Outcomes of Treatment with Opioids

the role of clinical, pharmacokinetic and genetic factors

Astrid Oosten

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Uitkomsten van behandeling met opioïden – de rol van klinische, farmacokinetische en genetische factoren

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Colofon

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Een doel is de wegwijzer van het leven,
maar als je er bent, geniet er dan van

Contents

Chapter 1

General introduction and outline of this thesis

General introduction

Cancer-related pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, according to the widely used definition from the International Association for the Study of Pain (1). The prevalence of pain is high in patients with cancer. In a meta-analysis of 52 studies, a pooled prevalence rate of 53% was found; ranging from 33% of patients after curative treatment, to 64% of patients with advanced stages of disease. More than one-third graded their pain as moderate or severe (2). In a later published pan-European survey study, 72% of 4947 cancer patients approached, reported moderate to severe pain at least monthly (3).

Although the prevalence differs among cancer types, pain can occur in all types of cancer. In up to 90% the pain is caused by the cancer itself, while in about 20% the treatment of cancer (surgery, radio-or chemotherapy) is the cause of pain (4). Pain can also be associated with general debility or with concurrent conditions unrelated to the cancer. The majority of patients suffer from more than one pain, and a median of 3 different pain sites has been reported (5-7).

Pain can have a large impact on daily life and leads to distress in about two thirds of patients. In the European survey study, 51% reported difficulties in concentrating or thinking, 69% in performing normal activities in daily life, 52% in work performance and 30% in caring for self or others. In addition, 43% felt that their pain made them an increased burden to others (3).

Several factors influence the subjective experience of pain. These factors can be broadly divided into three domains: physical processes, thoughts and feelings and behaviour (8). Within the physical domain, peripheral (pain receptors, sensory nerves) and central mechanisms as well as modulating systems (e.g. gate control theory, sensitisation, neurotransmitters) can influence the pain sensation (8).

Opioids

An opioid is any agent that binds to opioid receptors. The original opiates, morphine and codeine, were derived from opium. In search of a better balance between analgesia and side-effects, numerous (semi-) synthetic opioids have been developed. In the Netherlands, commonly prescribed opioids are morphine, oxycodone, fentanyl, methadone and hydromorphone. Opioids act by binding to opioid receptors that can be found throughout the nervous system, but also in sites unrelated to pain modulation such as the intestinal tract. There are three principal classes of receptors, named mu (μ), delta (δ) and kappa (κ) receptors, all G-coupled protein receptors. The effects of an opioid depend upon the receptor to which it binds, its affinity for that receptor, and whether the opioid is an agonist or an antagonist.

The available opioids each have their own pharmacological characteristics, are available for different routes of administration and are metabolized through different pathways (Table 1). Differences in bioavailability, production of active metabolites and elimination are likely to influence outcomes of treatment.

Treatment of cancer-related pain

The World Health Organisation three-step analgesic ladder (9) (Figure 1) forms the basis for the treatment of cancer-related pain. By using this stepped approach, satisfactory pain relief can be reached in 80-90% of patients (10-12).

According to the WHO Pain ladder, strong-acting opioids are the treatment of choice for moderate to severe cancer-related pain after failure of treatment with a weak-acting opioid. In daily practice, step II opioids are often omitted and low doses of morphine or oxycodone are introduced after step I. This two-step strategy is supported by a recently published randomized trial showing that low doses of morphine reduced pain intensity significantly as compared to weak (step II) opioids with similar tolerability (13).

Based on currently available evidence, it is unknown which type of opioid is best to start treatment with. The evidence based guidelines from the European Association for Palliative Care (EAPC) state that 'data show no important differences between morphine, oxycodone, and hydromorphone given by the oral route) and permit a weak recommendation that any one of these three drugs can be used as the first choice step III opioid for moderate to severe cancer pain (14).

Unfortunately, in 25-40% of patients, first line treatment is unsuccessful due to insufficient pain control and/or the occurrence of severe side effects limiting (further) dose escalations (15, 16). Common opioid induced side effects are gastro-intestinal (e.g. nausea, vomiting, constipation), central (e.g. drowsiness, hallucinations, delirium, myoclonus, respiratory depression), autonomic (e.g. dry mouth) and cutaneous (e.g. sweating, itch) effects (15). Central side effects, such as drowsiness and confusion and gastro-intestinal side effects are most frequently reported as dose limiting adverse effects (16, 17). In these cases opioid rotation is reported to be successful in about two-thirds of patients (18, 19). In clinical practice, several drugs may need to be tried in order to find the one with the best balance between analgesic and adverse effects. In addition, doses need to be carefully titrated to avoid overdosing and toxicity. As there is no standard or maximal dose, in each patient, the dose must be titrated based on clinical effects. Thus, due to the wide variability in treatment effects and doses, treatment with opioids for managing cancer-related pain needs to be individualized. As it is unknown which factors can guide treatment, a trial- and-error approach is used in clinical practice. This takes time, which is unwanted in a population with often limited life-expectancy. There is therefore an urgent need of expanding our knowledge and finding predictive factors that can help in guiding treatment.

This thesis describes research that was performed in order to expand our knowledge of the effects of treatment with individual opioids and to better understand causes of variations in treatment outcomes.

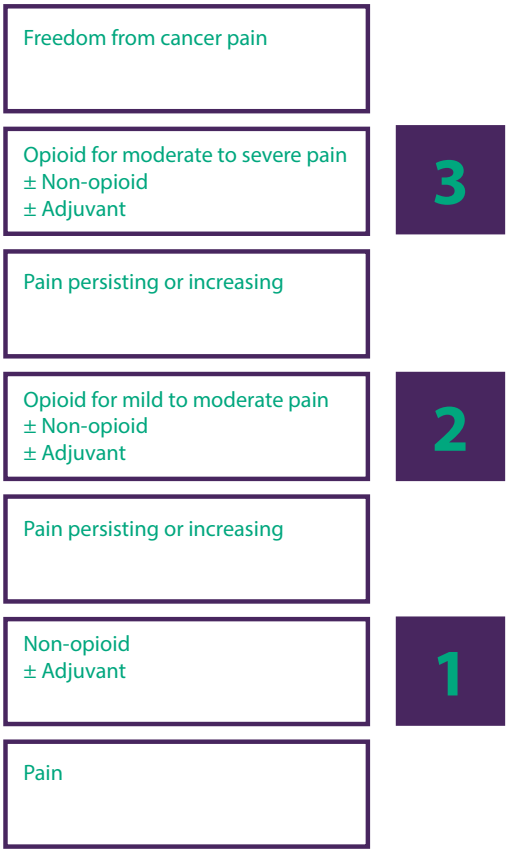

Figure 1. World Health Organisation Pain ladder

Table 1. Overview of characteristics of commonly used opioids (20-23)

Type of opioid	*Route of administration*	*Equi-analgesic dose*	*Summary of metabolism*	*Notes*
Pure μ agonists				
Morphine	IM/IV/SC Oral (SR, IR) (spinal, rectal)	20 mg 60 mg	Phase 2; Glucuronidation by UGT2B7 Main Metabolites: morphine-6-glucuronide (M6G; 10-15%, active) and morphine-3-glucuronide (M3G; 45-55%, active?) Elimination: urinary; 75% M3G, 10% morphine T ½: 1.5-3 h, increased in renal failure	Extensive first-pass metabolism Minor metabolism to hydromorphone No potential drug-drug interactions identified
Oxycodone	IM/IV/SC Oral (SR, IR)	20 mg 40 mg	Phase 1; CYP3A4 and to a lesser extent CYP2D6 Main metabolites: Noroxycodone (80% -active), oxymorphone (10% - active) Elimination: 72% urinary (metabolites) T ½ : 2-3 h	Conflicting evidence on effects of CYP3A4 and CYP2D6 genotypes Probably also an agonist for the Kappa2b opioid receptor (24)
Fentanyl	IV/SC Transdermal Nasal/buccal/ sublingual	25 mcg/h 25 mcg/h –	Phase 1, CYP3A4 Main metabolite: Norfentanyl (inactive) Elimination: 75% urinary (metabolites) T ½ : 7-12 h (parenteral)	High lipid solubility Only 0.4-6% excreted unchanged T ½ up to 22 h after repeated patches (25)
Hydromorphone	IM/IV/SC Oral (SR, IR)	3-4 mg 15 mg	Phase 2, glucuronidation by UGT2B7 and to a lesser extent UGT1A2 Main metabolite: hydromorphone-3 glucuronide (active) Elimination: urinary excretion T ½ : 2-3 h	Extensive first pass metabolism In our hospital used mainly for continuous parenteral administration in patients failing treatment with high doses of other opioids
Methadone	IM/IV/SC Oral	20 mg 40 mg	Controversial, Phase 1, CYP3A4, CYPD2B6 Main metabolite: EDDP (inactive) Elimination: variable; 50-75% urinary (methadone, EDDP), faecal elimination T ½ : 12-150 h (longer after prolonged administration)	Also antagonizes the NMDA-receptor and functions as serotonin and norepinephrine reuptake inhibitor Elimination half-live and potency highly variable
Partial μ agonist				
Buprenorphine	IM/IV/SC Transdermal Sublingual	0.6 mg +- 35 mcg/hr	Phase 1 CYP3A4 (30%) CYP2C8 &Phase 2 glucuronidation UGT2B7, UGT1A1 Main metabolite: norbuprenorphine (active) T ½ : 1-7 h Elimination: 70% faecal as conjugated metabolites, 14-30% urinary	Antagonist kappa and delta receptors May precipitate opioid withdrawal effects when administered after recent use of opioid agonists. Possible ceiling effect

IM = intramuscular; IV = intravenous; SC = subcutaneous; SR= slow-release; IR= immediate-release; UGT = Uridine 5'-diphospho-glucuronosyltransferase; CYP= Cytochromes P450; EDDP = 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine; NMDA = N-methyl-D-Aspartate

The aims of this thesis are:

1. To study the role of treatment with opioids and other medication in patients with an indication for palliative sedation due to severe, refractory symptoms.

2. To report the incidence of side effects of opioids in patients naive to strong acting opioids and to study possible differences in the incidence of side effects between the opioids.

3. To gain more insight in the pharmacokinetics of morphine and fentanyl administered by different routes.

4. To explore whether variability in pharmacokinetics of morphine and fentanyl is associated with treatment outcomes and to translate pharmacokinetic findings to clinical practice.

5. To study the effects of clinical and demographic factors and genetic variations on outcomes of treatment with opioids.

Outline of this thesis

In chapter 2, we studied a population of patients with a particularly bad outcome, namely patients who died on our specialized unit for palliative care after continuous palliative sedation because of severe, refractory symptoms. To explore the possible role of opioids and other medication in this setting, we studied differences in medication use between these patients and patients who died without an indication for palliative sedation.

In chapter 3, a systematic review of studies reporting adverse events of morphine, fentanyl, oxycodone and methadone in patients with cancer-related pain not treated with any of these opioids before is reported. The aim of this review was to describe the incidence of adverse events per type of opioid and to compare these rates in order to find possible differences that can help to guide treatment.

In chapter 4, we present results from a population pharmacokinetic study on fentanyl administered by the subcutaneous and transdermal routes. Although titration with subcutaneous fentanyl is safe and effective, pharmacokinetic data are lacking. We therefore aimed to describe the pharmacokinetics of subcutaneous and transdermal fentanyl in one cohort of patients. Secondly, we aimed to evaluate rotations from subcutaneous to transdermal fentanyl.

In chapter 5, we describe results from a population pharmacokinetic study on morphine administered subcutaneously and orally. Secondly, we studied the effects of several clinical and genetic factors on the clearance of morphine and metabolites and explored whether variability in clearance of morphine and metabolites was related to treatment outcome.

In chapter 6, results from an explorative analysis are presented, in which we compared patients in whom treatment with opioids and/or specific opioids failed with patients in whom these treatments did not fail and explored a range of clinical and genetic factors for associations with treatment failure.

Chapter 7 summarises the studies described in this thesis and addresses possibilities for future studies.

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Chapter 2

Higher doses of opioids in patients who need palliative sedation prior to death: cause or consequence?

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Eur J Cancer. 2011 Oct;47(15):2341-6

Abstract

Background:

Palliative sedation (PS) is necessary in a significant percentage of patients dying on an acute palliative care unit (PCU). Common indications are terminal restlessness, pain and dyspnoea. On our PCU, terminal restlessness was the main indication for PS but pain was the most prevalent symptom during admission. Because delirium is often drug induced in terminal cancer patients and opioids are amongst the most frequently implicated drugs, we hypothesised that the underlying pain problem and its treatment might have been related to the need for sedation.

Patients and methods:

To test this hypothesis, we did a retrospective analysis on the use of medication with potential cognitive side effects, focusing on analgesics, in 68 patients who died on the PCU after PS and 89 patients who died without PS.

Results:

Ultimately sedated patients used opioids in significantly higher doses; they were more often treated with a rotation to another opioid and with amitriptyline. The dose of opioids used at various time points between admission and death was strongly related to the probability of PS.

Conclusions:

Our findings support the hypothesis that, although pain was not the main indication for PS, pain and its treatment might have been primarily related to the need for palliative sedation in this patient cohort.

Introduction

Palliative sedation (PS) is the monitored use of medication intended to induce varying states of unconsciousness, but not death, in order to relieve refractory and unendurable symptoms in patients in whom death is imminent (1). This implies that PS is only justified when unendurable symptoms are present that cannot be controlled with appropriate measures.

Common indications for PS are pain, terminal restlessness/delirium/confusion and dyspnoea. In some reported series delirium or confusion/restlessness was the most frequent indication for PS (2-4) while in other series dyspnoea (5, 6) or pain (7-9) were found to be the most frequent indications.

The practice of palliative sedation in our specialised unit for acute palliative care in a university cancer hospital in the Netherlands has been reported by Rietjens et al (10). They described 157 patients who died at this unit, and studied differences between 68 sedated and 89 non-sedated patients. They found that terminal restlessness was the most common indication for PS (60%), followed by dyspnoea (46%) and pain (26%). Pain, however, was the most prevalent symptom on admission (up to 87%), and its prevalence remained high during admission – both for patients who died after PS as for patients who were not sedated before death. Prior to the onset of sedation, sedated patients more often suffered from delirium as compared to non-sedated patients at similar periods before death.

As it is known that delirium is often drug induced in advanced cancer patients and, more specifically, that opioids are amongst the most frequently implicated drugs (11-14), it is possible that the underlying pain problem and its treatment were primarily related to the need for sedation. In this new retrospective analysis, we therefore studied differences in the use of medication with potential cognitive side-effects, with special attention for opioids and other, adjuvant, drugs used in the treatment of complex pain, between patients who were ultimately sedated prior to death and patients dying without sedation.

Patients and methods

We conducted a new retrospective analysis of data from the same cohort of patients that was studied by Rietjens et al (10). The cohort consisted of all patients who died on our specialised acute palliative care unit (PCU) in a tertiary cancer hospital in Rotterdam, The Netherlands between October 2001 and October 2005.

The main goal during admission to the PCU is to provide symptom control for cancer patients with advanced disease. Daily multidisciplinary meetings are held with medical oncologists, nurses, an anesthesiologist, a neurologist and a psychiatrist present; other specialists are consulted when needed.

Pain is treated stepwise following the WHO pain medication ladder (15). Of note, because many patients on the PCU are admitted with complex pain problems, high doses of opioids, opioid rotation, parenteral administration of opioids and/or adjuvant analgesics are often needed. In patients with severe pain, we generally use parenteral morphine or fentanyl for titration, if possible subcutaneously. Doses are titrated whilst closely monitoring the effect on pain and side-effects. Patients are monitored for the development of delirium using the Delirium Observation Screening (DOS) scale, a Dutch-developed 13 point nurse observation scale filled out three times daily (16). For all patients who score ≥ 3 points or when delirium is suspected on clinical grounds, the psychiatrist is consulted. In case of dose-limiting side-effects that cannot be controlled with symptomatic therapy and/or inadequate effect on pain, opioid rotation to another type of opioid is used. We reserve the use of parenteral hydromorphone for patients whose pain cannot be controlled with high doses of other opioids, when dose-limiting side-effects occur related to other opioids or when problems related to the administration of large volumes subcutaneously arise. In these circumstances, ketamine may also be used as an adjuvant drug.

A decision to use palliative sedation in a dying patient is discussed in a multidisciplinary meeting. In case of sedation, opioids are continued at the dose level used at the start of the sedation, according to (inter)national guidelines.

A detailed description of the data collection and analysis is given in the original article (10). In summary, the database was built in four time frames: admission (T0), 72-49 h before death (T1), 48-25 h before death (T2) and 24-0 h before death (T3). Baseline variables were scored on admission, other variables in the three time frames prior to death. The start of palliative sedation was not per se related to the time frames but could take place between admission and time of death.

Regarding medication, we studied the use of: acetaminophen/NSAIDs, opioids, ketamine, amitriptyline, anti-convulsants, corticosteroids, benzodiazepines, anti-hypertensive drugs, diuretics, anti-emetics and acid reflux/stomach medication. In the category of opioids we differentiated various types of opioids in the time frames prior to death and registered rotations to another type of opioid .

Per time frame, doses of all opioids administered (continuous, slow release and immediate release products) were recalculated to the morphine equivalent daily dose (MED) per 24 h. This was done according to published equianalgesic dose tables: oral morphine 60 mg/d = parenteral morphine 20 mg/d = transdermal fentanyl 25 mcg/h = parenteral fentanyl 25 mcg/h = oral oxycodone 30 mg/d = oral hydromorphone 8 mg/d = parenteral hydromorphone 4 mg/d (17-19). Conversion rates for tramadol, methadone and epidurally or intrathecally administered opioids are not included in these tables. For tramadol we used a conversion rate of 4:1 (tramadol:morphine), according to results of a study by Wilder-Smith in 1994 (20). For oral methadone we used a conversion factor

of 1: 4.7 (methadone:morphine), according to data from a study by Walker et al (21). For epidurally or intrathecally administered opioids no relevant studies could be found. We therefore decided to use conversion factors of 1:30 (epidural:oral morphine) and 1:300 (intrathecal:oral morphine), respectively, factors based on theory and clinical experience of pain specialists from the department of anaesthesiology in our hospital.

Statistical analyses

Data were analysed using STATA version 10. Descriptive statistics were used to describe patients' characteristics. Reported p-values are two-tailed and $p < 0.05$ was considered to be statistically significant. To assess the association between the MED and the probability of PS logistical regression analysis was used. For each interval we calculated logistic regression of sedation (yes or no) versus log (MED). So, we obtained the probability of sedation for each MED-value and for all time periods.

Results

Patient characteristics of 68 sedated and 89 non-sedated patients are given in Table 1. In case of sedation, it was started in the last 24 hrs before death in a majority of patients (68%).

Symptom prevalence on admission and the indications for palliative sedation are shown in Table 2. There was a high prevalence of pain in both groups.

One patient in the sedated group was excluded from further analyses, because no information on used medication could be found.

No statistically significant differences were found in the percentage of patients using anti-convulsants, corticosteroids, anti-hypertensive drugs, diuretics, anti-emetics and acid reflux/stomach medication in T0-T3. Significantly more patients in the ultimately sedated group used benzodiazepines at T0, 10/68 (22%) sedated versus 2/89 (3%) non-sedated patients ($p = 0.002$). For T1-3 data could not be used as the indication for benzodiazepines was not registered, so they could then also be used for the purpose of PS.

The use of pain medication is shown in Figure 1. No significant differences were found in the percentage of patients using WHO step 1 pain medication and opioids (Figure 1a). The figure shows that the percentage of patients using WHO step 1 medication decreased with time, whilst the percentage of patients using opioids increased in both groups.

Figure 1b shows that sedated patients more frequently used amitriptyline in T0-2. ($p = 0.02$, $p = 0.002$, $p = 0.004$, respectively). Between T0 and T1 the percentage of patients using ketamine in the ultimately sedated group increased from 4.5% to 13.4%, whereas it remained stable in the non-sedated group (differences NS).

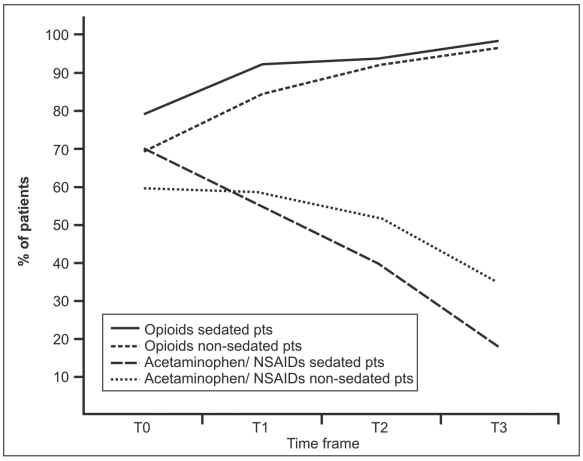

Figure 1. Differences in the use of pain medication and haloperidol between sedated and non-sedated patients.

Figure 1A: WHO step 1& 3 pain medication

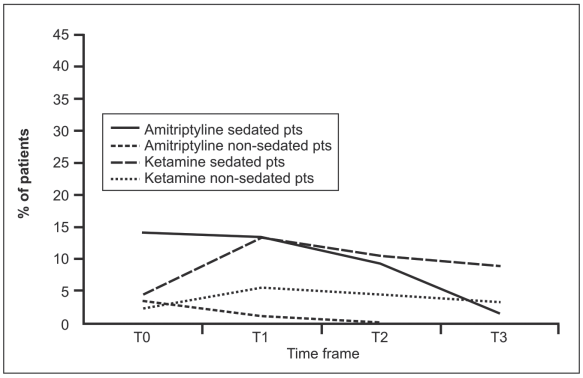

Figure 1B: adjuvant analgesics

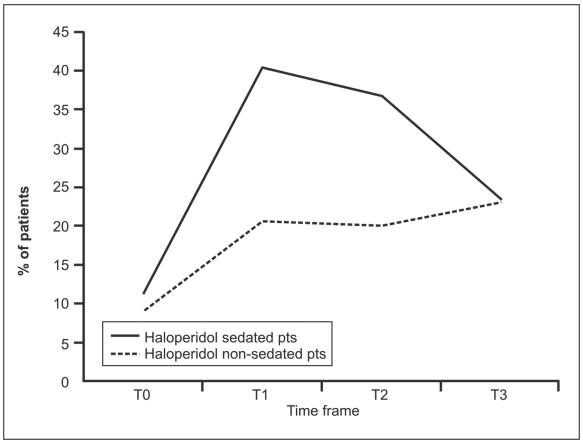

Figure 1C: haloperidol

Table 1. Patient characteristics

	Sedated patients N = 68		*Non sedated patients N = 89*		*p-value*
	N	%	*N*	%	
Male	31	46	40	45	0.87
Age median (range)	57	(27-89)	61	(25-80)	0.03
Primary tumor					
Lung	15	22	12	13	0.19
Gastro-intestinal	14	21	5	6	< 0.01
Breast	11	16	22	25	0.16
Genito-urinary tract	7	10	17	19	0.13
Head and neck	5	7	5	6	0.66
Melanoma	8	12	6	7	0.27
Sarcoma	5	7	7	8	0.91
Other/(A)CUP	3	4	15	17	0.02

Table 2. Symptom prevalence on admission and indications for palliative sedation (Main results of previous analyses)

	Sedated patients N = 68		*Non sedated patients N = 89*		*p- value*
Symptom prevalence on admission	*N*	%	*N*	%	
Pain	59	87	69	78	0.2
Dyspnea	20	29	28	31	0.7
Delirium	8	12	9	10	0.8
Anxiety	6	9	6	7	0.7
Indication for palliative sedation					
Pain	18	26	-	-	
Pain as the only indication for PS	7	10	-	-	
Terminal restlessness	41	60	-	-	
Dyspnea	31	46	-	-	
Other	10	15	-	-	

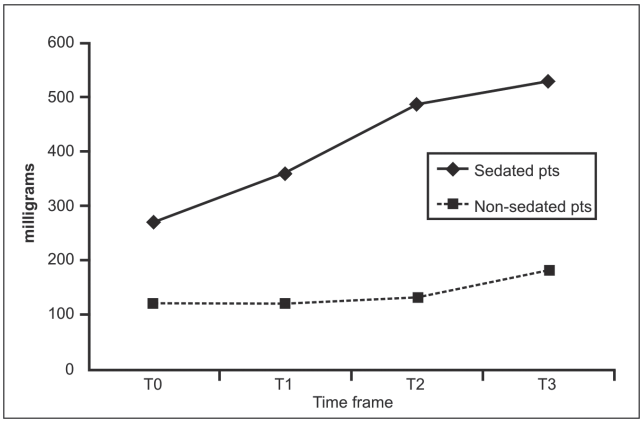

Figure 2. Median equianalgesic dose of opioids per time frame.

Figure 1c shows that about 40% of the ultimately sedated patients used haloperidol in T1 and T2, whereas this percentage was about 20% for the non-sedated group ($p = 0.02$ and $p = 0.034$ respectively).

Variations regarding the use of specific types of opioids and the various routes of administration were studied per time frame. At T0, patients from the ultimately sedated group and the non-sedated group used similar types of opioids. Many patients were rotated from oral to parenteral opioids during admission, but especially between T0 and T1, without differences between the groups. Between T0 and T1, rotation to another type of opioid was more often used in the group of patients who were ultimately sedated than in the non-sedated group: in 30/68 pts (44%) and 19/89 pts (22%), respectively ($p < 0.005$). In particular, more patients were set on hydromorphone (9.3 versus 1.2%, $p = 0.017$) or spinal pain medication (4.5 versus 1.2%, NS) during this period. There were no significant differences in the use of opioid rotations between sedated and non-sedated patients during the last 72 h of life.

The median morphine equivalent daily dose (MED) of opioids in T0-3 for sedated and non-sedated patients is shown in Figure 2. Sedated patients used significantly higher doses of opioids in all time frames ($p = 0.025$, $p = 0.001$, $p < 0.001$, $p < 0.001$, respectively).

One patient was found to use extremely high doses of opioids. Because the possibility of an error in noting the dose could not be excluded, this patient was excluded for the analyses on equianalgesic doses of opioids.

Figure 3 shows the probability of dying with PS in relation to the logarithm of the MED of opioids at T0 using logistic regression analysis. The figure shows that there was a strong relationship between the dose of opioids at T0 and the probability of becoming

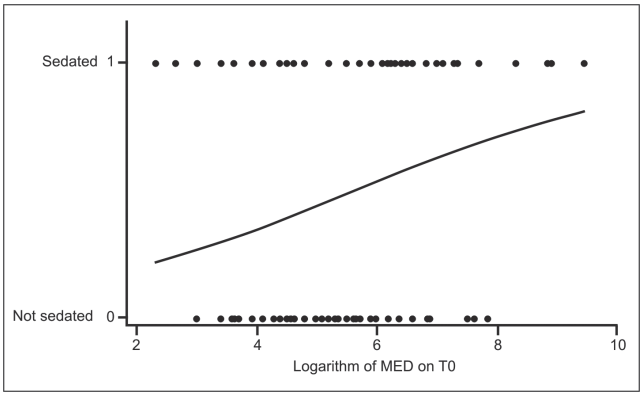

Figure 3. Probability of PS in relation to the MED of opioids on T0, logistic regression analysis.

sedated before death (p = 0.017). Similar results were obtained for time frames T1 and T2 (p = 0.004) and p < 0.001).

Discussion

PS is necessary in a significant percentage of patients dying on an acute PCU (3, 5). These patients suffer from treatment refractory symptoms distressing them as well as their family members and care givers. The setting in which PS is performed, is therefore always difficult and stressful, making it all the more important to better understand the trajectory leading to PS and the factors that may influence it.

As mentioned in the introduction of this article, in some settings delirium or terminal restlessness/confusion is the main indication for PS whilst in others dyspnoea or pain is the main indication. To our knowledge, studies on predictors for the occurrence of refractory symptoms in the dying phase have not been performed.

In our cohort of patients pain was one of the main indications for PS in 26% of patients, and the only indication in 10% of patients - although pain was very prominent. This reflects the fact that we have the facilities and the experience to treat patients with severe and difficult pain problems. However, pain and its treatment might very well be indirectly related to the need for PS as it is known that delirium is often drug induced. Because in our cohort of patients, delirium/terminal restlessness was the main indication for PS, we studied differences in medication with potential cognitive side-effects between ultimately sedated patients and non-sedated patients. We found some striking differences in the

use of pain medication. The ultimately sedated patients used opioids in significantly higher doses; they were more often treated with a rotation to another type of opioid - in some to hydromorphone - and with adjuvant amitriptyline. Furthermore, ketamine and spinal medication were used more frequently, although differences were not statistically significant. These results support our hypothesis of more difficult pain problems in the ultimately sedated group compared to the non-sedated patients. Although it is likely that sedated patients had more severe pain, we unfortunately have no data to substantiate this as the severity of pain was not registered in the database in this study period. However, in our previous analyses in this same group of patients we already found indications to suggest a more aggressive course of the underlying cancer in the sedated patients, which is also compatible with the assumption of more difficult pain problems in this group of patients (10). Thus, ultimately sedated patients are likely to have had more difficult pain problems, leading to more intense treatment with a higher risk of terminal restlessness/ delirium.

Differences in pharmacokinetics and pharmacodynamics of pain medication between the groups may also be important. It is possible that ultimately sedated patients had less analgesic effects and/or more side-effects from the used medication. Large inter-individual differences in the metabolism of morphine have indeed been described (22, 23) and genetic variability is assumed (24). Results of studies on the relation between morphine metabolites and delirium in cancer patients are conflicting, however (25-28). Furthermore, a recently published large European study could not find an association between genetic variability and opioid dose (29). More research on the effects of pharmacokinetic and pharmacogenetic variability on analgesic and side-effects of opioids is needed.

To our knowledge, this is the first study addressing the possible role of pharmacological interventions for the treatment of complex pain in the need for PS in a group of terminally ill cancer patients. Although the retrospective design of our study is an important limitation, our findings indicate that more insight in the pathophysiologic mechanisms of refractory symptoms in the dying phase is needed.

In conclusion, our findings suggest that ultimately sedated patients had more difficult pain problems and/or had a disturbed dose-effect relationship for opioids. The more intensive treatment of these patients could have led to a higher rate of treatment refractory delirium/terminal restlessness, sometimes necessitating PS. Although pain was not the main indication for PS in our cohort of patients, its treatment might very well have been related to the need for PS. This emphasizes the need for more individualised treatment schemes, to minimise the risk of adverse events.

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Chapter 3

A systematic review of prospective studies reporting adverse events of commonly used opioids for cancer-related pain: a call for the use of standardized outcome measures

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Abstract

Data on the tolerability of opioids in patients with cancer-related pain are limited. Here, we report a systematic review that includes all published prospective studies reporting adverse events (AEs) of morphine, oxycodone, fentanyl, methadone, or hydromorphone for cancer-related pain in patients naive for these opioids. We included 25 studies describing 31 treatment cohorts, made an overview of study characteristics, and reported rates of AEs per type of opioid. The frequency of the most commonly reported AEs varied widely: nausea from 3 to 85%, vomiting from 4 to 50%, constipation from 5 to 97%, drowsiness from 3 to 88%, and dry mouth from 1 to 94%. There was a large heterogeneity among included studies, especially regarding the assessment and reporting of AEs. We describe how differences in assessment and reporting influence outcome rates. Although AEs are an important issue in daily clinical practice, realistic incidence rates of AEs per type of opioid are unknown because of the immense heterogeneity among studies.

Introduction

Pain is prevalent in patients with cancer in all stages of the disease, with the highest prevalence seen in patients with advanced or metastatic disease: 2 of 3 patients experience pain, with more than one-third of these patients grading their pain as moderate or severe (1). The analgesic ladder as published by the World Health Organization (WHO) is the foundation for the treatment of cancer-related pain. WHO follows a stepwise approach, with weak-acting or step 2 opioids as second-line choice for moderate pain and strong-acting step 3 opioids as third-line choice for moderate to severe pain (2). This review focuses on the strong-acting opioids (referred to as opioids in this article), which are also used as a first-line opioid in low doses.

Commonly prescribed opioids in the Western world are morphine, oxycodone, fentanyl, and, to a lesser extent, hydromorphone and methadone. Choosing among these opioids is not easy. Only a few randomized controlled trials (RCTs) directly comparing different opioids have been published, and no significant differences in efficacy and tolerability profiles have been shown, with the exception of the finding of less constipation with fentanyl compared with morphine (3-5). The European Association for Palliative Care guidelines state that morphine, oxycodone, or hydromorphone can be used as the first-choice opioid and that fentanyl may be an alternative in some patients, for example in cases of problematic oral intake, renal insufficiency, or severe constipation. Methadone should be used only by experienced professionals (6).

