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Development of a pharmacokinetic and pharmacodynamic model for intranasal administration of midazolam in older adults: a single-site two-period crossover study

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Abstract

Background: Intranasal midazolam can produce procedural sedation in frail older patients with dementia who are unable to tolerate necessary medical or dental procedures during domiciliary medical care. Little is known about the pharmacokinetics and pharmacodynamics of intranasal midazolam in older (>65 yr old) people. The aim of this study was to understand the pharmacokinetic/pharmacodynamic properties of intranasal midazolam in older people with the primary goal of developing a pharmacokinetic/pharmacodynamic model to facilitate safer domiciliary sedation care.
Methods: We recruited 12 volunteers: ASA physical status 1–2, aged 65–80 yr, and received midazolam 5 mg intravenously and 5 mg intranasally on two study days separated by a 6 day washout period. Concentrations of venous midazolam and 1'–OH–midazolam, Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score, bispectral index (BIS), arterial pressure, ECG, and respiratory parameters were measured for 10 h.
Results: Time to peak effect of intranasal midazolam for BIS, MAP, and SpO_2 were 31.9 (6.2), 41.0 (7.6), and 23.1 (3.0) min, respectively. Intranasal bioavailability was lower compared with intravenous administration (F_{abs} 95%; 95% confidence interval: 89–100%). A three-compartment model best described midazolam pharmacokinetics following intranasal administration. A separate effect compartment linked to the dose compartment best described an observed time-varying drug-effect difference between intranasal and intravenous midazolam, suggesting direct nose-to-brain transport.
Conclusions: Intranasal bioavailability was high and sedation onset was rapid, with maximum sedative effects after 32 min. We developed a pharmacokinetic/pharmacodynamic model for intranasal midazolam for older persons and an online tool to simulate changes in MOAA/S, BIS, MAP, and SpO_2 after single and additional intranasal boluses.
Clinical trial registration: EudraCT (2019-004806-90).

Keywords: geriatric anaesthesia; intranasal sedation; midazolam; pharmacokinetic–pharmacodynamic modelling; procedural sedation

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Editor's key points

- The pharmacokinetic and pharmacodynamic properties of intranasal midazolam in older people have not been described previously.
- This study describes a pharmacokinetic/pharmacodynamic model and an online simulation tool for intranasal midazolam in older people to facilitate safer domiciliary sedation care.
- Pharmacokinetic modelling of the time-varying drug-effect difference between intranasal and intravenous midazolam suggests direct nose-to-brain transport.
- Intranasal bioavailability of midazolam was high with onset of maximum sedation at 32 min.

Intranasal administration of midazolam, with a formulation optimised for this route, offers a minimally invasive option for provision of sedation to patients with fear of medical treatment or those lacking the cognitive abilities to cope with the anxiety and discomfort associated with medical interventions. In children and younger adults, intranasal midazolam administration rapidly produces adequate sedation with a predictable onset time and plasma concentration profile.[1,2] However, comparable information is lacking for older people. Within the population of older people, the group of patients with major neurocognitive disorder or dementia is rapidly increasing. According to data from the WHO, the number of people suffering from dementia will rise globally from 78 million people in 2030 to 139 million in 2050.[3,4] Older patients with major neurocognitive disorder are a challenging group for medical and dental practitioners, as they have an impaired ability to care for their personal and dental hygiene. They have limited abilities to understand the rationale for treatment and to communicate pain experiences. For these and other reasons, they are commonly fearful and unable to tolerate and cooperate with medical procedures.[5–7] Recently, there has been an increased awareness that the incidence of undetected painful medical or dental conditions is disproportionately high in this group and that their pain may be more severe because of the structural brain damage accompanying this syndrome.[6,8,9]

When options for non-pharmacological measures to improve comfort and cooperation have been exhausted, procedural sedation might be indicated, for instance with intranasal midazolam. Age has been shown to influence the pharmacokinetics (PK) and pharmacodynamics (PD) of midazolam when administered intravenously.[10–13] Information on the effect of age on midazolam PK and PD after intranasal administration is lacking. If intranasal administration is to be used, it is important that the pharmacological profile is well understood in this vulnerable group of patients, many of whom must be considered as frail. This is especially true for patients with major neurocognitive disorder, who need domiciliary medical care when transportation to a hospital facility is considered unfeasible or an intolerable burden to the patient. The possibility of domiciliary procedural sedation care is seldom mentioned in the literature or considered to be an option by healthcare professionals because of fears of complications.

We designed a single-site two-period crossover study to evaluate the PK and PD properties of intranasal midazolam (IN-MDZ) in older (aged 65 yr and older) volunteers. After developing a comprehensive PK/PD model for IN-MDZ in older persons, we developed a freely accessible online tool to simulate the effects of single administrations of IN-MDZ and of additional boluses. The model and the tool should help caregivers titrate IN-MDZ to a safe and effective sedation level for older patients to facilitate essential dental or medical treatment.

