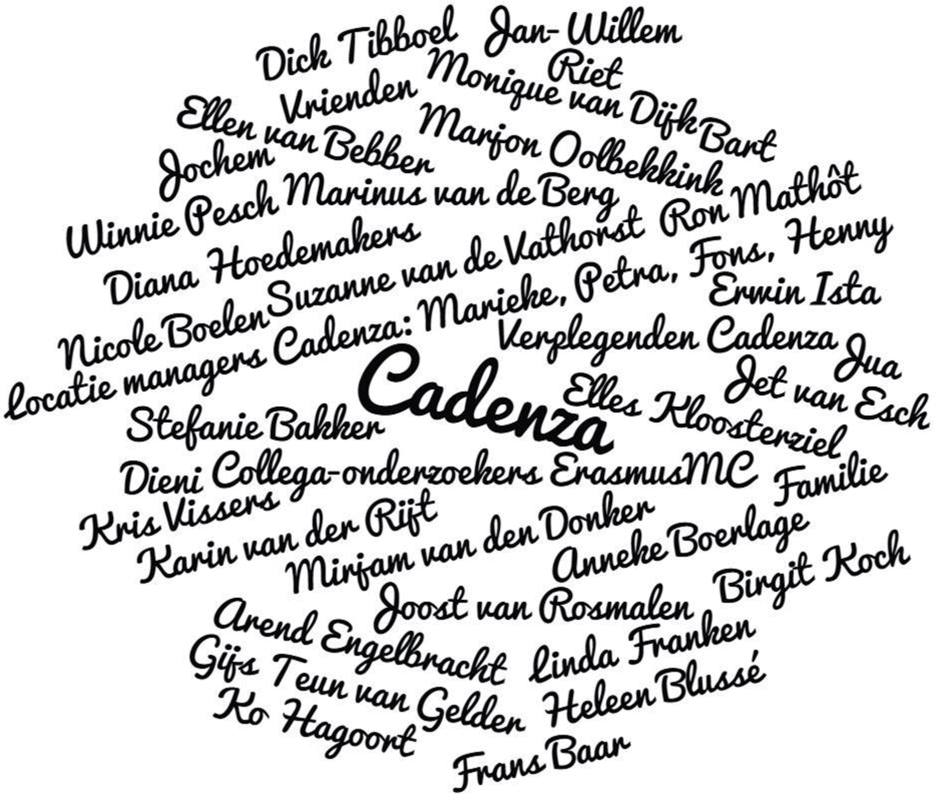

CURRICULUM VITAE


Anniek Masman was born on the 2nd of January 1983 in 't Harde, the Netherlands. She went to a Christian primary school until 1995. That year, she moved with her parents and brother to live in Hapert and started secondary education at the Pius X College in Bladel. In the first year, her mother was diagnosed with gastric cancer, but was cured against all expectations. This was the year that Anniek's interest in medical topics was very notable and this only grew thereafter.

She graduated from secondary school in 2001 and in the same year started her medical training at Leiden University, the Netherlands. In her second year she participated in an exchange program at the Karolinska Institutet in Stockholm, Sweden, for six months. During her medicine study she was actively involved in the L.M.D. Forestus society of the medical students association (M.F.L.S.). She was president of this society during one year. During her paediatrics internship she met a PhD-student from the department led by Prof. Dick Tibboel. This piqued her interest in research on patients unable to communicate verbally and the drugs physicians have to prescribe in off-label manner.

After finishing her internships she started research at the Erasmus Medical Center in Rotterdam, the Netherlands; first as a medical student (2007-2008) and later as a PhD-student (from June 2008). Anniek performed the research presented in this thesis at the Laurens Cadenza Palliative Care Center in Rotterdam, the Netherlands. There, she was the first researcher ever and created, in close collaboration with Frans Baar, elderly care physician and consultant palliative care, a setting equipped for research within this hospice.

In March 2014 she started training as a general practitioner at the Erasmus Medical Center in Rotterdam. Anniek lives together with Bart van de Ven and is the mother of Gijs (born in March 2013).