The effect on pain and the occurrence of side effects in an individual patient are assumed to be the result of a complex interplay between pharmacokinetics and pharmacodynamics. Pharmacogenetics may further complicate existing pharmacokinetic-pharmacodynamic relationships Therefore, much research is conducted with the aim of finding clinical, pharmacokinetic, or genetic determinants that will enable true personalized treatment. However, results of such studies have not yielded specific markers or profiles that can guide treatment decisions for individual patients (7-9).

As a result, finding the right opioid in the right dose at the right moment is a matter of trial and error in daily clinical practice. The choice for the opioid to start with in an opioid-naive patient is mainly based on expert opinions, clinical experience, personal preference, and sometimes clinical factors (ie, accessible routes of administration, renal failure). All opioids have shown equal rates of pain control (6, 10) but data about side effects are scarce. Obviously, if one of the opioids had a better side effect profile, this opioid would be preferred. Also, differences in the incidence of specific side effects can be relevant in patients who already present with or are at risk for various symptoms. The prevalence and severity of symptoms are high in patients with cancer-related pain and increase with each step up the WHO treatment ladder (11). In one study, patients not using any opioids

experienced a mean of 2.9 (standard deviation [SD] 1.9) symptoms. Among the most prevalent symptoms were insomnia (58%), anorexia (40%), constipation (25%), and nausea (21%) (12). We conducted a systematic review including prospective studies in patients with cancer naive for morphine, oxycodone, fentanyl, methadone, and hydromorphone in which side effects of these commonly used opioids were reported. The objective of this review was to create an overview of the incidence of side effects after starting treatment with opioids for cancer-related pain and to study whether the incidence of (specific) side effects differs among different types of opioids.

Methods

We performed a systematic review in which we included prospective studies reporting on the occurrence of side effects after the start of morphine, oxycodone, fentanyl, methadone, or hydromorphone for cancer-related pain in patients who were naive for these opioids. Pretreatment with codeine phosphate, dihydrocodeine, dextropropoxyphene, or tramadol was allowed.

The following databases were searched up until March, 2015: MEDLINE (PubMed), Embase, Web of Science, and the Cochrane Database of Systematic Reviews. No year limits were applied to the searches and therefore they extend as far back as the year range of each database. Retrievals in Ovid MEDLINE go back to 1976, EMBASE to 1985, Web of Science to 1950, and the Cochrane Library to 1966.

The search terminology included different terms and medical subject headings for cancer, side effects and specific side effects (constipation, nausea, vomiting, delirium, hallucinations, myoclonus, sweating, drowsiness, and dry mouth), all types of trials, and morphine, fentanyl, oxycodone, methadone, and hydromorphone. The search strategies were developed specifically for each database. The search was performed by a staff member of the Medical Library and one of the authors (A.W.O.). In addition, reference lists of relevant studies and reviews found were checked.

Two reviewers (A.W.O., W.H.O.) independently assessed all titles with or without abstracts identified by the search. In case of potentially relevant articles, the full text was obtained to judge if they fulfilled the criteria: 1) it had to be a prospective study; 2) treatment with morphine, oxycodone, fentanyl, methadone, or hydromorphone for cancer-related pain was required; 3) patients had to be naive for these opioids before inclusion in the study; 4) data on specific side effects (constipation, nausea, vomiting, delirium, hallucinations, myoclonus, sweating, drowsiness, and/or dry mouth) were given; and 5) only full-text articles published in English, German, Dutch, or French were considered. When the same cohort of patients was described in multiple articles, the article describing the largest

cohort or fulfilling our inclusion criteria best was chosen, provided that no information on adverse events (AEs) was lost.

For studies fulfilling our inclusion criteria, data were extracted independently by 2 authors (A.W.O., W.H.O.), after which extracted data were compared. Disagreements were resolved by discussion between the 2 reviewers. When necessary, a third reviewer (C.C.D.R.) decided. All studies were assessed in a standardized manner. For each trial included, information was extracted on study design, number of patients who fulfilled the inclusion criteria, opioid treatment (type, route of administration, dosing, and titration), previous analgesic treatment, length of follow-up and loss to follow-up, AE (types of AEs, severity grade of AEs, method and frequency of assessment, number of patients with AEs), and confounding factors (eg, comedication, type of rescue medication, antitumor treatment). For studies including a wider group of patients than defined, only data for the patients fulfilling the inclusion criteria were reported. Opioid doses were recalculated to the median morphine equivalent daily dose (MEDD) (mg/d) according to published equianalgesic dose tables: oral morphine 60 mg/d = parenteral morphine 20 mg/d = transdermal fentanyl 25 µg/h = oral oxycodone 40 mg (6). For oral methadone, we used a dose conversion ratio of 1:4 (methadone/morphine) (13).

Data on the specific AEs were reported as the percentages of patients with the respective AE. For studies that did not report on the number or percentage of patients with AEs or when there were uncertainties about the data, the corresponding author was contacted with a request for additional information. When available, data on AEs during the first week of treatment with the opioid were used. When AEs were given on multiple days during the first week, we used the highest percentage. We aimed to study the percentages of mild AEs and the percentages of moderate to severe AEs separately.

Results

The literature search provided a total of 7,077 citations. Figure 1 shows the selection process. Thirty-six studies fulfilled our inclusion criteria. In 10 of these studies, data on the number of patients with AEs could not be extracted because they reported the mean/median AE severity scores or the proportion of days with AEs only. After contacting the authors of these articles, data on the number of patients with AEs were supplied for 5 of these 10 studies. After excluding 6 more studies for various reasons (Figure 1), 25 studies (9 RCTs and 16 cohort studies) describing 31 treatment cohorts with different opioids were included in our analysis (14-38). An overview of included studies is given in Table 1. Thirteen studies reported on morphine, 9 on fentanyl, 6 on oxycodone, and 3, all from the same investigator, on methadone. No studies with hydromorphone were included.

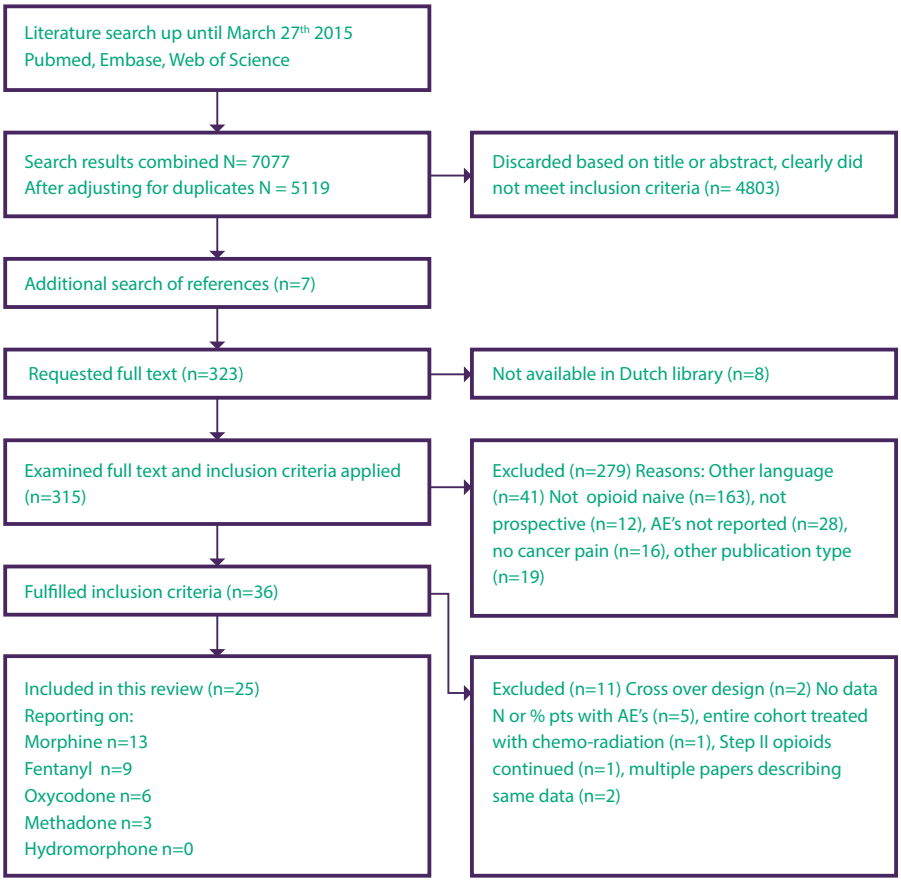

Figure 1. CONSORT diagram of the literature search and selection process.

Most studies reported data for nausea and constipation. Vomiting, drowsiness, and dry mouth were reported less frequently, and just a few studies reported data on confusion, sweating, or pruritus. None of the studies reported on hallucinations or myoclonus (Table 1). For only a few studies, the occurrence rates per severity grade (mild, moderate to severe) of some AEs were available (18-20, 22, 23, 31, 32). We decided to pool all grades because data were insufficient for a comparison of mild versus moderate to severe AEs.

Because the included studies were found to be very heterogeneous, Table 2 gives an overview of study characteristics relevant for interpreting the reported occurrence rates of AEs. The first characteristic is pretreatment with weak-acting (WHO step 2) opioids, which was allowed in 7 studies (14-16, 22, 29, 32, 34), was an inclusion criterion in 6 studies (19, 20, 23, 27, 35, 36), was not allowed in 6 studies (17, 18, 21, 28, 30, 33) and

was unreported in another 6 studies (24-26, 31, 37, 38). The second characteristic is the starting dose of treatment and subsequent titration rate (shown as dose after titration and days needed for titration), for which sometimes large differences were seen. The median MEDD at the start was 60 mg, which was also the highest starting dose. In 5 oxycodone studies, substantially lower doses were given at the start (range in MEDD = 15-30 mg) but also after titration (range in MEDD = 25-48.6 mg). In 1 oxycodone study, the starting dose was unknown, but doses after titration were high (MEDD = 198 mg) (37). In 7 of 9 fentanyl cohorts, the MEDD at the start was 60 mg, and in all 3 methadone cohorts, the starting dose was close to 60 mg. The largest variation in treatment doses was seen between the morphine cohorts. The third characteristic is differences in the reporting and the assessment of AEs. Because there was no uniformity in the description of how the AEs were measured, we cited the described methods from each study briefly. In 1 study, AEs were reported only on day 28 (23), and 6 studies reported AEs over the entire follow-up period (range = 14 days to 3 months) (15, 18, 25, 34, 35, 37). For all other studies, except 1 with unknown time of follow-up and reporting(38), AEs were available for the first 3 to 10 days of treatment.

We could not include information about comedication and concurrent treatments in Table 2 because of limited data. In some studies antiemetics (23), laxatives (15), or both (16) were given as standard, and 1 study (21) recommended the use of both. In other studies, comedication was given as clinically indicated (18, 25, 27, 29, 32, 35, 38, 39). One study (33) examined the combination of oxycodone with or without the antiemetic prochlorperazine. For the other studies, no data on comedication/adjuvants were reported. Four studies (19, 20, 29, 36) reported the number of patients treated with chemotherapy, radiotherapy, or both during the study period.

Figure 2 shows the percentage of patients experiencing any grade of nausea, constipation, drowsiness, and dry mouth per study and per type of opioid (red dots, morphine; green, oxycodone; blue, fentanyl; and black, methadone). Each dot represents a treatment cohort of patients treated with a specific type of opioid, and therefore the included studies can be found in the figures more than once if they reported on multiple treatment cohorts. The studies are arranged from left to right in ascending opioid starting doses and, in case of similar starting doses, doses after titration. A solid black ring around a dot signifies that only AEs ascribed to the studied opioid were reported (14, 21, 30, 31, 34, 35), whereas a spotted black ring around a dot signifies that this was likely the case but could not be determined for certain based on the information provided (29, 33, 36). Studies reporting all AEs regardless of causality with the studied opioid are not circled. In the following section, we describe the information gathered per type of AE, which is summarized in Figure 2.

Table 1. Overview of Included Studies Reporting AEs as an Outcome of Treatment With Opioids for Cancer-Related Pain

Reference	*Year*	*Country*	*Study type*	*Number*	*Male (%)*	*Treatment*	*Rescue medication*	*Follow-up (days)*	*Number evaluable (day 7)*	*AEs Reported*
De Conno et al (14)	2008	Italy	Cohort	159	65	Mo IR	Mo	5	135	N, V, Cs, Dr, Cf
Eyelade et al (15)	2012	Nigeria	Cohort	182	19	Mo IR	Mo	90	166	Cs, Dr, DM
Harris et al (16)	2003	India	RCT	62	76	Mo IV vs IR	Mo IV/IR	7	52	N, V, Cs, Dr, Pr
Hemati et al (17)	2015	Iran	Cohort	86	56	Fe td	?	3	86	N/V, Cs, Dr, Pr
Kang et al (18)	2015	Korea	Cohort	98	64	Fe td	*	25	?	N, V, Cs, Dr, DM
Klepstad et al (19)	2000	Norway	Cohort	40	53	Mo IR / Mo SR	Ke	12	35	N, V, Cs, Sw
Klepstad et al (20)	2003	Norway	RCT	40	56	Mo IR vs SR	Ke	4	34	N, V, Cs
Koizumi et al (21)	2004	Japan	Cohort	22	86	Ox CR	Mo	7	22	N, Cs, Dr
Ljuca and Husic (22)	2010	Bosnia and Herzegovina	Cohort	35	57	Mo IR	Mo	10	35	Cs, Dr, DM
Luczak et al (23)	2002	Poland	Cohort	72	63	Fe td	Mo	28	?	N, V, Cs
Matsui et al (24)	2009	Japan	Cohort	18	50	Fe td	*	9	18	N, V, Cs, Dr, Pr
Mercadante et al (25)	1998	Italy	RCT	20 20	50 45	Mo SR Me	? ? 	y y 	20 20	N, Cs, Dr, DM, Cf
Mercadante et al (26)	1999	Italy	Cohort	45	47	Me	?	y	45	N, Cs, Dr, DM, Cf, Sw
Mercadante et al (27)	2008	Italy	RCT	36 36 36	45[z] 56[z] 52[z]	Mo SR Fe td Me	Mo Mo Mo	28 28 28	22 25 23	N/V, Cs, Dr, DM, Cf
Mercadante et al (28)	2010	Italy	RCT	30 30	41[z] 41[z]	Ox CR Mo SR	Mo Mo	56 56	24 21	N, Cs, Dr, DM, Cf
Mystakidou et al (29)	2004	Greece	Cohort	1507	49	Fe td	Mo	276	1505	N, V, Cs, Sw, Pr
Pan et al (30)	2007	China	Cohort	216	58	Ox CR	?	28	216	N, V, Cs, Dr
Rodriquez et al (31)	1994	Spain	RCT[x]	42	76	Mo IR	Pcm/cod	7	35	N, Cs, Dr
van Seventer et al (32)	2003	Netherlands	RCT	64 67	70 60	Mo SR Fe td	Mo Mo	28 28	47 63	N, V, Cs, Dr

Table 1. Continued

Reference	*Year*	*Country*	*Study type*	*Number*	*Male (%)*	*Treatment*	*Rescue medication*	*Follow-up (days)*	*Number evaluable (day 7)*	*Aes Reported*
Suzuki et al (33)	2008	Japan	Cohort	37	0	Ox CR	Mo	20	37	N, Cs, Dr, Cf
Tawfik et al (34)	2004	Egypt	Cohort	157	38	Fe td	Mo	28	157	N, V, Cs, Dr, DM
Vielvoye et al (35)	2000	Netherlands	Cohort	28	?	Fe td	Mo	28	28	N, V, Cs
Vijayaram et al (36)	2000	India	Cohort	223	34	Mo IR	Mo	68	223	N/V, Cs, Pr
Xiao et al (37)	2014	China	RCT	60	?	Ox CR	?	14	60	N/V, Cs, Dr, Pr
Zhang et al (38)	2014	China	RCT?	114 57	55	Mo SR Ox CR	Mo Mo	?	?	N, V, Cs

Abbreviations: Mo, morphine; IR, immediate release; N, nausea; V, vomiting; Cs, constipation; Dr, drowsiness; Cf, confusion; DM, dry mouth; IV, intravenous; Pr, pruritus; Fe, fentanyl; td, transdermal; Ke, ketobemidone; Ox, oxycodone; CR, controlled release; SR, slow release; Me, methadone; Sw, sweating; Pcm/cod, paracetamol/codeine; ?, unknown. *Rapid-type oral opioid agent. Y, Until death. Z Not at baseline, based on number of patients completing study. X Versus dypiridone

NOTE. Five studies were sponsored by a pharmaceutical company (18, 23, 32, 34, 35)

Table 2. Study Characteristics Relevant for the Assessment of Reported Incidences of AEs

Reference	*Year*	*Pretreatment with step 2 opioids number (%)*	*Treatment*	*Dose at start/ dose aftertitration (per 24 h, mean)*	*Dose in oral medd (mg/24 h, mean)*	*Duration of titration (Days)*	*Days or period (p) after start on which aes were reported*	*Assessment of AEs*
De Conno et al (14)	2008	122 (77)	Mo IR	30–60 / 59 mg	30–60 / 59	5	P0–5	The safety was assessed by the physician who recorded AEs related to treatment using an intensity scale from 1 to 3 (mild to severe)
Eyelade et al (15)	2012	33 (18)	Mo IR	30 / 47 mg	30 / 47	7	P0–90	Any reported AEs were documented
Harris et al (16)	2003	Y (?) Y (?)	Mo IV Mo IR	60 / 49.8 mg 30 / 43.2 mg	60 / 49.8 30 / 43.2	3	1, 2, 7	Groups were reviewed to assess AEs
Hemati et al (17)	2015	0	Fe td	25 / 25 mg	60 / 60	3	P0–3	The severity of side effects was evaluated
Kang et al (18)	2015	0	Fe td	12.5 / 26 mg	30 / 62	8	P0–25	Phone inquiries every 3 d. Investigators used mild, moderate, and severe to describe the intensity of the AEs
Klepstad et al (19)	2000	40 (100)	Mo IR/ Mo SR	60 / 97 mg	60 / 97	2	1, 2, 3, 4, 5, 6, 7	The EORTC-QLQ-C30 questionnaire was administered 3 times during the study
Klepstad et al (20)	2003	20 (100) 20 (100)	Mo IR Mo SR	60 / 94 mg* 60 / 82 mg*	60 / 94* 60 / 82*	2	1, 2, 3, 4, 5, 6, 7	AEs were reported on a VRS (not at all to very severe)
Koizumi et al (21)	2004	0	Ox CR	10 /16.7 mg	15 / 25.2	2	P0–7	By questioning/examining the patients, reviewing patient diaries. Severity (slight to severe) assessed by investigators
Ljuca and Husic (22)	2010	20 (57)	Mo IR	48 / 71.3 mg	48 / 71.3	4–6	P0–10	Side effects were monitored. Dry mouth/ drowsiness on a scale of 0–10, constipation grade 0–3
Luczak et al (23)	2002	72 (100)	Fe td	25 / 44.3 mg	60 / 106	7	1, 28	A diary was used. Nausea/vomiting was assessed daily using scale absent to severe
Matsui et al (24)	2009	?	Fe td	12.5 / ? mg	30 / ?	?	2, 7	AEs were classified using CTC 3.0
Mercadante et al (25)	1998	? ?	Mo SR Me	32.5 / 109.5 mg 13.6 / 25.2 mg	32.5 / 109.5 54.4 / 100.8	? ?	P0–50	The symptoms were assessed by the patient using a scale 0–3 (not at all to awful)

Table 2. Continued

Reference	*Year*	*Pretreatment with step 2 opioids number (%)*	*Treatment*	*Dose at start/ dose aftertitration (per 24 h, mean)*	*Dose in oral medd(mg/24 h, mean)*	*Duration of titration (Days)*	*Days or period (p) after start on which aes were reported*	*Assessment of AEs*
Mercadante et al (26)	1999	?	Me	14.4 / 27.2 mg	57.6 / 108.8	?	P0–U	The symptoms were assessed by the patient using a scale 0–3 (not at all to awful)
Mercadante et al (27)	2008	36 (100) 36 (100) 36 (100)	Mo SR Fe td Me	60 / 68.2 mg 25 / 39.1 mg 15 / 15.6 mg	60 / 68.2 60 / 94 60 / 62.4	7 7 7	P0–7	The symptoms were assessed by the patient using a scale 0–3 (not at all to awful), unless for constipation, which was monitored on an institutional scale
Mercadante et al (28)	2010	0 0	Ox CR Mo SR	20 / 23.8 mg 30 / 35.0 mg	30 / 35.7 30 / 35.0	7 7	P0–7	The symptoms were assessed by the patient using a scale 0–3 (absent to severe), constipation using an institutional scale
Mystakidou et al (29)	2004	1239 (82)	Fe td	25 / 50 mg*	60 / 120	7	0, 2, 7	Side effects were graded according to the CTC
Pan et al (30)	2007	0	Ox CR	10–20 / 21.1 mg	15–30 / 31.7	2	P0–7	All drug-related AEs encountered were reported on the CRF using a scale mild–very serious
Rodriquez et al (31)	1994	?	Mo IR	60 / ? mg	60 / ?	7	P0–7	Possible AEs as a result of drugs administered were recorded using a checklist. Severity was classified by investigators mild to moderate to severe.
van Seventer et al (32)	2003	42 (66) 48 (72)	Mo SR Fe td	60 / 105 mg 25 / 67 mg	60 / 105 60 / 160	7 7	1, 7, 28	Assessed by investigators using scale 1–4 (not at all to very much), questionnaire about bowel function
Suzuki et al (33)	2008	0	Ox CR	10 / 18.9 mg	15 / 28.4	2.3	P0–7	?

Table 2. Continued

Reference	*Year*	*Pretreatment with step 2 opioids number (%)*	*Treatment*	*Dose at start/ dose aftertitration (per 24 h, mean)*	*Dose in oral medd(mg/24 h, mean)*	*Duration of titration (Days)*	*Days or period (p) after start on which aes were reported*	*Assessment of AEs*
Tawfik et al (34)	2004	84 (54)	Fe td	25 / 39.8–43.6 mg	60 / 96–106	28	P0–28	All AEs reported by the patient were recorded and rated by the investigator (mild–severe). Severity of nausea assessed by patient using scale absent–severe. Bowel function was evaluated normal, constipated, diarrhea, stool frequency, bloating, laxative use)
Vielvoye et al (35)	2000	14 (50)	Fe td	25 / 50 mg	60 / 120	28	P0–28	Any AE that was either mentioned by the patient or reported after a nonleading question was noted by the investigator. Severity mild– severe
Vijayaram et al (36)	2000	223 (100)	Mo IR	50 / 140 mg	50 / 140	4	P0–10	Side effects were evaluated by patient report
Xiao et al (37)	2014	?	Ox CR	? / 54–132 mg	? / 81–198	14?	P0–14?	Side effects should be recorded in detail
Zhang et al (38)	2014	?	Mo SR Ox CR	60 / 87.5 mg 20 / 32.4 mg	60 / 87.5 30 / 48.6	? ?	? ?	The adverse reactions were observed

Abbreviations: Mo, morphine; IR, immediate release; Y (?), yes, numbers unknown; IV, intravenous; Fe, fentanyl; td, transdermal; SR, slow release; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life C30; VRS, verbal rating scale; CR, controlled release; Me, methadone; Ox, oxycodone; CRF, clinical registration form; ?, unknown; U, follow-up untill death, mean duration of follow-up unknown; CTC, common toxicity criteria. / signifies titration.
*Median dose.

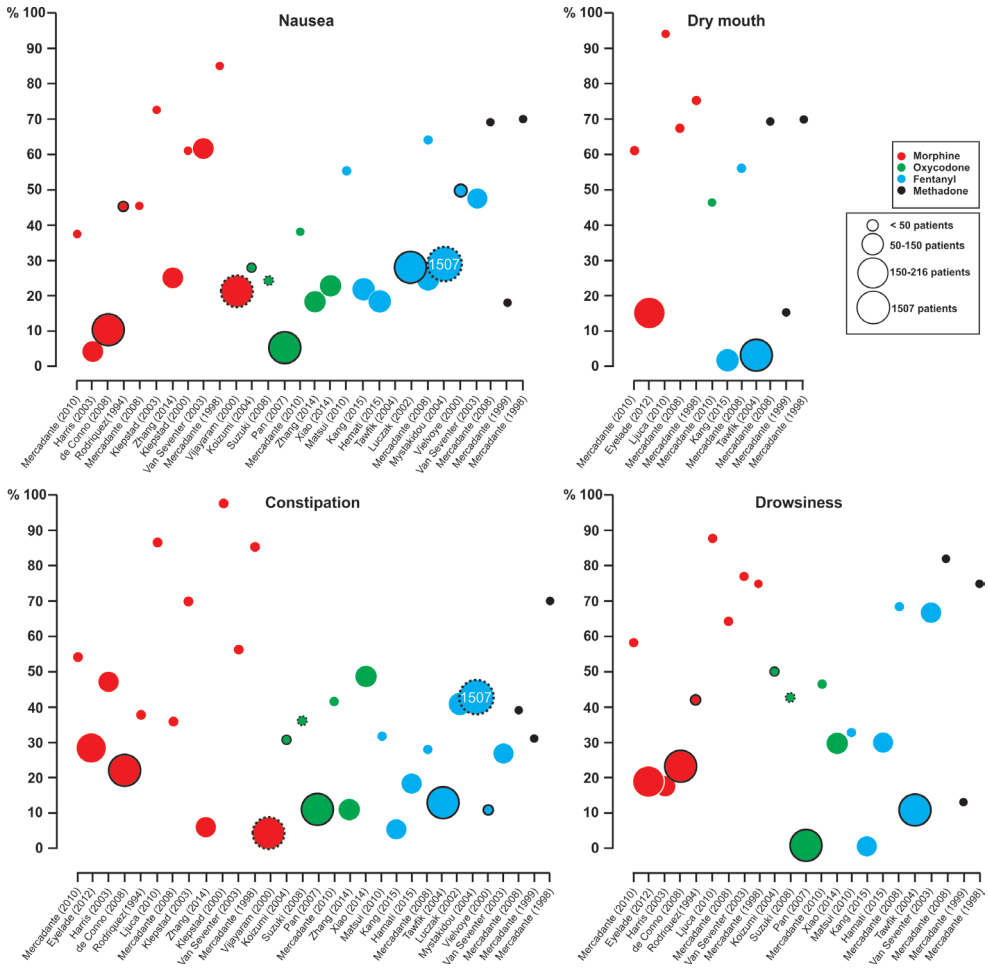

Figure 2. Incidence rates of nausea, dry mouth, constipation, and drowsiness as the percentage of patients with any grade of the AE per study. Studies are arranged per type of opioid and in ascending order of treatment doses (starting and/or doses after titration). For studies reporting only AEs ascribed to treatment, the dots are circled with a solid black ring or a spotted black ring (probably reporting only AEs ascribed to treatment).

Nausea

As shown in Figure 2, the reported rates of occurrence of nausea varied from 3 to 85 % (16, 25). In all treatment cohorts in which only AEs ascribed to the opioid were reported, the occurrence of nausea was ≤50%, whereas in 8 of 20 cohorts reporting all AEs, rates above 50% were reported. Remarkably low rates were reported in the study by Harris et al (16), who reported nausea in 3.5% of patients but vomiting in 14.5%. Because studies are arranged in ascending starting/titration doses from left to right, we see a trend in the morphine studies (red dots) showing higher rates of nausea as treatment doses become higher. An exception is the study by Vijayaram et al (36), who reported a low rate of nausea (21.5%) despite the high morphine doses after titration. In this study, no systematic assessment for AEs was performed, and only AEs spontaneously reported by patients were registered. In the oxycodone, fentanyl, and methadone cohorts, there was less variation in treatment doses; we can see no trend in Figure 2 because the occurrence of nausea varied widely regardless of treatment doses.

At first glance, nausea seems to be less likely to occur in the oxycodone studies. However, low starting and titration doses were used in most of these studies (Table 2), and 3 of the 6 studies reported not all AEs but only AEs ascribed to oxycodone. The heterogeneity among the studies made comparisons between the different opioid types impossible. Although the rates of nausea were high in 2 of 3 methadone studies (25, 27) the rate of nausea was remarkably low in the third methadone study (26), although these studies seemed similar with respect to dose and assessment method.

Vomiting

Although vomiting was explicitly reported in fewer studies compared with nausea, in general, the occurrence of vomiting paralleled that of nausea (data not shown), with a broad range of 4-50%.(20, 30). Four studies reported nausea/vomiting as one AE (17, 27, 36, 37) and in 3 other studies (14, 16, 29) the reported rate of vomiting was higher than for nausea. Based on these data, we were not able to make a comparison between the different opioids.

Constipation

The rate of constipation also ranged widely, from 5 to 97% (19, 36). The pattern of distribution of reported rates was in line with that of nausea. A dose-effect relationship could be seen for the morphine studies and possibly also for the fentanyl studies. The lowest rates were seen in the studies reporting AEs ascribed to opioid treatment (11–38%) and in studies in which no systematic assessment of AEs was performed and only AEs spontaneously reported by patients were given (5–29%) (15, 35, 36). Regarding differences between the types of opioids, in all fentanyl cohorts, the reported percentage of patients

with constipation was <50%, whereas in 6 of 13 morphine cohorts the percentage was > 50% (19, 20, 22, 25, 28, 32). The reported rates of constipation were also low (10.5–49%) in the oxycodone studies, but as mentioned for nausea, treatment doses were low and 3 out of 6 studies reported only AEs ascribed to treatment.

Drowsiness

Drowsiness was reported for 23 treatment cohorts from 18 studies (Figure 2) and the rates ranged from 3 to 88% (18, 22). The rates again seemed highest in the studies with the highest treatment doses. The lowest rates (3–50%) were seen in studies reporting AEs ascribed to the opioid use (14, 21, 30, 31, 33, 34) or in studies reporting only AEs spontaneously reported by patients (15). Compared with the low rates of nausea and constipation in the oxycodone cohorts, the rate of drowsiness was relatively high in 3 of 5 oxycodone studies (43–50%), despite the low treatment doses and the reporting of only treatment-related AEs in 2 of these studies (21, 30).

Dry Mouth

Dry mouth was reported in 12 treatment cohorts from 8 studies (Figure 2), and its occurrence varied from 1 to 94% (18, 22). Despite this huge variation, the rate was ≥48% (median = 68.8%) in 8 of these 12 cohorts. Three studies with low incidence rates (4.5–15.6%) reported either AEs ascribed to the treatment or only AEs spontaneously reported by patients without systematic assessment (15, 26, 34). The reason for the low rate (1%) in the study by Kang et al (18) is unknown to us. Overall, the reported rates of dry mouth are high compared with the rates of the other AEs.

Other AEs

Confusion as an AE after starting opioids was reported only in studies by de Conno et al (14) and Mercadante et al.(25-28), and the reported rates ranged from 7 to 80% (data not shown). Sweating was reported in 4 studies and ranged from 5 to 66% of patients (19, 29). Itching was reported in 6 studies and ranged from 0-9% (24, 36) (data not shown).

We did not find lower rates of AEs in study cohorts pretreated with codeine, tramadol, or dextropropoxyphene compared with cohorts in which the studied opioids were started directly. In general, studies performed in non-Western countries (China, Korea, Iran, India, Nigeria, and Egypt) reported lower rates of AEs compared with studies performed in Western countries and Japan.

