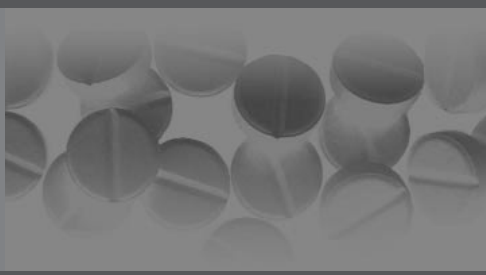
Pharmacodynamics of midazolam in pediatric intensive care patients

Chapter 11



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Summary

Aim To aim of the study was to determine the pharmacodynamics of midazolam in pediatric intensive care patients using the COMFORT scale as validated sedation scale.

Methods The pharmacodynamics of midazolam and its metabolites were determined in 21 pediatric intensive care patients with ages between 2 days and 17 years who received a continuous infusion of midazolam (0.05-0.4 mg/kg/h) for 3.8 hours to 25 days for conscious sedation. The rate of midazolam infusion was titrated according to sedation level, using the COMFORT scale as a validated tool for the assessment of sedation. Blood samples were taken at different time points during and after midazolam infusion for determination of midazolam, 1-OH-midazolam and 1-OH-midazolam-glucuronide with HPLC-UV assay.

Results In twenty out of the 21 patients the rate of midazolam infusion could be effectively titrated to the desired level of sedation. However, the COMFORT scale ranges, as previously validated to reflect an adequate level of sedation, could not be applied to all patients as in specific disease states a deeper level of sedation was clinically indicated. A relationship between pharmacokinetic and pharmacodynamic assessment using the COMFORT scale could not be detected

Discussion Desired levels of sedation could be reached with midazolam in almost all pediatric intensive care patients. Based on our findings that there is no relationship between pharmacokinetic parameters and pharmacodynamic outcome, we recommend that midazolam dosing should be titrated according to the desired clinical effect with the use of the COMFORT scale.

Introduction

Most pediatric intensive care patients are in pain, fearful and anxious. This impairs cooperation with treatment and negatively influences clinical outcome (1) (2). Sedation is, therefore, often required in children in the intensive care unit.

One of the most widely used drugs in the pediatric intensive care is the short-acting benzodiazepine midazolam. The efficacy of continuous midazolam infusion for sedation in pediatric intensive care patients has been shown by several investigators (3) (4) (5) (6). These studies demonstrated that midazolam resulted in effective sedation in the majority of patients studied. Unfortunately, all these studies show limitations with respect to the overall usefulness of their results for midazolam dosing in pediatric intensive care patients. The two main limitations of these studies are the concomitant administration of other sedative-analgesic drugs and the use of non-validated sedation scores, varying from the subjective assessment of sedation by the patient's nurse to a 5-item sedation scale. (4) (5) (6)

The COMFORT scale is specifically validated to assess sedation in pediatric intensive care patients and postoperative neonates (1) (7) (8). This scale has been successfully used to investigate the pharmacodynamics of other drugs for continuous sedation or analgesia in pediatric intensive care patients (9). Hence, the COMFORT scale appears to be a useful surrogate measure for the efficacy of midazolam infusion in pediatric intensive care patients.

The aim of this study is to investigate the pharmacodynamics of midazolam and its metabolites in pediatric intensive care patients, using the COMFORT scale as a validated tool for measurement of sedation.

Methods

Patient recruitment

Patients were recruited from the Pediatric Intensive Care Unit of the Sophia Children's Hospital, Rotterdam, The Netherlands. The institutional review board approved this research protocol. Written, informed consent was obtained from patients and/or parents or legal guardians prior to enrollment in the study.

Patients were eligible for study entry if they were between 0 and 18 years old, needed midazolam for conscious sedation and already had an indwelling arterial catheter placed for purposes of medical care. Patients were excluded if they (1) received concomitant neuromuscular blockade drugs, (2) were exposed to midazolam for longer than 12 hours prior to start of the investigation, (3) were exposed to midazolam prior to start of the investigation without exact information on midazolam dosing, (4) were exposed to recent (i.e. < 24 hours prior to dosing) or chronic treatment with medications known or suspected to alter the pharmacokinetics of midazolam. Since midazolam is a substrate for cytochrome P450 3A enzymes, potential patients were evaluated for exposure to drugs known to affect CYP3A activity (e.g. erythromycin, phenobarbital, dexamethasone, and cisapride) (10). Severity of illness during the first 24 hours of ICU stay was assessed with the Pediatric Risk Mortality score (PRISM) (11).

