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THERAPEUTICS

Population pharmacodynamic modelling of midazolam induced sedation in terminally ill adult patients

Correspondence Linda G. Franken, Department of Hospital Pharmacy, Erasmus Medical Centre, Wytemaweg 80 NA-206, 3015 CN Rotterdam, The Netherlands. Tel.: +31 1 0703 3202; Fax: +31 1 0703 2400; E-mail: l.franken@ersmusmc.nl

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Linda G. Franken[1], Brenda C. M. de Winter[1], Anniek D. Masman[2,3], Monique van Dijk[3], Frans P. M. Baar[2], Dick Tibboel[3], Birgit C. P. Koch[1], Teun van Gelder[1] and Ron A. A. Mathot[4]

[1]Department of Hospital Pharmacy, Erasmus Medical Centre, Rotterdam, The Netherlands, [2]Palliative Care Centre, Laurens Cadenza, Rotterdam, The Netherlands, [3]Intensive Care, Department of Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, and [4]Hospital Pharmacy – Clinical Pharmacology, Academic Medical Centre, Amsterdam, The Netherlands

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AIMS

Midazolam is the drug of choice for palliative sedation and is titrated to achieve the desired level of sedation. A previous pharmacokinetic (PK) study showed that variability between patients could be partly explained by renal function and inflammatory status. The goal of this study was to combine this PK information with pharmacodynamic (PD) data, to evaluate the variability in response to midazolam and to find clinically relevant covariates that may predict PD response.

METHOD

A population PD analysis using nonlinear mixed effect models was performed with data from 43 terminally ill patients. PK profiles were predicted by a previously described PK model and depth of sedation was measured using the Ramsay sedation score. Patient and disease characteristics were evaluated as possible covariates. The final model was evaluated using a visual predictive check.

RESULTS

The effect of midazolam on the sedation level was best described by a differential odds model including a baseline probability, Emax model and interindividual variability on the overall effect. The EC50 value was 68.7 $\mu g\ l^{-1}$ for a Ramsay score of 3–5 and 117.1 $\mu g\ l^{-1}$ for a Ramsay score of 6. Comedication with haloperidol was the only significant covariate. The visual predictive check of the final model showed good model predictability.

CONCLUSION

We were able to describe the clinical response to midazolam accurately. As expected, there was large variability in response to midazolam. The use of haloperidol was associated with a lower probability of sedation. This may be a result of confounding by indication, as haloperidol was used to treat delirium, and deliria has been linked to a more difficult sedation procedure.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In terminally ill patients, pharmacokinetic variability can be reduced by taking in to account a patients' albumin levels and estimated glomerular filtration rate.
- There is large interindividual variability in clinical response to midazolam.
- Delirious patients are regarded as more difficult to sedate in general, as well as in the case of palliative sedation.

WHAT THIS STUDY ADDS

- Using a population approach with categorical sedation scores, we were able to describe the pharmacodynamics of midazolam accurately in terminally ill patients.
- Haloperidol as comedication was associated with lower Ramsay scores, and therefore a less sedative state.
- With this population pharmacodynamic model target levels of midazolam can be attained that can be used in the development of an individualized dosing algorithm.

Table of Links

LIGANDS
Midazolam

This Table lists key ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

Introduction

In terminally ill end-of-life patients, the most important goal is to provide adequate symptom relief [2–4]. When symptoms are so severe that none of the conventional modes of treatment are effective within a reasonable time frame and/or these treatments are accompanied by unacceptable side effects, i.e. in case of refractory symptoms, palliative sedation may be initiated. In a hospice setting palliative sedation is commonly used. Several studies looked at how often palliative sedation was initiated and showed that on average 46% (range 22–67%) of the terminally ill patients in a hospice were being sedated for refractory symptoms at the end of life [5–9]. The drug of choice to achieve palliative sedation is midazolam [5, 10]. Although midazolam has been shown to be effective in achieving adequate sedation, the response between patients varies widely. In clinical practice, the midazolam dose is titrated according to clinical response which results in a wide range of both effective dose and time to adequate sedation [11, 12]. Furthermore, the study by Morita *et al.* showed that almost half of the patients awoke at least once from the sedated state [12].

A more individualized dose could therefore potentially lead to more adequate sedation in these patients. To investigate this, a population pharmacokinetic (PK) model was developed which demonstrated large interindividual variability (IIV) on clearance of both midazolam and its metabolites with values ranging from 49 to 61% [13]. It also showed that IIV could be significantly reduced if patients' serum albumin levels and estimated glomerular filtration rate (eGFR) were to be taken into account. This suggests that a dosing regimen based on albumin levels and eGFR may result in better clinical outcome. However, such a PK model only predicts midazolam concentrations and does not include the pharmacodynamic (PD) variability, which is likely to be considerable and may vary with age, sex or disease severity [14–16]. This information is crucial when generating an individualized dosing advice.

To investigate the clinical response to midazolam plasma concentration on sedation level, to assess the amount of variability and to find clinically significant covariates, we performed a population PD study in terminally ill adult patients using the Ramsay sedation score.

Methods

Study design

The study (NL32520.078.10) was approved by the Medical Ethics Committee of the Erasmus University Medical Centre Rotterdam and was performed in accordance with the principles of the Declaration of Helsinki and its later amendments. The design of the study and study population are presented in detail in the article of Franken *et al.* in which the population PK model of midazolam is described [13]. Parts of the methods are briefly mentioned in this article when relevant. The study design with sparse regimen of random PK and PD sampling is shown in Figure 1.