Discussion

To our knowledge, this is the first review providing an overview of AEs after starting treatment with morphine, oxycodone, fentanyl, or methadone for cancer-related pain. In general, we found that the occurrence rates of AEs (of any grade) were high, although there was a broad range in reported rates of all AEs. AEs have a negative impact on quality of life, and the number of symptoms has been shown to be associated with heightened psychological distress and poorer quality of life (40). Symptoms that seem to be of particular impact are drowsiness and dry mouth because both have a high prevalence and are rated as moderate to severe by many patients (11, 41). Both symptoms have been shown to be "quite a bit" or more distressing in about 20% of patients experiencing them (40). Drowsiness and other central side effects (hallucinations, confusion) frequently contribute to opioid failure (42, 43). Our data indicated a dose-effect relation, with higher rates of AEs reported in studies with higher opioid starting doses and/or higher doses after titration, but this effect was mainly seen in the morphine cohorts because the variation in treatment doses was less in the studies with fentanyl, oxycodone, and methadone. The striking heterogeneity among included studies made it difficult to compare AEs between the different opioids. Despite this, the rate of constipation seemed to be lower for fentanyl than for morphine, a finding that has previously been reported (3-5, 44). Also, the rate of drowsiness was high in the oxycodone cohorts, especially given the fact that low oxycodone treatment doses were used, which probably explains the low rates of nausea and constipation in these cohorts. However, no definite conclusions can be drawn because despite our inclusion criteria, we were confronted with a large heterogeneity among the included studies, leading to broad ranges of reported rates of AEs. Differences in assessment of and subsequent reporting of AEs seem to be of significant influence on the reported rates of AEs. Studies reporting only AEs ascribed to the studied opioid described lower rates than studies reporting all AEs, regardless of the causality with the studied opioid. This is not surprising, because we know that the prevalence of symptoms that can be seen as side effects of opioid treatment is high in patients with cancer, regardless of their treatment with opioids (11, 12). Also, in studies in which no systematic assessment of AEs was performed and only AEs spontaneously mentioned by patients were reported (15, 35, 36), low occurrence rates were found, especially for constipation and dry mouth. We can speculate that patients mention these AEs less freely than other AEs when no direct assessment is used. Contrary to what we assumed and experience in clinical practice, we could not identify a protective effect of pretreatment with codeine phosphate, dihydrocodeine, dextropropoxyphene, or tramadol. However, if we looked at individual studies in which AEs were reported separately for opioid-naive patients and for patients pretreated with codeine or tramadol, pretreated patients had lower rates of

AEs than opioid naive patients, with the exception of constipation (29, 34, 35). Therefore, the fact that overall rates of AE's were not lower in pretreated versus naive patients is probably due to the heterogeneity between the studies.

Our data are in line with findings from previous studies. In a meta-analysis by Reid et al (45) which included 4 studies, 3 comparing oral oxycodone with oral morphine and 1 comparing oral oxycodone with oral hydromorphone, the rate of nausea ranged from 42 to 74%, constipation from 21 to 70%, dry mouth from 33 to 74%, and drowsiness from 31 to 90% in patients treated with oxycodone, morphine, and hydromorphone. No differences were found in AE profiles. A systematic review on RCTs comparing oral morphine with other opioids or placebo concluded that the lack of data in opioid-naive and nonselected populations limited the ability to draw conclusions. However, similar patterns of side effects were seen for morphine, oxycodone, and hydromorphone (46). A recently published RCT in opioid-naive patients also concluded that side effects between morphine and oxycodone did not differ (43). A meta-analysis of 3 studies comparing fentanyl with morphine (4) showed lower rates of AEs with fentanyl and morphine (nausea, 19–32% with fentanyl and 22–25% with morphine; constipation, 6–30% with fentanyl and 15–55% with morphine; and drowsiness, 17–25% with fentanyl and 19–52% with morphine) than we have found. One (32) of the three studies was also included in our review; the others did not meet our inclusion criteria because of pretreatment with strong-acting opioids, which probably explains the lower rates. In a recent Cochrane review (47) on the impact of morphine, fentanyl, oxycodone, or codeine on patient consciousness, appetite, and thirst, the reported rates of nausea ranged from 14 to 23%, vomiting from 7 to 15%, constipation from 17 to 30%, somnolence from 13 to 24%, and dry mouth from 3 to 47%. This review included only RCTs, and the investigators were also confronted with multiple major problems with AE reporting. The authors call for "the development of definitions for AE's that have a spectrum of severity or importance, and the development of appropriate measurement tools for recording such events to aid clinical practice and clinical research'. research. In 2 other recent Cochrane reviews (44, 48), the investigators conclude that the quality of the evidence is limited because of important risk of bias, and both studies call for the use of standardized outcome measures. This need was further supported in a study showing that the number of symptoms reported using systematic assessment was eightfold higher than the number of symptoms reported spontaneously (49). Also, low agreement has been shown between toxicity rates of chemotherapy reported by physicians (using common toxicity criteria) and patients (using a 4-point Likert scale). Lower rates were reported by physicians, supporting the use of patient reported outcomes (50).

A strength of our review is that we chose to include only patients naive for the opioids studied to minimize bias, because patients with an indication for opioid rotation form a

selection of patients not responding well to the previous opioid(s). This selection criterion meant that no studies with hydromorphone could be included, because in none of the studies was hydromorphone used as a first-line opioid. Because hydromorphone is a potent opioid, usually reserved for patients failing treatment with other types of opioids, this was not unexpected.

We must also acknowledge several limitations. First is our decision not to use a scale, checklist, or tool to assess the quality and risk of bias of selected studies. The use of such tools is advocated, and many exist for the assessment of randomized trials. However, we could not find any tools for the assessment of nonrandomized cohort studies, as were most of the selected studies. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria automatically allocate observational studies as generating (very) low-quality evidence (51). We therefore chose to systematically describe all included studies. Also, because AEs were seldom the primary outcome of included studies, we were not able to study the incidence of AEs because some studies reported all symptoms, whereas others reported only symptoms probably related to the opioids. We were therefore able to describe only the occurrence rates of side effects. Despite the large variation in study size, we weighed all studies equally because there were many other differences in possible influencing factors among the studies. Nevertheless, we made the variation in study size visible in Figure 2. Also, we excluded studies in which AEs were reported as changes in mean or median symptom intensity only, although this is probably the most reliable method for assessment, assuming that other causes of symptoms remain stable. Because these studies did not report the number of patients with AEs, we could not compare them with the other studies. Furthermore, the number of studies using symptom intensity scales was too small to make a separate comparison on the occurrence of mild versus moderate to severe AEs. Another limitation is the inevitable heterogeneity in patient populations. Study populations differed in patient characteristics (ie, tumor type, gender, race, body weight) and concurrent treatments (comedication, chemotherapy, and radiotherapy). However, data were too scarce to include these characteristics in this review.

Nausea, vomiting, constipation, drowsiness, and dry mouth are the most reported AEs in patients with cancer-related pain starting with morphine, oxycodone, fentanyl, or methadone; rates of these AEs were found to be high. There seems to be a dose-effect relation, with high starting doses and/or higher doses after titration leading to more side effects. There is a lack of well-performed clinical studies in patients with cancer-related pain in which a systematic assessment with validated scoring systems for AEs is used. Although side effects are important in daily clinical practice, data are insufficient and the true incidence of side effects is still unknown. Future studies should use standardized methods for the assessment and reporting of AEs; consensus on the use of these assessment methods is eagerly awaited.

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Chapter 4

Treatment with subcutaneous and transdermal fentanyl: results from a population pharmacokinetic study in cancer patients

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Abstract

Purpose:

Transdermal fentanyl is effective for the treatment of moderate to severe cancer-related pain but is unsuitable for fast titration. In this setting, continuous subcutaneous fentanyl may be used. As data on the pharmacokinetics of continuous subcutaneous fentanyl are lacking, we studied the pharmacokinetics of subcutaneous and transdermal fentanyl. Furthermore, we evaluated rotations from the subcutaneous to the transdermal route.

Methods:

Fifty-two patients treated with subcutaneous and/or transdermal fentanyl for moderate to severe cancer-related pain participated. A population pharmacokinetic model was developed and evaluated using non-linear mixed-effects modelling. For rotations from subcutaneous to transdermal fentanyl, a 1:1 dose conversion ratio was used while the subcutaneous infusion was continued for 12 h (with a 50% tapering after 6 h). A 6-h scheme with 50% tapering after 3 h was simulated using the final model.

Results:

A one-compartment model with first-order elimination and separate first-order absorption processes for each route adequately described the data. The estimated apparent clearance of fentanyl was 49.6 L/h; the absorption rate constant for subcutaneous and transdermal fentanyl was 0.0358 and 0.0135 h-1, respectively. Moderate to large inter-individual and inter-occasion variability was found. Around rotation from subcutaneous to transdermal fentanyl, measured and simulated plasma fentanyl concentrations rose and increasing side effects were observed.

Conclusions:

We describe the pharmacokinetics of subcutaneous and transdermal fentanyl in one patient cohort and report several findings that are relevant for clinical practice. Further research is warranted to study the optimal scheme for rotations from the subcutaneous to the transdermal route.

Introduction

For the treatment of moderate to severe cancer-related pain, strong opioids are the treatment of choice (1, 2). Fentanyl is a synthetic opioid with a high affinity for the μ-opioid receptor and is 75-100 times more potent than morphine (3, 4). According to international guidelines, fentanyl is not the opioid of first choice (2), but nonetheless, it is widely used for the treatment of cancer-related pain. Fentanyl is recommended in patients with renal failure (2). Furthermore, because the incidence of constipation is lower in fentanyl compared to morphine (5-7) and it can be administered through a patch, it is a popular drug for the treatment of cancer-related pain. Fentanyl can also be used if an opioid rotation is necessary after failure on another type of opioid. Its low molecular weight and high lipid solubility make it suitable for transdermal delivery (8). Although the first patches used a reservoir design carrying risks of drug leakage or abuse, currently available patches have a matrix design. They release fentanyl at a proposed rate of 12.5–100 μg/h and the amount delivered is proportional to the surface area of the patch. As a gradient is needed between the patch and the skin, the patch contains more fentanyl than is released. A mean bioavailability of 92% (57–146%) has been reported (9). Reservoir and matrix patches and different types of matrix patches have been shown to have similar pharmacokinetic profiles (10, 11). The slow decrease in fentanyl concentrations after transdermal patch removal and the delay before achieving the maximum plasma concentrations (both reflecting slow release of fentanyl) make transdermal fentanyl (patches) unsuitable for fast titration in patients with severe pain. In this setting, parenteral titration is therefore preferred. Subcutaneous administration has been proven to be safe and effective (12, 13) and has advantages over the intravenous route as no vascular access is needed, making it easier to change sites and avoiding complications associated with indwelling intravenous catheters. In addition, subcutaneous administration can also be applied safely in an out-of-hospital-setting (14).

In our cancer institute, patients with severe pain are preferably titrated with continuous subcutaneous opioids, and in this setting, fentanyl is frequently used. However, little is known about the pharmacokinetics of subcutaneously (sc) administered fentanyl as opposed to the transdermal (td) route. As part of a larger prospective pharmacologic opioid project, we studied the pharmacokinetics of fentanyl in hospitalized cancer patients with moderate to severe cancer-related pain. The purpose was to study the pharmacokinetics of fentanyl administered via the subcutaneous and transdermal routes to cancer patients. A second aim was to evaluate rotations from the subcutaneous to the transdermal route.

Patients, materials and methods

Between January 2010 and November 2013, patients admitted to the Erasmus MC Cancer Institute (Rotterdam, The Netherlands) and treated with fentanyl for moderate to severe cancer-related nociceptive pain were asked to participate in the study. Fentanyl Sandoz® Matrix patches were used in available doses of 12/25/50/75/100 µg/h and patches could be combined. Patches were applied to the chest wall or upper arm and were replaced every 72 h. The starting dose in opioid-naive patients was 12 µg/h and doses in other patients were based on previous treatment. In case of severe pain, patients were titrated by continuous sc infusion with the possibility of an extra bolus every hour. The dose of the bolus usually parallels the dose given per hour. Doses were titrated based on clinical effects. When pain control was reached and doses were stabilized, patients could be rotated to fentanyl (td) patches depending on the clinical setting. For the rotation of sc to td fentanyl, a 1:1 dose conversion ratio was used, based on data from previous studies (15, 16). After applying the patch, the sc administration was continued in the same dose for 6 h, after which 50% of the dose was given during an extra 6 h (17). After 12 h of patch application, the sc administration was stopped. Patients treated with a patch were prescribed medication for the treatment of breakthrough pain, mostly oral morphine or oxycodone in an immediate release formulation but not rapid onset opioids. For all patients, co-medication was screened for the concurrent use of strong CYP3A4 inhibitors or inducers. Also, liver function was checked based on the laboratory values of bilirubin, alanine aminotranferase (ALT), aspartate aminotransferase (AST) and albumin. The study was approved by the medical ethics review board (MEC 09.332) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. The trial was registered in the Dutch Trial Register (Trial registration ID: NTR4369).

Pharmacokinetic sample collection

Patients were included in the study as soon as possible after admission to the ward or after the start of fentanyl. Blood samples for pharmacokinetic analysis were taken during a maximum of 72 h after the start of fentanyl and after each change in the opioid regimen (dose, route of administration). The protocol prescribed sampling twice a day, around 8 am and 8 pm, a baseline plasma sample before every change in the regimen and a series of samples maximally once a day around the administration of an extra subcutaneous bolus at baseline, 5, 15, 30 and 60 min after administration. Samples were collected using potassium EDTA tubes. After centrifugation of the tube, the supernatant was collected and stored at 70 °C until analysis at the laboratory of Translational Pharmacology (Erasmus MC Cancer Institute).

Measurements of fentanyl plasma concentrations

Fentanyl in plasma was quantitated using a validated UPLC-MS/MS method consisting of a Waters Acquity UPLC sample manager coupled to a triple quadruple mass spectrometer operating in the multiple reaction monitoring mode (MRM) with positive ion electrospray ionization (Waters, Etten-Leur, The Netherlands). The multiple reaction monitoring transitions was set at 337 → 188 for fentanyl and 342 → 188 for the internal standard fentanyl-d5.

Chromatographic separations were achieved on an Acquity UPLC® BEH C18 1.7 µm 2.1 x 100 mm column thermostated at *T*=50 °C. A gradient at a flow rate of 0.350 mL/min was achieved with mobile phase A, composed of 2 mM ammonium formate and 0.1% formic acid, and mobile phase B, composed of methanol with 0.1% formic acid. A linear gradient was used, with 90% mobile phase A from 0-0.50 min followed by 90–0% mobile phase A, from 0.50 to 2 min, holding on 0% mobile phase A (i.e. 100% mobile phase B) for 2 min. This was succeeded by a linear gradient back to 90% mobile phase A from 4.0 to 4.1 min, which was held for 1.9 min to re-equilibrate. The overall cycle time of the method was 6 min. The calibration curves were linear over the range of 0.100 to 10.0 ng/mL with the lower limit of quantitation validated at 0.100 ng/mL for fentanyl. The extraction of 200 µL of plasma involved a deproteinization step with 100 µL of internal standard solution in acetonitrile and 100 µL of acetone followed by a simple liquid–liquid extraction with 1-mL ethyl acetate after the addition of 100 µL of 4% ammonium hydroxide. For fentanyl (linear calibration range 0.100–10.0 ng/mL), the within- and between-run precisions at five tested concentrations, including the lower limit of quantitation (LLQ), were ≤5.52 and ≤6.12%, respectively, while the average accuracy ranged from 88.5 to 94.0%. No adsorption of fentanyl was observed to the sampling and/or storing tubes. The inter-day coefficient of variation (CV) at five tested concentrations, including the LLQ, were ≤7.5% in individual validation runs.

Population pharmacokinetic model for fentanyl

The analysis of log-transformed concentration–time data was carried out with non-linear mixed-effects modelling in NONMEM (version 7.3; Icon Development Solutions, Hanover, MD) by means of the first-order conditional estimation method with or without eta-epsilon interaction (18). Model building was assisted by Perl-speaks-NONMEM (PsN version 4.2.0, http://psn.sourceforge.net/) (19, 20) and the graphical evaluation with R (version 3.0.3, http://www.r-project.org/) and Xpose (version 4.4.1, http://xpose.sourceforge.net/) (21).

As a starting point, a one-compartment model with first-order absorption preceded by a lag time was used. Several model components were evaluated, including one- versus two-compartment disposition models, alternative absorption models following transdermal administration (first- versus zero-order), differences between the two administration

routes in absorption parameters, i.e. absorption rate constant (*k*a) and lag time (*t*lag), and inclusion of allometrically scaled body weight on disposition parameters. Concentrations below the lower limit of quantification comprised less than 1% of the data and were discarded from the analysis.

Inter-individual variability (IIV) in pharmacokinetic parameters was modelled using log-normal models. An occasion was defined as a transdermal dose followed by at least one observation, and inter-occasion variability (IOV) was evaluated on absorption parameters as proposed by Karlsson and Sheiner (22):

$$P_{ik} = P \cdot e^{\eta i + \kappa ik}$$

where P_{ik} represents the parameter *P* for the *i*th individual on occasion *k*, *P* is the typical parameter for the studied population, η_i is the patient-specific random effect describing the discrepancy between the typical and individual parameter and κ_{ik} is the random effect accounting for the IOV. η_i and κ_{ik} are assumed to be normally distributed with mean zero and estimated variance ω^2 and π^2, respectively.

Alternative residual error models were evaluated, including homoscedastic or heteroscedastic residual errors as well as a model combining both types of error.

Model evaluation

The selection between alternative models during the modelling process was based on scientific plausibility and statistical significance. Statistical evaluation comprised the analysis of goodness-of-fit plots, precision of parameter estimates, condition number and the likelihood ratio test based on the change of the objective function value (OFV). The OFV is given by minus twice the log likelihood, and a difference in OFV (ΔOFV) between nested models is approximately χ^2 distributed. A ΔOFV of 3.84, 6.64 and 10.8 corresponds to *p* values of 0.05, 0.01 and 0.001, respectively, when one parameter is added to the model (1 *df*). The Akaike information criterion (AIC) was used to compare non-hierarchical models. The magnitude of η- and ε- shrinkage was computed according to Karlsson and Savic (23) to judge the reliability of various diagnostic plots. The uncertainty of parameter estimates was assessed using the non-parametric bootstrap procedure in PsN (1000 bootstrap datasets). The predictive performance of the final model was evaluated with a population prediction-corrected visual predictive check (pcVPC) through 1000 simulations of the dataset (24).

Results

Patients

Plasma samples for pharmacokinetic analysis were available for 52 patients (Table 1). Three patients participated in the study twice. Treatment with td and sc fentanyl in relation to the observations for all patients is shown in Supplemental figure 1. In 13 patients, samples were available during sc treatment without previous td administration; in 9 patients, samples were available during treatment with td fentanyl without previous or concurrent sc treatment, and in 32 patients, samples were available during treatment with sc or td fentanyl, but the other treatment route was given until shortly before sampling (semi-simultaneous treatment) or simultaneously. The majority of patients (*n*=33) already used transdermal fentanyl before admission. In total, 942 fentanyl plasma samples were

Table 1. Patient characteristics

Characteristics (n=52)	*No. (%)*
Median age (years) – range	63 (23-80)
Sex	
Male	33 (63)
Female	19 (37)
Race	
Caucasian	47 (90)
Other	1 (2)
Unknown	4 (8)
WHO performance status	
0	0
1	19 (37)
2	17 (33)
3	4 (8)
Unknown	12 (23)
Median body mass index –range	25 (18-40)
Median NRS in rest at start of fentanyl or on admission – range	5 (2-10)
Primary tumour localization	
Breast	8 (15)
Colorectal	5 (10)
Prostate	7 (13)
Soft tissue sarcoma/GIST	6 (12)
Urinary tract (including the kidney)	8 (15)
Other	18 (35)
Median albumin – range	39 (29-49)
Median AST (U/l) – range	31 (13-216)
Median ALT (U/l) – range	22 (7-131)
Median total bilirubin (umol/L) - range	7 (3-16)

available with a median of 15 sparse samples per patient (range 1-86) and a median concentration of 1.33 ng/mL (range 0.122–10.7 ng/mL). One patient used a strong CYP3A4 inducer — carbamazepine 200 mg — during his study period. In none of the patients, the combination of AST and/or ALT above upper limit of normal (ULN), bilirubin above ULN and albumin below lower limit of normal was found, and therefore it was concluded that none of the patients had liver failure. Doses for the transdermal route varied from 12 to 400 µg/h (median 50 µg/h), and doses for the continuous subcutaneous infusion ranged from 10 to 300 µg/h (median 75 µg/h).

Fentanyl pharmacokinetics

The pharmacokinetics of fentanyl-administered sc and td were best described by a one-compartment model with first-order elimination and separate first-order absorption processes for each route. The residual error was most adequately described by a heteroscedastic model parameterised as an additive model on the log-scale. Due to the sparse sampling design, we were unable to estimate all model parameters satisfactorily, particularly with respect to parameters describing the absorption part. Hence, the apparent volume of distribution (*V/F*) was fixed to 280 L (25). A sensitivity analysis carried out with values of *V/F* ±50% fixed in 10% increments showed the model to be insensitive to the value and other parameter estimates to be stable within the tested range, with only t_{lag} and *k*a,sc varying slightly (less than ±25% deviation from the final PK parameter values). Inclusion of allometrically scaled body weight on CL/*F* and *V/F* was found to explain some variability and was kept to increase model stability. The final population model parameters including bootstrap results are presented in Table 2.

The estimated population value for CL/*F* in a 70-kg subject was 49.6 L/h. The estimation of a t_{lag} for td administration led to an improvement of the model fit (*p* value <0.001) with the final value of 4.73 h. In contrast, the inclusion of a *t*lag was not relevant for sc administration. The model was compared with a model with zero-order absorption for td fentanyl, and the AIC was clearly in favour of the first-order absorption (AIC more than 60 points lower). The estimated absorption rate constant for subcutaneous fentanyl was 0.0358 h-1 and for transdermal fentanyl 0.0135 h-1.

IIV was included on k_a for both routes (93.5 and 42.4 % for sc and td, respectively), td bioavailability and apparent clearance (CL/*F*). Bioavailability of td fentanyl was allowed to differ between individuals with an estimated variability of 42.3%. IOV on td *k*a resulted in a significant improvement of the model ($p < 0.01$) with an estimated value of 32.8 %. The consequence for rate and extent of absorption following td administration, given these characteristics, is illustrated in Figure 1.

Table 2: Typical population pharmacokinetic parameter estimates for subcutaneous and transdermal fentanyl and bootstrap analysis results

Parameter (units)	*NONMEM estimate*	*(%RSE)*	*Bootstrap mean*	*(95% CI)a*
Structural model parameters				
k_a subcutaneous (h^{-1})	0.0358	(24.4)	0.0374	(0.0248, 0.0555)
t_{lag} transdermal (h)	4.73	(21.2)	4.65	(2.25, 6.98)
k_a transdermal (h^{-1})	0.0135	(16.8)	0.0140	(0.0105, 0.0188)
V_{70kg}/F (L)[b]	280	(fix)	-	
CL_{70kg}/F ($L.h^{-1}$)[c]	49.6	(9.36)	50.4	(40.9, 61.6)
Inter-individual variability (%CV)				
k_a subcutaneous	93.5	(15.2[d])	91.1	(59.6, 119)
F transdermal	42.3	(30.0[d])	45.7	(19.7, 67.8)
k_a transdermal	42.4	(23.9[d])	41.4	(10.5, 59.2)
CL/F	43.2	(15.2[d])	41.6	(27.1, 53.9)
Inter-occasion variability (%CV)				
k_a transdermal	32.8	(51.1[d])	39.2	(12.0, 77.0)
Residual unexplained variability (%CV)				
Proportional residual error	23.4	(5.17[e])	23.2	(20.6, 25.6)

[a] Mean and 95 % bootstrap percentile confidence intervals. Runs with estimates near a boundary (n = 150), rounding errors (n = 165) or crashed (n = 3) were skipped when calculating results.

[b] V_{70kg}/F= 280 x (WT/70)

[c] CL_{70kg}/F= estimate x $(WT/70)^{0.75}$

[d] %RSE is reported on the approximate standard deviation scale (standard error/variance estimate)/2. η-shrinkage for inter-subject variability ranged between 14.6-48.4% and η-shrinkage for inter-occasion variability was >35%

[e] *ε-shrinkage was 5.97%.*

[f] The condition number of the final model was 24.99.

CI, confidence interval; CL_{70kg}/F, apparent clearance for a subject with 70 kg; *%CV*, percent coefficient of variation, reported as sqrt(variance) x 100%; *F* bioavailability; *k*a, absorption rate constant; *%RSE*, relative standard error; t_{lag}, absorption lag time; V_{70kg}/F, apparent volume of distribution for a subject with 70 kg; *WT*, weight (kg).

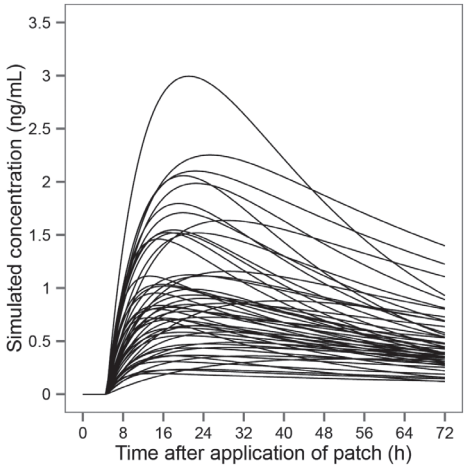

Figure 1. Stochastic simulation of fentanyl plasma concentrations versus time after application of a transdermal patch with a delivery rate of 50 µg/h in 52 patients.

The model was found to describe the observed concentrations well (Figure 2). The performance of the model to predict median concentrations was good as illustrated by a pcVPC shown in Figure 3. Additional goodness-of-fit plots can be found in Supplemental data.

Evaluation of rotations from subcutaneous to transdermal fentanyl

For 14 patients, multiple plasma samples were available shortly before and after rotation from sc to td fentanyl using the 12 h scheme. In 12 of these patients, a rise in plasma fentanyl concentrations was seen after application of the first patch. Furthermore, the intensity of side effects increased in 9 patients while in 3 patients, severe fentanyl-related toxicity occurred, necessitating adjustment of treatment. The severe toxicity consisted of respiratory depression, severe drowsiness and nausea.

By using the final model, fentanyl plasma concentrations expected around and after rotation were predicted for a population of 52 patients through stochastic simulation. Figure 4 illustrates plasma fentanyl concentrations during the rotation from a sc infusion of 50 µg/h to a td patch with a delivery rate of 50 µg/h using the 12-h scheme. After the application of the td patch, the simulated median peak concentration is higher than the steady-state concentration of subcutaneous fentanyl. In addition, concentrations immediately after the end of the rotation scheme, i.e. 12 h after the application of the patch, are very variable with the 10^{th} and 90th percentiles equal to 0.87 and 3.22 ng/mL (median value 1.68 ng/mL). Simulated fentanyl plasma concentrations using a 6-h scheme (26) produced similar results, and comparative plots can be found in Supplemental data.

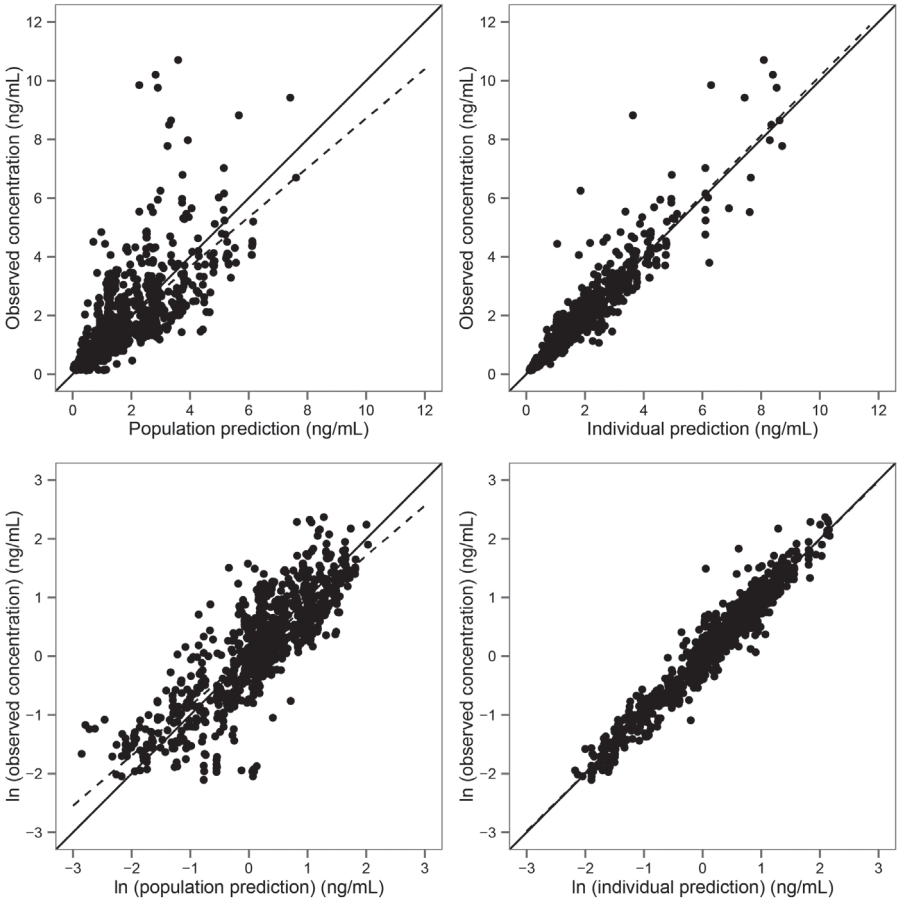

Figure 2. Goodness-of-fit plots for the final model. Observed fentanyl plasma concentrations versus population predictions (*left panels*) and individual predictions (*right panels*) in normal (*top panels*) and logarithmic scale (*bottom panels*). The *solid line* represents the line of identity ($x = y$) and the *dashed line* represents a linear regression line.

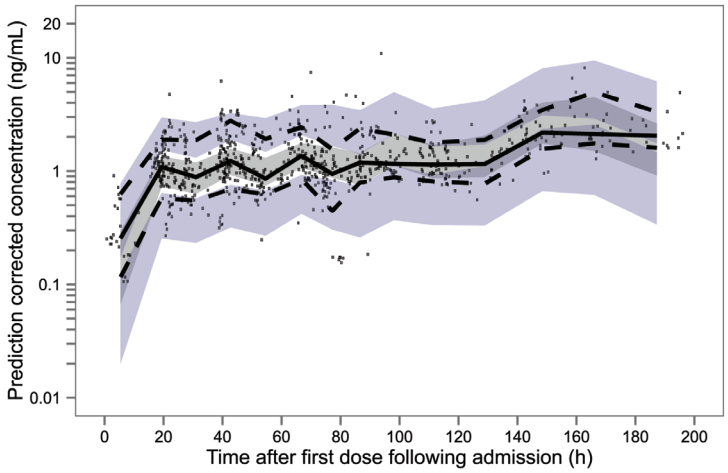

Figure 3. Population prediction-corrected visual predictive check for the final model for subcutaneous and transdermal fentanyl. The *x*-axis represents the time after the first recorded dose of fentanyl after admission. Dots are the population predicted-corrected individual observations, and the *solid* and *dashed lines* represent the median and the 10th and 90th percentiles of the observed data, respectively. The *shaded areas* represent the simulation-based 95% confidence interval for the simulated data percentiles.

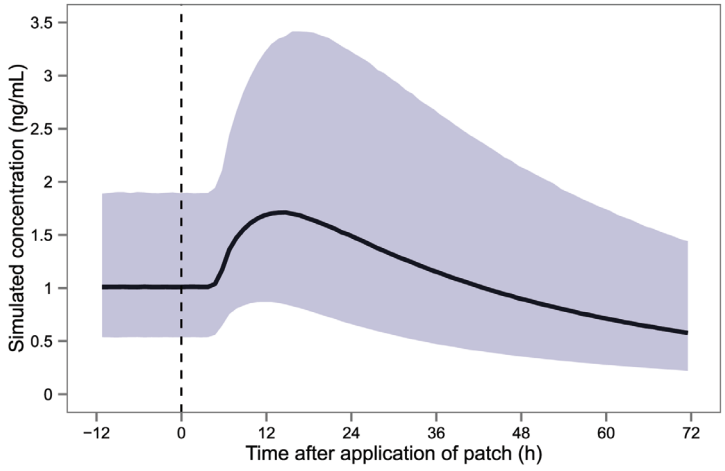

Figure 4. Simulated fentanyl plasma concentrations during the rotation from a subcutaneous infusion of 50 µg/h at steady state to a transdermal patch with a delivery rate of 50 µg/h using the 12-h scheme (1000 simulations of 52 subjects). Following this scheme, the subcutaneous administration is continued in the same dose for 6 h after applying the transdermal patch, after which 50% of the dose is given during an extra 6 h. The simulated *solid line* represents the median of the simulated data, and the *shaded area* represents the 80 % prediction interval. The vertical dashed line (schuin) represents the time of patch application.