Sedation assessment

The COMFORT scale was used as primary measure of effectiveness of midazolam (Table 1). The COMFORT scale rates eight behavioral or physiologic dimensions of distress (1). Each dimension is scored on a subscale from 1 to 5 by a trained observer. Six individuals were trained as observer and were allowed to score children for the study when interrater reliability was acceptable as described by Van Dijk et al. (7). For the non-ventilated patients, an item on crying replaced the item 'respiratory response'(7). Each observation consisted of a 2-min period of intensive observation of the patient. After each observation, the trained observer calculated the COMFORT score (minimal score 8, maximal score 40). COMFORT scores of < 17 were considered reflective of oversedation, scores between 17 and 26 as effective/optimal sedation and scores of >26 as distressed, undersedated and in need of further intervention (1).

Study design

We used a midazolam dosing schedule to obtain optimal sedation as assessed by the COMFORT scale. If the patient's COMFORT score was <17 or >26 during the midazolam infusion the dose was either reduced or increased, respectively. The midazolam infusion was continued until the attending physician decided that additional sedation was no longer needed (e.g. when extubation was anticipated that same day). The time of end of study was determined by completion of wash-out sampling, removal of the arterial line, discharge from the ICU, a midazolam infusion rate > 1.0 mg/kg/h, neuromuscular blockade, death or by request of the patients parent/guardian

Midazolam dosing and pharmacodynamic assessment

Drug dosing was started with midazolam, 0.1 mg/kg in glucose 5%, (Dormicum®, Roche, Mijdrecht, The Netherlands) as an intravenous bolus followed immediately by an intravenous midazolam infusion of 0.1 mg/kg/h into a peripheral vein or central catheter. COMFORT scores were determined before, 2 and 30 minutes after start of the infusion.

If midazolam infusion was already started before study entry, the midazolam infusion was continued and a baseline COMFORT score was determined. Next, for all patients, COMFORT scores were determined every 8 hours (at 8 am, 4 pm and 12 pm) and, in addition, when the nurse considered the patient to be not optimally sedated at any other time. The infusion rate was adjusted according to the COMFORT score as follows: if a patient was in distress (COMFORT>26), a bolus dose midazolam (0.1 mg/kg) was given, followed by an immediate increase in infusion rate of 0.05 mg/kg/h. If a patient was considered oversedated (COMFORT<17), the infusion rate was decreased by 0.05 mg/kg/h. Additional COMFORT scores were determined, 2 and 30 minutes after an increase in midazolam infusion rate and 60 minutes after a decrease in midazolam infusion rate. Deviations from the protocol were allowed at the discretion of the attending physician as based on clinical needs.

If sedation was no longer clinically needed, the infusion rate was decreased by 0.1 mg/kg/h every 12 hours. Immediately prior to and 10, 30 minutes, 1, 2, 4, 6, 12 and 24 hours after discontinuation of the infusion, COMFORT scores were determined.