PHD PORTFOLIO


SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

PhD training	Year	Workload (ECTS)
General academic and research skills		
Good Clinical Practice / BROK cursus; Erasmus MC	2008	1.0
Workshop literatuur zoeken (basis); Medisch Bibliotheek Erasmus MC	2009	0.3
Statistics: classical methods for data-analysis; Nihes course	2009	5.7
Research Management; MolMed course	2010	1.5
Workshop literature search (advanced); Medisch Bibliotheek Erasmus MC	2011	0.3
EndNote course; Medisch Bibliotheek Erasmus MC	2011	0.3
English biomedical writing and communication; Erasmus MC	2011	1.2
Proefschrift schrijf drie daagse; Louter Promoveren	2012	1.5
In-depth courses (e.g. Research school, Medical Training)		
Basiscursus Palliatieve zorg voor verpleeghuisartsen; Leerhuizen Palliatieve Zorg	2007	2.5
Advanced course Palliatieve zorg verpleeghuisartsen; Leerhuizen Palliatieve Zorg	2009	0.7
Pharmacokinetics; LACDR course	2009	1.0
Teaching the teacher in palliatieve zorg; Leerhuizen palliatieve zorg	2010	1.3
Principles of Clinical Pharmacology; NIH web course	2010-2011	2.0
Presentations, seminars and workshops		
Haalbaarheidsonderzoek naar meetinstrumenten, Laurens Cadenza; 7e Vlaams Nederlands onderzoeksforum palliatieve zorg	2010	2.0
Evaluatie van het Zorgpad Stervensfase in Laurens Cadenza; Nationaal congres palliatieve zorg	2010	2.0
Haalbaarheidsonderzoek van meetinstrumenten in Laurens Cadenza: Onderzoek doen verbetert direct de zorg!; Nationaal congres palliatieve zorg	2010	1.5
Train de trainer bijeenkomst REPOS; Laurens Cadenza, Rotterdam	2010	1.5
Voorbeeld van onderzoek vanuit een Leerhuis: 'Farmaprofiel bij terminale patiënten'; Universitair Verpleeghuis netwerk Zuid Holland, Leiden	2011	1.5
Pijn bij ouderen herkennen en meten; Verenso, Rotterdam	2011	1.0
Supervising practicals and excursions		
Teaching nursing pain consultants (pijnspecialisten); Laurens Antonius IJsselmonde and Cadenza, Rotterdam	2009, 2010	2.5
Implementation pain observation scale REPOS and supervising nurses in practice; Laurens Cadenza, Rotterdam	2009, 2010	3.0
Other		
Multiple oral presentations for a weekly Pharmacology Research Meeting; Erasmus MC	2008-2012	2.0
Secretary/organizing activities for a weekly Pharmacology Research Meeting; Erasmus MC	2009	2.0
Organizing 'pain-week'; Cadenza, Rotterdam	2010	1.5
CME- online cursus: Pijn bij verpleeghuisbewoners met een uitingsbeperking (+ update)	2010, 2012	7.5

LIST OF PUBLICATIONS


THIS THESIS

Masman AD, Boerlage AA, Baar FPM, Tibboel D, van Dijk M; *The Rotterdam Elderly Pain Observation Scale (REPOS) is reliable and valid for non-communicative end-of-life patients*; BMC Palliative care 2016 (Submitted)

Masman AD, van Dijk M, van Rosmalen J, Blussé van Oud-Alblas HJ, Ista E, Baar FPM, Tibboel D; *Bispectral index (BIS) monitoring in terminally ill patients – a validation study*; Journal of Pain and Symptom Management 2016 (Accepted for publication)

Masman AD, van Dijk M, Tibboel D, Baar FPM, Mathôt RA; *Medication use during end-of-life care in a palliative care centre*; International Journal of Clinical Pharmacy 2015 Oct; 37(5):767-75

Masman AD, Tibboel D, Baar FPM, van Dijk M, Mathôt RA, van Gelder T; *Prevalence and implications of abnormal laboratory results in patients in the terminal phase of life*; Journal of Palliative Medicine 2016 (Accepted for publication)

Franken LG*, **Masman AD***, de Winter BC, Koch BC, Baar FPM, Tibboel D, van Gelder T, Mathôt RA; *Pharmacokinetics of Morphine, Morphine-3-Glucuronide and Morphine-6-Glucuronide in Terminally Ill Adult Patients*; Clinical pharmacokinetics 2015 Dec 29 (Epub ahead of print)
*L.G. Franken and A.D. Masman contributed equally to this work.

OTHER PUBLICATIONS

Boerlage AA, **Masman AD**, Hagoort J, Tibboel D, Baar FPM, van Dijk M; *Is pain assessment feasible as a performance indicator for Dutch nursing homes? A cross-sectional approach*; Pain Management Nursing 2013 Mar; 14(1):36-40

van Dijk M, **Masman AD**, Baar FPM; *CME Online 'Pijn bij verpleeghuisbewoners met een uitingsbeperking, cursus voor specialisten ouderengeneeskunde*; 2010 (e-learning, schriftelijke nascholingsmodule)
Masman AD, van Dijk M, Baar FP; *CME-Online 'Diagnostiek van pijn bij uitingsbeperkten'*; 2012 (revisie van e-learning voor verpleegkundig specialisten)