Discussion

This prospective study in Caucasian cancer patients treated with fentanyl provides us with new insights into the pharmacokinetics of fentanyl which are relevant for clinical practice. Firstly, we developed a population pharmacokinetic model for sc and td fentanyl from a high number of sparse samples in this patient cohort. We found that a one-compartment model adequately describes the pharmacokinetics of sc and td fentanyl, similarly to the results of previous studies with td fentanyl (27, 28). We were able to distinguish inter-individual variability between absorption and elimination pharmacokinetic parameters that along with inter-occasion and residual variability explain the high variability in plasma concentrations and possibly also clinical effects.

Similar PK models have been described following td administration previously (27, 28). In our study, the CL/F was estimated to 49.6 L/h, which is similar to the values of 40.8 and 42.4 L/h obtained in previous PK studies (10, 29). Furthermore, in line with previous models, the absorption from td patches over 72 h was found to be closer to a first-order than to a zero-order process, with a potential to lead to fluctuations in plasma concentrations during treatment. Indeed, fluctuation in plasma concentrations has been reported in several studies (30-33); however the clinical relevance of this finding was never widely acknowledged. In clinical practice, however, many patients report either lower pain scores and/or more side effects after patch change, and on the other hand, worsening of pain during the third day, a patch is used (16, 34).

The estimated absorption rate constant and absorption lag time are in agreement with the values found by Bista et al. (28) (0.013 h^{-1}, k_a) and Kokubun et al. (27) (0.0145 h^{-1} and 4.93, k_a and lag time) for td fentanyl. Such slow absorption relative to elimination (absorption and elimination half-lives 51.3 h and 3.91 h, respectively) results in that the decline in plasma concentrations after achieving the peak following transdermal administration reflects absorption rather than elimination. The *t*max predicted by our model in a typical patient was about 20.5 h after the administration of a patch. This value is known to vary substantially between patients and values in the range 12–48h have been reported (35). The td absorption with large variability is illustrated in Figure 1.

For sc fentanyl, published PK data are limited. In the only other study in patients treated with continuous infusion of sc fentanyl, only one plasma sample was taken showing considerable variability, but no PK parameters were presented (36). Capper et al. (37) described the pharmacokinetics of fentanyl after a bolus of 200 µg fentanyl sc in nine healthy volunteers and reported a CL/*F* of 53.7 L/h, similar to our estimate, and a rapid absorption (*t*max 10–30 min). We found a slow absorption with substantial IIV in a situation in which fentanyl dosages were titrated using continuous infusion with extra boluses as needed for pain control. The estimation of a separate *k*a following sc boluses was tested

but not supported by the data. In addition, the model was evaluated with a fast absorption process following sc administration by fixing *k*a for this route (2 h-1). However, goodness-of-fit plots and the fit of the model was statistically significantly worse ($p < 0.001$). In four patients in our study, plasma samples were available after stopping sc fentanyl because of rotation to another type of opioid. In all, a slow decrease in fentanyl plasma concentrations was noticeable which supports our data. It may be that also after subcutaneous treatment, some subcutaneous dose depot is formed, as has been reported for td fentanyl (9), but there are no firm data following sc infusion. Thus, our model describes sc infusion data, but mechanistic conclusions should not be drawn. However, if the absorption would be that slow, it suggests that continuous fentanyl is less suitable for fast titration.

High to moderate variability in PK parameters and plasma concentrations has been reported before for td fentanyl, but literature on sc fentanyl is scarce. Kokubun et al. and Bista et al. (28) estimated moderate IIV on CL/*F* to 43.5 and 38.5%, respectively, following td patches. Although there are differences in patch type (reservoir versus matrix) and study populations, i.e. regarding the amount of sc fat/body mass index and hepatic metabolism, IIV was in agreement with our estimate of 43.2%. The IIV on *k*a in the study of Kokubun was substantially greater (71.9 %) than the 42.4 % we obtained, but we also found different occasions as a significant source of variability (IOV, 32.8 %). Other studies have reported substantial variation in bioavailability (range 60 to 97 %), in the measured rate of absorption (e.g. 12.5 to 60.4 µg/h with a patch of 50 µg/h) (29) and in inter- and intra-subject variability in plasma fentanyl concentrations (50.7 and 34.4 %, respectively) (30).

Lastly, this is to our knowledge the first evaluation of rotations from sc to td fentanyl, using the scheme described by Kornick et al. (17) who studied rotations from the intravenous (iv) to the transdermal route. More recently, a scheme using a two-step taper of iv fentanyl in 6 h was found to be safer than the 12-h method (26). In a PK study by the same group, using the 6-h scheme, a rise in plasma concentrations was seen after 3 h but without adverse effects (38). According to the current study, the use of the 12-h scheme, and a 1:1 dose conversion may lead to a rather steep rise in plasma concentrations for some patients and clinically evident toxicity. Based on the final model, we simulated rotations using the 6-h scheme. This scheme may also lead to a rise in plasma levels and therefore potential toxicity. This is probably caused by the fact that plasma concentrations fall slower after stopping a sc administration than after an iv administration and by the finding that absorption following td administration appears to follow a first-order process. For confirmation of our findings, we have planned a prospective pharmacokinetic evaluation study of different rotation schemes without overlap of routes and with or without dose reduction of the first patch.

Strengths of our study are the longitudinal data that we assembled in one patient cohort and the large number of samples available for PK analysis. One limitation in our study

was that, although we were able to estimate IIV and IOV variability in PK parameters, due to a limited sample size, we did not investigate possible sources of variability through covariate modelling. Furthermore, due to semi-simultaneous administration following different routes of administration, the observed concentrations were the sum of those obtained following each route. Especially, many patients started on sc fentanyl after hospital admission while they already used fentanyl td at home, and sc bolus injections for rescue were frequently administered over the full study period. Although the semi-simultaneous administration was accounted for in modelling, the study design was not optimal for modelling purposes.

In conclusion, this study describes the pharmacokinetics of sc and td fentanyl in one patient cohort. Findings relevant for clinical practice are the moderate to large IIV and IOV and that absorption following td administration potentially may lead to fluctuations in plasma concentrations. Furthermore, published rotation schemes for rotations from intravenous to transdermal fentanyl might not be applicable on rotations from subcutaneous to transdermal fentanyl.

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Supplemental material

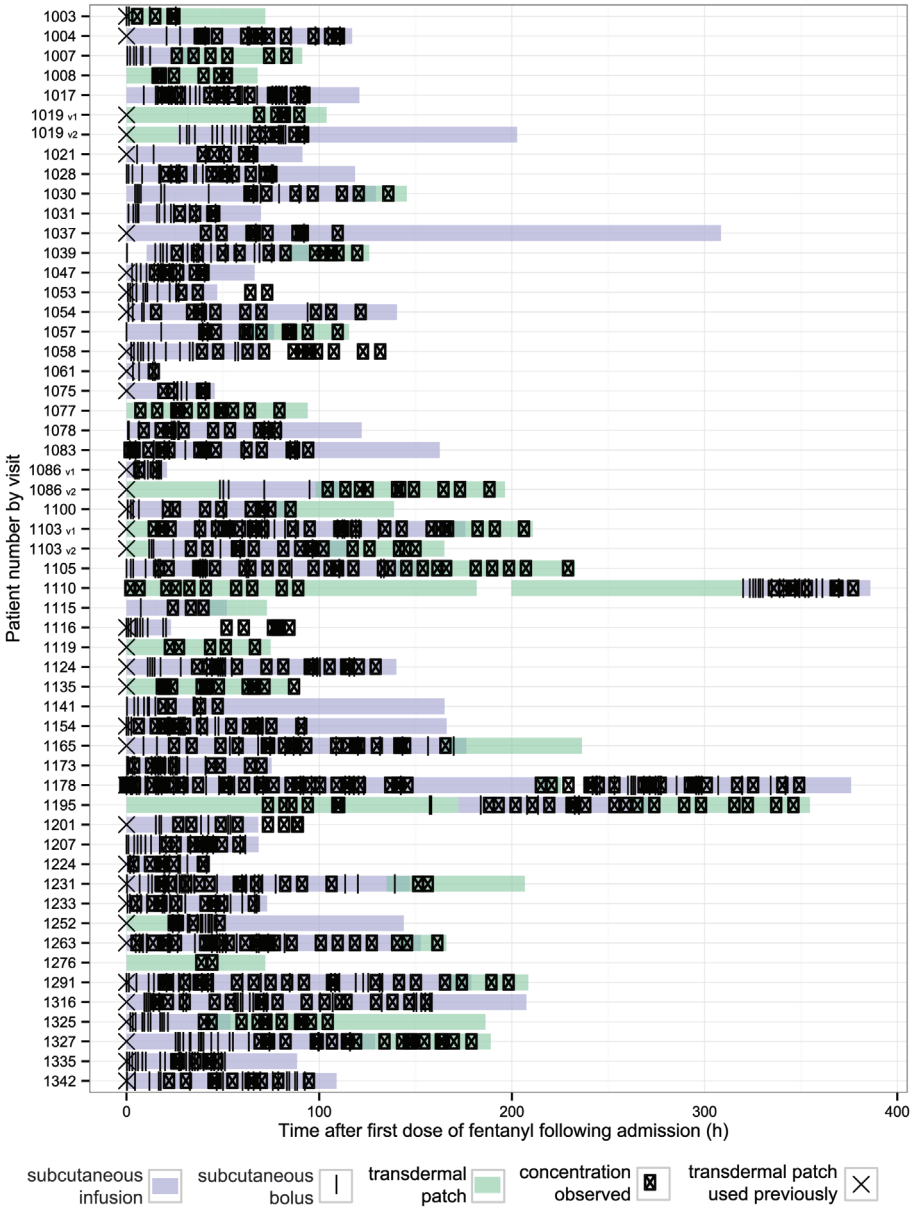

Figure 1. Treatment with transdermal and subcutaneous fentanyl in relation to the observations for all patients.

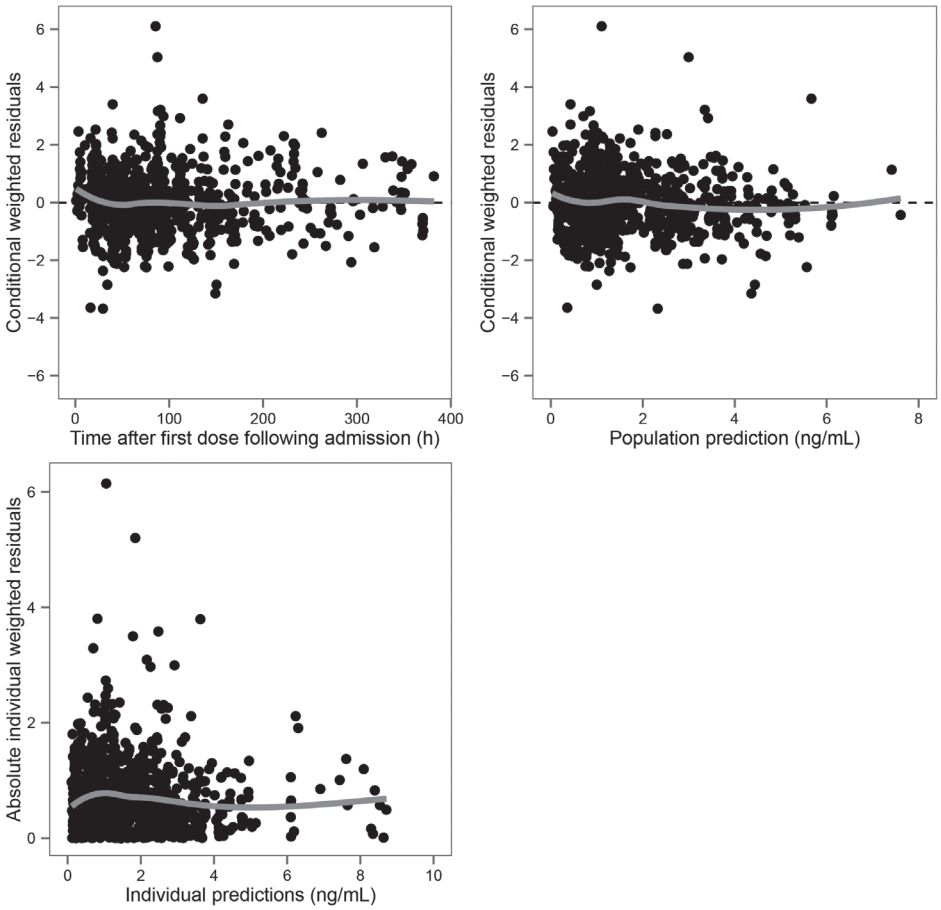

Figure 2. Additional goodness-of-fit plots for the final model. Conditional weighted residuals versus time after the first recorded dose of fentanyl following admission (upper left panel), conditional weighted residuals versus population predictions (upper right panel) and absolute individual weighted residuals versus individual predictions (lower left panel). The grey line is a tendency line.

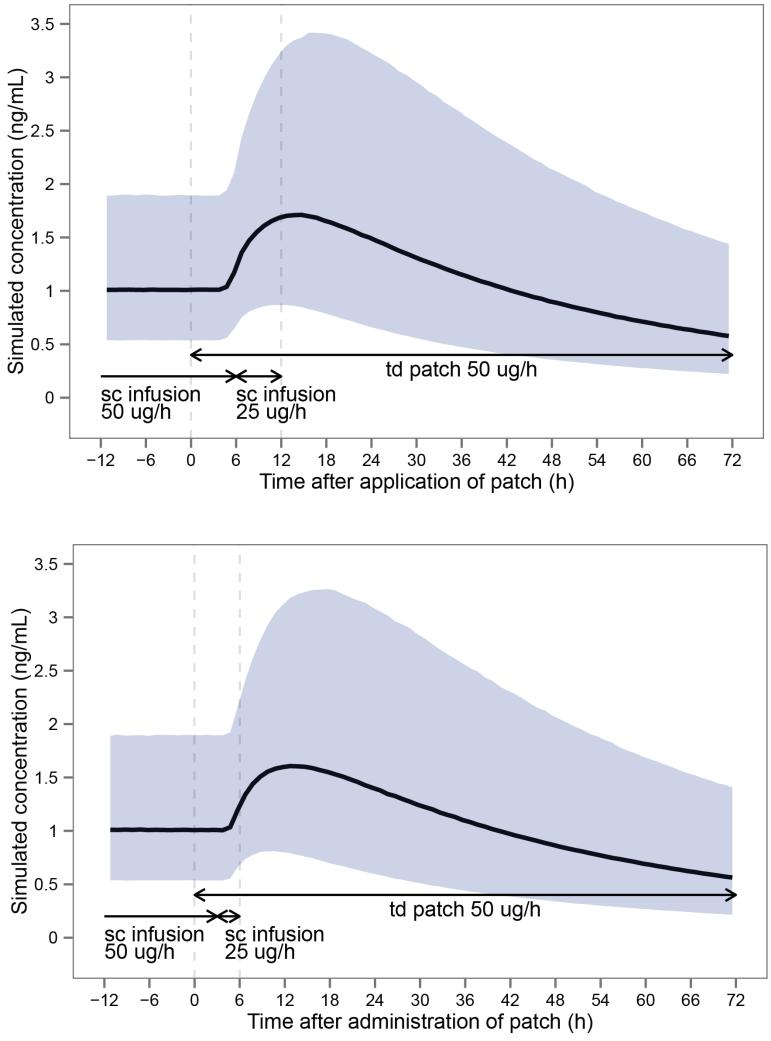

Figure 3. Simulated fentanyl plasma concentrations during the rotation from a subcutaneous (sc) infusion of 50 µg/h at steady-state to a transdermal (td) patch with a delivery rate of 50 µg/h using the 12-hour scheme (upper panel) and the 6-hour scheme (lower panel). In the 12-hour scheme, the sc administration is continued in the same dose for 6 hours after applying the td patch, after which 50% of the dose is given during an extra 6 hours. In the 6-hour scheme, the sc administration is continued in the same dose for 3 hours after applying the td patch, after which 50% of the dose is given during an extra 3 hours. The vertical dashed lines represent the start and the end of the rotation scheme. The simulated solid line represents the median of the simulated data and the shaded area represents the 80% prediction interval (1,000 simulations of 52 subjects).

Chapter 5

A prospective population pharmacokinetic study on morphine metabolism in cancer patients

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Abstract

Background & Objectives:

Oral and subcutaneous morphine is widely used for the treatment of cancer-related pain. However, solid pharmacokinetic data on this practice are lacking. Furthermore, it is largely unknown which factors contribute to the variability in clearances of morphine and its metabolites and whether morphine clearance is related to treatment outcome.

Methods:

Blood samples from 49 cancer patients treated with oral and/or subcutaneous morphine were prospectively collected and used to develop a population pharmacokinetic model for morphine, morphine-3- and 6-glucuronide (M3G, M6G). The influence of age, gender, renal function and several polymorphisms possibly related to the PK of the three compounds was investigated. The relation between treatment failure and morphine and metabolite clearances was explored.

Results:

A one-compartment model including an extensive first-pass effect adequately described the morphine and metabolites data. Estimated mean AUC ratios following oral vs. subcutaneous administration were: M3G/Morphine 29.7:1 vs. 11.1:1; M6G/Morphine 5.26:1 vs. 1.95:1; M3G/M6G 5.65:1 vs. 5.70:1. Renal function was significantly correlated with clearance of the metabolites, which increased 0.602 L/h per every 10 mL/min/1.73 m^2 increase of eGFR, reaching a plateau for eGFR > 90 mL/min/1.73 m^2. The clearance of morphine or metabolites was not found to be correlated with treatment failure.

Conclusion:

Influence of age, gender and PK related polymorphisms was not identified on the PK of morphine. Clearance of morphine or metabolites was not found to explain treatment outcome. However, large variations in plasma concentrations of morphine, M3G and M6G, support further studies on the relation between plasma concentrations and treatment outcome.

Introduction

Morphine is a widely used opioid analgesic and is one of the preferred treatment options for the treatment of cancer-related pain (1).

After an intravenous (iv) administration, morphine is rapidly distributed from the central compartment to highly perfused tissues (distribution $t_{1/2}$= 0.9-2.5 min) and thereafter the plasma concentrations versus time decay in a biphasic way with a short mean terminal elimination half-life of 1.4-3.4 hours that is similar for intravenous, subcutaneous and oral administrations (2, 3). After oral administration, morphine undergoes extensive hepatic first-pass metabolism (2, 3). Morphine is predominantly metabolised through glucuronidation in the liver into the conjugates morphine-3-glucuronide (M3G; 45-55%) and morphine-6-glucuronide (M6G; 10-15%) (4-6). While M6G is thought to contribute to the analgesic effects (7-9), the effects of M3G are unclear. It has been associated with (central) side effects and the development of tolerance to the analgesic effects in rats (10, 11), but direct administration to humans did not produce any clinical effects (12).

Morphine is available for different routes of administration. For fast titration in case of severe pain, we mainly use continuous subcutaneous administration. This has been found to be safe and effective (13, 14), has advantages over the intravenous route and can also be applied safely in an out of hospital setting (13, 15).

Little is known about the pharmacokinetics (PK) of morphine after continuous subcutaneous administration in cancer patients and solid PK data after oral administration are also lacking. Furthermore, while substantial inter- and intra-individual variability in plasma concentrations of morphine, M3G and M6G has been reported after oral as well as subcutaneous administration (16, 17), the causes for this variability and its effects on clinical outcomes of treatment are incompletely understood. Although treatment with morphine is unsuccessful in about 30% of patients (18), it is unknown what causes these treatment failures. A number of clinical factors such as age and gender as well as genetic factors have been associated with variability in pharmacokinetics and/or dynamics of morphine (19-22) but data are sparse and so far only a small part of variability can be explained at best.

The objectives of the current population pharmacokinetic analysis were to describe the pharmacokinetics and metabolic ratios of morphine, M3G and M6G following subcutaneous and oral administration of morphine. As a second objective, the influence of age, gender, renal function and polymorphisms in several PK related genes on the PK of morphine, M3G and M6G was investigated. Finally, the relation between outcome of treatment and the clearance of morphine and metabolites was explored.

Patients, materials and methods

Between February 2010 and March 2014, patients admitted to the Erasmus MC Cancer Institute (Rotterdam, the Netherlands) and treated with morphine for moderate to severe cancer-related nociceptive pain were asked to participate in the study. All patients treated with morphine were eligible, i.e. patients already treated with morphine before admission but also opioid naive patients or patients rotating to morphine after failure of treatment with another type of opioid. Morphine was available as hydrochloride-3-water (molecular weight 375.84 mg/mmol) 10 mg/mL for parenteral administration and as 5-sulphate-water (molecular weight 758.83 mg/mmol) extended release (tablet 10, 20, 60, 100 mg) and immediate release formulation (liquid 20 mg/mL or dose unit 10, 30 mg) for oral administration. The starting dose in opioid naive patients is usually 10 mg BID or 1 mg/hr parenterally depending on the clinical circumstances. Doses in non-naive patients are based on previous treatments. Patients treated with a fentanyl patch who were prescribed immediate release oral morphine for treatment of breakthrough pain could also be included in the study. In case of severe pain, patients were titrated by continuous subcutaneous infusion with the possibility of an extra bolus every hour. Doses were titrated based on clinical effects. When pain control was reached and doses were stabilized, patients could be rotated to oral extended release (ER) morphine with immediate release (IR) morphine prescribed as needed, using a 1:3 dose conversion ratio (23). Gender, age and weight (kg) at study entry were recorded as well as baseline creatinine values (µmol/L). The Modification of Diet in Renal Disease (MDRD)-formula was used to calculate the glomerular filtration rates for all patients and values >90 mL/min/*1.73 m²* were truncated.

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times (0.0113 \times S_{cr\ [\mu mol/L]})^{-1.154} \times age_{\ [years]}^{\ -0.203} \times (0.742\ if\ female).$$

For every patient treated with long-acting or continuous morphine, the outcome of treatment was classified as failure or non-failure. The response was classified as failure in case of a rotation to another type of opioid or treatment with intrathecal opioids because of insufficient pain control and/or side effects *or* the use of palliative sedation because of refractory symptoms associated with opioid treatment in the dying phase.

Pharmacokinetic sample collection

Patients were included in the study as soon as possible after hospital admission or after the start of morphine. Blood samples for pharmacokinetic analysis were taken during a maximum of 72 hours after the start of morphine and after each change in the opioid regimen (dose, route of administration). The protocol prescribed sampling twice a day,

just before the administration of oral ER morphine or around 8 am and 8 pm in case of continuous administration, a baseline sample before every change in the regimen and a series of samples maximally once a day around the administration of a subcutaneous bolus or oral IR formulation at baseline, 5, 15, 30 and 60 minutes after administration. Samples were collected using potassium EDTA tubes. After centrifugation of the tube, the supernatant was collected and stored at -70°C until analysis at the laboratory of Translational Pharmacology (Erasmus MC Cancer Institute).

Measurements of plasma concentrations of morphine, M3G and M6G

Morphine and its metabolites in plasma were quantitated using a validated UPLC-MS/MS method consisting of a Waters Acquity UPLC sample manager coupled to a triple quadruple mass spectrometer operating in the multiple reaction monitoring mode (MRM) with positive ion electro spray ionization (Waters, Etten-Leur, The Netherlands). The multiple reaction monitoring transitions were set at 286→201 and 462→286 for morphine and M3G and M6G respectively.

Chromatographic separations for morphine were achieved on an Acquity UPLC® BEH C18 1.7 µm 2.1 x 100 mm column eluted at a flow-rate of 0.350 mL/min on a gradient of methanol. The overall cycle time of the method was 6 minutes. The calibration curves were linear over the range of 1.00 to 100 ng/mL with the lower limit of quantitation (LLQ) validated at 1.00 ng/mL for morphine. The within and between-run precisions at five tested concentrations, including the LLQ, were ≤ 10.3 and ≤ 8.67%, respectively, while the average accuracy ranged from 91.9 to 96.9%. The interday coefficient of variation (CV) at five tested concentrations, including the LLQ, was ≤ 11.8% in individual validation runs. The extraction of 200 µL of plasma involved a deproteinization step with acetone followed by a simple liquid extraction with ethyl acetate. For M3G and M6G chromatographic separations were achieved on a VisionHT C18-P 3 µm 2.1 x 50 mm column eluted at a flow-rate of 0.250 mL/min on a gradient of acetonitrile. The overall cycle time of the method was 10 minutes. The calibration curves were linear over the range of 10.0 to 1000 ng/mL for M3G and 2.00 to 200 ng/mL for M6G with the LLQ validated at 10.0 ng/mL for M3G and 2.00 ng/mL for M6G. In patients with metabolite concentrations above these values, samples were adequately diluted in blank human plasma prior to processing until the signal fell within the calibration range. The within and between-run precisions at five tested concentrations in human potassium EDTA plasma for M3G, including the LLQ, were ≤ 5.16 and ≤ 2.18%, respectively, while the average accuracy ranged from 84.0 to 96.5%. For M6G, the within and between-run precisions at five tested concentrations, including the LLQ, were ≤ 16.2 and ≤ 9.12%, respectively, while the average accuracy ranged from 87.0 to 105.5%. The interday CV at five tested concentrations, including the LLQ, were ≤ 8.1% and ≤ 8.2% for M3G and M6G respectively in individual validation runs. The morphine

glucuronides were extracted from 100 µL aliquots of plasma after the addition of 850 µL ammonium carbonate buffer pH 8.8 followed by a solid-phase extraction using Oasis® HLB 1cc (30 mg) SPE columns.

SNP analysis

Single nucleotide polymorphisms (SNPs) which have been related to morphine PK were studied (Table 1). DNA was isolated from 1 mL EDTA blood on the MagNA Pure LC 2.0 instrument (Roche Diagnostics®), with further analysis performed on the 7500 Real-Time PCR System (Life Technologies®). Hardy-Weinberg (HW) equilibrium was calculated with the chi-squared – test. Additionally, the observed minor allele frequency (MAF) was compared with the European MAF from HapMap in dbSNP (National Center for Biotechnology Information). The *SLC22A1* haplotype (consisting of either 2 active alleles, a combination of 1 active vs. 1 inactive allele or 2 inactive alleles) was estimated based on the expectation-maximization (EM) logarithm with R (version 3.1.1) haplo.stats package, using a posterior probability > 0.98.

Population pharmacokinetic modelling

The analysis of concentration-time data of morphine and its metabolites was conducted with the first-order conditional estimation method with eta-epsilon interaction through non-linear mixed effects modelling in NONMEM (version 7.3; Icon Development Solutions, Hanover, MD) (24). Model building was supported by Perl-speaks-NONMEM version 4.2.0, Xpose version 4.4.1 (25) and R version 3.2.0.

Concentration data and doses of morphine were expressed as free base in molar units (nmol/L and nmol, respectively), the latter calculated taking into account the salt administered. All dosing history concerning administration of morphine before and during the period of sampling was included in the dataset. Concentrations below the LLQ comprised 7.6%, 0.7% and 0.9% of the data of morphine, M3G and M6G, respectively, and were discarded from the analysis (26).

First, a pharmacokinetic model was developed for morphine following subcutaneous and oral administration, starting out from previously published models (27, 28). Oral bioavailability was estimated under the assumption of complete subcutaneous bioavailability as indicated in the current literature (29-31). Thereafter, the model was extended to describe also the pharmacokinetics of the metabolites. The rate of appearance of the metabolites was parameterized as a fraction of the rate of elimination of morphine, with fractions fixed to literature values (4-6). The inclusion of first-pass formation of metabolites following oral morphine was assessed in the model and the sum of the estimated fractions of morphine reaching the systemic circulation unchanged or undergoing first-pass metabolism to metabolites was constrained to a maximum of 1. The

Table 1. Summary of selected genetic variants

UGT2B7
• Uridine 5′-diphospho-glucuronosyltransferase 2B7 (UGT2B7) is a phase II (glucuronidation) metabolizing enzyme encoded by the *UGT2B7* gene.
• UGT2B7 is involved in the conversion of morphine into M3G and M6G.
• The G-allele of polymorphism -900G>A (rs7438135), which is in complete linkage disequilibrium (LD) with polymorphism 802C>T, has been associated with a decreased glucuronidation (56, 57).
SLC22A1
• Organic cation transporter 1 (OCT1) is encoded by the *SLC22A1* gene.
• OCT1, expressed at the sinusoidal membrane of the human liver, mediates the cellular uptake of morphine [51].
• Healthy volunteers with *SLC22A1* polymorphisms have reduced morphine uptake in the hepatocytes (54).
• Children with 2 loss-of-function *SLC22A1* alleles have lower morphine clearance than carriers of the active *SLC22A1* alleles (55).
ABCC3
• ATP-binding cassette C3 (ABCC3) is an organic anion transporter encoded by the *ABCC3* gene.
• ABCC3, expressed on the basolateral membranes of hepatocytes, mediates the efflux of M3G and mostly likely also M6G into the bloodstream (58).
• *ABCC3* polymorphism -211C>T (rs4793665) was associated with a significantly altered mRNA expression (59, 60).
• Children with the −211CC genotype had significantly higher M3G and M6G levels (~40%) than carriers of the -211T allele (55).

influence of age and gender on the PK profiles was explored and the relationship between eGFR and clearance of the metabolites was assessed.

Inter-individual variability (IIV) in PK parameters was modelled using log-normal models. Homoscedastic, heteroscedastic and combined residual errors models were evaluated. The correlation between parent drug and metabolite concentrations from the same sample was taken into account utilizing the L2 data item in NONMEM.

Selection between alternative models was based on scientific plausibility, statistical significance, precision in parameter estimates and visual inspection of goodness-of-fit plots. Statistical significance was determined with the likelihood ratio test using the NONMEM objective function value (OFV). The OFV is given by minus twice the log likelihood and a difference in OFV (ΔOFV) between nested models is approximately χ^2 distributed. A ΔOFV of 6.64 and 10.8 corresponds to p-values of 0.01 and 0.001, when one parameter is added to the model (1 *df*). The reliability of various diagnostic plots was judged based on magnitude of η- and ε- shrinkage (32). The precision of the model parameter estimates was obtained with the Sampling-Importance-Resampling (SIR) method (33). In addition to the general advantages of SIR (e.g. fast runtimes as it does not require estimation steps, flexibility in addressing asymmetric confidence intervals), SIR was deemed more appropriate than the bootstrap in this case because it is less sensitive to sample size and does not require stratification of the data, which is particularly useful with unbalanced study designs involving a few subjects. Further details on the

SIR procedure are presented in Electronic Material (supplemental text material). The predictive performance of the final model was evaluated with visual predictive check (VPC) or population prediction-corrected VPC (pcVPC) (34) for the observed concentrations as well as for concentration ratios. The concentration ratios M3G:M, M6G:M and M3G:M6G following uniquely the subcutaneous or the oral route of administration were calculated by dividing the respective observed or simulated concentrations.

Influence of genetic variants and assessment of treatment failure

After finalization of the population PK model, the influence of *UGT2B7* (rs7438135), *SLC22A1* (rs72552763, rs12208357, rs34130495, rs34059508) and *ABCC3* (rs4793665) genetic variants were explored on total morphine clearance and morphine metabolic clearances to M3G and M6G; *ABCC3* (rs4793665) was also studied in relation to the clearance of the metabolites. In addition, the model was used to assess whether failing treatment was related to a difference in clearance of morphine or metabolites. The influence of failing treatment was tested in the model as a binominal variable on the clearance of morphine and metabolites, not with the purpose of explaining parameter variability but to identify a possible association between failing the treatment and clearance.

Results

Patients

The dataset contained 410 samples from 49 patients **(**Table 2**)**. Treatment with oral and subcutaneous morphine in relation to the observations for all patients is shown in supplemental figure 1 and observations in relation to time after first dose in supplemental figure 2. The median treatment doses were 2 mg/h for continuous and bolus subcutaneous morphine (ranges 0.6-14 mg/h and 0.6-10 mg), 40 mg BID for oral ER morphine (range 10-150 mg) and 10 mg for oral IR morphine (range 5-60 mg). Creatinine values were missing for 4 patients and were imputed based on linear regression of the available values of eGFR on age and gender. In 7 patients baseline eGFR was between 30-60 mL/min/1.73 m² (range 33-57 mL/min/1.73 m², median 43 mL/min/1.73 m²). All other patients (n=38) had an eGFR ≥ 60mL/min/1.73 m². In twelve out of 43 patients treated with long-acting/continuous morphine, the outcome of treatment was classified as failure, in all due to the occurrence of dose limiting side effects.