Table 1 *(adapted with permission from van Dijk et al. (7)*

Scale item	Score
Alertness	
Deeply asleep	1
Lightly asleep	2
Drowsy	3
Fully awake and alert	4
Hyperalert	5
Calmness	
Calm	1
Slightly anxious	2
Anxious	3
Very anxious	4
Panic	5
Respiratory response	
No coughing and no spontaneous respiration	1
Spontaneous respiration with little or no response to ventilation	2
Occasional cough or resistance to ventilator	3
Actively breathes against ventilator or coughs regularly	4
Fights ventilator; coughing or choking	5
Crying	
Quiet breathing, no crying	1
Sobbing or gasping	2
Moaning	3
Crying	4
Screaming	5
Physical movement	
No movement	1
Occasional, slight movement	2
Frequent, slight movements	3
Vigorous movement limited to extremities	4
Vigorous movements including torso and head	5
Muscle tone	
Muscles totally relaxed; no muscle tone	1
Reduced muscle tone	2
Normal muscle tone	3
Increased muscle tone and flexion of fingers and toes	4
Extreme muscle rigidity and flexion of fingers and toes	5
Facial tension	1
Facial muscles totally relaxed	2
Facial muscle tone normal; no facial muscle tension evident	3
Tension evident in some facial muscles	4
Tension evident throughout facial muscles	5
Facial muscles contorted and grimacing	
Blood pressure	1
Blood pressure below baseline	2
Blood pressure consistent at baseline	3
Infrequent elevations of 15% or more above baseline (1-3 during 2 minutes observation)	4
Frequent elevations of 15% or more above baseline (> 3 during 2 minutes observation)	5
Sustained elevations of 15% or more	
Heart rate	
Heart rate below baseline	1
Heart rate consistent at baseline	2
Infrequent elevations of 15% or more above baseline (1-3 during 2 minutes observation)	3
Frequent elevations of 15% or more above baseline (> 3 during 2 minutes observation)	4
Sustained elevations of 15% or more	5

'Crying' is used instead of 'respiratory response' if a patient is not mechanically ventilated

Blood sampling and drug assay

Blood samples were taken for later analysis of midazolam and 1-OH-midazolam and 1-OH-midazolam-glucuronide concentrations. Blood samples were taken simultaneously with the COMFORT scores: i.e.:

1 before, 2 and 30 minutes after each midazolam loading dose
2 before and 60 minutes after each decrease in midazolam infusion rate
3 every morning at 8.00 AM, but not at 4 PM and 12 PM
4 prior to and 10, 30 minutes, 1, 2, 4, 6, 12 and 24 hours after discontinuation of the infusion.

Plasma was separated from whole blood by centrifugation (1000 X g for 10 minutes) and then stored at -80°C until analysis. Plasma samples were analyzed for midazolam and 1-OH-midazolam by validated high-pressure liquid chromatography (HP G13 series, Agilent, Amstelveen, The Netherlands) with diode array UV detection. (HP G1315A, Agilent, Amstelveen, The Netherlands) The column used was Novapak C18 (Waters, Ettenleur, The Netherlands). Diazepam (12.5 ng/100µl H_2O, Bufa, Uitgeest, The Netherlands) was added to each sample as internal standard and solid phase extraction was performed using alkalic extraction (pH=9) with dichloromethane (Rathburn, Walkerburn, Switzerland)

The inter-day coefficients of variation at the low standard concentration (20 ng/ml) were less than 6.9% and 10.3% for midazolam and 1-OH-midazolam, respectively. The lower limit of quantitation was 20 ng/ml for both midazolam and 1-OH-midazolam using 0.5 ml plasma volume (12).

Table 2 *Patient characteristics*

	Sex	Age	Weight (kg)	Origin	ICU admission reason	PRISM (11)
Patient						
1	Male	0.04 mths	3.5	Caucasian	Congenital heart disease	14
2	Male	0.12 mths	3.8	Caucasian	Congenital heart disease	23
3	Female	0.36 mths	3.6	Caucasian	Congenital heart disease	9
4	Male	0.48 mths	2.8	African	Postcardiac surgery	22
5	Female	0.60 mths	3.7	Caucasian	Congenital heart disease	17
6	Female	0.96 mths	4.3	Mediterranean	Respiratory insufficiency eci	30
7	Female	1.9 mths	4.8	Afro-Caribbean	Upper airway infection	14
8	Male	2.0 mths	3.6	Caucasian	Upper airway infection	20
9	Male	4.1 mths	7.5	Caucasian	Meningitis	19
10	Male	8.2 mths	20	Caucasian	Upper airway infection	6
11	Male	1.1 yrs	9.3	Asian	Pneumonia	19
12	Male	2.8 yrs	13	Asian	Empyema	7
13	Male	3.9 yrs	15	Afro-Caribbean	Acute laryngotracheobronchitis	14
14	Female	4.5 yrs	19	Caucasian	Pulmonary hypertension	24
15	Female	5.5 yrs	24	Caucasian	Staphylococcal scalded skin syndrome	11
16	Female	8.9 yrs	22	Middle-Eastern	Pulmonary hypertension	2
17	Male	9.1 yrs	25	Caucasian	Measles pneunomia	9
18	Female	13.1 yrs	40	Caucasian	Final stage ALL with multiple organ failure	20
19	Male	14.8 yrs	50	Caucasian	Ebstein-Barr virus infection	5
20	Female	15.1 yrs	52	Hispanic	Malignant hypertension	12
21	Male	17.0 yrs	60	Mediterranean	Postcardiac surgery	4

