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. Franken1, Brenda C. M. de Winter1, An niek D. Masman2,3, Monique van Dijk3, Frans P. M. Baar2, Dick Tibboel3, Birgit C. P. Koch1, Teun van Gelder1 and Ron A. A. Mathot4

1Department of Hospital Pharmacy, Erasmus Medical Centre, Rotterdam, The Netherlands, 2Palliative Care Centre, Laurens Cadenza, Rotterdam, The Netherlands, 3Intensive Care, Department of Paediatric Surgery, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands, and 4Hospital 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 μg l\(^{-1}\) for a Ramsay score of 3–5 and 117.1 μg 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.
WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
- In terminally ill patients, pharmacokinetic variability can be reduced by taking into account a patient’s 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
determined by a 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 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).

\[
P (\text{Ramsay} = n) = P(\text{Ramsay} \geq n) - P(\text{Ramsay} \geq n + 1)
\] (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
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.

\[
\logit(Ramsay' n) = Base_n + \frac{Emax - Base_n}{CP + EC50_n} + IIV
\]

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

### 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 sedative 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 medication 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.

\[
\text{Covariate effect} = 1 - \left( \frac{\text{cov}_i}{\text{cov}_m} \right)^{\theta_{cov}}
\]

\[
\text{Covariate effect} = 1 - \theta_{cov} \text{ cov}_i
\]

with \( \text{cov}_i \) being the individual covariate value, \( \text{cov}_m \) represents the median covariate value and \( \theta_{cov} \) the covariate coefficient. In the equation for categorical covariates \( \text{cov}_i \) 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 (\( \theta_\lambda \)) and a second theta the rate (\( \theta_{rate} \)) at which the change takes place.

\[
\text{Covariate effect} = \theta_\lambda \exp(\theta_{rate} \text{ TTD})
\]
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 IV 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

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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, ml min⁻¹ 1.73 m⁻² | 69.4 (6–328) |
| C-reactive protein, U l⁻¹ | 128 (1–625) |

**Comedication used**

| Other benzodiazepines, n (%) | 8 (18.6) |
| Haloperidol, n (%)           | 18 (41.9) |
| Levomepromazine, n (%)       | 2 (4.7) |
| Dexamethasone n (%)          | 13 (30.2) |
| Anti-epileptic drugs, n (%)  | 3 (7.0) |
| Anti-depressant drugs, n (%) | 2 (4.7) |

**Morphine, μg l⁻¹ (median, range)**

| 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
acalculated using the abbreviated MDRD equation;
dduring the same day when Ramsay observations were collected;
bBenzodiazepines used included lorazepam, oxazepam and temazepam;
Antiepileptic drugs used included levetiracetam and pregabalin;
Antidepressant drugs included only amitriptyline

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*Table 1: Patient characteristics of terminally ill patients receiving midazolam.*

- **Characteristics**
  - **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, ml min⁻¹ 1.73 m⁻²:** 69.4 (6–328)
  - **C-reactive protein, U l⁻¹:** 128 (1–625)

- **Comedication used:***
  - **Other benzodiazepines, n (%):** 8 (18.6)
  - **Haloperidol, n (%):** 18 (41.9)
  - **Levomepromazine, n (%):** 2 (4.7)
  - **Dexamethasone n (%):** 13 (30.2)
  - **Anti-epileptic drugs, n (%):** 3 (7.0)
  - **Anti-depressant drugs, 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)
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 delirium has been mentioned to be a risk factor for a difficult sedation process [29, 30]. The IIIV 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 IIIV 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.

### Table 2
Covariate effects in univariate analysis compared to the structural model

| Covariate          | Parameter value | ΔOFV | ΔIIV | 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 | 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

**Note:** 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)
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
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

| Parameter                  | Structural model | Final model | RSE % | Shrinkage % | Bootstrap of the final model |
|----------------------------|------------------|-------------|-------|-------------|------------------------------|
| **Baseline**               |                  |             |       |             |                              |
| B2                         | 1.22             | 1.47        | 32    |             | 1.33                         |
| B3-5                       | –0.91            | –0.72       | 19    |             | –0.81                        |
| B6                         | –1.93            | –1.76       | 38    |             | –1.83                        |
| **Emax model**             |                  |             |       |             |                              |
| Emax                       | 4.08             | 4.62        | 24    |             | 4.54                         |
| EC502 (μg l⁻¹)             | 30.1             | 39.5        | 69    |             | 33.4                         |
| EC503 (μg l⁻¹)             | 62.8             | 68.7        | 51    |             | 62.8                         |
| EC506 (μg l⁻¹)             | 111.6            | 117.1       | 50    |             | 109.4                        |
| **Covariate effect**       |                  |             |       |             |                              |
| haloperidol                | 1.76             | 18          |       |             | 1.74                         |
| **Interindividual variability** |              |             |       |             |                              |
| Overall effect             | 0.81             | 0.92        | 29    | 18          | 0.94                         |

Bn, baseline logit for a Ramsay score of n; Emax, maximum effect; EC50n, 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.
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% chance 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 concentrations 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

| Dosing regimen* (mg) | - haloperidol | + haloperidol |
|----------------------|--------------|--------------|
|                      | albumin 15 g L⁻¹ | albumin 25 g L⁻¹ | albumin 15 g L⁻¹ |
| Midazolam concentration (μg L⁻¹) | 7.5 / 1 | 25 / 4 | 7.5 / 2 | 25 / 7 | 10 / 1.5 | 75 / 12 | 10 / 3 | 75 / 21 |
| Ramsay ≥ 3 Mean (95% CI; %) | 50 | 200 | 60 | 200 | 75 | 600 | 85 | 600 |
| Ramsay = 6 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) |

*dosing regimen in loading dose / additional doses every 4 h
CI, confidence interval
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 symptoms is needed.

Competing Interests

There are no competing interests to declare.

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