Table 2. Baseline characteristics

Characteristics (n=49)	*No*	*% or range*
Median age (years) – range	60	38 - 80
Gender		
Male	27	55
Female	22	45
Median Weight (kg)	83	53 - 140
Body Mass Index (kg/m2)		
Underweight < 18.5	1	2
Normal range 18.5-25	13	27
Overweight 25-30	20	41
Obese 30-40	13	27
Severely obese >40	2	4
Race		
Caucasian	44	90
Latin-American	1	2
Unknown/other	4	8
Median WHO Performance Status - range	2	(0 - 3)
Primary tumor localization		
Breast	11	22
Colorectal	7	14
Prostate	6	12
Sarcoma	4	8
Other	21	43
Distant metastasis present	44	89
Median creatinine (µmol/l)	72	25 - 190
Median estimated glomerular filtration rate (mL/min/1.73 m^2)	81	33 - >90
Median serum albumin (g/L)	40	28-47
Routes of administration during sampling		
Subcutaneous	28	57
Oral extended and immediate release	12	24
Oral immediate release only	6	12
Both oral and subcutaneous consecutively	3	6
UGT2B7 G>A		
- GG (wild type)	14	29
- GA (heterozygous)	26	53
- AA (variant)	9	20
SLC22A1		
- 2 active alleles	26	53
- 1 active allele/1 inactive allele	18	37
- 2 inactive alleles	5	10
ABCC3 C > T		
- CC (wild type)	5	10
- CT (heterozygous)	28	57
- TT (variant)	16	33

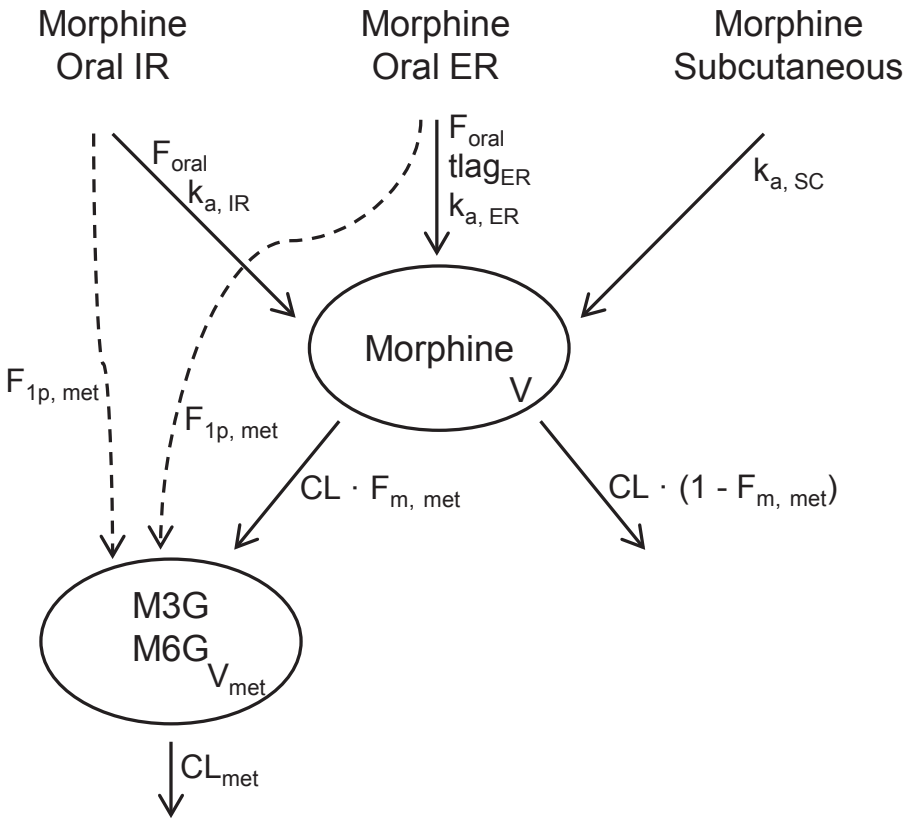


Figure 1. Schematic figure of the pharmacokinetic model developed to describe plasma concentrations of morphine and metabolites (M_3G and M6G) following oral immediate-release (IR), oral extended-release (ER) and subcutaneous administration. Abbreviations: CL morphine clearance; CL_{met} metabolites clearance; $F_{1p,\ met}$ fraction of morphine converted to metabolites in first-pass effect; $F_{m,\ met}$ fraction of morphine clearance forming metabolites; F_{oral} oral bioavailability; k_a, *ER* absorption rate constant for oral extended-release morphine; k_a, *IR* absorption rate constant for oral immediate-release morphine; k_a, *SC* absorption rate constant for subcutaneous morphine; $tlag_{ER}$ absorption lag-time for oral extended-release morphine; V morphine volume of distribution; V_{met} metabolites volume of distribution.

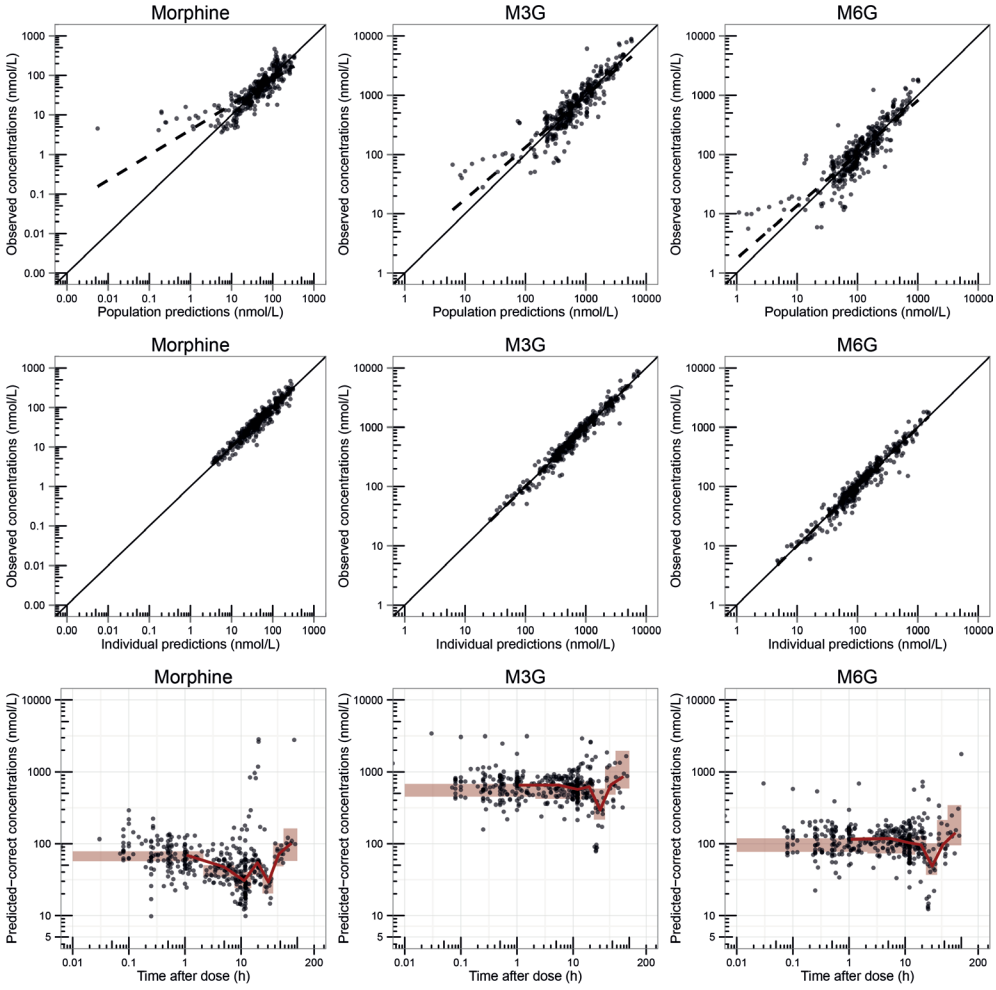


Figure 2. Prediction- and simulation-based diagnostics for the final population pharmacokinetic model. Observed concentrations of morphine, M3G and M6G vs. population predictions (upper panel) and observed concentrations vs. individual population predictions (middle panel); the *solid line* is a unity line and the *dashed line* is a linear tendency line. Prediction-corrected visual predictive checks (lower panel) through 1000 replications; *dots* are the predicted-correct concentrations of each entity, the *solid red line* represents the observed median and the *shaded area* represents the 95% confidence interval for the simulated median.

Table 3. Population pharmacokinetic parameter estimates for morphine, M3G and M6G following subcutaneous and oral administration of morphine

Parameter (units)	*Description*	*Estimate*	*SIR RSEa (%)*	*SIR 95%CI*	
Morphine					
$t_{lag, ER}$ (h)	absorption lag-time for oral extended-release	0.25 fixed	na	na	
$k_{a, SC}$ (h-1)	absorption rate constant for subcutaneous	3.96 fixed	na	na	
$k_{a, IR}$ (h-1)	absorption rate constant for oral immediate-release	6.00 fixed	na	na	0.306
$k_{a, ER}$ (h-1)	absorption rate constant for oral extended-release	0.221	17.7	0.155	0.306
$F_{r, oral}$ (%)[b]	oral bioavailability	0.372	na	na	99.9
CL_{70kg} (L/h)[c]	clearance	91.9	3.91	85.8	99.9
V_{70kg} (L)[c]	volume of distribution	278	12.3	221	351
M3G and M6G					
$F_{m, M3G}$	fraction of morphine clearance forming M3G	0.573 fixed	na	na	
$F_{m, M6G}$	fraction of morphine clearance forming M6G	0.104 fixed	na	na	
θ_1[b]	parameter estimated to derive F_{oral}, $F_{1p\ M3G}$ and $F1_{p\ M6G}$	0.170	10.4	0.136	0.206
θ_2[b]	parameter estimated to derive F_{oral}, $F_{1p\ M3G}$ and $F_{p\ M6G}$	0.953	8.95	0.796	1.14
θ_3[b]	parameter estimated to derive F_{oral}, $F_{1p\ M3G}$ and $F_{p\ M6G}$	0.565	30.3	0.310	1.01
$F_{1p, M3G}$[b]	fraction of morphine converted to M3G in first-pass effect	0.355	na	na	
$F_{1p, M6G}$[b]	fraction of morphine converted to M6G in first-pass effect	0.0631	na	na	
$CL_{met, 70kg}$ (L/h)[c,d]	clearance (common for metabolites)	4.71	5.24	4.24	5.20
$V_{met, 70kg}$ (L)[c]	volume of distribution (common for metabolites)	25.8	6.12	22.8	29.0
eGFR on $CL_{met, 70kg}$	fractional change in $CL_{met, 70kg}$ per mL/min/1.73 m^2 eGFR relative to $CL_{met, 70kg}$ for subject with eGFR of 81 mL/min/1.73 m^2	0.0128	12.9	0.00924	0.0156

Table 3. Continued

Inter-individual variability					
$k_{a,all}$ (%CV [η-shrinkage])		71.0 [25.3]	na	na	
CL_{70kg} (%CV [η-shrinkage])		22.2 [17.9]	12.9	16.9	27.8
V_{70kg} (%CV [η-shrinkage])		74.7 [21.4]	9.71	60.4	88.6
CL_{M3G} (%CV [η-shrinkage])		36.2 [6.28]	10.6	29.5	44.4
CL_{M6G} (%CV [η-shrinkage])		36.8 [7.00]	11.8	29.6	46.2
correlation CL_{M3G} - CL_{M6G}[e]		0.912	11.8	0.864	0.952
V_{M3G} (%CV [η-shrinkage])		24.7 [30.7]	18.4	17.0	34.0
V_{M6G} (%CV [η-shrinkage])		24.3 [39.0]	20.5	16.3	34.6
θ_1 (%CV [η-shrinkage])		15.0 [62.7]	18.7	8.91	19.9
θ_3 (%CV [η-shrinkage])		98.2 [57.1]	25.1	50.1	146
Residual variability					
morphine (%CV [ε-shrinkage])	proportional residual error for morphine	28.6 [8.45]	4.31	26.5	31.2
M_{3G} (%CV [ε-shrinkage])	proportional residual error for M_{3G}	20.0 [8.00]	4.14	18.5	21.7
M_{6G} (%CV [ε-shrinkage])	proportional residual error for M_{6G}	23.9 [8.00]	4.04	22.2	26.0
correlation morphine - M3G[e]		0.420	7.11	0.340	0.504
correlation morphine - M6G[e]		0.386	7.57	0.302	0.477
correlation M3G - M6G[e]		0.918	4.29	0.901	0.934

[a] For inter-individual and residual variability, %RSE is reported on the standard deviation scale

[b] $F_{oral} = 1 / (1 + \theta1 + \theta2 + \theta3)$; F1p, $M3G = \theta2 / (1 + \theta1 + \theta2 + \theta3)$; F1p, $M6G = \theta1 / (1 + \theta1 + \theta2 + \theta3)$

[c] value for a 70-kg patient calculated as *parameter*70kg = estimate · (weight / 70)[a] for volumes or 0.75 for clearances

[d] value for a patient with eGFR = 81 mL/min/1.73 m²

[e] η-shrinkage varied between 6.28 and 62.7% and ε-shrinkage varied between 8.00 and 8.45 %

[f] correlation of the off-diagonal estimate calculated as cov(omega1, omega2)/sqrt(var(omega1) · var(omega2)) or cov(sigma1, sigma2)/ sqrt(var(sigma1) · var(sigma2))

Abbreviations: CI, confidence interval; CV, coefficient of variation; na, not available; RSE, relative standard error; SIR, sampling importance resampling.

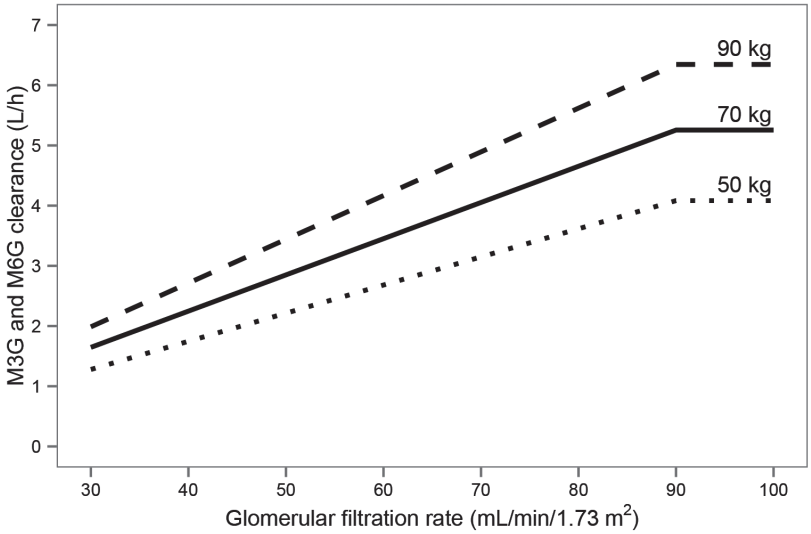
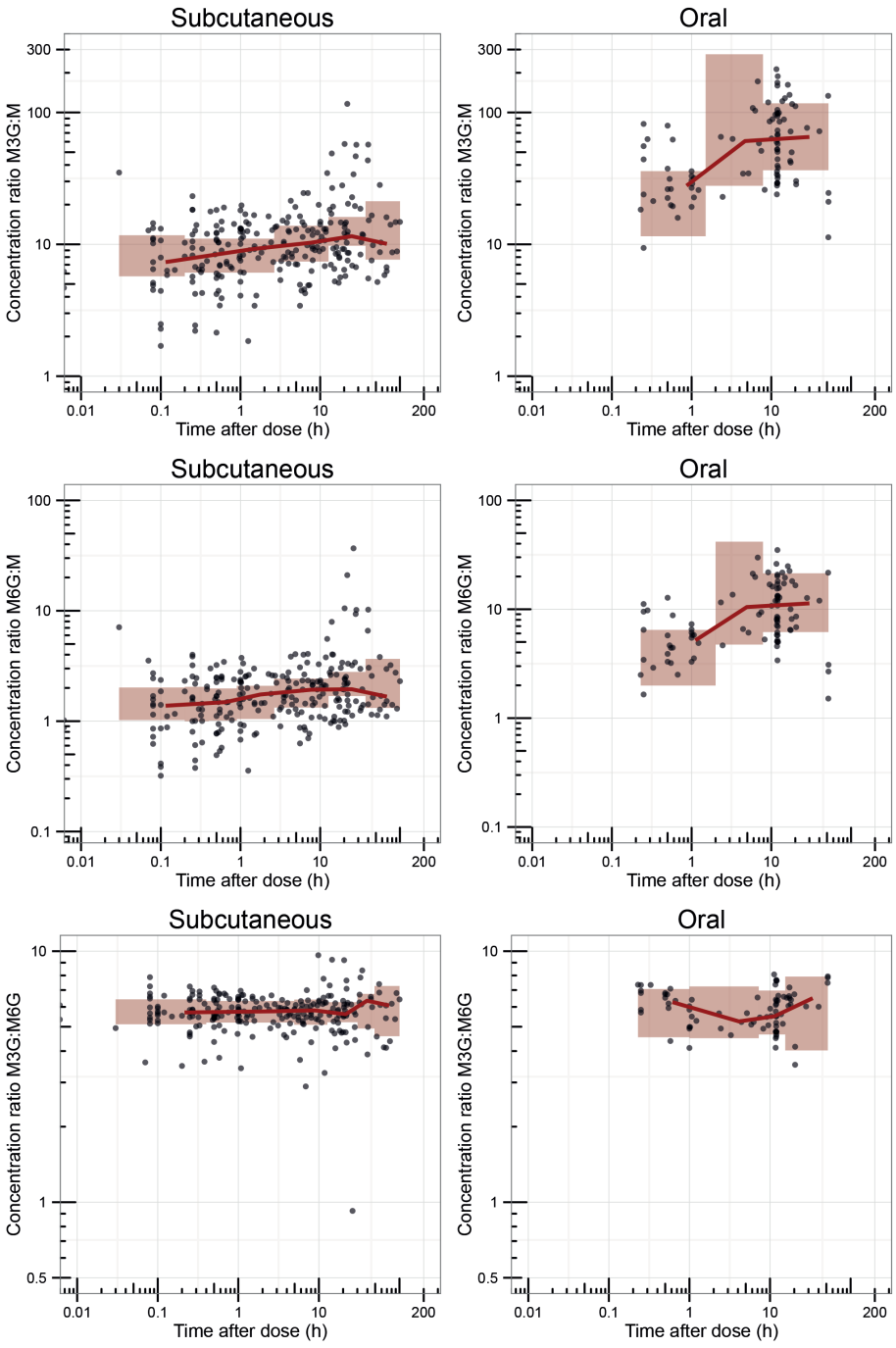


Figure 3. Illustration of M3G and M6G clearance in relation to glomerular filtration rate (eGFR) and body weight.

Figure 4. Observed and simulated (1000 replications) metabolic concentration ratios (M3G:morphine, M6G:morphine and M3G:M6G) over time stratified by route of administration; dots are the observed metabolic concentrations ratios, the *solid red line* represents the observed median and the *shaded area* represents the 95% confidence interval for the simulated median.


Subcutaneous
Oral
Concentration ratio M3G:M
Concentration ratio M6G:M
Concentration ratio M3G:M6G
Time after dose (h)
0.01
0.1
1
10
200
300
100
10
1
0.5
0.1

Morphine pharmacokinetics

The pharmacokinetics of subcutaneous and oral morphine was adequately described by a one-compartment model with separate first-order absorption processes for each route. Parameters describing the absorption phases for subcutaneous and oral immediate-release morphine were fixed to literature values (27, 28) and the value of the absorption rate constant for oral extended-release morphine was estimated (p-value < 0.001 when compared to a fixed value of 0.8 h^{-1}). The fractions of total morphine clearance forming M3G and M6G were fixed to 0.57 and 0.10, respectively (4-6).

The pharmacokinetics of M3G and M6G were appropriately described by first order systemic and additional first-pass formation and first order elimination according to a one-compartment model (figure 1). Note that given the parameterisation of the model (fixed and estimated fractions of formation) the estimated disposition parameters reflect true, and not apparent, values. The inclusion of first-pass metabolism statistically significantly improved the fit of the parent-metabolite model (p-value < 0.001). The metabolites disposition parameters were estimated to common values and the estimation of separate clearance and volume parameters for each metabolite was not found to be statistically significant (p-value > 0.01). The final population model parameters for morphine, M3G and M6G are presented in table 3.

The model was found to fit the data well as shown by the absence of major systematic trends in the goodness-of-fit plots and pcVPCs (figure 2). Allometric body weight with theory-based exponents was included *a priori* on all disposition parameters of all entities (35). Age did not statistically significantly improve the model fit (p-value > 0.01). The inclusion of an effect of gender on clearance of morphine resulted in a decrease of 17.0% for females (p-value > 0.01) but was not retained in the model. The clearance of the metabolites was found to change with eGFR (p-value < 0.001) and increased 0.602 L/h with every increase in eGFR of 10 mL/min/1.73 m^2 up to an eGFR of 90 mL/min/1.73 m^2, above which clearance was constant (figure 3).

The mean area under the plasma concentration-time curve (AUC) molar ratios for a typical patient (with 70 kg and eGFR of 81 mL/min/1.73 m^2) following oral morphine compared with the subcutaneous route of administration for the same dose were: M3G/Morphine 29.7:1 vs. 11.1:1; M6G/Morphine 5.26:1 vs. 1.95:1; M3G/M6G 5.65:1 vs. 5.70:1. The concentration ratios over time and respective model predictions by route of administration are shown in figure 4.

Influence of genetic variants

An effect of *UGT2B7*, *SLC22A1* and *ABCC3* SNPs on total clearance of morphine and morphine metabolic clearances to M3G or M6G could not be identified (p-value > 0.01). Similarly, an effect of *ABCC3* genotype on the clearance of the metabolites was not found (p-value > 0.01).

Assessment of treatment failure in relation to metabolism

Differences in clearance of morphine, M3G and M6G in patients in whom treatment with morphine failed (n=12) compared with patients in whom treatment did not fail (n= 31) could not be identified ($p > 0.01$ in all cases).

Discussion

First, we developed a population pharmacokinetic model for morphine, M3G and M6G following subcutaneous and oral morphine administration from a high number of sparse samples. We found that a one-compartment model with separate first-order absorption processes for each route adequately describes the plasma concentrations of morphine and a one-compartment model following first-order systemic and additional first-pass formation from morphine appropriately describes plasma concentrations of the metabolites. Our results are in line with literature data.

PK data after subcutaneous administration are scarce. The basis for the morphine model was the model by Upton et.al.(27) who reported a CL of 79.8 L/h in a population of 22 post-operative patients aged 50 years or over. In a study by Stuart-Harris et.al (29) in 6 healthy volunteers, CL of 83.1 L/h (subcutaneous bolus), 95 L/h (iv) and 127.5 L/h (subcutaneous infusion) were reported. In a recent publication, a lower CL of 47.5 L/h was reported in a slightly older and terminally ill population, with – compared to our cohort – lower serum albumin values (median 26 g/L), shorter survival (median 33 days) and most likely lower body weight (not reported), and these factors may suggest lower metabolic capacity and explain the lower CL in that study (36). Thus, CL in our study estimated to 92.9 L/h for a patient weighing 70 kg is in reasonable agreement with previous data.

Clearance for the metabolites was estimated to a common value of 4.71 L/h for a subject weighing 70 kg and with eGFR 81 mL/min/1.73m^2. The estimation of separate disposition parameters for M3G and M6G did not statistically significantly improve the model, suggesting that these entities might have the same clearance and volume of distribution, or that the model cannot distinguish the difference. Thus, the different PK profiles of the metabolites depend exclusively on the fraction of systemic (subcutaneous and oral) and first-pass formation (oral) of the metabolites. This is in line with the observed strong correlation (R^2=0.963) of the metabolites, as reported in other studies (37, 38). Furthermore, the values of CL and V for intravenous M3G in healthy volunteers, 10.1 L/h and 23.1 L (39), are in agreement with previously published values for intravenous M6G (40, 41) and corroborate the similarity found in the disposition PK parameters of metabolites in our study. Furthermore, CL and V of M6G in cancer patients following intravenous administration of M6G was found to be 5.8 L/h and

22 L, respectively, thus in good agreement with our estimates and supporting our findings (42).

Concentration-time data following the administration of subcutaneous and oral morphine allowed the estimation of the oral morphine bioavailability (37.2%) and, in addition, the fractions of the oral morphine dose that undergo first-pass metabolism to M3G (35.5%) and M6G (6.31%). It is not expected that the fractions are in agreement with the Fm, i.e. the fractions of morphine clearance forming the two metabolites. The fraction of the dose formed into a metabolite in the first pass is dependent on several factors; whether metabolism occurs in the intestinal wall in addition to the liver, whether all metabolites are formed in the first passage (i.e. whether total clearance is equal to hepatic clearance) and the blood-to-plasma ratio of morphine. The values estimated are in line with only hepatic first pass metabolism (for all pathways) but it is not solid evidence of lack of intestinal wall formation.

As expected, the subcutaneous route of administration, which avoids first-pass metabolism, resulted in lower metabolite:morphine concentration ratios compared to the oral route. According to Hasselstrom et.al.(5) and supported by our data, this difference is due to higher morphine plasma concentrations and therefore the AUCs of the metabolites formed following both routes of morphine administration are similar. The observed and model-predicted ratio M3G:M6G remained constant regardless of level of renal impairment or route of administration. The clinical consequences of the differences in metabolite:morphine ratios are uncertain. We could only find one study comparing oral and subcutaneous administration using a cross-over design (23). This study reported less nausea and somnolence during treatment with subcutaneous morphine, a finding that we recognize from our daily clinical practice. The relationship between plasma concentrations of morphine and metabolites and clinical effects is unsure however, because some studies have failed to show a correlation (43-45), while others did report an association (9, 37, 46). Although we did not perform a full pharmacokinetic-pharmacodynamic analysis, we tried to identify an association between outcome of treatment and clearance of morphine. The outcome of treatment may not be associated with a different clearance of morphine and other factors may be more important in this regard. The relation between clearances and plasma concentrations of morphine and the metabolites and outcomes of treatment deserves further study.

Secondly, in an attempt to explain variability in PK parameters, we studied the role of several clinical and genetic covariates on the clearances of morphine and the metabolites. In our study, inclusion of both age and gender did not statistically significantly improve the model, although we estimated a 17% lower clearance in females. Reported data on the effects of age, are conflicting. Age was reported to predict post-operative morphine requirements (47) and PK studies have reported either lower clearances and volume of

distribution in elderly patients (20) or higher plasma concentrations of M6G and/or M3G (48, 49), while others found no significant impact of age (50). A possible explanation for these findings is the fact that in most studies renal function – which declines with age – was not taken into account. However, in the study by Klepstad *et.al* (49), serum creatinine and age were found to be independent contributors to outcome in a multivariable analysis. Regarding gender, in a systematic review and meta-analysis, Niesters et.al (21) found that women display greater opioid analgesia than men and this effect was largest when the analysis was restricted to patient-controlled analgesia studies with morphine. It is unsure however, if this gender difference can be attributed to pharmacokinetic differences. While McQuay et.al (48), found lower plasma concentrations of morphine and M6G in men compared to women, the effect of gender was also non-significant in other modelling studies (27, 50).

Furthermore, clearance of the metabolites was found to be a function of body weight and renal function (figure 3), while no correlation was found between these two (data not shown). The consequence of this combined finding for dose recommendation is not clear, and would demand to take into account the systemic exposure of morphine and metabolites simultaneously. Although accumulation of M3G and M6G in patients with impaired renal function is widely reported (51), data on the clinical effects of morphine treatment in these patients are scarce and conflicting. Reducing the frequency of administration or the dose are carefully suggested in guidelines (1, 52), but opioid rotation to an opioid without renally excreted active metabolites, such as fentanyl, should also be considered.

We did also not identify significant effects of genetic variants in transporters (*OCT1*, *ABCC3*) and the phase-II metabolizing enzyme (*UGT2B7*) on morphine PK. Remarkably, almost all of the previously identified effects of these genetic variants were found in children and mainly in small patient populations (Table 1). In our adult population, we were unable to confirm previously identified effects. This may be caused by lower rates of glucuronidation in children and possibly overcapacity in adult livers. Additionally, the absence of a genotypic OCT1 effect could be due to construction of the OCT1 haplotype in the current study. Recently, a study addressing worldwide genetic variability within this gene and assessing the effect of several genetic variants (a.o. *SLC22A1**2-*6 alleles) on 10 probe compounds, found that the effect of the *2 allele on the transport function is substrate dependent (53). This makes the *2 allele rather a reduced function allele against morphine than total loss-of-function, as previously suggested (54, 55).

Conclusions

We found that a one-compartment model adequately described the pharmacokinetics of morphine after subcutaneous and oral administration and a one-compartment model following first-order systemic and additional first-pass formation from morphine appropriately described the plasma concentrations of the metabolites. The estimated relative bioavailability of 37.2% for oral morphine confirms the dose conversion ratio of 1:3 when converting subcutaneous to oral morphine. Age and gender did not significantly influence the clearance of morphine, while the clearance of the metabolites was found to be a function of body weight and glomerular filtration rate. We found no significant effects of polymorphisms in *UGT2B7*, *SLC22A1* and *ABCC3* and no difference in morphine and metabolite clearance between patients in whom treatment failed vs patients in whom treatment did not fail. Further research is therefore needed to explain the variability in treatment doses as well as clinical outcomes.

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Supplemental material

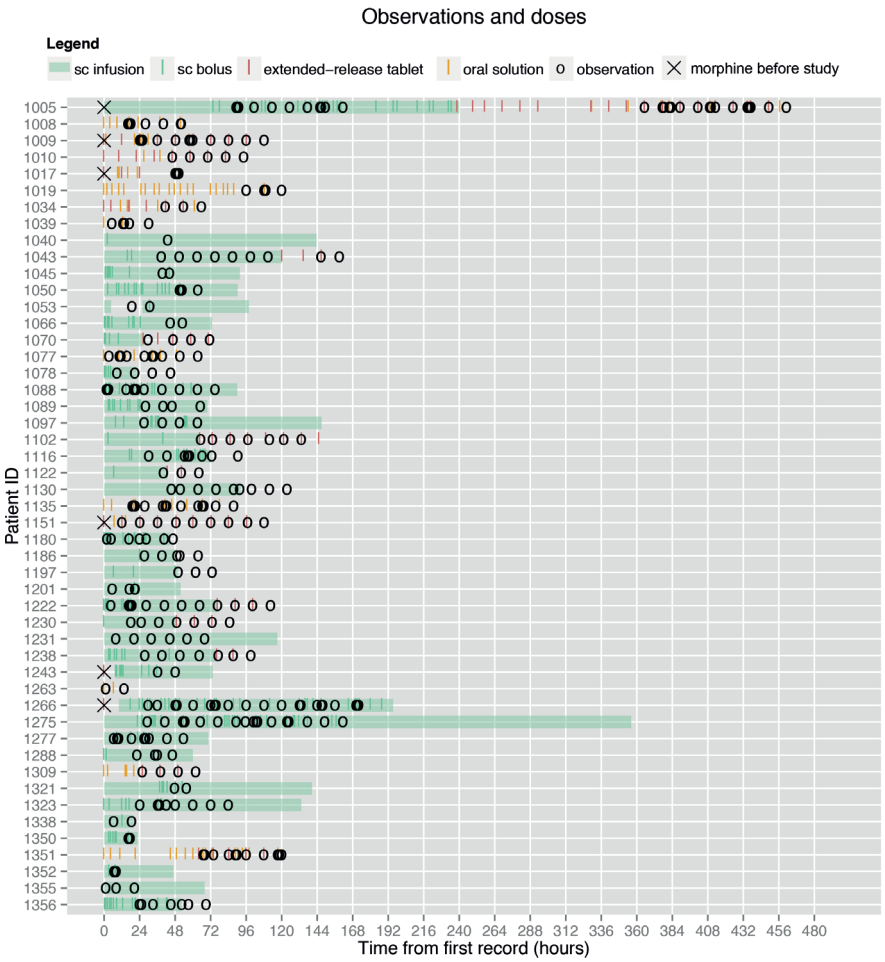

Figure 1. Treatment with oral and subcutaneous (SC) morphine in relation to the observations.