ALL = acute lymphatic leukemia, PRISM = pediatric risk of mortality score, mths = months, yrs = years

To measure 1-OH-midazolam-glucuronide in plasma, 50 µl β-glucuronidase was added to plasma samples (IBF Biotechnics, Villeneuve-la-Garenne, France, 100.000 Fishmann units/ml) and incubated at 40°C for 16 hours. Samples were processed and quantitated for total 1-OH-midazolam (conjugated plus unconjugated) in the same manner as described before. 1-OH-midazolam-glucuronide concentrations were then determined by using the following equation: [1 -OH-MG] = d[1-OH-M] x [M 1-OH-MG/M 1-OH-M], where: [1-OH-MG] = 1-OH-midazolam-glucuronide concentrations, d[1-OH-M] = concentration difference of 1-OH-midazolam before and after hydrolysis, M 1-OH-MG = molecular weight of 1-OH-midazolam-glucuronide (517,9) and M 1-OH-M = molecular weight of 1-OH-midazolam (341,8).

Statistical analysis

COMFORT scores of patients who had a baseline score and a minimum of one 'post-infusion rate change' score were included in the analysis relating dose-adjustments to sedation level. The proportion of patients at each sedation level group was determined before and two and 30 minutes after the initial midazolam dose, during steady state, before and two and 30 minutes after each midazolam dose increment, before and 60 minutes after midazolam dose reduction and during the wash-out period. The paired student t-test was used to compare COMFORT scores, drug and metabolite concentrations before and after start of the infusion. The effect of time-points on the parameters COMFORT score, midazolam, 1-OH-midazolam and 1-OH-midazolam-glucuronide concentrations were determined using a mixed model ANOVA allowing for inter- and intra-patient differences. The relationship between COMFORT score, sedation level category (i.e. oversedated, sedated or distressed) and drug or metabolite concentrations was also determined using a mixed model ANOVA. Data are expressed as mean ± SD unless stated else. These statistical analyses were obtained using SPSS software (version 9.0.0, SPSS Inc., Chicago, Ill) and SAS software [PROC MIXED (version 6.12 SAS institute, Inc, Cary, N.C)]. α =0.05 was considered the limit of significance.

Results

Patient clinical characteristics

21 patients in the age range of 2 days to 17 years were enrolled in the study. The characteristics of the individual patients are listed in Table 2. As reflected by the PRISM score, disease severity among our patients varied considerable. All patients received concomitant drug therapy inherent to intensive care treatment. Seven patients required analgesia (morphine, codeine, fentanyl and acetaminophen) during the midazolam infusion. Data from these patients are included in the analysis unless stated otherwise. Although the prescription of a drug known to affect CYP3A activity, was an exclusion criteria before entry in the study, two patients received CYP3A substrates after inclusion in the study. One patient (no 8) received a bolus of the CYP3A4 inducer dexamethasone (corticosteroid) on the second and third study day before a planned extubation (12). One patient (no 11) received both the CYP3A4 inhibitor erythromycin (macrolide antibiotic) and the CYP3A4 substrate/inhibitor fentanyl (analgesic) during the whole study period (13-15).

In eleven patients study participation ended before the washout period for the following reasons: a) neuromuscular blockade (n=1), b) death (n=1), c) removal of the arterial line (n=4) and d) discharge from the intensive care unit (n=4). One patient (no 4) was withdrawn from the study by his guardian. From one patient no COMFORT score immediately before cessation of the infusion was determined. Hence, in nine patients a (partial) washout curve could be established.

Midazolam dosing

The median duration of midazolam infusion was 3.4 days (range 3.8 hours to 25 days) with a median infusion rate of 0.09 mg/kg/h (range 0.05 – 0.4 mg/kg/h). The median total dose of midazolam infused was 2.9 mg/kg (range 0.40 – 46.0 mg/kg). On average, patients needed two (range 0 – 5) midazolam dose increments and one (range 0 – 3) infusion rate reductions.