Data collection

Demographic characteristics (age, sex, ethnicity, primary diagnosis and time of death) were extracted from the electronic medical records. Midazolam administration times were recorded in the patient record as well as any concomitant medication. Sparse blood samples were collected at random time points during both the preterminal and terminal stage of the disease. Using these samples, midazolam and its two major metabolites, 1-hydroxymidazolam (1-OH-M) and 1-hydroxymidazolam glucuronide (1-OH-MG) were

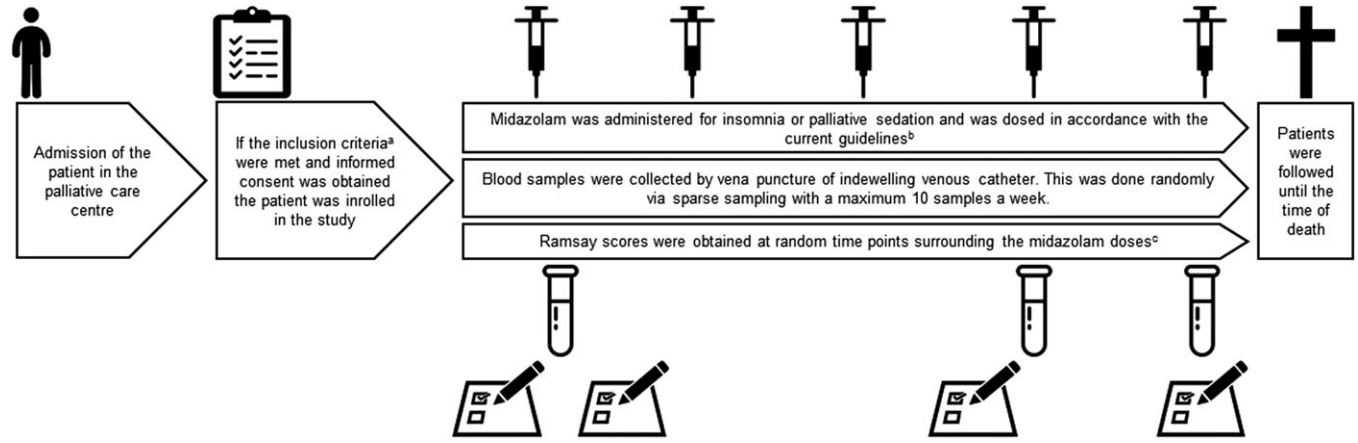

Figure 1

Regimen of pharmacokinetic and pharmacodynamic sampling. (A) The inclusion criteria for this study were terminal illness, a survival prognosis of more than 2 days and less than 3 months, administration of midazolam. (B) The current Dutch guidelines states that midazolam can be administered either as subcutaneous bolus injection (with a starting dose of 10 mg followed 5 mg every 2 h if necessary) or as a continuous subcutaneous infusion (with a starting dose of 1,5–2.5 mg h^{-1} and the possibility to up the dose if sedation was insufficient with 50% every 4 h in combination with a 5-mg bolus injection). (C) In general, the Ramsay score was obtained at the start of the midazolam treatment with consecutive assessments at 2-h intervals

determined by an liquid chromatography–tandem mass spectrometry method described before [13]. Blood samples for clinical chemistry were taken at the same time and serum levels of albumin, creatinine, urea, bilirubin, γ-glutamyl transpeptidase, alkaline phosphatase, alanine transaminase, aspartate transaminase and C-reactive protein were determined. Sedation was assessed using the Ramsay sedation score and was typically scored at the start of the midazolam treatment with consecutive assessments at 2-h intervals [17]. This scale consists of six sedation levels: 1, patient is anxious and agitated or restless; 2, patient is cooperative, orientated and tranquil; 3, patient is drowsy or asleep and responds to commands only; 4, patient is asleep and has a brisk response to a light glabellar tap or loud auditory stimulus; 5, patient is asleep and has a sluggish response to a light glabellar tap or loud auditory stimulus; 6, patient is asleep and has no response to a glabellar tap or loud auditory stimulus. The Ramsay sedation score has been used before in a palliative care setting and enables doctors and nursing staff to assess the level of sedation as self-reporting is usually not possible [18, 19]. The Ramsay score was measured by a trained and experienced nurse, using a standard operating procedure.

PK data integration

A previously described population PK model was used to predict PK profiles for all individual patients [13]. This model was based on the same study population and contained data from 45 patients and 139 collected blood samples. This model was systematically developed based on minimum objective function value (OFV), parameter precision, error estimates, shrinkage values and visual inspection of the goodness of fit plots, bootstrapping and normalized prediction distribution errors analyses. In summary the model was a one-compartment model for both midazolam, 1-OH-M and 1-OH-MG and contained two covariates albumin levels on midazolam clearance and eGFR on 1-OH-MG clearance. Since all 43 patients for whom Ramsay scores were available, were also included in the PK dataset, the individual PK parameters together with the midazolam doses were used as input for the sequential PD model. From the remaining two patients, no Ramsay scores were available and they were excluded from the PD model.

Population PD method

A population PD analysis using nonlinear mixed effect models was performed with NONMEM® 7.2, in combination with Pirana (version 2.9.2) for the model building process and R (version 3.3.0) and PsN (version 4.6.0) to generate diagnostic plots.