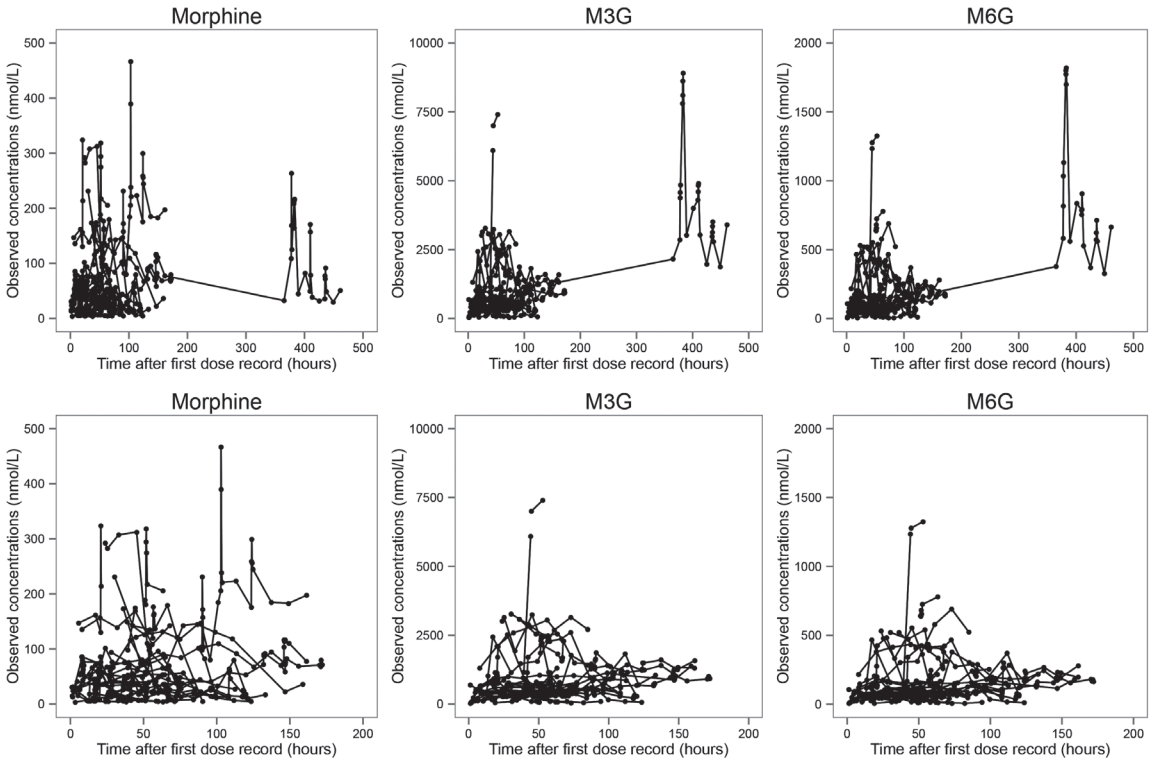

Figure 2. Observed concentrations of morphine, M3G and M6G vs. time after first dose record (upper panel) and the same data with the x-axis truncated to 200 hours (lower panel).

Chapter 6

Opioid treatment failure in cancer patients: the role of clinical and genetic factors

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Abstract

Aim:

To identify clinical and genetic factors associated with outcome of opioid treatment.

Patients & methods:

We performed an exploratory analysis in a cohort of 353 patients treated with fentanyl, morphine, oxycodone, and/or hydromorphone for cancer-related pain, exploring selected clinical and (pharmaco-)genetic factors for a correlation with treatment failure for all and per type of opioid.

Results:

Use of adjuvant pain medication, intensity of pain at rest and age were associated with treatment failure in the various cohorts. Only the genetic variants rs12948783 (*RHBDF2)* and rs7016778 *(OPRK1)* correlated statistically significant in univariate, but not in multivariable analysis.

Conclusions:

Several clinical and genetic factors were identified that warrant further study to clarify their role and use in opioid treatment.

Introduction

Opioids are the cornerstone of treatment for moderate to severe cancer-related pain. Although treatment is successful in the majority of patients, 25-40% does not achieve sufficient pain control and/or experiences serious side effects limiting dose escalation (1, 2). In these cases, opioid rotation is successful in about two-thirds of patients. However, opioid rotation is time-consuming, which is unwanted in a population with limited life-expectancy (3, 4). As we are currently unable to predict the clinical response to specific opioids for an individual patient, finding the right type and dose of opioid is still a matter of trial and error. The effects on pain and the occurrence of side effects are the result of a complex interplay between clinical / demographic, pharmacokinetic and -genetic factors (5, 6). So far, factors related to treatment-failure of individual opioids that can be used to guide treatment decisions (2, 7-10) have not been identified.

Studies in twins, separating environmental from genetic influences, have demonstrated that up to 60% of the inter-individual variation in pain perception and analgesia can be attributed to a person's genetic predisposition (11, 12). In the last decade, a large number of studies have found associations between genetic variants of drug metabolizing enzymes (*CYP3A4, CYP2D6*), membrane drug transporters (*ABCB1, ABCC3, OCT1*), molecules involved in opioid receptor signaling (*OPRM1, OPRK1, OPRD1, KCNJ6*) and pain modulators (*COMT*) on the one hand and opioid efficacy, required dose, and toxicity on the other hand (5, 13). These studies mostly had a small sample size, focused solely on morphine, or data from various types of opioids were pooled. The European Pharmacogenetic Opioid Study (EPOS) included a large number of cancer patients and studied the influence of genetic variability on opioid dose, during opioid treatment. No statistically significant associations were found between 112 single nucleotide polymorphisms (SNPs) in 25 candidate genes and opioid dose (14). Sub studies from the EPOS patient cohort focused on pharmacokinetics of fentanyl (15), pharmacokinetics of oxycodone (16), occurrence of nausea and vomiting (17) and constipation (18). The study on pharmacokinetics of fentanyl reported that the *CYP3A4*22* and *CYP3A5*3* variants accounted for a small proportion of the variability in pharmacokinetics of fentanyl (15). For oxycodone, *CYP2D6* genotypes were shown to influence the pharmacokinetics of oxycodone, but not the pharmacodynamics (16). For nausea and constipation, although a correlation was found with 8 and 5 SNPs, respectively, only two SNPs (rs1672717 in the 5-Hydroxytryptamine (Serotonin) Receptor 3B (*HTR3B*) for nausea (17); and rs2020917 in the enzyme Catechol-O-methyltransferase (*COMT*) for constipation (18)) passed the Benjamini-Hochberg criterion for a 10% false discovery rate. However, EPOS was a cross-sectional study, in which outcomes were studied at a random time point during opioid treatment. To our knowledge, no studies have assessed whether a combination of clinical

and genetic factors is related to the efficacy or failure of treatment with individual opioids, whereas this information could help to personalize pain management in cancer patients (19).

With the aim to identify clinical and genetic factors related to treatment failure of opioids, we performed an exploratory prospective study in patients treated with morphine, oxycodone, fentanyl, or hydromorphone for cancer-related pain.

Patients and methods

Patients admitted to the department of Medical Oncology of Erasmus MC Cancer Institute (Rotterdam, the Netherlands), who were treated with opioids for moderate-severe nociceptive cancer-related pain (with or without a neuropathic component) were included in this prospective study. Patients with an expected duration of hospitalisation < 72 h and patients unable to give informed consent were excluded from the study. Patients were admitted to our specialised acute palliative care unit (PCU) or one of two general oncology wards. Pain was treated stepwise following the World Health Organisation analgesic ladder (20) and only patients treated with strong-acting (step III) opioids were eligible. Treatment was given in line with our institutional protocol for the treatment of oncological pain, which is based on (inter-) national guidelines. Of note, because many patients on the PCU are admitted with complex pain problems; high doses of opioids, opioid rotation, parenteral administration of opioids and/or adjuvant analgesics were often necessary. In general, the type of opioid used before hospital admission was continued unless dose escalation was not possible due to side effects or problems related to administration. In patients with severe pain, we generally used subcutaneous morphine or fentanyl for titration. Doses were titrated while closely monitoring the effect on pain (by numeric rating scale 0-10 twice daily) and side-effects (10 most common side effects assessed using a 4-point Likert scale twice daily). Opioid rotation was performed in case of insufficient pain control despite adequate dose escalation and/or dose limiting side-effects and/or the occurrence of other dose limiting events, such as volume related problems with subcutaneous infusions. Adjuvant pain medication was started in case of an insufficient effect of opioids in patients with mixed nociceptive-neuropathic pain. Selection of the opioid of first, second or third choice was based on clinical factors (i.e. renal function, possibility for use of oral route) and treatment history. In opioid naive patients, our protocol advises oxycodone as a first choice.

Clinical and demographic data were collected. All data were registered in an electronic database (©2004-2012 OpenClinica, LLC and collaborators). Patients were categorised in treatment groups according to the type of opioid(s) they received. In case of rotations

between different types of opioids, patients were included in all the specific treatment groups.

For the analysis, we defined T_0 as the start of the clinical titration period for the opioid of study. In case of pain requiring opioid titration at admission, To was set at the time of hospitalisation irrespective of the use of opioids before referral. When an opioid was started after hospitalisation, To was set at the moment of that start. In case of an opioid rotation, a new titration period started. Therefore, at To, patients could be opioid naive, already using the respective opioid (before hospitalisation) or starting a new opioid after rotation. For every patient, the treatment response per opioid was classified as failure or non-failure. The response was classified as failure in case of: 1) a rotation to another type of opioid because of insufficient pain control and/or side effects, 2) a treatment with intrathecal opioids because of persistent pain and/or side effects, *or* 3) the use of palliative sedation because of refractory symptoms associated with opioid treatment in the dying phase. In all other patients the response was classified as non-failure. A rotation from oxycodone to another type of opioid given parenterally was considered as failure only if the reason for rotation included adverse events. We excluded patients rotating solely because of a need for (fast) parenteral titration, as oxycodone for parenteral use is not available in our hospital. The study was approved by the Erasmus MC medical ethics review board (study ID: MEC 09.332) and conducted in accordance with the Declaration of Helsinki. The trial was registered at the Dutch Trial Registry (Trial registration ID: NTR4369). Written informed consent was obtained from all participants, with separate informed consent for the DNA analysis.

Analyses of SNPs

Blood samples for pharmacogenetic analysis were collected concurrent with the first venepuncture for blood sampling for a medical indication and after obtaining informed consent. DNA was isolated from 1 mL EDTA blood on the MagNA Pure LC 2.0 instrument (Roche Diagnostics®). Genetic variants were selected based on evidence from literature, taking into account allele frequency, clinical impact and reproducibility of effect. The analysis was performed with the TaqMan allelic discrimination method on the 7500 Real-Time PCR System (Life Technologies®). *CYP2D6* duplication and deletion (*5 allele) were determined on the ProFlex™ PCR system (Life Technologies®) and visualized via gel electrophoresis on 1% agarose gel.

Violation of Hardy-Weinberg (HW) equilibrium was calculated for all genetic variants with the chi-squared – test. Additionally, the observed minor allele frequency (MAF) was compared with the MAF from HapMap in dbSNP (National Center for Biotechnology Information). The *COMT, CYP2D6* and *OCT1* haplotypes were estimated based on the expectation-maximization (EM) logarithm with R (version 3.1.1) haplo.stats package,

using a posterior probability > 0.98. Patients genotyped GGC (rs4680, rs4818, rs4633 resp.) for *COMT* were categorized in the low pain sensitivity (LPS) group, ACT genotype in average pain sensitivity (APS) group and GCC in high pain sensitivity (HPS) group, as previously this haplotype has been related with experimental pain sensitivity (21) and opioid consumption (22{Tan, 2016 #5836, 23, 24). The LPS group consisted of patients with the LPS/LPS or LPS/APS alleles, APS from APS/APS or LPS/HPS alleles and HPS from the alleles HPS/HPS or APS/HPS.

Statistical analysis

Data were analysed using STATA® version 13. Descriptive statistics were used to summarize patients' characteristics. Statistical analyses were performed for the whole group of patients and per type of opioid. For the analysis of all patients, the first opioid that was used for titration during admission for which an observation period of at least 24 hours was available, was selected. Logistic regression analysis was used with treatment failure as the dependent variable and the SNPs described in the previous paragraph and clinical/demographic factors as covariates. For the analysis in the whole group of patients only SNPs in genes related to pharmacodynamics or pain sensitivity were tested. The following clinical/demographic factors were explored: gender, age, radiotherapy on any tumour localisation related to the pain for which opioid treatment was initiated (either 1-8 weeks before To or 1 week before - during hospitalisation), use of adjuvant pain medication (pregabalin, gabapentin, or amitriptyline) or use of corticosteroids started before To and continued or started on To or during hospitalisation, pain at rest and worst pain at To (rated using Numeric Rating Scale (NRS 0-10) and divided into categories mild (NRS 0-4), moderate (NRS 5-6) and severe pain (NRS 7-10) and opioid dose at To. For the analysis of all patients, doses were recalculated to the median oral morphine equivalent daily dose (MEDD) according to published equianalgesic dose tables: oral morphine 60mg/d = parenteral morphine 20 mg/d = transdermal fentanyl 25 mcg/h = oral oxycodone 40 mg/d = parenteral hydromorphone 4 mg/d (25). For the whole group, as well as the opioid specific groups, doses were divided into 2, 3 or 4 equally sized dose level groups based on the appropriate quantiles (Q)). For the ordinal factors (pain, opioid dose) each category was analysed using the first category as reference. Patients already using opioids before admission, who were rotated within 24 hours after admission were excluded for the analysis of time-dependent variables for the opioid used at admission. Reported p-values are two-sided and because of the exploratory nature of this analysis, factors with a p-value < 0.10 in univariate analysis were entered into the multivariable analysis. The 'backward elimination' method was used to find the combination of clinical and genetic factors associated with treatment failure. Again, we used a threshold of 0.1 for significance. Resulting p-values were not corrected for multiple testing because of the

exploratory nature of this analysis. The multivariable analysis was performed twice, with and without adjustment for opioid dose at To.

Results

Between January 2010 and April 2014, a total of 356 individual patients were included in this study. Three patients were not evaluable because they used different opioids simultaneously during the entire study period and therefore 353 patients were analysed. The median age of the patients was 61.5 years (range 24-86) and 168 (48%) patients were male. The most frequent tumour origins were the urinary tract (20%), gastro-intestinal tract (18%) and breast (16%). Most patients had advanced stages of cancer (80%) and the median WHO performance status was 2. The median duration of hospitalisation – and therefore follow-up – was 9 days (range 1-48). For all but 2 patients the duration of follow-up exceeded 72 hours.

The majority of patients (n= 214) was treated with a single type of opioid, whereas 113 patients were treated with 2 opioids, 22 patients with 3 and only 4 patients with 4 opioids (figure 1). In the fentanyl group, most patients (66%) already used fentanyl before hospital admission, while in the morphine group patients were mostly rotated from another type of opioid (58%). In the oxycodone cohort most patients were either opioid naive (38%) or

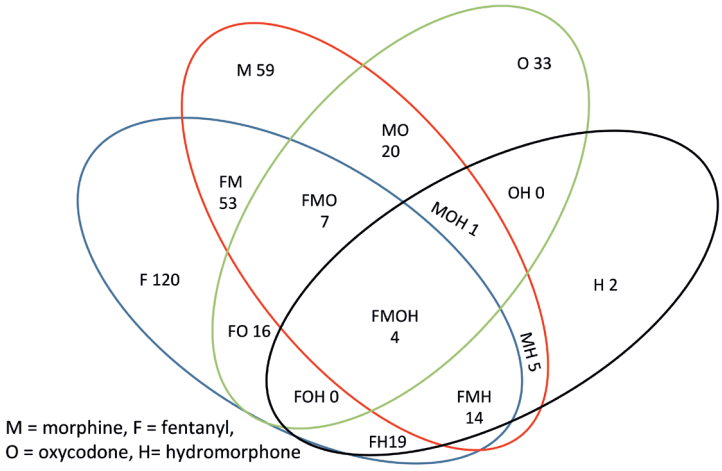

Figure 1. A Venn diagram showing the numbers of patients treated with the specified opioids consecutively throughout the study. For example, 20 patients were treated with both morphine and oxycodone and studied in both cohorts.

already used oxycodone (43%) before study entry. As expected, the hydromorphone cohort contained mostly patients in whom treatment with other opioids had failed (89%). A wide range of treatment doses was observed for all types of opioids. Regarding the median morphine equivalent daily dose (MEDD), doses were quite similar in the fentanyl (120 mg) and morphine group (101 mg) but lower treatment doses were given in the oxycodone cohort (30 mg), whereas, as expected, MEDD was highest in the hydromorphone group (504 mg). The number of patients in whom treatment failed divided by the total number of patients per group was 104/353 (29%) for all patients, 59/233 (25%) for fentanyl, 56/163 (34%) for morphine, 27/81 (33%) for oxycodone and 9/45 (20%) for hydromorphone.

Genotype distributions

From the total cohort, written informed consent for DNA-analysis and a blood sample were available for 346 patients. The undetermined genotype results ranged from 0.9-2.3% per assessed genetic variant. None of the SNPs violated HW equilibrium ($p > 0.05$), nor were there large differences observed between the study and MAFs reported in the literature (Supplementary table 1).

Association of treatment failure with clinical and genetic factors in univariate and multivariable analysis

All patients: In univariate analysis, factors associated with failure of treatment were age (Odds ratio (OR) 0.58, 95% Confidence Interval (CI) 0.39–0.97, p = 0.039), use of adjuvant pain medication started on T0 or later (OR 3.04, 95% CI 1.76–5.24, p = 0.000), use of corticosteroids started on T0 or later (OR 1.95, 95% CI 1.15–3.29, p = 0.012), pain at rest (category severe pain OR 3.13, 95% CI 1.29–7.56, p = 0.011) and worst pain at T0 (category severe pain OR 3.21, 95% CI 1.19–8.69, p = 0.022), the MEDD at T0 (Q3: OR 2.27, 95% CI 1.04–4.92, p = 0.038 and Q4: OR 3.10, 95% CI 1.45–6.63, p = 0.004) and the rs12948783 SNP in *RHBDF2* (OR 0.55, 95% CI 0.32–0.96, p = 0.035). Of these, the use of adjuvant pain medication (OR 3.49, p = 0.000), severe pain at rest (OR 2.67, p = 0.048) and the rs12948783 SNP in *RHBDF2* (OR 0.37, p 0.056) were (possibly) independent as shown in multivariable analysis (tables 1-3). When the analysis was corrected for opioid dose, results were unchanged.

Table 1. Distribution of clinical factors between patients in whom treatment failed/did not fail for all patients and per type of opioid

	All - NF N=249 (%)	*All - F N=104 (%)*	*Fe - NF n = 174 (%)*	*Fe - F n = 59 (%)*	*Mo - NF n = 107 (%)*	*Mo - F n = 56 (%)*	*Ox - NF n= 54 (%)*	*Ox - F n=27 (%)*	*H - NF n=36 (%)*	*H - F n=9 (%)*
Male	124 (50)	44 (42)	84 (48)	26 (44)	49 (46)	25 (45)	25 (46)	11 (41)	23 (64)	4 (44)
Median age	61	59 *	63	58 ‡	63	60 ‡	61	61	55	58
Excluding patients rotating < 24 h	*n=237 (%)*	*n=76 (%)*	*n= 172 (%)*	*n= 40 (%)*	*n= 106 (%)*	*n= 49 (%)*	*n= 54 (%)*	*n= 16 (%)*	*n= 36 (%)*	*n=9 (%)*
Radiotherapy										
- 1-8 weeks before T_0	42 (17)	11 (15)	33 (19)	6 (15)	15 (14)	7 (14)	8 (15)	1 (6)	7 (19)	5 (56)*
- up to 1 week before T_0 / during treatment	38 (16)	12 (16)	34 (20)	11 (28)	20 (19)	9 (18)	4 (7)	2 (13)	6 (17)	0
Adjuvant pain medication										
- Used before T_0 - continued	4 (2)	2 (3)	11 (6)	4 (10)	8 (8)	5 (10)	5 (9)	1 (6)	12 (33)	3 (33)
- Started on T_0 or later	52 (22)	35 (46)*	43 (25)	18 (45)*	26 (25)	22 (45)*	6 (11)	7 (44)*	14 (39)	1 (11)
Corticosteroids										
- Used before T_0 - continued	7 (3)	3 (4)	11 (6)	2 (5)	7 (7)	3 (6)	7 (13)	1 (6)	8 (22)	0
- Started on T_0 or later	95 (40)	43 (57)*	63 (37)	25 (63)*	39 (37)	26 (53) ‡	24 (44)	7 (44)	13 (36)	5 (56)
Pain at rest (NRS)										
- Mild (NRS 0-4)	77 (64)	20 (49)	54 (68)	11 (55)	35 (60)	17 (53)	19 (66)	3 (50)	11 (58)	1 (33)
- Moderate (NRS 5-6)	28 (23)	8 (20)	19 (24)	2 (10)	16 (28)	9 (28)	6 (21)	1 (17)	8 (42)	1 (33)
- Severe (NRS 7-10)	16 (13)	13 (32)*	6 (8)	7 (35)*	7 (12)	6 (19)	4 (14)	2 (33)	0	1 (33)
- Missing	116	35	93	20	48	17	25	10	17	6
Worst pain (NRS)										
- Mild (NRS 0-4)	34 (18)	5 (8)	23 (17)	1 (3)	16 (19)	3 (7)	10 (24)	3 (21)	3 (12)	2 (25)
- Moderate (NRS 5-6)	48 (25)	9 (14)	44 (32)	6 (19)	16 (19)	10 (24)	10 (24)	3 (21)	7 (27)	1 (13)
- Severe (NRS 7-10)	108 (57)	51 (78)*	72 (52)	24 (77) ‡	51 (61)	28 (68)	22 (52)	8 (57)	16 (62)	5 (63)
- Missing	47	11	33	9	23	8	12	2	10	1
Opioid dose on T0										
- Q1: 1st quarter/third/half	79 (33)	12 (16)	48 (28)	5 (13)	59 (56)	19 (39)	35 (65)	7 (44)	17 (47)	6 (67)
- Q2: 2nd quarter/third/half	75 (32)	22 (29)	46 (27)	9 (23)	33 (31)	15 (31)	19 (35)	9 (56)	19 (53)	3 (33)
- Q3: 3rd quarter/third	50 (21)	20 (26) *	45 (26)	16 (40)*	14 (13)	15 (31)*				
- Q4: 4th quarter	33 (14	22 (29) *	33 (19)	10 (25) ‡						

*Abbreviations: NF = not failing; F = failing, Fe= fentanyl, Mo – morphine, Ox = oxycodone, H = hydromorphone; * = p < 0.05, ‡ = p < 0.1*

Table 2. Distribution of genotypes between patients in whom treatment failed/did not fail for all patients and per type of opioid

	All – NF *N= 249*	*All – F* *N=104*	*Fe - NF* *n = 174*	*Fe - F* *n = 59*	*Mo - NF* *n = 107*	*Mo - F* *n = 56*	*Ox - NF* *n= 54*	*Ox - F* *n=27*	*H - NF* *n=36*	*H – F* *n=9*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
***OPRM1* (rs1799971)**										
118AA	187 (79)	82 (80)	126 (76)	51 (88)	87 (84)	40 (73)	43 (81)	21 (81)	26 (72)	9 (100)
118G carrier	50 (21)	20 (20)	39 (24)	7 (12) ‡	17 (16)	15 (27)	10 (19)	5 (19)	10 (28)	0
***COMT* haplotype**										
LPS	123 (53)	51 (51)	82 (50)	30 (53)	56 (54)	30 (54)	25(47)	11 (42)	22 (65)	5 (56)
APS	80 (34)	37 (37)	57 (35)	20 (35)	35 (34)	20 (36)	20 (38)	12 (46)	12 (35)	2 (22)
HPS	31 (13	13 (13)	25 (15)	7 (12)	12 (12)	5 (9)	8 (15)	3 (12)	0	2 (22)*
***KCNJ6* (rs2070995)**										
1032GG	155 (66)	60 (60)	106 (64)	35 (61)	66 (63)	29 (54)	33 (67)	17 (65)	22 (61)	7 (78)
1032A carrier	80 (34)	40 (40)	59 (36)	22 (39)	38 (37)	25 (46)	16 (32)	9 (35)	14 (39)	2 (22)
***RHBDF2* (rs12948783)**										
GG	162 (68)	81 (79)	116 (69)	44 (76)	77 (75)	43 (78)	34 (64)	23 (88)	23 (64)	8 (89)
A carrier	76 (32)	21 (21)*	51 (31)	14 (24)	26 (25)	12 (22)	19 (36)	3 (12)*	13 (36)	1 (11)
***HTR3B* (rs1672717)**										
TT	88 (37)	44 (43)	61 (37)	25 (43)	40 (38)	23 (42)	21 (40)	10 (38)	16 (44)	5 (56)
TC	106 (45)	44 (43)	80 (49)	23 (40)	41 (39)	25 (45)	21 (40)	11 (42)	14 (39)	3 (33)
CC	43 (18)	14 (14)	23 (14)	10 (17)	23 (22)	7 (13)	11 (20)	5 (19)	6 (17)	1 (11)
***OPRK1* (rs7016778)**										
AA	175 (74)	79 (78)	123 (76)	46 (79)	81 (78)	42 (78)	33 (62)	22 (85)		
T carrier	61 (26)	22 (22)	39 (24)	12 (21)	23 (22)	12 (22)	20 (38)	4 (15)*		
***OPRK1* (rs7824175)**										
CC	191 (81)	80 (78)	131 (79)	42 (72)	81 (79)	47 (85)	46 (88)	20 (77)		
G carrier	45 (19)	22 (22)	34 (21)	16 (28)	22 (21)	8 (15)	6 (12)	6 (23)		

Table 2. Continued

	All – NF N= 249	All – F N=104	Fe - NF n = 174	Fe - F n = 59	Mo - NF n = 107	Mo - F n = 56	Ox - NF n= 54	Ox - F n=27	H - NF n=36	H – F n=9
	n (%)		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
***CYP3A4* (rs2242480)**										
***1/*1**			130 (78)	45 (82)			38 (72)	23 (88)		
***1/1G**			31 (19)	10 (18)			12 (23)	3 (12)		
***1G/*1G**			6(4)	0			3 (6)	0		
***CYP3A4* (rs35599367)**										
***1/*1**			146 (88)	50 (91)			46 (87)	24 (92)		
***1/*22**			20 (12)	5 (9)			7 (13)	2 (8)		
***OCT1* phenotype**										
EM					56 (54)	32 (58)				
IM					42 (40)	21 (38)				
PM					6 (6)	2 (4)				
***ABCC3* (rs4793665)**										
-211CC					26 (25)	12 (22)				
-211CT					51 (50)	24 (44)				
-211TT					25 (25)	19 (35)				
***UGT2B7* (rs7438135)**										
-900GG					34 (33)	15 (27)			11 (31)	5 (56)
-900GA					49 (47)	28 (51)			16 (44)	3 (33)
-900AA					21 (20)	12 (22)			9 (25)	1 (11)
***CYP2D6* phenotype**										
PM							4 (8)	2 (8)		
IM							23 (47)	9 (35)		
EM							20 (41)	14 (54)		
UM							2 (4)	1 (4)		

Where numbers do not add up to the numbers indicated per column, data are missing (supplemental table 1). Abbreviations: NF = not failing; F = failing, LPS = low pain sensitivity, APS = average pain sensitivity, HPS = high pain sensitivity; EM = extensive metaboliser, IM = intermediate metaboliser, PM = poor metaboliser, UM = ultra-rapid metaboliser; * = $p < 0.05$, ‡ = $p < 0.1$

Table 3. Results of univariate and multivariable analyses for all patients and per type of opioid

	Univariate analysis			*Multivariable analysis*		
	Odds ratio	**95% Confidence Interval**	***P***	**Odds ratio**	**95% Confidence Interval**	***P***
All						
- Age	0.58	0.39 – 0.97	0.039			
- Adjuvant pain medication ≥ T_0	3.04	1.76 – 5.24	0.000	3.49	1.87 – 9.29	0.000
- Corticosteroids ≥ T_0	1.95	1.15 – 3.29	0.012			
- Pain at rest						
Mild pain	1			1		
Moderate pain	1.1	0.44 – 2.78	0.840	1.25	0.47 – 3.34	0.656
Severe pain	3.13	1.29 - 7.56	0.011	2.67	1.01 – 7.04	0.048
- Worst pain						
Mild pain	1					
Moderate pain	1.28	0.39 – 4.14	0.686			
Severe pain	3.21	1.19 – 8.69	0.022			
- Dose at T_0						
Q1	1					
Q2	1.91	0.91 – 4.02	0.086			
Q3	2.27	1.04 – 4.92	0.038			
Q4	3.10	1.45 – 6.63	0.004			
- rs12948783 (RHBDF2)						
A carrier	0.55	0.32 - 0.96	0.035	0.37	0.14 – 1.03	0.056
Fentanyl						
- Age	0.98	0.95 - 1.00	0.071	0.95	0.91 - 1.01	0.081
- Adjuvant pain medication ≥ T_0	2.45	1.20 - 5.00	0.013	2.82	0.93 - 8.54	0.067
- Corticosteroids ≥ T_0	2.88	1.42 - 5.87	0.004			
- Pain at rest						
Mild pain	1			1		
Moderate pain	0.52	0.10 – 2.55	0.42	0.53	0.10 - 2.74	0.448
Severe pain	5.72	1.61 - 20.37	0.007	5.68	1.52 - 21.28	0.010
- Worst pain						
Mild pain	1					
Moderate pain	3.14	0.36 - 27.64	0.30			
Severe pain	7.67	0.98 - 59.84	0.052			
- Dose at T_0						
Q1	1					
Q2	1.87	0.59 - 6.02	0.289			
Q3	3.41	1.16 - 10.09	0.026			
Q4	2.90	0.91 - 9.29	0.072			
- rs1799971 OPRM1						
118G carrier	0.44	0.19 - 1.06	0.066			

Table 3. Continued

	Univariate analysis			*Multivariable analysis*		
	Odds ratio	**95% Confidence Interval**	***P***	**Odds ratio**	**95% Confidence Interval**	***P***
Morphine						
- Age	0.97	0.94 - 1.00	0.081	0.96	0.93 - 0.99	0.047
- Adjuvant pain medication ≥ T_0	2.50	1.23 - 5.13	0.012	2.51	1.22 - 5.19	0.013
- Corticosteroids ≥ T_0	1.94	0.98 - 3.86	0.058			
- Dose at T_0						
Q1	1	-				
Q2	1.41	0.63 – 3.14	0.40			
Q3	3.33	1.36 - 8.13	0.008			
Oxycodone						
- Adjuvant pain medication ≥ T_0	6.22	1.69 - 22.88	0.006	11.18	2.21 - 56.40	0.003
- rs12948783 (RHBDF2) A carrier	0.23	0.06 - .88	0.032	0.19	0.03 - 1.12	0.066
- rs7016778 (OPRK1) T carrier	0.30	0.09 - 1.00	0.050	0.20	0.04 - 1.09	0.063

≥ T_0: started on To or during hospitalization, Q1 first quantile, Q2 second quantile, Q3 third quantile, Q4 fourth quantile

Fentanyl: In univariate analysis, factors associated with failure of fentanyl treatment were age (Odds ratio (OR) 0.98, 95% Confidence Interval (CI) 0.95–1.00, p = 0.071), use of adjuvant pain medication started on T0 or later (OR 2.45, 95% CI 1.20–5.00, p = 0.013), use of corticosteroids started on T0 or later (OR 2.88, 95% CI 1.42–5.87, p = 0.004), pain at rest (category severe pain OR 5.72, 95% CI 1.61–20.37, p = 0.007) and worst pain at T0 (category severe pain OR 7.67, 95% CI 0.98–59.84, p = 0.052), the dose of fentanyl at T0 (Q_3: OR 3.41, 95% CI 1.16–10.09, p = 0.026 and Q_4: OR 2.90, 95% CI 0.91–9.29, p = 0.072) and the rs1799971 SNP in *OPRM1* (OR 0.44, 95% CI 0.19–1.06, p = 0.066). Of these, age (OR 0.95, p = 0.081), the use of adjuvant pain medication (OR 1.83, p = 0.067), and severe pain at rest (OR 5.68, p = 0.010) were independent as shown in multivariable analysis (tables 1-3). When the analysis was corrected for opioid dose the use of adjuvant pain medication was no longer significant (p = 0.106).