In all cases of a COMFORT score >26 (n=14), the midazolam dosing was increased according to the protocol. Two times, midazolam dosing was increased, while the COMFORT score was less than 26, because a deeper level of sedation was clinically needed. All downward adjustments of the infusion rate were in keeping with a COMFORT score of <17. At 30 occasions (of which 9 and 5 times in two patients) of a COMFORT <17, the midazolam infusion was not decreased, because the clinicians judged a deeper level of sedation necessary.

Pharmacokinetic-pharmacodynamic relationship

Plasma drug sampling and associated sedation assessment sufficient to permit an evaluation for possible pharmacokinetic-pharmacodynamic relationships were performed in all 21 patients (242 data pairs) and in patients without analgesic co-administration (n=14, 200 observations). The relationship between sedation level category was compared with corresponding drug and metabolite concentrations (Table 3). No significant relationship between sedation level category and drug or metabolite concentrations was found. Midazolam concentrations associated with a COMFORT score between 17 and 26 varied from 100 ng/ml (25th percentile value) and 450 ng/ml (75th percentile value) in patients without analgesic co-medication.

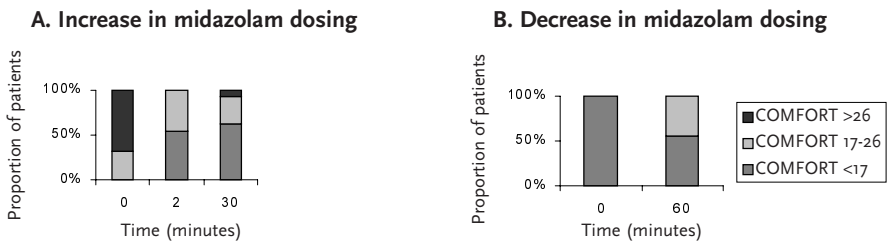
Sedation level

Only five patients did not receive any midazolam twelve hours prior to study enrollment. The COMFORT scores prior to midazolam dosing were <26 in all patients. Two and 30 minutes after midazolam dosing (bolus and start infusion), two and five patients became oversedated (COMFORT <17), respectively. Their mean COMFORT score prior to any study drug administration was 19.8 ± 4.0, which decreased significantly to 16.2 ± 3.0 two minutes and to 12.2 ± 2.7 (p=0.012) 30 minutes thereafter.

The effect of midazolam dosage adjustments during the infusion period on the proportion of patients in each sedation category is shown in Figure 1. The mean COMFORT scores were 26.6 ± 1.3 prior to midazolam dosage increment and decreased significantly to 17.7 ± 1.4 (p<0.01), 2 minutes, and to 15.9 ± 1.3 (p<0.01), thirty minutes thereafter. The mean COMFORT score increased significantly from 12.9 ± 1.1 to 17.0 ± 1.1 (p=0.01) one hour after decrease of the midazolam infusion rate with 0.05 mg/kg/h.

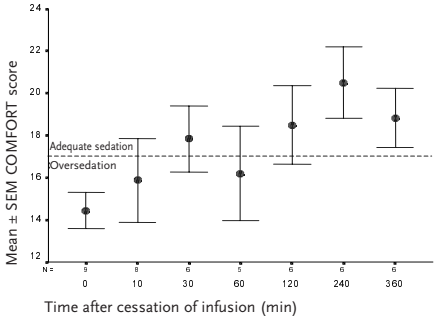
From only six patients COMFORT score were available up to six hours after

Figure 1 *Effect of midazolam dosage adjustment on sedation level in pediatric intensive care patients*



a. midazolam bolus dose (0.1 mg/kg) followed immediately by an infusion rate increase with 0.05 mg/kg/h (16 times, n=6)
b. midazolam infusion rate decrease with 0.05 mg/kg/h (24 times, n=13). The X-axis represents time (minutes) before (0) and after midazolam dosage adjustment. The Y-axis represents proportion of patients in each sedation level category.

Figure 2 *Effect of midazolam infusion cessation on COMFORT score in pediatric intensive care patients.*



The X-axis represents time (minutes) after cessation of the midazolam infusion. The Y-axis represents the mean (± SEM) COMFORT score.