Population PD model development

Both a proportional odds model and a differential odds model were tested for the possibilities of observing a certain Ramsay sedation score. These methods have been described before by Kjellsson *et al*. and the difference between these models was tested by dichotomising the data and performing logistic regression [20]. In short, these methods estimate the logit and corresponding probability of the Ramsay score being equal or greater than a particular value. At any given concentration, there is a finite probability of having a Ramsay score of 1, 2, 3, 4, 5 and 6 with the sum of these probabilities being 1. The probability (P) of a particular sedation score (n) follows from calculating the difference of two consecutive scores, as is shown in equation (1).

$$P\,(Ramsay = n) = P(Ramsay \geq n) - P(Ramsay \geq n+1) \qquad (1)$$

To describe the clinical response to midazolam concentrations on the probability of a certain Ramsay score linear models, log linear models, Emax models and a sigmoidal Emax models were tested both direct and indirect [21]. Model evaluation was based on objective function value (OFV), parameter precision, shrinkage values and visual predictive

checks (VPC). Pharmacodynamic parameter estimates were obtained using the Laplacian estimation method. To evaluate the effect of the midazolam metabolites, 1-hydroxy midazolam (1-OH-M) and 1-hydroxy midazolamglucuronide (1-OH-MG) an additive interaction model (equation (2)) was used with equal maximal effect (Emax) for midazolam and the metabolite of interest. In this equation, $EC_{50,1}$ $EC_{50,2}$ represent the half maximal effective concentrations of midazolam and the metabolite respectively and C_1 and C_2 represent the concentrations of midazolam and the particular metabolite.

$$Effect = Emax_{1,2}{}^{*}\frac{\left(\frac{C_1}{EC_{50,1}}+\frac{C_2}{EC_{50,2}}\right)}{1+\left(\frac{C_1}{EC_{50,1}}+\frac{C_2}{EC_{50,2}}\right)} \quad (2)$$

Covariate model development

Patient characteristics (age and sex), disease characteristics [albumin levels, C-reactive protein levels, eGFR and time to death (TTD)], all concomitant medication with sedatory effects and the time of day were evaluated as possible covariates in the PD model. Significance of a covariate was evaluated using a forward inclusion, backward elimination method with *P*-values of 0.05 and 0.001 respectively. Continuous covariates were incorporated using equation (3) and categorical covariates using equation (4). All concomitant medication, with the exception of morphine, was tested as a categorical covariate with the value being 1 if the patients used that type of comedication on the day of the Ramsay observations. Morphine concentrations as well as the concentrations of the morphine metabolites, morphine-3-glucuronide and morphine-6-glucuronide were tested as a continuous covariate. This was possible since the patients in this study were also included in a population PK study on morphine and its metabolites [22]. This PK model was used to predict the morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations at the time of the Ramsay observation.

$$Covariate\ effect = 1-\left(\frac{\mathrm{cov}_i}{\mathrm{cov}_m}\right)^{\theta_{cov}} \quad (3)$$

$$Covariate\ effect = 1-\theta_{cov}{}^{\mathrm{cov}_i} \quad (4)$$

with $\mathrm{cov_i}$ being the individual covariate value, $\mathrm{cov_m}$ represents the median covariate value and θcov the covariate coefficient. In the equation for categorical covariates $\mathrm{cov_i}$ is either 1 or 0. The covariate effect that was obtained with this equation was added to the sum of the logits. Because of the transformation used, a negative covariate coefficient described a positive correlation and *vice versa*. The difference in time between the observation and the recorded time of death was tested as a covariate using equation (3) as well as using a first order equation. In this second equation (equation (5)) one theta represents the maximum effect (θ_Δ) and a second theta the rate (θ_{rate}) at which the change takes place.

$$Covariate\ effect = \theta_\Delta{}^{*}\exp(\theta_{rate}{}^{*}TTD) \quad (5)$$

Model evaluation

The intermediate and final models were evaluated using the objective function value, parameter precision and shrinkage values. As the PD model predicts probabilities rather than actual sedation scores, residual errors could not be calculated and the standard observed *vs*. predicted plots could not be generated. We therefore used visual predictive checks to visually evaluate the goodness of fit.

Results

A total of 941 Ramsay sedation scores from 43 patients were available, with a median of 14 (interquartile range 7–30) observations per patient. The number of observations for the Ramsay categories of 1–6 were 68 (7.2%), 161 (17.1%), 31 (3.3%), 30 (3.2%), 146 (15.5%) and 505 (53.7%), respectively. Since there were very few data in categories 3 and 4, these were taken together with category 5. This decision was made as, for clinical outcome, a score of 3 or more will be sufficient in most cases. For a complete overview of the patient characteristics see Table 1.

Structural model

Sedation in the terminally ill patients, using the Ramsay sedation scores, was best described by a differential odds model including a baseline probability, midazolam effect and IIV. The effect of midazolam on the sedation was best described by a direct Emax response model. IIV was tested on baseline, EC50 and overall effect, where the latter gave the best results. Incorporating more than one IIV in the model resulted in large eigenvalues, indicating over-parameterisation. This resulted in the structural model as shown by equation (6). In this model, *n* represents a particular Ramsay score. Per Ramsay score there are different baseline values and EC50 values, but the Emax is the same for all scores.

$$\begin{aligned} logit(Ramsay^{3}n) &= Base_n+\frac{E\max - Base_n{}^{*}CP}{CP+EC50_n}+IIV \\ P(Ramsay^{3}n) &= e^{logit}/2+e^{logit} \end{aligned} \quad (6)$$

Implementing the concentrations of the metabolites 1-OH-M and 1-OH-MG did not improve the model. The final structural model resulted in baseline probabilities of 0.23, 0.49, 0.16 and 0.13 for Ramsay scores of 1, 2, 3–5 and 6 respectively and the following EC50 values 30.1, 62.8 and 111.6 μg l^{-1} for Ramsay scores of 2, 3–5 and 6. In the structural model the value for IIV on overall effect was 0.81 on the logit scale. Calculating the probability from that it means that 1SD is equal to a probability of 69% (equation (6)).