Morphine: For morphine, age (OR 0.97, 95% CI 0.94–1.00, p = 0.081), use of adjuvant pain medication started on T0 or later (OR 2.50, 95% CI 1.23–5.13, p = 0.012), use of corticosteroids started on T0 or later (OR 1.94, 95% CI 0.98–3.86, p = 0.058) and the dose of morphine at T0 (Q_3 OR 3.33, 95% CI 1.36–8.13, p = 0.008) were found to be correlated with treatment failure in univariate analysis. None of the genetic variants correlated with failure of treatment (all: $p > 0.10$). In multivariable analysis use of adjuvant pain medication (OR 2.51, $p < 0.013$) and age (OR 0.96, p = 0.047) were found to correlate with treatment failure (tables 1-3). As for fentanyl, when the analysis was corrected for opioid dose, the use of adjuvant pain medication was no longer significant (p = 0.10).

Oxycodone: For oxycodone, use of adjuvant pain medication started on T0 or later (OR 6.22, 95% CI 1.69–22.88, p = 0.006) and the SNPs rs12948783 (*RHBDF2)* (OR 0.23, 95% CI 0.06–0.88, p = 0.032) and rs7016778 *(OPRK1)* (OR 0.30, 95% CI 0.09–1.00, p = 0.050) were identified in univariate analysis. In multivariable analysis, all three variables remained in the model, without and with correction for opioid dose on T0. (adjuvant pain medication OR 11.18, p = 0.003); rs12948783 in *RHBDF2*: OR 0.19 p = 0.066; rs7016778 in *OPRK1*: OR 0.20, p = 0.063) (tables 1-3).

Hydromorphone: The number of patients in the hydromorphone group was considered too small for further analyses and to draw conclusions.

Discussion

In this cohort of cancer patients treated with opioids, we found that in 20–34% treatment with fentanyl, morphine, oxycodone or hydromorphone failed because of insufficient pain control and/or dose limiting side effects. This is in line with previously reported data (1, 2, 26, 27). Clinical factors associated with treatment failure were the use of adjuvant

pain medication started after T_0 and severity of pain at rest at To. In the morphine and fentanyl cohorts, younger age was also associated with a worse outcome. For the selected SNPs, we identified rs12948783 (*RHBDF2)* and rs7016778 *(OPRK1)* as factors to be explored further in a future study. Previous studies assessing clinical risk factors for the need of opioid rotation have yielded variable results. In a large and prospective study, 118/345 (34.2%) patients underwent opioid rotation and no association between the need for rotation and pain type, use of adjuvant drugs or opioid doses was found (28). In another, retrospective, analysis, 103/273 patients (37.5%) rotated from their first line opioid. Although no correlation with age, type of pain or co-analgesics was found, the use of corticosteroids was associated with a significantly lower rate of opioid rotation (29). In our study, the use of corticosteroids was correlated with higher rates of failure, but only in the univariate analyses. A possible explanation is that in our cohort of patients, corticosteroids were given to patients with severe complex pain. It is also possible that corticosteroids may alter pharmacokinetics (e.g. by induction of CYP3A4) and pharmacodynamics of opioids. The association with the use of adjuvant pain medication is complex. Adjuvant drugs are preferentially used when a neuropathic mechanism may contribute to the clinical presentation. Neuropathic pain is more difficult to treat, as was shown in a validation study of the Edmonton Classification System for Cancer Pain. In that study, neuropathic pain and initial severity of pain were found to be significant predictors of pain complexity and positively correlated with the number of days needed to achieve stable pain control, the use of more adjuvants and higher doses of opioids (30). In another study in cancer patients using morphine, neuropathic pain was associated with a higher opioid escalation index (31). In our study, all patients had nociceptive pain but patients with a neuropathic component, were eligible. Adjuvant drugs were prescribed in case of a suspected neuropathic pain component, which were usually more complex pain syndromes. Further studies should assess neuropathic pain using validated tools. The correlation with age has been observed before. Ericson *et al.* reported a decrease in risk of treatment failure of 3% per 10-year increase in age. Above the age of 65 the risk decreased even 13% per 10-year increase (32). In the present analysis, the correlation between age and failure to morphine and fentanyl remained unchanged when the multivariable analysis was corrected for opioid dose at To and therefore the association cannot be explained by lower treatment doses in elderly patients. We can speculate that differences in opioid metabolism play a role or even that elderly patients and/or their doctors are less likely to report insufficient pain control or severe side effects because they are less demanding and/or more often fear dose escalation. Finally, the association with pain intensity at rest was not unexpected and was reported before (30).

The genetic analysis was also set-up as an exploratory analysis in order to identify candidate SNPs associated with treatment failure of (specific) opioids. While the frequencies of the

studied SNPs followed widely reported prevalence rates, none of the selected genetic variants were found to be significantly correlated with failure of treatment in the entire cohort and the fentanyl, morphine and oxycodone cohorts in the multivariable analysis. We did however find an association between the variant upstream of the *RHBDF2* gene (rs12948783) and treatment outcome ($p<0.10$). In a previous genome wide association study (GWAS), this SNP was found to be significantly associated with decreased pain relief from opioids (33). As this gene is coding for inactive rhomboid protease, an enzyme that has been associated with cancer growth (34, 35), the found hit could be due to cancer demographics of the analyzed cohort, which were not specified in the GWAS study. In our cohort we observed a trend in the opposite direction, i.e. a lower rate of treatment failure. The distribution of tumor types might have been different which, combined with low number of patients, may explain these seemingly contradictory findings. Although the genetic variation (rs1672717) in the *HTR3B* gene, coding for the serotonin receptor subtype 3B, was previously associated with opioid induced nausea and vomiting in more than 1,500 Caucasian cancer patients (17), we did not find an association with opioid failure. Opioid failure is a composite endpoint and although a substantial part of patients failing treatment had dose limiting adverse events, the proportion of patients with severe nausea and vomiting as the main reason for treatment failure was probably too low to detect an association.

Interestingly, we found no correlation between the frequently investigated *OPRM1* SNP (rs1799971) and opioid failure. A meta-analysis has illustrated the relevance of this SNP for opioid requirement in postoperative patients, especially within Asians treated with morphine for visceral pain (36), but the results have been conflicting for opioid response in cancer induced pain (14, 17, 37-43). Although genetic variation in the *KCNJ6* gene has been previously associated with increased opioid requirement in postoperative pain (44) and a tendency toward less opioid effectiveness in chronic pain (45), this variant does not seem to predict opioid failure in our cohort. The minor allele of *OPRK1* rs7016778 SNP has been previously associated with an increased experimental pain threshold (46). This could be caused by increased expression of the kappa receptor and as a consequence a higher affinity for endogenous opioids. Since oxycodone may exert (part of) its analgesic effect primarily via the kappa receptor (47), it is expected that *OPRK1* genetic variants could alter the response and thus the need to switch to a non-kappa-binding opioid. While the relevance of the kappa receptor above the mu-opioid receptor for oxycodone has been discussed (48), in our cohort carriers of the minor allele had a (non-statistically significant) lower risk of treatment failure with oxycodone, which is in line with the decreased pain sensitivity reported in the experimental pain setting. Lastly, none of the SNPs related to metabolism of specific opioids (*CYP3A4, CYP2D6, OCT1, UGT2B7* and *ABCC3)* correlated with failure of treatment in our analysis. This might be due to our limited sample size.

Furthermore, up till now little is known about the effect of changes in pharmacokinetics on pharmacodynamics.

*A*lthough we assembled longitudinal data in a large group of cancer patients and studied a clinically relevant endpoint we must also acknowledge some limitations. Per treatment group numbers were small and the included population was heterogeneous in terms of treatment phase with opioids and opioid dose at T_0. Furthermore we compared patients in whom treatment failed with patients in whom treatment did not fail. Although we strictly defined failure of treatment, we categorised all other patients as not failing treatment although some may not have been successfully treated. Also, we studied failure as a composite endpoint although analgesia and (central) side effects may be independent treatment outcomes (38). Sample size did not allow us to create subgroups according to the reason(s) of failure.

In conclusion, we have identified that the use of adjuvant pain medication, pain intensity at rest and age were associated with failure of treatment with fentanyl, morphine, oxycodone and hydromorphone in this exploratory study. Furthermore, a trend to a negative correlation with treatment failure was seen for the single nucleotide polymorphisms rs12948783 (*RHBDF2)* in all patients and the oxycodone cohort and for rs7016778 *(OPRK1)* in the oxycodone cohort. As these factors are not opioid specific, they cannot be used to guide treatment and the choice for a specific type of opioid. The variant rs7016778 *(OPRK1)* warrants further research with this respect. Ideally, future studies should include large and homogeneous patient populations and protocolise treatments strictly. However, such a trial will be difficult – if not impossible – to perform in a palliative clinical care setting.

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Supplemental material

Supplementary Table 1. Genotype frequencies and HW-equilibrium

SNP	n	MAF study (%)	MAF Literature (%)	HW (p-value)
***CYP3A4* rs2242480 (*1G)**		12	7	0.07
***1/*1**	175			
***1/*1G**	41			
***1G/*1G**	6			
***CYP3A4* rs35599367 (*22)**		6	5	0.37
***1/*1**	196			
***1/*22**	25			
***22/*22**	0			
***CYP2D6* rs35742686 (*3)**		4	2	0.68
***1/*1**	71			
***1/*3**	7			
***3/*3**	0			
***CYP2D6* rs3892097 (*4)**		21	28	0.34
***1/*1**	48			
***1/*4**	23			
***4/*4**	5			
***CYP2D6* deletion (*5)**		2	5	0.86
Negative	76			
Positive	3			
***CYP2D6* rs5030655 (*6)**		2	1	0.86
***1/*1**	76			
***1/*6**	3			
***6/*6**	0			
***CYP2D6* rs28371725 (*41)**		9	9	0.71
***1/*1**	65			
***1/*41**	13			
***41/*41**	1			
***CYP2D6* XN**		2	3	0.86
Negative	76			
Positive	3			
***UGT2B7* rs7438135**		45	50	0.79
GG	49			
GA	77			
AA	33			
***OCT1* rs72552763 (*2)**		21	15	0.45
***1/*1**	247			
***1/*2**	86			
***2/*2**	10			
***OCT1* rs12208357 (*3)**		8	10	0.31
***1/*1**	298			
***1/*3**	43			
***3/*3**	3			

Supplementary Table 1. Continued

SNP	n	MAF study (%)	MAF Literature (%)	HW (p-value)
***OCT1* rs34130495 (*4)**		4	2	0.47
***1/*1**	319			
***1/*4**	26			
***4/*4**	0			
***OCT1* rs34059508 (*5)**		1	1	0.81
***1/*1**	336			
***1/*5**	9			
***5/*5**	0			
***ABCC3* rs4793665**		52	49	0.59
CC	38			
CT	75			
TT	44			
***COMT* rs4680**		51	48	0.28
GG	85			
GA	160			
AA	95			
***COMT* rs4818**		37	42	0.07
CC	141			
CG	144			
GG	56			
***COMT* rs4633**		51	48	0.35
CC	83			
CT	161			
TT	97			
***OPRM1* rs1799971**		11	16	0.77
AA	269			
AG	68			
GG	5			
***KCNJ6* rs2070995**		79	80	0.22
AA	9			
AG	112			
GG	217			
***RHBDF2* rs12948783**		15	15	0.99
CC	246			
CT	89			
TT	8			
***HTR3B* rs1672717**		60	58	0.23
CC	57			
CT	152			
TT	133			
***OPRK1* rs7016778**		13	12	0.38
AA	255			
AT	81			
TT	4			
***OPRK1* rs7824175**		10	10	0.73
CC	274			
CG	64			
GG	3			

Chapter 7

Summary, discussion and future perspectives

Summary and discussion

The prevalence of pain is high in patients with cancer during all stages of their disease. The highest rates, more than 70%, are seen in patients with advanced stages of cancer. Pain is also one of the most feared symptoms by patients, as well as their families. In unselected cohorts, pain is adequately controlled in only 50% of cancer patients (1). We therefore face a major challenge when it comes to improving the treatment of cancer-related pain. In this process, many steps are important, starting with identifying patients with pain and overcoming barriers hindering adequate management of cancer pain, such as knowledge deficits, inadequate pain assessment and misconceptions regarding pain (2). We also face many challenges when it comes to pharmacologic interventions for cancer-related pain. The optimal sequence and combinations of non-opioid, opioid, and adjuvant analgesics are largely unknown due to the current lack of high quality clinical trials. Although opioids are the backbone in the treatment of moderate to severe pain, the causes for the variable treatment outcomes are incompletely understood and from the variety of available opioids we try to find the best type and dose for an individual patient by trial and error. In order to improve and personalize treatment we need to expand our knowledge. The studies described in this thesis, were performed with the intention to expand our knowledge of the outcomes of treatment with various opioids and to find clinical, pharmacokinetic and (pharmaco-) genetic factors associated with variations in treatment outcomes. Ideally, these factors can then be used to guide treatment.

The study described in chapter 2 can be seen as the basis for the other studies in this thesis. We performed a retrospective analysis in a cohort of 157 cancer patients who died during a hospitalisation on our specialised unit for acute palliative care. In this cohort, 68 patients had an indication for continuous palliative sedation prior to death. From a previous analysis (3), we knew that the most common indication for palliative sedation in this cohort of patients was terminal restlessness (60%) and that ultimately sedated patients more often suffered from delirium as compared to non-sedated patients. Moreover, we knew that in both groups of patients, pain was the most prevalent symptom on admission and that it's prevalence remained high during admission (3). As a delirium is often drug induced and opioids are amongst the most frequently implicated drugs, we studied differences in pain medication and other medication with potential cognitive side effects between ultimately sedated and non-sedated patients. We found some striking differences between the use of pain medication between the two groups. Patients in the ultimately sedated group, were already treated with higher doses of opioids on admission (Median Equianalgesic daily dose (MEDD) 270 mg versus 120 mg) and the differences between the MEDD increased further in the final 72h before death.

Furthermore, ultimately sedated patients were switched to other opioids more often (44 versus 22%) and were more frequently treated with adjuvant analgesics.

These data support the assumptions that in a subset of patients, pain is more complex and difficult to treat, that a disturbed dose-effect relationship for opioids may exist in these patients and that intensive treatment of pain may have severe consequences for these patients. These findings raise some important new questions.

Although it is known that in about 30% of patients, treatment with a first opioid is unsuccessful due to the occurrence of dose-limiting side effects and/or insufficient pain control (4, 5), and that opioid rotation can be successful in these cases, we do not know in how many patients treatment with various opioids consecutively is ultimately unsuccessful. More importantly, we do not know which patient will have unwanted outcomes of treatment and what distinguishes them from patients who can be treated successfully. And why treatment with a specific opioid is successful in some patients but unsuccessful in others. Are there differences in clinical effects between the various opioids? What are the main causes for the large differences in required doses? And can we find factors that can be used to guide opioid treatment in individual patients? Or can we identify a subgroup of patients in whom treatment with all opioids is likely to fail? With the aim of answering some of these questions, the other studies described in this thesis, were performed.

To start with, we went back to the basics in chapter 3 where we tried to answer the question whether the incidence of specific side effects differs among frequently used types of opioids. We conducted a systematic review, including only prospective studies reporting adverse events (AEs) in patients treated with the opioids morphine, oxycodone, fentanyl, methadone or hydromorphone for cancer-related pain. Furthermore, we selected studies including patients naive to treatment with step III opioids. We included 25 studies, reporting on 31 treatment cohorts and made an overview of reported rates of AEs per type of opioid. In general, reported rates of AEs were high but we were confronted with very broad ranges in reported rates of all AEs. With the available data, it was not possible to create an overview of the true incidence of AEs per type of opioid and to compare these rates for the various opioids.

This was due to large heterogeneity between the studies, especially regarding the assessment and reporting of AEs. Furthermore, there is a lack of studies in opioid naive patients and – surprisingly – little attention is given to AEs when performing clinical trials. In many studies, there was no systematic assessment of AEs and even when AEs were reported as outcome parameter, most studies reported only a fraction of AEs frequently encountered in daily clinical practice. The most frequently reported AEs were nausea, vomiting, constipation, drowsiness and dry mouth. However, other AEs may also be prevalent and have a high(er) impact on quality of life. For example, itching, myoclonus,

hallucinations and confusion are AEs quite common in clinical practice (6, 7) but were only rarely assessed and reported. And although dry mouth seems to be one of the most frequently occurring AEs with a high impact on quality of life (7) , only 8 out of 25 studies reported this AE.

Next, we performed two pharmacokinetic studies, described in chapters 4 and 5. In chapter 4 we published the results from a population pharmacokinetic study in a cohort of patients treated with fentanyl administered subcutaneously by continuous and bolus infusion and/or transdermally. By inclusion of 942 samples from 52 cancer patients, a non-linear mixed effects model (NONMEM) was built. A one-compartment model with first-order elimination and separate first-order absorption processes for each route best described the data. For 14 patients clinical and pharmacokinetic data were available around rotations from subcutaneous to transdermal fentanyl using a 12-hour rotation scheme, and by using the final model we also simulated a 6-hour rotation scheme. Several findings from this study may be relevant for clinical practice and warrant further studies. Firstly, we report moderate to high variability in PK parameters and plasma concentrations for transdermal as well as for subcutaneous fentanyl. Assuming a correlation between plasma concentrations of fentanyl and clinical effects, these data emphasize the need for individual dose titration. Secondly, when treating patients with transdermal fentanyl it is crucial to consider that fluctuations in plasma concentrations occur during the recommended treatment period of 72 hours per patch, as absorption seems to be closer to a first-order (i.e. concentration dependent) than to a zero-order (i.e. concentration independent) process. This may lead to changes in pain control and/or the occurrence of side effects during the 72 h application period. Thirdly, we estimated a rather low absorption rate constant for subcutaneous fentanyl. If this finding can be confirmed, we may conclude that continuous subcutaneous fentanyl may not be as suitable for fast titration as previously assumed. It may be, that for fast titration, intravenous fentanyl should be preferred, while – for example – in patients in an outpatient setting without an indication for fast titration, continuous infusion of subcutaneous fentanyl may be preferred in case of a contra-indication for patches. Lastly, we observed a rise in plasma concentrations of fentanyl when rotating the route of administration from subcutaneous to transdermal, and this led to toxicity in 12 out of 14 patients with pharmacokinetic and clinical data available around this rotation. As the simulated 6-hour scheme produced similar results (i.e. a similar rise in plasma concentrations of fentanyl), we suggest that overlap in routes should not be used, while earlier performed studies with rotations from intravenous to transdermal fentanyl recommended a 6 hour overlap of routes (8, 9).

In chapter 5, we report results from a population pharmacokinetic study in a cohort of patients treated with continuous and bolus subcutaneously and/or orally (slow-release and/or immediate release) administered morphine. Data were again analysed by using

NONMEM. Plasma concentrations of morphine and metabolites (morphine-3- and 6-glucuronide; M3G and M6G) were best described by a one-compartment model with the metabolites formed via first-order elimination as well as first pass metabolism. We were able to estimate bio-availability of oral morphine to 37.2%, thereby confirming the recommended dose conversion ratio of 1:3 for rotations from subcutaneous to oral morphine. Furthermore, we report AUC ratios (M3G:morphine; M6G: morphine and M3G:M6G) for oral compared to subcutaneous administration. As expected, the subcutaneous route of administration, which avoids first-pass metabolism, resulted in a lower ratio of M3G:morphine and M6G: morphine. The ratio M3G:M6G remained constant. Substantial intra- and inter-individual variability in PK parameters was found. We therefore studied the effect of several clinical and genetic covariates on the clearances of morphine and the metabolites. We also explored whether the variability in morphine clearance is related to treatment outcome. Age, gender, renal function and genetic variants in genes coding for the metabolizing enzyme *UGT2B7* (rs7438135) and the membrane drug transporters *OCT1* (rs72552763, rs12208357, rs34130495, rs34059508) and *ABCC3* (rs4793665) were not found to be significant predictors of the clearance of morphine, and/or the clearances of M3G and M6G. The clearance of M3G and M6G however was found to be a function of body weight and renal function. The clearance of morphine did not differ significantly between patients failing treatment with morphine and patients not failing treatment. The effects of the large variations in concentrations of morphine, M3G and M6G on clinical outcomes should be further explored, as this may have consequences for treatment.

Limitations from both studies mainly arise from the fact that both studies were performed in a real life clinical setting and by following clinical practice. Therefore, most patients were being titrated with fentanyl/morphine during study participation and the frequent dose changes and use of rescue medication made the analyses of PK data more complex. Also, in many patients plasma samples were taken after semi-simultaneous administration of opioids by different routes. For example, the majority of patients treated with subcutaneous fentanyl was treated with a patch before, which, due to the long terminal half-life made it difficult to estimate the contribution of each route of administration to the measured plasma level.

In chapter 6, we report an analysis that was performed with the aim to find clinical and (pharmaco-) genetic factors associated with treatment outcome. Here, we selected several factors from the literature and tested these for a correlation with treatment failure in the entire cohort consisting of 356 patients and after categorising each patient in cohorts per type of opioid patients were treated with. Treatment failure was defined as a rotation to another type of opioid, treatment with intrathecal opioids, both because of insufficient pain control and/or side effects, *or* the use of palliative sedation because of refractory

symptoms associated with opioid treatment in the dying phase. In all other patients the outcome of treatment was considered as non-failure. As this was an explorative analysis, factors with a p-value of < 0.10 in univariate analysis were entered into multivariable analysis and data were not corrected for multiple testing. In multivariable analysis, younger age, the use of adjuvant pain medication, and pain intensity at rest were associated with failure of treatment with fentanyl, morphine and oxycodone. Furthermore, the single nucleotide polymorphisms (SNPs) rs12948783 (*RHBDF2*) and in the oxycodone cohort rs7016778 (*OPRK1*) showed a trend to a negative correlation with treatment failure. The role of these two genetic variants should be further explored, noting that the *RHDBF2* SNP was identified in a genome wide association study (GWAS) that reported patients carrying the studied variant had decreased pain relief from opioids while in our analysis we found a trend towards a lower rate of treatment failure. The associations between the clinical factors and treatment failure were not unexpected, although the relationship between age and treatment outcome is interesting. None of these factors, except maybe the *OPRK1* SNP, seem to be opioid specific and can therefore not be used to guide treatment with individual opioids.

Importantly, none of the SNPs related to metabolism of specific opioids (*CYP3A4*, *CYP2D6*, *OCT1*, *UGT2B7* and *ABCC3*) correlated with failure of treatment in our analysis, which supports the data reported in chapter 5.

General conclusions and future perspectives

Despite all efforts described above, we are still far away from truly individualising opioid treatment based on prognostic and predictive factors. This seems to be due, at least partly, to our incomplete understanding of the mechanisms of action involved in opioid treatment. These actions can be defined at the level of the receptor, the cell, and in the modulation of circuitry within the nervous system. Although much progress has been made in the past decades, the challenge to integrate the various areas of investigation remains (12). Once we have unravelled all factors that may be of influence on treatment outcomes, we can study the effects of variations in these factors using a more structured approach. We should learn from the abundance of cancer research, in which the biology of cancer is being unravelled step by step, leading to highly targeted treatment approaches and combinations.

The lack of well performed studies with opioids limits the ability to draw firm conclusions on the role of clinical factors for specific opioids. There is a need for investigator driven, high quality clinical trials with opioids. In order to make this possible, such studies should be subsidised by independent parties and we should renounce the notion that performing

research in a palliative care setting is either unethical or too difficult to perform. The inclusion of participants in palliative care studies has no unique risk factors, although there is more often an accumulation of factors hampering inclusion. Preparing for these by use of a specifically created checklist might prevent or at least reduce problems with inclusion (13).

Furthermore, international consensus should be sought on the use of validated assessment tools for pain and adverse events specific to palliative care, as has been suggested in a recent Cochrane review as well (14).

Regarding the pharmacokinetic studies, one of the difficulties is the fact that the opioid receptors are mainly located in the central nervous system. As the effects of opioids are dependent on the concentrations available at the receptor sites, we should possibly first explore the correlation between drug concentrations in cerebrospinal fluid (CSF) versus plasma. Although some efforts have been made in this area (15-18), our knowledge for the various opioids is still insufficient. To minimise patient burden, such studies could be performed in healthy volunteers or we should consider collecting samples from patients with another indication for a lumbar puncture. Furthermore, when performing pharmacokinetic studies, the challenge should be to design studies with a limited number of well-timed samples, while limiting disturbing factors (such as dose changes or extra doses of medication). The challenge will be to disrupt clinical practice as little as possible in order to minimize the burden of study participation for patients, while optimizing circumstances for performing studies. Future clinical studies could, for instance, focus on exploring the relationship between plasma and/or CSF concentrations of opioids and clinical outcomes, on finding ways to create more stable plasma concentrations during treatment with transdermal fentanyl and on optimising opioid rotation schemes for changes in route of administration and types of opioids.

To study the effects of genetic variations in more detail, we should ideally expand our knowledge on factors influencing the outcomes of opioid treatment first, so that we can study (pharmaco-) genetic variations more focused on specific pathways. As the outcome of treatment seems to be the result of a complex interplay of clinical, genetic and pharmacokinetic factors, it seems unlikely that one SNP will significantly influence treatment outcome. We may therefore need to focus on finding 'gene panels' by including combinations of SNPs involved in any step of the involved pathways. As long as our knowledge on these pathways is insufficient, GWAS might help to identify relevant SNPs and pathways. Such GWAS should ideally be performed in large, homogeneous patient populations and require objective criteria for defining treatment failure. Such studies will therefore be difficult to perform.

Lastly, as research on opioids is not frequently performed and is too specific for cancer journals, we experienced some difficulties in finding appropriate journals for the

publication of our results. In our opinion this is partly due to the fact that palliative care belongs to no one while it should belong to everyone. As the prevalence of pain is high in cancer patients, all physicians involved in treatment of patients with cancer, should also have knowledge on treatment of cancer-related pain. Hopefully, the current attention for palliative care in the political domain but also in the public domain, will yield more attention for (clinical) research performed in this area and lead to better possibilities for publications that reach a wide medical audience.

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7

Appendix 1

Samenvatting, discussie en aanbevelingen

Samenvatting, discussie en aanbevelingen

Pijn komt veel voor bij patiënten met kanker, gedurende alle stadia van de ziekte. Vooral bij patiënten met gevorderde stadia van kanker komt pijn veel voor, bij meer dan 70%. Daarnaast is pijn één van de symptomen die – zowel door patiënten als door hun naasten – het meest gevreesd worden. In niet geselecteerde groepen van patiënten met kanker, bleek bij slechts 50% van hen de pijn voldoende gestild te zijn (1). Het verbeteren van de behandeling van kanker-gerelateerde pijn is daarom een enorme uitdaging. Hierbij zijn vele stappen belangrijk, te beginnen met het vinden en herkennen van patiënten met pijn en het overwinnen van barrières die adequate behandeling van pijn bemoeilijken; zoals gebrek aan kennis, inadequate beoordeling van pijn en misvattingen aangaande pijn (2). Ook op het gebied van medicamenteuze behandeling van kanker-gerelateerde pijn, zijn er vele uitdagingen. De optimale volgorde en combinaties van niet-opioïde-, opioïde- en aanvullende pijnmedicatie zijn grotendeels onbekend als gevolg van een gebrek aan goed opzette klinische studies. Hoewel opioïden de basis vormen van de behandeling van matig tot ernstige pijn, is onvoldoende bekend wat de oorzaken zijn voor de wisselende uitkomsten van behandeling. We proberen voor een individuele patiënt het beste middel in de optimale dosering te vinden door 'trial and error' – oftewel door wanneer dat nodig is verschillende middelen en doseringen uit te proberen. Om de behandeling te kunnen verbeteren en meer op de individuele patiënt af te stemmen, is meer kennis nodig. De onderzoeken die beschreven staan in dit proefschrift, zijn uitgevoerd met als doel onze kennis omtrent uitkomsten van behandeling met opioïden te verbeteren, en om klinische, farmacokinetische en (farmaco-)genetische factoren te vinden die geassocieerd zijn met variaties in uitkomsten van behandeling. Idealiter, kunnen deze factoren vervolgens gebruikt worden om te helpen bij het maken van keuzes in de behandeling.

De studie die beschreven staat in hoofdstuk 2, kan gezien worden als een basis voor de rest van de onderzoeken in dit proefschrift. We voerden een retrospectieve analyse uit, in een groep van 157 patiënten met kanker die overleden tijdens een ziekenhuisopname op onze gespecialiseerde unit voor palliatieve zorg. Binnen deze groep, bestond er bij 68 patiënten een indicatie voor continue palliatieve sedatie tot aan het overlijden. Uit een eerdere analyse van ditzelfde cohort (3), wisten we dat terminale onrust de meest voorkomende indicatie was voor palliatieve sedatie (60%) en dat patiënten die uiteindelijk gesedeerd moesten worden vaker een delier hadden dan patiënten zonder indicatie voor sedatie. Ook wisten we dat – in beide groepen – pijn het meest voorkomende symptoom was bij opname en dat de prevalentie van pijn hoog bleef gedurende de opname (3). Omdat een delier vaak veroorzaakt wordt door medicatie, waarbij opioïden een veel genoemde oorzaak zijn, onderzochten we verschillen in het gebruik van pijnmedicatie en andere medicatie die cognitieve bijwerkingen kan veroorzaken, tussen uiteindelijk gesedeerde

en niet gesedeerde patiënten. We vonden daarbij opmerkelijke verschillen in het gebruik van pijnmedicatie tussen de twee groepen.

Patiënten in de uiteindelijk gesedeerde groep, werden al bij opname met hogere doseringen van opioïden behandeld (Mediane Equianalgetische dag dosering (MEDD) 270 mg versus 120 mg), waarbij de verschillen in de MEDD verder opliepen in de laatste 72 uur voor het overlijden. Ook vond bij de gesedeerde patiënten vaker een opioïd rotatie plaats (44 versus 22%) en werden deze patiënten vaker met aanvullende pijnmedicatie behandeld.

Deze data geven steun aan de aannames dat bij een deel van de patiënten pijn meer complex en moeilijker behandelbaar is, dat er bij deze patiënten een verstoorde balans bestaat tussen de dosis en de effecten van opioïden en dat intensieve behandeling van pijn bij deze patiënten ernstige gevolgen kan hebben. De bevindingen roepen belangrijke, nieuwe vragen op.

Hoewel bekend is dat, bij ongeveer 30% van de patiënten, behandeling met een eerste opioïd niet succesvol is ten gevolge van het ontstaan van dosis-limiterende bijwerkingen en/of onvoldoende pijncontrole (4, 5), en dat een opioïd rotatie (verandering naar een ander soort opioïd) bij deze patiënten succesvol kan zijn, is niet bekend bij hoeveel patiënten behandeling met opeenvolgende, verschillende opioïden uiteindelijk niet succesvol is. Belangrijker is nog, dat ook niet bekend is bij welke patiënten dit zal gebeuren en wat hen onderscheid van patiënten die wel succesvol behandeld kunnen worden. En waarom behandeling met een specifiek opioïd bij de ene patiënt wel, en bij de andere patiënt niet succesvol is. En of er verschillen zijn in de klinische uitkomsten van de verschillende opioïden of wat de belangrijkste oorzaken zijn voor de grote verschillen in benodigde doseringen. En kunnen we factoren vinden die we kunnen gebruiken om sturing te geven aan behandeling met opioïden bij individuele patiënten? Of kunnen we die patiënten identificeren bij wie behandeling met alle opioïden waarschijnlijk zal falen? De andere onderzoeken, die beschreven staan in dit proefschrift, werden uitgevoerd met het doel een deel van deze vragen te beantwoorden.