Table 3 *Relationship between sedation level category and midazolam or metabolite concentrations in pediatric intensive care patients.*

	COMFORT scale ranges			
	<17	**17-26**	**>26**	**p-value**
Midazolam	**Concentrations**			
All patients	553 ± 164	577 ± 169	572 ± 210	0,96
Patients without co-medication#	370 ± 56	311 ± 57	258 ± 78	0,08
1-OH-Midazolam				
All patients	49 ± 11	49±11	47±14	0,97
Patients without co-medication	37 ± 8	35 ± 9	27 ± 11	0,40
1-OH-Midazolam-glucuronide				
All patients	593 ± 105	622 ± 110	549 ± 154	0,83
Patients without co-medication	649 ± 140	624 ± 142	587 ± 192	0,90

All drug concentrations are expressed in ng/ml. COMFORT scale <17: oversedated, 17-26 effectively sedated, >26 undersedated, #=other sedative-analgesic drugs.

cessation of the infusion (Figure 2). The mean COMFORT score of these patients increased from 13.9 ± 5.6 before to 20.8 ± 4.2 (p=0.03 Wilcoxon's test, n=6) four hours after cessation of the infusion.

Outliers.

Two patients needed very high concentrations of midazolam to achieve an adequate level of sedation. Patient 18 was terminally ill due to an aspergillus infection secondary to ALL and died within 24 hours after inclusion in the study. She was very restless (i.e. tried to remove her central venous and arterial lines and her tube several times) and needed several midazolam infusion rate increments to a maximum infusion rate of 0.4 mg/kg/h. In contrast to our expectations, her midazolam concentrations were disproportional high (up to 8200 ng/ml), probably due to reduced midazolam metabolism secondary to hepatic failure. Patient 11, a patient with Down's syndrome, experienced recurrent episodes of breakthrough agitation during concomitant midazolam and fentanyl infusions, despite high midazolam concentrations (mean 1590 ng/ml).

Discussion

We determined the pharmacodynamics of midazolam in a heterogeneous group of intensive care patients with different clinical diagnoses. In most patients, we were able to establish a level of sedation that would allow the children to remain sedated during mechanical ventilation or spontaneous breathing, as well as during nursing activities. Moreover, in most patients, there was no need for additional drugs as opioids to achieve effective sedation. The ranges of midazolam infusion rates associated with effective sedation in our study (0.05-0.4 mg/kg/h) were in agreement with data from a study in 24 pediatric intensive care patients who were between 26 days and 5 years old (0.05-0.5 mg/kg/h) (5). Midazolam infusion rates associated with effective sedation were lower in two other studies in pediatric intensive care patients (0.02-0.4 mg/kg/h) (3, 16). However in both studies frequent temporary midazolam infusion rate increments or single doses of other sedative-analgesic drugs were needed. The results of studies in pediatric cardiac surgery patients are not well comparable with our results because midazolam infusion was used in conjunction with the administration of morphine (6) (17) (18). Hence, the observed sedative effect is the result of the synergistic action of both drugs, as discussed by Somma et al. (19).

Since mean COMFORT scores change considerably after a midazolam dosage adjustment a concentration-effect relationship appears to be present in individual patients. However, no significant concentration-effect relationship could be detected when data from all patients are taken together. This lack of a significant relationship between midazolam or metabolite concentrations and sedation is in agreement with other studies in pediatric and neonatal intensive care patients (5, 17, 20). Interestingly, Hartwig et al. (5) found a significant concentration-effect relationship during the first 24 to 48h of midazolam infusion, but no longer after 80-120 h of infusion duration. In healthy adult volunteers and pediatric patients (21, 22), a significant relationship between midazolam concentrations and sedation is apparent after a single bolus dose midazolam. In pediatric intensive care patients, a concentration-effect relationship may be obscured by several