Covariate analysis

The forward inclusion step of the covariate analysis resulted in three significant ($P < 0.05$) covariates. These were age, time of day (night-time *vs*. daytime) and concomitant use of haloperidol. After the backward elimination step only comedication with haloperidol remained significant ($P < 0.001$). The coefficient for this effect was 1.76. Due to the transformation used (equation (4)) patients who were also

Table 1

Patient characteristics of terminally ill patients receiving midazolam

Characteristics	*n* = 43
Age, years (median, range)	71 (43–93)
Male, *n* (%)	22 (51.2)
Female, *n* (%)	21 (48.8)
Ethnic origin, *n* (%)	
Caucasian	39 (90.7)
Afro-Caribbean	3 (7.0)
Unknown	1 (2.3)
Primary diagnosis, *n* (%)	
Neoplasm	42 (97.7)
Disease of the respiratory system	1 (2.3)
Daily dose midazolam, mg day^{-1} (range)	2.5–180
Blood chemistry, serum levels at admission (median, range)	
Albumin, g l^{-1}	24 (13–38)
eGFR[a], ml min^{-1} 1.73 m^{-2}	69.4 (6–328)
C-reactive protein, U l^{-1}	128 (1–625)
Comedication used[b]	
Other benzodiazepines[c], *n* (%)	8 (18.6)
Haloperidol, *n* (%)	18 (41.9)
Levomepromazine, *n* (%)	2 (4.7)
Dexamethasone *n* (%)	13 (30.2)
Anti-epileptic drugs[d], *n* (%)	3 (7.0)
Anti-depressant drugs[e], *n* (%)	2 (4.7)
Morphine, μg l^{-1} (median, range)	41.9 (0–609.2)
M3G, μg l^{-1} (median, range)	825.9 (0–5433.5)
M6G, μg l^{-1} (median, range)	119.9 (0–826.5)
Blood samples collected, *n* (median, range)	2 (1–10)

eGFR, estimated glomerular filtration rate; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide
[a]calculated using the abbreviated MDRD equation;
[b]during the same day when Ramsay observations were collected;
[c]Benzodiazepines used included lorazepam, oxazepam and temazepam;
[d]Antiepileptic drugs used included levetiracetam and pregabaline;
[e]Antidepressant drugs included only amitriptyline

treated with haloperidol had a lower probability for the sedation scores 2 or higher compared to patients without haloperidol coadministration. The coefficients, decrease in OFV and effect on IIV in the univariate analysis of all three covariates are shown in Table 2. The final model including the use of haloperidol as a covariate resulted in baseline probabilities of 0.18, 0.48, 0.18 and 0.15 for Ramsay scores 1, 2 3–5 and 6 in patients without haloperidol use and baseline probabilities of 0.33, 0.57, 0.06 and 0.04 for Ramsay scores 1, 2 3–5 and 6 in patients with concomitant use of haloperidol (Figure 2). The EC50 values of the final model were the following for all patients with and without haloperidol: 39.5, 68.7 and 117.1 μg l^{-1} for Ramsay scores of 2, 3–5 and 6. Figure 3 shows the probabilities of the different Ramsay scores as a function of the midazolam concentration. From the upper two graphs it can be seen that, without the use of haloperidol (Figure 3A), the probability of a Ramsay score of 3 or more is 80% at a midazolam concentration of about 50 μg l^{-1}, whereas with the concomitant use of haloperidol this concentration is around 80 μg l^{-1}. From the bottom left graphs it is clear that at a concentration of 30 μg l^{-1} (and no haloperidol comedication) the probabilities for a Ramsay score of 2, 3–5 and 6 are almost equal. To also show the effect of the high IIV in the model simulations were performed. Figure 4 shows the probabilities of a Ramsay score of 3 or more and the probability of a Ramsay score of 6 with their corresponding 95% confidence intervals. As mentioned before, these confidence intervals are large and as a result, the confidence intervals of both scores overlap.

Model evaluation

Of the initial bootstrap of 500 runs, just over 70% resulted in a successful covariance step and were used to calculate the 95 confidence intervals. The median values and 95% confidence intervals of the bootstrap are shown in Table 3. The VPC of the final model showed good model predictability with the observations (line) laying within 95% confidence interval of the model predictions (shaded area) for most of the Ramsay scores (Figure 5). In the VPC plot it can, however, also be seen that at midazolam concentrations of around 150–350 μg l^{-1}, Ramsay scores of 3–5 are somewhat over predicted while Ramsay scores of 6 are somewhat under predicted.

Discussion

To our knowledge this is the first study to describe the clinical response to midazolam in terminally ill patients with a population PD model. Our study population consisted primarily of patients with cancer, admitted to a hospice, for terminal care in the last phase of life. Others have done PD studies with midazolam in populations of critically ill patients admitted to intensive care units [23, 24]. For the lower Ramsay scores, the EC50 values found in our study are in accordance with the results of Somma *et al*. who studied the effect of midazolam in patients after heart surgery [23]. However, the EC50 value for the highest Ramsay score in our study was less than half of that found in the study of Somma *et al*. (118 *vs*. 352 μg l^{-1}). A possible explanation for this difference may be the different study populations. In our terminally ill patients, high doses of morphine were used, which may have increased the sedative effect of midazolam. However as both other studies also had opiates as comedication a more likely explanation may lay the advanced illness itself. As a consequence of their advanced illness, terminally ill patients may be unable to respond thereby causing the overall Ramsay scores to be higher. Furthermore, environmental factors may play a role. A hospice setting offers more tranquillity than a hospital's intensive care unit (with more medical equipment and noises), as described in the study of Somma *et al*. [23]. A more stressful situation is also one of the arguments Swart and colleagues