In hoofdstuk 3, zijn we bij de basis begonnen doordat we hebben geprobeerd een antwoord te vinden op de vraag of er een verschil is in de incidentie van specifieke bijwerkingen tussen verschillende, veel gebruikte opioïden. We hebben daarom een systematische review uitgevoerd, waarin we alleen prospectieve studies includeerden die bijwerkingen rapporteerden van patiënten die voor kanker-gerelateerde pijn werden behandeld met morfine, oxycodon, fentanyl, methadon of hydromorfon. We selecteerden alleen studies waarin patiënten werden geïncludeerd die niet eerder met deze opioïden behandeld waren, omdat gewenning op kan treden en zodat patiënten die vanwege falen op een eerder opioïd roteerden, niet meegenomen werden. We konden 25 studies includeren, die rapporteerden over 31 behandel groepen, waarna we per type opioïd, een overzicht

maakten van het gerapporteerde aantal bijwerkingen. Hoewel gemiddeld genomen bij grote aantallen patiënten bijwerkingen gerapporteerd werden, was de spreiding erg groot. Met de beschikbare gegevens lukte het niet om per type opioïd een overzicht te maken van de daadwerkelijke incidentie van bijwerkingen (het aantal nieuw ontstane symptomen/bijwerkingen na start van een opioïd) en om deze incidenties te vergelijken. Dit kwam door grote verschillen tussen de studies, vooral aangaande het beoordelen en rapporteren van bijwerkingen. Er is een tekort aan studies die zijn uitgevoerd bij niet eerder met opioïden behandelde patiënten en – tot onze verbazing – is er maar weinig aandacht voor bijwerkingen binnen klinische studies. In veel studies was geen systematische beoordeling van bijwerkingen gedaan, en wanneer wel bijwerkingen werden gerapporteerd, betrof het vaak slechts een fractie van de bijwerkingen die in de dagelijkse praktijk veel gezien worden. De meest gerapporteerde bijwerkingen waren misselijkheid, braken, obstipatie, sufheid en droge mond. Andere bijwerkingen komen echter ook veel voor en kunnen een grote(re) invloed hebben op de kwaliteit van leven. Zo komen bijvoorbeeld jeuk, myoclonieën, hallucinaties en verwardheid regelmatig voor (6, 7), maar werden deze bijwerkingen slechts zelden uitgevraagd en gerapporteerd. En hoewel droge mond één van de meest voorkomende bijwerkingen lijkt te zijn met een grote invloed op kwaliteit van leven (7), rapporteerden slechts 8 van de 25 studies deze bijwerking.

Vervolgens hebben we twee farmacokinetiek (PK) studies uitgevoerd, die worden beschreven in hoofdstukken 4 en 5. In hoofdstuk 4 zijn resultaten gepubliceerd uit een populatie farmacokinetiek studie in een patiënten cohort dat behandeld werd met continue en bolus subcutaan (onderhuidse) en/of transdermaal (via de huid, pleister) toegediende fentanyl. Door inclusie van 942 samples verkregen van 52 patiënten met kanker, kon een non-linear mixed effects (NONMEM) model worden gebouwd. Dit is een wiskundig model dat om de data heen wordt gebouwd en waarin rekening wordt gehouden met een niet rechtlijnig verband tussen onderzochte variabelen en uitkomsten en met verschillende bekende maar ook onbekende factoren, die invloed kunnen hebben op de farmacokinetiek. Met een 1-compartiment model met 1e orde eliminatie (per tijdseenheid wordt een constante fractie van de nog aanwezige stof uitgescheiden of omgezet in een andere stof, een metaboliet) en aparte 1e orde absorptie (absorptie snelheid afhankelijk van concentratie) voor beide routes konden de data het beste worden beschreven. Bij 14 patiënten waren klinische en farmacokinetische gegevens beschikbaar rondom rotaties van subcutaan naar transdermaal fentanyl met een 12-uur durende overlap van de routes, en met het uiteindelijke model kon ook een schema met 6 uur overlap worden gesimuleerd. Meerdere bevindingen uit deze studie kunnen belangrijk zijn voor de dagelijkse praktijk en verdienen verder onderzoek. Ten eerste rapporteren we matige tot hoge variatie in PK parameters en plasma concentraties van fentanyl, zowel

voor de transdermale als de subcutane route. Wanneer we aannemen dat er een verband is tussen de plasma concentratie van fentanyl en de klinische effecten, onderstrepen deze data dat de dosering altijd individueel getitreerd moet worden. Ten tweede is het belangrijk dat we ons realiseren dat plasma concentraties van fentanyl niet stabiel zijn gedurende de aanbevolen behandelduur van 72 uur per pleister. Dit komt doordat de absorptie via een 1e orde proces lijkt te verlopen (afhankelijk van concentratieverschil) in plaats van via een oe orde proces (niet afhankelijk van concentratieverschil). De schommelingen in plasma concentraties kunnen leiden tot veranderingen in pijncontrole en bijwerkingen gedurende de 72 uur dat een fentanyl pleister geplakt blijft. Ten derde, is de door ons geschatte absorptieconstante voor subcutaan fentanyl vrij laag. Als deze bevinding kan worden bevestigd, kan dit betekenen dat continue subcutaan toegediende fentanyl minder geschikt is voor snelle titratie. Daarvoor moet dan misschien intraveneus fentanyl gebruikt worden, terwijl bijvoorbeeld bij poliklinische patiënten waarbij er geen reden is voor snelle titratie, continue subcutane infusie de voorkeur kan hebben wanneer behandeling met pleisters niet lukt of niet mogelijk is. Tenslotte, zagen we een stijging in plasma concentraties van fentanyl bij rotaties van subcutaan naar transdermaal fentanyl. Bij 12 van de 14 patiënten waarvan zowel PK als klinische gegevens beschikbaar waren, leidde dit tot (een toename van) bijwerkingen. Omdat het gesimuleerde schema met 6 uur overlap eenzelfde stijging liet zien van de plasma concentratie, suggereren we dat het continueren van de subcutane infusie na aanbrengen van de pleister vermeden moet worden, terwijl eerdere studies rondom rotaties van intraveneus naar transdermaal fentanyl juist adviseerden om de intraveneuze toediening dan nog 6 uur te continueren (8, 9).

In hoofdstuk 5, beschrijven we de resultaten van een populatie farmacokinetiek studie in een cohort van patiënten met kanker die werden behandeld met continue en bolus subcutaan en/of oraal (vertraagde of onmiddellijke afgifte) toegediende morfine. De data werden wederom geanalyseerd met NONMEM. Morfine en de metabolieten (morfine-3- en 6-glucuronide; M3G en M6G) konden het beste worden beschreven door een 1-compartiment model waarbij de vorming van de metabolieten plaats vond via 1e orde eliminatie van morfine en waarin het effect van de eerste leverpassage (First pass effect) was meegenomen. De biologische beschikbaarheid van oraal morfine kon worden geschat op 37.2%, waarmee de aanbevolen verhouding in dosering van 1:3 bij omzetting van subcutaan naar oraal morfine kan worden bevestigd. Ook rapporteren we AUC (area under the curve) ratio's (M3G:morfine, M6G:morfine en M3G:M6G) voor oraal vergeleken met subcutaan toegediende morfine. Zoals verwacht, zijn de ratios M3G:morfine en M6G:morfine lager na subcutane toediening doordat het effect van de eerste leverpassage vermeden wordt. De verhouding M3G:M6G blijft wel constant. We rapporteren behoorlijke variatie in PK parameters tussen verschillende patiënten maar

ook binnen dezelfde patiënten. Daarop hebben we het effect van verschillende factoren op de klaring van morfine en de metabolieten onderzocht en het verband tussen klaring van morfine en uitkomst van behandeling geëxploreerd. We vonden dat leeftijd, geslacht, nierfunktie en genetische variaties in genen die coderen voor het metaboliserende enzym *UGT2B7* (rs7438135) en de membraneuze drug transporters *OCT1* (rs72552763, rs12208357, rs34130495, rs34059508) en *ABCC3* (rs4793665) geen significante voorspellers waren van de klaring van morfine. De klaring van de metabolieten bleek een funktie van lichaamsgewicht en nierfunktie te zijn. De klaring van morfine verschilde niet significant tussen patiënten bij wie de behandeling met morfine faalde en patiënten bij wie deze behandeling niet faalde. De invloed van de aanzienlijke variaties in concentraties van morfine, M3G en M6G op de uitkomsten van behandeling moeten verder onderzocht worden.

Beperkingen van beide studies komen vooral voort uit het feit dat beide werd uitgevoerd door het volgen van de dagelijkse praktijk tijdens een ziekenhuisopname. Als gevolg daarvan, werden veel patiënten gedurende hun deelname aan de studie getitreerd met fentanyl/morfine waarbij frequente dosisaanpassingen en gebruik van extra (rescue) doseringen nodig waren. Dit maakte de analyse van de PK data ingewikkelder. Ook werden bij veel patiënten samples verkregen na semi-gelijktijdige toediening van opioïden via verschillende routes. Zo was de meerderheid van de patiënten die behandeld werden met subcutaan fentanyl daarvoor met fentanyl pleisters behandeld. Door de lange halfwaardetijd was het daardoor moeilijk om de bijdrage van iedere route aan de gemeten plasma concentratie te schatten.

In hoofdstuk 6 beschrijven we een analyse die werd uitgevoerd met als doel om klinische en (farmaco-) genetische factoren te vinden die samenhangen met de uitkomsten van behandeling.

We selecteerden daarvoor verschillende factoren vanuit de literatuur en testten vervolgens of deze verband hadden met falen van de behandeling in het gehele cohort van 353 patiënten en na het verdelen van de patiënten in behandelcohorten per type opioïd. Het falen van een behandeling was gedefinieerd als de noodzaak tot een rotatie naar een ander type opioïd of behandeling met intrathecale opioïden (via een ruggenprik) vanwege onvoldoende pijncontrole en/of dosis beperkende bijwerkingen of het toepassen van palliatieve sedatie vanwege onbehandelbare symptomen ten gevolge van een behandeling met opioïden in de stervensfase. Bij alle andere patiënten werd de uitkomst van behandeling als niet falen beschouwd. Omdat dit een exploratief (verkennend) onderzoek was, werden factoren met een p-waarde van < 0.10 in de univariate analyse, geïncludeerd in de multivariabele analyse en werden de data niet gecorrigeerd voor multiple testing (hoe meer factoren onderzocht worden, hoe groter de kans dat er verschillen gevonden worden). Met multivariabele analyse vonden we dat

lagere leeftijd, het gebruik van aanvullende pijnmedicijnen en de ernst van pijn in rust geassocieerd waren met het falen van behandelingen met fentanyl, morfine en oxycodon. Ook werd bij de single nucleotide polymorphisms (SNP's; een variatie in het DNA van één enkele nucleotide lang) rs12948783 *(RHBDF2)* en alleen in het oxycodon cohort bij rs7016778 *(OPRK1)* een trend gezien in de richting van een negatief verband met falen op behandeling. De rol van deze twee genetische variaties moet verder worden onderzocht, temeer omdat de *RHDBF2* SNP ontdekt is in een genoom brede associatie studie waarin patiënten met de bestudeerde variant minder goede pijnstilling hadden van opioïden terwijl in onze analyse het tegenovergestelde werd gevonden, namelijk een lagere kans op falen van behandeling bij dragers van deze genetische variant. De verbanden tussen de klinische factoren en het falen van behandeling waren niet onverwacht, hoewel de relatie tussen leeftijd en uitkomst van behandeling interessant is. Geen van de gevonden factoren, behalve misschien de *OPRK1* SNP is specifiek voor een bepaald type opioïd, waardoor deze factoren de keuze voor een bepaalde behandeling niet kunnen sturen. Belangrijk is ook, dat geen van de SNP's die gerelateerd zijn aan het metabolisme van specifieke opioïden *(CYP3A4, CYP2D6, OCT1, UGT2B7 en ABCC3)* een samenhang vertoonden met falen van behandeling in deze analyse, hetgeen de bevindingen die in hoofdstuk 5 werden beschreven ondersteunt.

Algemene conclusies en aanbevelingen voor de toekomst

Ondanks alle hierboven beschreven inspanningen, zijn we nog ver weg van het echt individualiseren van behandeling met opioïden door gebruik te maken van prognostische en predictieve factoren. Dit lijkt tenminste deels een gevolg te zijn van ons onvolledige begrip van de werkingsmechanismen van opioïden en daarbij betrokken pathways (routes). Deze bevinden zich op het niveau van de receptoren, de cellen en in de modulerende systemen binnen het centraal zenuwstelsel. Hoewel er veel vooruitgang is geboekt in de afgelopen jaren, blijft het een uitdaging om de bevindingen vanuit de verschillende onderzoeksgebieden te integreren (10). Zodra we alle factoren kennen die de uitkomsten van behandeling kunnen beïnvloeden, kunnen we de effecten van variaties in deze factoren op de uitkomsten van behandeling meer gestructureerd onderzoeken. Hierbij kunnen we leren van de veelheid aan onderzoeken bij kanker, waarbij de biologie van kanker stap voor stap is ontrafeld waardoor gerichte behandelingen en combinaties van behandelingen konden worden ontwikkeld.

Het gebrek aan goed opgezette studies met opioïden maakt het onmogelijk om harde conclusies te trekken over de rol van klinische factoren bij specifieke opioïden. Er is

behoefte aan door onderzoekers opgezette klinische studies van hoge kwaliteit. Om dit mogelijk te maken, moeten dergelijke studies gefinancierd worden door onafhankelijke partijen en moeten we de aanname dat onderzoek doen bij patiënten in de palliatieve fase onethisch of moeilijk uitvoerbaar is, loslaten. Het includeren van patiënten in palliatieve zorg studies kent geen unieke risicofactoren, hoewel er wel vaker een opeenstapeling is van factoren die de inclusie bemoeilijken. Voorbereiding hierop, bijvoorbeeld door middel van een speciaal voor dit doel gemaakt checklist, kan problemen voorkomen of tenminste verminderen (11). Verder moet internationaal consensus gezocht worden over het gebruik van gevalideerde beoordelingsschalen voor pijn en bijwerkingen specifiek voor palliatieve zorg, zoals ook gesuggereerd werd in een recent verschenen Cochrane review (12).

Aangaande de farmacokinetiek studies is een van de moeilijkheden dat de opioïd receptoren zich voornamelijk in het centrale zenuwstelsel bevinden. Omdat de effecten van opioïden afhankelijk zijn van de concentratie van opioïden bij deze receptoren, zou wellicht eerst onderzocht moeten worden wat het verband is tussen de concentraties in plasma (bloed) en liquor (hersenvocht). Hoewel er beperkt onderzoek is gedaan op dit gebied (13-16), is onze kennis voor de verschillende opioïden momenteel niet toereikend. Om de belasting voor patiënten zo laag mogelijk te houden, zouden studies waarbij liquor en plasma worden onderzocht uitgevoerd kunnen worden bij gezonde vrijwilligers of zouden samples kunnen worden afgenomen bij patiënten die opioïden gebruiken en om een andere reden een ruggenprik moeten ondergaan. Verder zou bij het opzetten van PK studies de uitdaging moeten zijn de studie zo op te zetten dat het aantal samples zo beperkt mogelijk gehouden kan worden, door goede timing en door het beperken van verstorende factoren (zoals aanpassingen in de dosering of extra doses). De uitdaging zal zijn om de klinische praktijk zo min mogelijk te verstoren en zo de belasting van studiedeelname voor patiënten zo laag mogelijk te houden, terwijl tegelijkertijd de omstandigheden voor uitvoering van de studie zo optimaal mogelijk zijn. Toekomstige studies kunnen zich bijvoorbeeld richten op het onderzoeken van het verband tussen spiegels van opioïden in bloed en liquor, op het vinden van methoden om een meer stabiele bloedspiegel van fentanyl te krijgen bij toediening door middel van pleisters en op het optimaliseren van rotatie schema's voor zowel veranderingen in toedieningsroute als in type middel. Om de effecten van genetische variaties beter te kunnen onderzoeken, zouden we idealiter eerst meer kennis moeten hebben van factoren in verschillende pathways die van invloed zijn op de uitkomsten van behandeling, zodat we gericht het effect van (farmaco-) genetische variaties in deze factoren kunnen onderzoeken. Doordat de uitkomsten van behandeling het gevolg lijken te zijn van een ingewikkeld samenspel tussen klinische, genetische en farmacokinetische factoren, lijkt het echter onwaarschijnlijk dat één SNP een significant effect zal hebben. Daarom moeten we ons misschien richten op het vinden van groepen van genen door combinaties van SNP's te maken die betrokken zijn bij de verschillende

pathways. Zolang we deze pathways echter onvoldoende kennen en begrijpen, kunnen genoom brede associatie studies (studies waarbij alle bekende genen onderzocht worden en waarbij naar verschillen tussen bepaalde groepen kan worden gezocht) helpen bij het vinden van relevante SNP's. Zulke studies moeten echter uitgevoerd worden in grote, homogene groepen van patiënten en vereisen objectieve criteria voor het vaststellen van falen op een behandeling. Dat maakt zulke studies moeilijk uitvoerbaar.

Tot slot hebben wij, doordat weinig onderzoek wordt gedaan naar opioïden en dit als te specifiek wordt gezien voor medische tijdschriften gericht op kanker, soms moeite gehad met het vinden van een geschikt tijdschrift om onze bevindingen in te publiceren. Wij zijn van mening dat dit deels het gevolg is van het feit dat niemand zich 'eigenaar' voelt van palliatieve zorg terwijl het juist voor vrijwel iedere behandelaar belangrijk is. Omdat pijn veel voorkomt bij patiënten met kanker, zouden alle behandelaars die betrokken zijn bij de behandeling van patiënten met kanker ook kennis moeten hebben over de behandeling van kanker gerelateerde pijn. Hopelijk leidt de huidige aandacht voor palliatieve zorg op het politieke, maar ook het publieke vlak, tot meer aandacht voor wetenschappelijk onderzoek op dit gebied en leidt dat weer tot betere publicatie mogelijkheden waarmee een breed medisch publiek kan worden bereikt.

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Appendix 2

Dankwoord

Dankwoord

In de afgelopen jaren is mij (heel erg) vaak gevraagd of er nog een 3e kind zou komen. En net zo vaak heb ik geantwoord dat dit boekje mijn 3e 'kind' zou worden. Dat leverde soms vragende of zelfs bezorgde blikken op. De analogie tussen het krijgen van een kind en het schrijven van een proefschrift is echter vaker getrokken, en terecht. Vreemd? Zeker niet, ik zal u uitleggen waarom aan de hand van eigen ervaringen tijdens mijn promotietraject.

Ten eerste: hoewel ik weldegelijk bij de totstandkoming van dit promotietraject betrokken was, is het me toch een beetje overkomen en was het aanvankelijk ook niet erg gewenst. (Om verwarring te voorkomen: mijn zwangerschappen waren zeer gewenst.) Maar toen ik eenmaal aan het onderzoek begonnen was kon en wilde ik niet meer terug. Ik raakte aan het idee gewend en begon steeds meer uit te kijken naar de resultaten. Het eindresultaat begon steeds meer vorm te krijgen: waar ik in het begin geen idee had waar al mijn inspanningen toe zouden leiden, kwam uiteindelijk dit tot in detail uitgewerkte boekje tot stand.

Ten tweede: hoewel het schrijven van dit proefschrift ietsje langer duurde dan 9 maanden, had ook het beloop overeenkomsten met een zwangerschap. De kern is eigenlijk dat het beloop nogal wisselt terwijl je daar niet of nauwelijks invloed op hebt. Het gaat zoals het gaat en het komt zoals het komt, je kunt je er maar het beste aan overgeven.

Ten derde: hoewel het heel verstandig is om voor je 40e, en bij voorkeur nog veel eerder kinderen te krijgen/ een proefschrift te schrijven, maken de omstandigheden soms dat de dingen anders lopen. En zo kan het zijn dat je toch na je 40e nog een kind krijgt of in mijn geval (net....) na je 40e promoveert.

Waar de vergelijking mank gaat is dat voor het 'maken' van een kind meestal slechts 2 mensen nodig zijn. Voor de totstandkoming van dit proefschrift waren dat er vele meer. Een aantal mensen wil ik in het bijzonder bedanken voor hun bijdrage in wetenschappelijke en/of persoonlijke sfeer.

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Siv Jönsson and João Abrantes. I don't know where to begin... When we started to work on the PK studies, I had never heard of NONMEM and had no experience with PK studies at all. Nonetheless, you have had the patience to teach me how to build a NONMEM dataset, correct endless mistakes in it and explain all steps in the analyses. You always remained calm and friendly, even when I was pressuring you because of time issues. It was a pleasure to work with you and I am very happy to finally meet you in person on the 9th of December.

Iedereen betrokken bij de PG analyses. Anne-Joy: jij beheerde de samples en wist ze op de juiste momenten ook weer snel te vinden, waarvoor dank! Maja, jij hebt me wegwijs gemaakt in de wereld van de SNP's en hebt alle genotyperingen uitgevoerd. Veel succes met de afronding van jouw promotietraject en wat daarna komt. Ron, dank voor het mogelijk maken van alle genotyperingen in jouw laboratorium.

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Iedereen die betrokken is geweest bij het (opnieuw) bouwen en vullen van de database: Kirsten, Rene, Nelly, Jessica, Regine, Caroline, Petra, Ellen, Tarik, Armina en Zubeyde. Het was een hele tour om een goede dataset te bouwen, te verhuizen, te corrigeren en te vullen. Maar het is gelukt! Veel dank voor alle uren die jullie daarin gestopt hebben.

Alle collega's die me de ruimte hebben gegeven om dit onderzoek te doen en jarenlang – of jullie dat nu wilden of niet – deelgenoot werden gemaakt van alle ups en downs. Ik kon altijd bij jullie terecht en velen van jullie hebben op enige wijze bijgedragen aan dit proefschrift. Ronald, Marijke, Agnes, Esther, Wim, Caroline, Stefan, Maja, Martijn, Marjolein, Stefan, Ate, Ferry, Lia en Ingrid: veel dank!

Alle dames van het secretariaat interne oncologie, in het bijzonder Gerdien. Hoewel ik altijd denk het allemaal zelf te kunnen, is het jullie toch gelukt om mij op vele manieren te ondersteunen in dit traject. Veel dank daarvoor en blijf vooral proberen!

Wendy, jij bent me op vele manieren tot steun geweest tijdens dit traject. Ten eerste heb je het kunnen opbrengen om meer dan 5000 titels te screenen voor ons systematische review waarna je de overgebleven papers tot in detail hebt uitgeplozen. Ook jouw bijdrage aan de beroemde stippenfiguur is onmisbaar geweest. Maar naast jouw bijdrage aan het review heb ik ook veel gehad aan jouw ervaring met onderzoek doen binnen de palliatieve zorg, en met promoveren. Fijn dat ik altijd bij je terecht kan om even te spuien.

Dan, alle promovendi die in de afgelopen jaren voorbij zijn gekomen. Als promoverend staflid was ik een vreemde eend in de bijt, toch was ik bij jullie altijd welkom. Jacqueline, veel dank voor je hulp bij het maken van en vervoeren van mijn poster en voor de vele gezellige momenten zowel in Rotterdam als Chicago. Je keuze voor de reumatologie blijft moeilijk te begrijpen, maar je hebt het in je om een goede reumatoloog te worden. Sander, jouw droge humor kwam vaak op het juiste moment. Ik zal voortaan voorzichtiger zijn bij het vullen van waterballonnen in jouw aanwezigheid. Roelof, jij ging mij eerder dit jaar voor, dank voor je praktische adviezen en de gezelligheid bij verschillende gelegenheden.

Jildou, Maureen en Laila en natuurlijk de mannen, Gerben, Roy en Eduard. Onze vriendschappen begonnen meer dan 20 jaar geleden (....) en hebben de tijd en de afstand overleefd. Hoewel we elkaar weinig zien, is het wanneer we elkaar zien altijd gelijk goed. Ik heb erg genoten van onze culinaire trips in de afgelopen jaren, laten we dat vooral blijven doen!

Evelien, geweldig dat je naast me staat op deze dag! Onze tijd samen in het Erasmus MC was kort maar krachtig. Het was heel fijn om met jou in hetzelfde schuitje te zitten, maar erg jammer dat onze duo-promotie niet is gelukt. Veel dank voor je gezelligheid, steun, opbeurende woorden en al het werk dat je gedaan hebt om mij tijd te geven voor onderzoek. Succes met het afronden van jouw promotietraject en met het opbouwen van mooie dingen in en rond Nijmegen.

Maike, wie anders dan jij moet er naast me staan op deze dag. Sinds dat 1e sigaretje en die oranje tuinbroek is er heel veel veranderd en toch ook weer niet. Onze vriendschap staat als een huis, ondanks het feit dat we elkaar maar weinig kunnen zien. Ik ben heel blij te weten dat je er altijd voor me bent. Door dik en dun.

Papa en mama, wat ben ik jullie veel dank verschuldigd. Jullie hebben mij altijd op alle mogelijke manieren ondersteund en mij mijn eigen keuzes laten maken. Dankzij jullie heb ik een onbezorgde jeugd en studententijd gehad. Ik, maar ook Bas en de kinderen, kunnen altijd op jullie rekenen. Dankzij jullie stabiele basis heb ik mezelf kunnen ontplooien en

daarvoor ben ik jullie zeer dankbaar.

Elsa en Olaf, hoewel ik dit boekje gekscherend mijn 3e kind heb genoemd, zijn jullie me heel veel dierbaarder. Jullie geven kleur aan mijn leven. Mama's boekje is eindelijk af, het is tijd voor feest!

Lieve Bas, zonder jou had ik dit echt niet kunnen doen. Ik ben je ontzettend dankbaar voor je onvoorwaardelijke steun, voor alle uren die je alleen met de kinderen doorbracht terwijl ik op zolder zat en voor het accepteren van onze beperkte actieradius in de weekeinden. Dit jaar is nogal tumultueus verlopen, gelukkig hebben we dat samen kunnen doorstaan. Ik wil niets liever dan samen met jou aan een volgend hoofdstuk beginnen.

En nu: tijd voor een drankje en een dansje!

A

Appendix 3

Curriculum Vitae

Curriculum Vitae

Astrid Oosten werd op 25 september 1976 geboren te Amsterdam. In 1994 behaalde zij haar VWO-atheneum diploma aan het Christelijk College Nassau Veluwe te Harderwijk. Daarna volgde een studie geneeskunde aan de Rijks Universiteit Groningen. In 2001 behaalde zij daar cum laude haar artsexamen. Van januari 2001 tot november 2002 werkte zij als AGNIO interne geneeskunde in de Isala Klinieken te Zwolle. In november 2002 startte de opleiding tot internist in het Martini Ziekenhuis in Groningen (opleider Dr. R.S. de Jong). Van juni 2006 tot februari 2007 werd de opleiding vervolgd in het Universitair Medisch Centrum Groningen (opleider Prof. Dr. R.O.B Gans). In februari 2007 startte zij met de opleiding binnen het aandachtsgebied interne oncologie (opleider Prof. Dr. J. Verweij) in het Erasmus MC te Rotterdam. Vanaf juni 2009 werkt zij als staflid binnen de afdeling interne oncologie van het Erasmus MC Kanker Instituut. In 2010 werd, onder begeleiding van Prof. Dr. C.C.D. van der Rijt en Prof. Dr. A.H.J. Mathijssen, een begin gemaakt met de onderzoeken die beschreven staan in dit proefschrift.

A

Appendix 4

Publications

Publications

Oosten AW, Sprenger HG, van Leeuwen JT, Meessen NE, van Assen S.
Bilateral renal aspergillosis in a patient with AIDS: a case report and review of reported cases.
AIDS Patient Care STDS. 2008 Jan;22(1):1-6. Review.

van Gool AR, van der Velden MT, **Oosten AW**, van Meerten E, Verhoeven WM, Loonen AJ.
Chemotherapy during clozapine treatment. Increased risk of agranulocytosis?
Tijdschr Psychiatr. 2008;50(10):673-8. Dutch.

Oosten AW, Seynaeve C, Schmitz PI, den Bakker MA, Verweij J, Sleijfer S.
Outcomes of first-line chemotherapy in patients with advanced or metastatic leiomyosarcoma of uterine and non-uterine origin.
Sarcoma. 2009 Article ID 348910, 6 pages

Oosten AW, Oldenmenger WH, van Zuylen C, Schmitz PI, Bannink M, Lieverse PJ, Bromberg JE, van der Rijt CC.
Higher doses of opioids in patients who need palliative sedation prior to death: cause or consequence?
Eur J Cancer. 2011 Oct;47(15):2341-6

Oosten AW, Oldenmenger WH, Mathijssen RH, van der Rijt CC.
A Systematic Review of Prospective Studies Reporting Adverse Events of Commonly Used Opioids for Cancer-Related Pain: A Call for the Use of Standardized Outcome Measures.
J Pain. 2015 Oct;16(10):935-46

Oosten AW, Abrantes JA, Jönsson S, de Bruijn P, Kuip EJ, Falcão A, van der Rijt CC, Mathijssen RH.
Treatment with subcutaneous and transdermal fentanyl: results from a population pharmacokinetic study in cancer patients.
Eur J Clin Pharmacol. 2016 Apr;72(4):459-67

Oosten AW, Matic M, van Schaik RH, Look MP, Jongen JL, Mathijssen RH, van der Rijt CC.
Opioid treatment failure in cancer patients: the role of clinical and genetic factors.
Pharmacogenomics. 2016. Aug;17(13):1391-403

Bins S, Eechoute K, Kloth JS, de Man FM, **Oosten AW**, de Bruijn P, Sleijfer S, Mathijssen RH. Prospective Analysis in GIST Patients on the Role of Alpha-1 Acid Glycoprotein in Imatinib Exposure.
Clin Pharmacokinet. 2016 Jul 26. [Epub ahead of print]

Appendix 5

PhD Portfolio

PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student: A.W. Oosten Erasmus MC Department: Medical oncology	PhD period: January 2010 – July 2016 Promotor(s): Prof dr. CCD van der Rijt and Prof. dr. A.H.J. Mathijssen	
1. PhD training		
	Year	Workload ECTS
General academic skills		
Research Integrity		
Good clinical practice	2010	0.4
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2011	1
BROK recertification	2015	0.5
In-depth courses (e.g. Research school, Medical Training)		
6-day Course Palliative care for medical specialists	2011	2
Presentations		
Oral presentation for Oncology TV	2011	0.5
Oral presentation Research meeting Expertise center for palliative care	2011	0.5
Oral presentation ZonMW meeting for researchers in palliative care	2012	1
Oral presentations Scientific Meeting dept. of Oncology	2011 & 2014	1
ASCO poster presentation (abstract number 9540)	2014	1
Interview oncology TV 'pharmacokinetics of fentanyl'	2014	0.5
Amsterdam symposium on palliative care	2015	0.5
Medical Oncology Research Meeting	2016	1
(Inter) National conferences		
Year symposium 'continuum oncology'	2010-2016	2
Research meetings Erasmus MC Medical Oncology	2010-2016	1.5
ECCO/ESMO conference (2010, Berlin, Germany)	2010	1.2
ESMO conference (2012, Vienna, Austria)	2012	1.2
'Internistendagen'	2013	0.6
Post-ASCO	2013/2015	0.8
ESMO conference (2013, Amsterdam)	2013	1.2
National conference 'cancer in the elderly'	2013	1
ASCO Annual meeting (2014, Chicago)	2014	1.2
'De dokter en de dood'	2015	1
Amsterdam symposium on palliative care 2015	2015	1
ASCO Annual meeting (2016, Chicago)	2016	1.2
Seminars and workshops		
Regional meeting Pain IKNL	2011	0.3
Workshop communicating with cancer patients	2011	0.3
OMBO courses dept. of medical oncology	2010-2016	1.5
Research meetings Expertise Center for palliative care	2010-2015	1
Seminar: 'U vraagt wij draaien'	2011	0.2
Workshop Stichting STEM	2012	0.2

1. PhD training		
Didactic skills		
Teach the teacher training	2010	1
Member Education Committee dept of Medical Oncology	2010 - 2015	2
Education ANIOS/AIOS Medical Oncology Erasmus MC	2009 - 2016	4
Trainer General Practitioners palliative care internship	2012 - 2016	2
2. Teaching activities		
Lecturing		
Oncology nurses teaching days, several lectures	2010 -2013	3
OIO meetings 'pharmacokinetics of fentanyl and morphine'	2012 and 2014	2
Monodisciplinary teaching sessions medical oncology	2011 - 2016	2
Case meetings Tumour working group pain	2012 - 2016	1
Nursing theme afternoon: Palliative care	2012	1
Zorgacademie Erasmus MC: Pain and pain control in palliative care	2013-2016	4
GIST patient support group contact day: Workshop palliative care	2014	1
Supervising practicals and excursions		
2nd year students elective course visit to palliative care unit	2010-2015	0.4
VSO skills in communicating bad news	2015	0.4
Other		
Supervising nurse practitioner palliative care in training	2013-2014	4
Medical coordinator and supervisor clinical unit for palliative care and symptom control	2010-2016	10
Coordinator of team 'Nursing Specialists in Palliative care and Home Technologies'	2010-2016	6