factors. First, mental status changes during sleep. Most persons alternate from awake to sedated to asleep during the day. Clearly, the level of sedation is not entirely a function of plasma concentrations. Second, in many studies, a possible concentration-effect relationship may be complicated by the concomitant administration of other sedative-analgesic drugs. In this study, the concentration-effect relationship seemed to improve after exclusion of the patients with co-medication (Table 3). Third, development of tolerance to midazolam after prolonged infusion may also obscure a concentration-effect relationship (2) (23). Due to the small number of patients in this study who received midazolam for more than 72 hours (n=6) we were, however, not able to investigate such an effect. Finally, the absence of adequate sedation despite high concentrations as observed in patient 11 may be associated with Down's syndrome (18). Children with Down's syndrome respond less predictable to sedative drugs and often need more than one drug to achieve adequate sedation (24). Concluding the lack of an overall concentration-effect relationship precludes the use of standardized dosing schedules to reach a similar sedative effect in all pediatric intensive care patients.

The use of standard COMFORT scale ranges (i.e. <17, >26) for all patients and consequent changes in midazolam dosing needs careful consideration. In our experience, these ranges are not valid for all patients with different needs of sedation. In more than half of the occasions with a COMFORT score of less than 17, the attending physician felt dose reduction not appropriate in view of the patient's clinical condition. Clinical conditions which warranted a deeper sedation level, to prevent breakthrough agitation, were e.g. pulmonary hypertension or systemic malignant hypertension.

Our results demonstrate that episodes of distress can be treated effectively and rapidly by a midazolam bolus dose in conjunction with an increase in infusion rate using the COMFORT scale as a measure of sedation (Figure 1a). If an immediate sedative effect is needed, a bolus dose is needed in addition to an increase in infusion rate, given the pharmacokinetics of midazolam. With the reported midazolam elimination half-lives between 1 to 4 hours (and possibly longer) in pediatric intensive care patients, a new steady-state midazolam concentration will only be reached after 3.5 to 16h (18) (17, 25) (26). Although frequently employed (16), the administration of other drugs to overcome breakthrough agitation, will complicate the titration of sedation afterwards by the effect of two drugs instead of one. Moreover, especially in newborn infants, the concomitant use of midazolam and opioids has been associated with hypotension (27).

Our results also show that a decrease in midazolam dosage or cessation of the midazolam infusion results in a relatively slow and variable increase in COMFORT score (less sedated), consequent to the wide interindividual variability in midazolam clearance (18) (17, 25) (26, 28). These data are in agreement with other studies in pediatric intensive care patients were a clinical state allowing extubation was achieved between two and four hours after cessation of the midazolam infusion (6, 18).

We also determined the concentrations of 1-OH-midazolam and 1-OH-midazolam-glucuronide in addition to midazolam, because these metabolites are also clinically active. The reasons for the lack of a pharmacokinetic-pharmacodynamic relationship for the metabolites by themselves, or when the sum of midazolam and metabolites was taken, are probably similar as discussed for midazolam. High 1-OH-midazolam-glucuronide concentrations may lead to prolonged sedation, when present in high concentrations as may occur patients with renal failure. Only one patient (no 20) in our patient sample

had serious renal failure. Although her 1-OH-midazolam-glucuronide/midazolam ratio was very high (data not shown), she did not become oversedated, probably because she received midazolam only for approximately 12 hours.

In conclusion, midazolam dosing can be successfully titrated using the COMFORT score to achieve adequate sedation in pediatric intensive care patients. The lack of a pharmacokinetic-pharmacodynamic relationship in pediatric intensive care patients forces midazolam dosing to be titrated according to its desired effect. Using the pharmacodynamic data generated in the current study, the following dosing schedule can be suggested. First, although the COMFORT score adequately reflects sedation in pediatric intensive care patients, individual COMFORT score ranges, based on each patient's clinical condition, should be defined reflecting adequate sedation. Second, this dosing scheme incorporates a single 0.1 mg/kg loading dose of midazolam to achieve immediate, effective sedation while simultaneously beginning a continuous infusion at a rate of 0.1 mg/kg/h. Further dosage increment, at least 30 minutes after a prior dosage increment consists of a single bolus dose (0.05-0.1 mg/kg) with a simultaneous increasing of infusion rate with 0.05 mg/kg/h. Downward dosage adjustment consists of a decrease of midazolam infusion rate with 0.05 mg/kg/h. Downward dosage adjustment at night or early morning should be done with care, as the COMFORT score may reflect sleep instead of sedation.

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