Table 2

Covariate effects in univariate analysis compared to the structural model

Covariate[a]	Parameter value[b]	ΔOFV[c]	ΔIIV[d]	Included after backward elimination
Age	−1.67	−5.776	- 8.0%	No
Use of haloperidol	1.76	−11.975	+ 6.3%	Yes
Day *vs.* night-time[e]	0.675	−4.919	+ 4.1%	No

[a]Covariates included in the full model after forward inclusion
[b]Parameter value, note that due to the transformation used, positive values are negative correlations and *vice versa*
[c]Decrease in objective function value (OFV) after the univariate analysis
[d]Decrease in interindividual variability (IIV) after the univariate analysis
[e]with daytime being the reference value

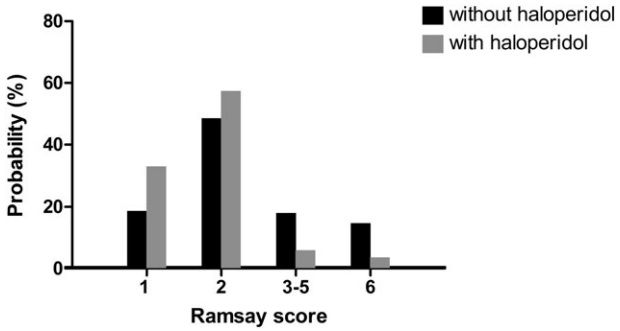

Figure 2

Baseline probabilities for Ramsay scores of 1, 2, 3–5 and 6 without the use haloperidol (black bars) and with concomitant haloperidol use (grey bars)

[25] used to explain why their study in IC patients found even higher EC50 values than Somma *et al.* [23].

In contrast to the two previously mentioned studies, we did not only investigate the response to midazolam but also analysed its two major metabolites 1-OH-M and 1-OH-MG. Interestingly neither of these metabolites showed an additive effect, while it is known from the literature that 1-OH-M is about 80% as effective as midazolam and 1-OH-MG has a potency of about 10% [25, 26]. The lack of an additive effect can be explained by the fact that 1-OH-M is a formation rate limited metabolite, and therefore closely follows the midazolam concentrations. As a result, it is impossible to separate the effect of these two substances. 1-OH-MG, by contrast, is elimination rate limited and it has been shown before that this metabolite can accumulate in patients with renal failure, causing prolonged sedation [27]. We did not see an effect of the 1-OH-MG concentrations or renal function on sedation in our study. The lack of an effect may be because the treatment period is relatively short (palliative sedation is usually given for around 48 h) and the dose low, compared to an ICU setting where the starting dose may be 10 times higher [28]. As result, the treatment period may have been too short for any significant accumulation to occur. Furthermore, in palliative sedation, midazolam is not discontinued, therefore high 1-OH-MG concentrations never occurred in the absence of midazolam concentrations and as the sedation scale has an upper limit an additive effect of 1-OH-MG may not be seen. Furthermore, renal function did not seem to be that severely affected in the population, with only 6% of the patients having an eGFR <30 ml min^{-1}, although it should be noted that estimating GFR in this population is difficult due to the possible low lean body weight and muscle atrophy.

The only covariate that showed a significant effect was the concomitant use of haloperidol. Patients who also used haloperidol had a higher probability of lower Ramsay scores, meaning that they were less likely to be sedated. A possible explanation is that this effect is a result of confounding by indication, as patients receive haloperidol to treat agitation or delirium, and deliria has been mentioned to be a risk factor for a difficult sedation process [29, 30]. The IIV did not decrease when haloperidol use was incorporated as a covariate. This can be caused by the fact that the use of haloperidol could change within an individual patient over time, and it is therefore not a reflection of the IIV but rather a result of interoccasion variability. Two other covariates – age and time of day – showed a significant effect in the forward inclusion that did not hold up or stay after the backward elimination. Age was positively correlated with sedation, meaning that elderly patients were more likely to be deeply sedated compared to younger patients. These data are in accordance with a study by Sun *et al.*, who showed sedation scores after midazolam treatment differed significantly with age [16]. However, as the age range of patients in this study is not that large, our patient numbers may have been too small to show a significant effect of age in the backward elimination step. Time of day was also not significant in the backward elimination step. This may be because its influence was tested using a fairly basic dichotomous equation, with night-time *vs.* daytime. A previous study by Peeters and colleagues used a more elaborate sinus equation to describe the circadian rhythm [31]. As our study had more sparsely collected data, this was not feasible in our model. No correlation was found between the sedation level and the time to death, or albumin levels, although we would have expected that if a patient is closer to the time of death (for which low albumin levels are also a marker), they would be more deeply sedated. Incorporating TTD and albumin as a covariate did show a trend (ΔOFV 3.27 for TTD and 3.32 for albumin). However, this did not meet the criteria of statistical significance. To further investigate this more continuous measurements of level of sedation may be helpful as the dying phase is a gradual process.

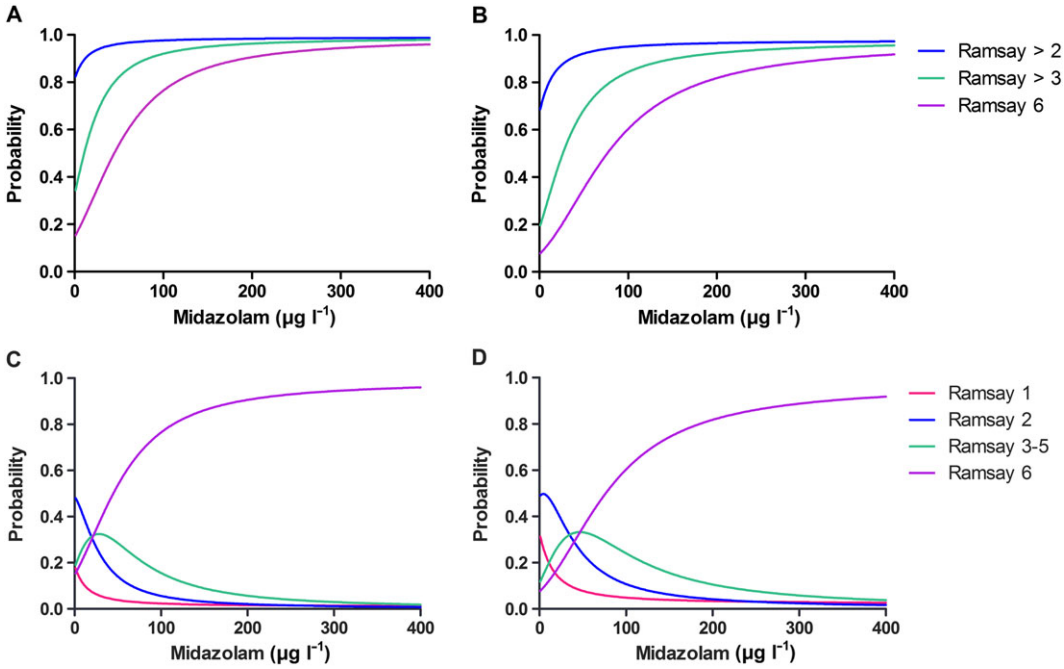

Figure 3

(A) Probabilities of a Ramsay score ≥2 (blue) ≥3 (green) and ≥6 (purple) without the use of haloperidol. (B) Probabilities of a Ramsay score ≥2 (blue) ≥3 (green) and ≥6 (purple) with concomitant haloperidol use. (C) Probabilities of a Ramsay score of 1 (red), 2 (blue), 3–5 (green) and 6 (purple) without the use of haloperidol. (D) Probabilities of a Ramsay score of 1 (red), 2 (blue), 3–5 (green) and 6 (purple) with concomitant haloperidol use

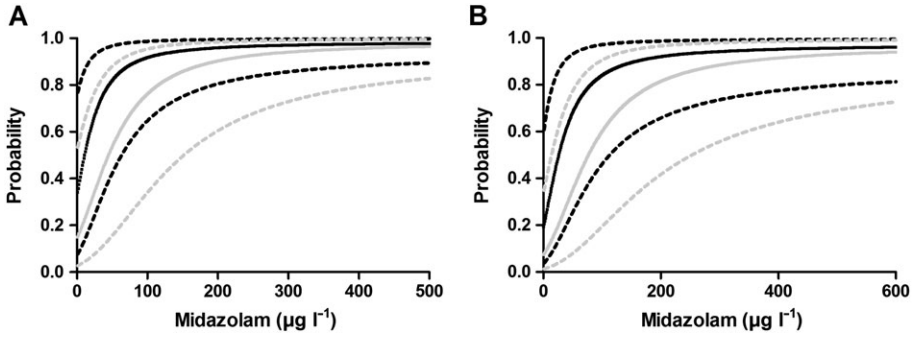

Figure 4

Simulations of the average probabilities and corresponding 95% confidence intervals (*dashed lines)* of Ramsay score 3 or more (*black*) and Ramsay score 6 (*grey*) without the use of haloperidol on the left (A) and with concomitant haloperidol use on the right (B)

Furthermore, we initially would have expected an effect of morphine (and possibly its metabolites) on sedation levels; however, this was not the case [32]. This could have been caused by the fact that in 88% of the Ramsay observations the patient also used morphine making the group of data without morphine too small for an adequate comparison. In addition, it is also possible that the sedative effect of morphine may be less prominent in patients who have used it for a prolonged period.

This study also a few limitations, firstly the Ramsay sedation score is not validated for terminally ill patients. In addition, the scores are measured only at certain time points, thereby making it difficult to evaluate a possible delay in response onset. Due to the limited number of observations shortly after a midazolam dose, we were unable to include an effect compartment and to estimate a first-order effect compartment rate constant (K_{e0}). Although midazolam has a rapid onset and we therefore would not expect a great variability in this K_{e0} value, it would be interesting to see if there is any variability on K_{e0} as this would impact the onset of sedation and is therefore of considerable clinical interest. To evaluate this, a more continuous PD observation method such as EEG measurements would be needed.

Another limitation in our model is that the Ramsay scores of 3, 4 and 5 were taken together as one category due to the limited data in the 3 and 4 categories. This is most likely also to be a consequence of the lack of observations shortly after a

Table 3

Population pharmacodynamic parameter estimates of the structural and final models

Parameter	Structural model	Final model	RSE %	Shrinkage %	Bootstrap of the final model		
					Average	95% CI (lower)	95% CI (upper)
Baseline							
B2	1.22	1.47	32		1.33	0.46	2.15
B3–5	−0.91	−0.72	19		−0.81	−2.53	0.98
B6	−1.93	−1.76	38		−1.83	−4.58	0.59
Emax model							
Emax	4.08	4.62	24		4.54	3.57	6.30
$EC50_2$ (μg l^{-1})	30.1	39.5	69		33.4	7.1	109.3
$EC50_{3–5}$ (μg l^{-1})	62.8	68.7	51		62.8	10.9	165.0
$EC50_6$ (μg l^{-1})	111.6	117.1	50		109.4	23.6	280.0
Covariate effect							
haloperidol		1.76	18		1.74	0.88	2.41
Interindividual variability							
Overall effect	0.81	0.92	29	18	0.94	0.45	1.63

B*n*, baseline logit for a Ramsay score of *n*; Emax, maximum effec; EC50*n*, concentration at half of the maximum effect for a Ramsay score of *n*

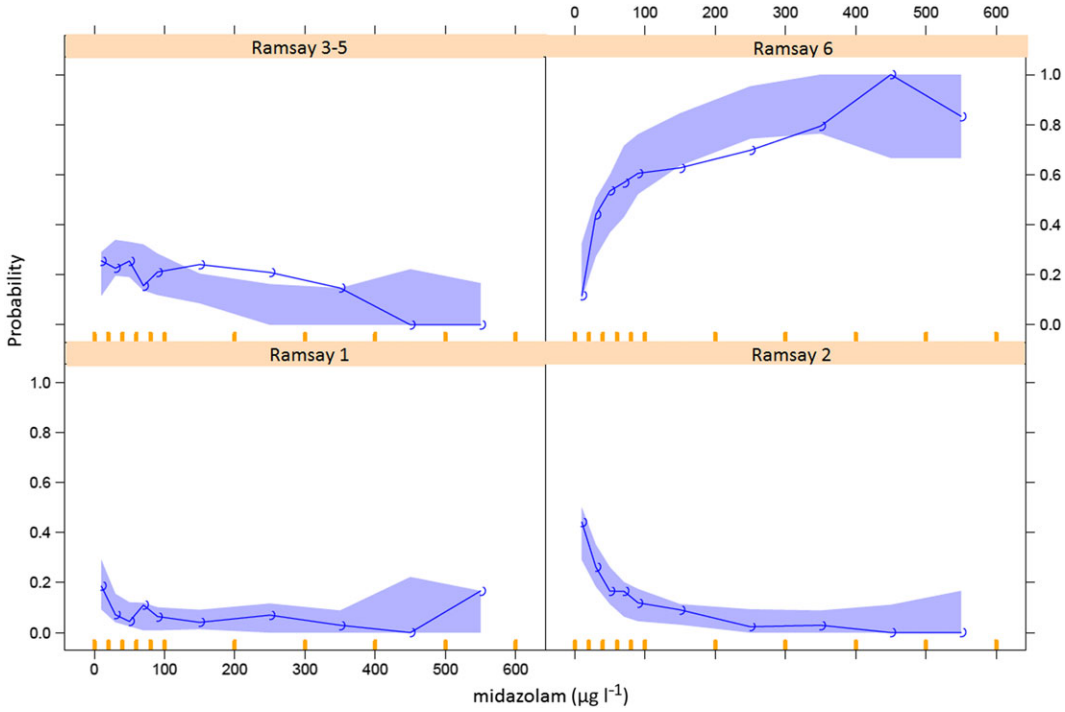

Figure 5

Visual predictive check of the final model for Ramsay scores of 1, 2, 3–5 and 6. With the line depicting the observed probabilities and the shaded area the 95% prediction interval of the model. Yellow lines are the concentration intervals

midazolam dose. We also tested a model with all categories separately, which resulted in similar parameter estimates and almost equal EC50 values and baseline probabilities for the scores 3, 4 and 5, as expected due to the low number of observations. This will not affect our results and conclusions. The main goal of palliative sedation is to make sure the patient is comfortable and although this is not exactly reflected by the Ramsay score, a score of 2 or 3 or more will be

sufficient. The distinction between scores 3–5 and 6 may be relevant from the point of view of the relatives and for side effects.

A third limitation of our study is that individual PK parameters were used from a previously performed PK modelling study, instead of a simultaneous PK/PD analysis. This may have led to some overestimation of the IIV in the PD model. Finally, previously performed PD studies on midazolam included a naive pooled analysis to assess the model accuracy [23, 33]. We instead used a VPC for the model evaluation, which is a newer evaluation method and has the additional benefit that it also shows the amount of variability in the model. In conclusion, we described the response to midazolam on sedation levels in terminally ill patients using a population PD model with the Ramsay sedation score as outcome variable.

Therapeutic implications

As expected, the variability in response was large. We found that the use of haloperidol was correlated with a lower response. This effect is best visualized by Figure 4, where the graph in 4A shows that without haloperidol use a typical individual (solid line) will have an 80% chance of a Ramsay score of 3 or more at midazolam concentration of around 50 μg l^{-1}. The graph also shows that due to the large interindividual variability, a concentration of around 200 μg l^{-1} would be needed to assure this same chance for 95% of the population (dashed line). The adjacent Figure 4B shows that with concomitant haloperidol, the midazolam concentration needed to give a typical patient (solid line) an 80% change of a Ramsay score of 3 or more would be around 80 μg l^{-1}. Again, to ensure this chance for 95% of the population a much higher concentration would be needed (of approximately 600 μg l^{-1}) due to the large IIV (dashed line, Fig 4). Of course, aiming for the higher midazolam concentrations will also increase the probability of Ramsay score of 6 (grey lines), which may not always be desirable.

Combining these results with our previous knowledge of the PK of midazolam we performed some simulation of dosing regimens for patients with and without the haloperidol as concomitant medication and different albumin levels. The results are shown in Table 4 and it can be seen that the loading dose depends on the use of haloperidol and the additional doses on the albumin concentrations. For instance, a loading dose of 7.5 mg followed by 2 mg every 4 h to a patient without haloperidol use and an albumin levels of 25 g l^{-1} will on average give an 85% of a Ramsay score of 3 or more (with its 95% confidence interval between 48 and 97%). This dose is slightly lower than the current guidelines. However, aiming for an 80% change of a Ramsay of 3 or more for 95% of the population would result in higher doses than the current guidelines, especially in patients with haloperidol as comedication. These values may be used as a reference in developing an individualized dosing regimen, which may improve clinical care for these terminally ill patients. However, it should be noted that with increasing the target concentration to ensure an adequate level of sedation for a larger proportion of the population, overdosing in part of the population would occur. It may therefore be advantageous to initially dose with the aim to achieve a 80% chance of an adequate sedation (Ramsay ≥3) for the typical patient and to titrate up according to the clinical response. To achieve an adequate response as soon as possible, the dose could be increased if adequate sedation is not yet reached at the time of the additional dose (after 4 h). For patients without haloperidol, increasing the additional dose with 50% with a bolus of 6 mg would ensure that the concentrations at which 95% of the population will have an 80% chance of adequate sedation will be reached within 12 h. For patients with haloperidol use, doubling the additional dose (with a maximum increase of 10 mg) in combination with an 8 mg bolus would ensure these higher concentration within around 16 h. Figure 6 shows the concentrations time profiles and corresponding probabilities that would be achieved with these dosing regimens. However, as the IIV remains high more research remains necessary to explore further the possible underlying causes. Other interests for future study arising from our results would be a PD study with a continuous observation to investigate variability in onset of sedation and the effect of haloperidol on sedation. A continuous measurement using a Bispectral Index Monitor (BIS) has been tested before in terminally ill patients. However, large variability in BIS values for patients with Ramsay scores of 6 were found [19]. Although it may give insight in the onset of sedation, BIS values may be more difficult to use for clinical recommendations. The same goes for other continuous PD measurements such as saccadic eye movement analysis [34]. With haloperidol it would be interesting to investigate if the correlating is due to the effect of deliria or because of a paradoxal response on

Table 4

Simulated dosing regimens and corresponding probabilities

	– haloperidol				+ haloperidol			
	albumin 15 g l^{-1}		albumin 25 g l^{-1}		albumin 15 g l^{-1}			
Dosing regimen[a] (mg)	7.5 / 1	25 / 4	7.5 / 2	25 / 7	10 / 1.5	75 / 12	10 / 3	75 / 21
Midazolam concentration (μg l^{-1})	50	200	60	200	75	600	85	600
Ramsay ≥ 3 Mean (95% CI; %)	82 (42–97)	96 (80–99)	85 (48–97)	96 (80–99)	78 (36–96)	96 (81–99)	81 (41–96)	96 (81–99)
Ramsay = 6 Mean (95% CI; %)	54 (16–88)	90 (60–98)	60 (19–90)	90 (60–98)	49 (13–86)	94 (73–99)	54 (16–88)	94 (73–99)

[a]dosing regimen in loading dose / additional doses every 4 h
CI, confidence interval

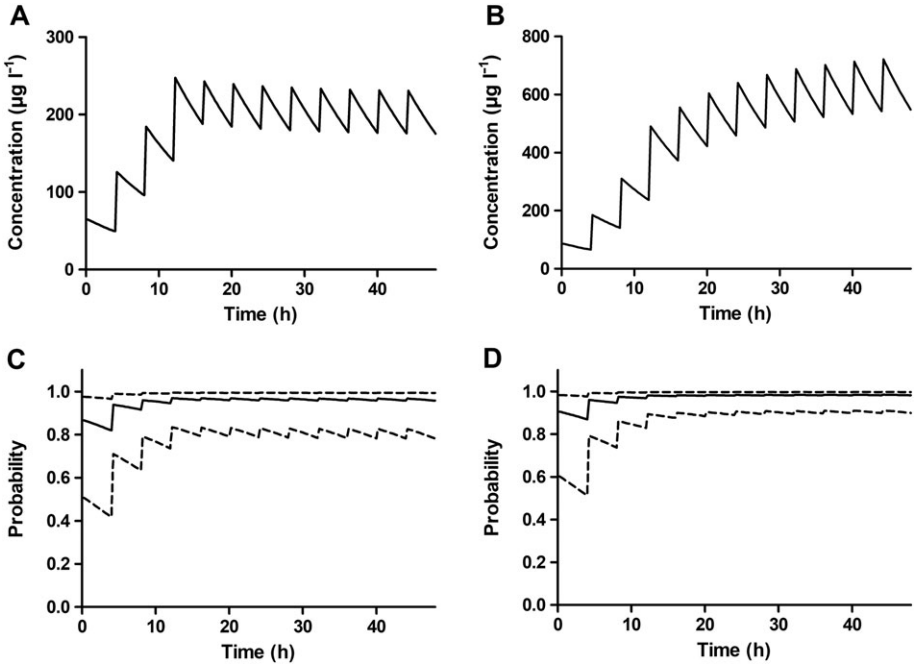

Figure 6

Concentration time profiles and corresponding probabilities (mean: solid line 95% confidence interval: dashed line) of a Ramsay score of 3 or more for a patient without haloperidol and albumin level of 25 g l^{-1} (A and C). For this patient a dosing regimen was simulated with an initial loading dose of 7.5 mg loading dose the additional dose of 2 mg every 4 h was increased 3 times with 50% together with a bolus dose of 6 mg to simulate a patient with inadequate response. B and D show the concentrations and probabilities (mean: solid line 95% confidence interval: dashed line) for a patient with haloperidol and albumin levels of 25 g l^{-1}. For this patient a dosing regimen was simulated with an initial loading dose of 10 mg loading dose the additional dose of 3 mg every 4 h was doubled 3 times together with a bolus dose of 8 mg to simulate a patient with inadequate response

haloperidol [35, 36]. Future research is complicated due to the complexity of the clinical setting in palliative care, such as the process of disease, comorbidities and the lack of validated rating scales. However, more insight is needed and more PK/PD research is needed to improve the care of these patients. Validated PD endpoints are necessary and a focus on relevant questions such as onset of sedation of relief of symtoms is needed.

Competing Interests

There are no competing interests to declare.

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