Methods

This single-site two-period crossover study was performed at the clinical research facility of QPS Netherlands B.V., Groningen, the Netherlands, in cooperation with the Departments of Anaesthesiology and Gerodontology of the University Medical Center Groningen, Groningen, The Netherlands. The study protocol was approved by the BEBO Ethics Committee (Stichting BEBO, Assen, The Netherlands) on February 6, 2020 (number NL72400.056.20) and registered as a Phase 1 trial on February 19, 2020, under EudraCT number 2019-004806-90, accessible at the Dutch regulatory authority.

All participants gave written informed consent. Inclusion criteria were persons 65–90 yr old, BMI $\geq$18 and $\leq$30 kg m^{-2}, and ASA physical status 1 or 2. Exclusion criteria were current use of midazolam, contraindications to the use of midazolam, history of any illness, nasal pathology, medication use that might confound the results of the study, or history or risk of difficult tracheal intubation. Additionally, participants were excluded from participation if they had surgery within 90 days before dosing, a history of alcoholism or drug abuse within the past 2 yr, or a history of severe osteoporosis or tendency to fall.

Study objectives

The primary objective of this study was to determine the PK and PD characteristics and to investigate the safety and sedative properties of IN-MDZ in older persons in comparison with intravenous midazolam (IV-MDZ). These data were used to develop an online educational tool to simulate the effects of IN-MDZ administration to participants aged 65–80 yr.

Study design

In total, 12 healthy participants (aged 65 yr and older) participated. The study took place on two separate study days for each participant. On one day, midazolam was administered intranasally (IN-MDZ) and on the other day intravenously (IV-MDZ). The sequence of administration per participant was determined by randomisation using a software-driven random number generator. Study days were separated by a washout period of at least 6 days.

Baseline PD measurements of arterial BP, HR, haemoglobin oxygen saturation, and Bispectral Index (BIS) were taken at least 5 min before midazolam administration. One 20G i.v. cannula was inserted on the IN-MDZ day and two 20G i.v. cannulas, on opposite arms, on the IV-MDZ day. The first cannula was used for blood sampling and could be used for administration of rescue medications, such as ephedrine, phenylephrine, atropine, or flumazenil. The second cannula was only used for IV-MDZ administration. On IN-MDZ days, the participants were administered a 2.5 mg dose of IN-MDZ in each nostril using a commercially available midazolam intranasal spray device that provides midazolam 2.5 mg per single puff of 75 μl (De Magistrale Bereider, Fagron, Hoogeveen, The

Netherlands). On IV-MDZ days, a single 5 mg bolus dose of IV-MDZ (midazolam hydrochloride 1 mg ml^{-1}; Actavis B.V., Baarn, The Netherlands) was administered through the dedicated intravenous cannula with an administration time of 30 s.

The participants were monitored by an anaesthesiologist and a physician assistant. After midazolam administration, the participants were placed in a supine position with a 30-degree head-up tilt. The participants remained in bed until they were fully awake (FA; defined as three consecutive Modified Observer's Assessment of Alertness/Sedation [MOAA/S] scores of 5) but for at least 2 h or as long as it took for full recovery (FR; defined as a modified *Aldrete* score [APRS] score of 9 or higher). Monitoring consisted of measurement of ECG and HR (beats min^{-1}), BP (mm Hg), ventilatory frequency (bpm), and end-tidal CO_2 (kPa), measured using a Smart Capnoline® (Oridion Medical Ltd, Jerusalem, Israel). These measurements were recorded at 2.5-min intervals for the first hour after administration and every 5 min during the second hour. Thereafter, measurements were recorded whenever blood samples were taken (see below). The MOAA/S scores and BIS values were recorded at 5-min intervals until the participants were FA.

Venous blood samples were taken from the designated intravenous cannula at 5, 10, 15, 20, and 25 min and 1, 2, 4, 6, 8, and 10 h after administration. At the end of each study day, the participants were asked to rate nasal mucosal irritation on a 5-point scale (0=no irritation up to 5=severe irritation or pain), and direct visual nasal mucosal inspection was performed. The participants were contacted by telephone on the day following each study day and were given a 5-item questionnaire comprising questions about possible excessive sleepiness, loss of concentration, nausea, dizziness, and nasal irritation.

Sample handling

Venous blood samples were collected in Li heparin tubes. Analysis was performed at the QPS Netherlands B.V. bioanalytical laboratory. Plasma samples were stored at −20°C until analysis. Sample preparation was by liquid–liquid extraction with a stable isotope labelled ^{13}C6 midazolam and ^{13}C6 1'–OH–midazolam. Samples were analysed with an API 4000™ liquid chromatography–tandem mass spectrometry system (LC–MS/MS; SCIEX, Framingham, MA, USA). The lower limit of quantitation of the assay was 0.100 ng ml^{-1} for both midazolam and 1'–OH–midazolam, and for a validated LC–MS/MS method the assay range was 0.100–100 ng ml^{-1}. Between-run imprecision and accuracy across the midazolam assay range were from 4.1% to 6.8% and from 95.8% to 122.1%, respectively.

Population PK modelling

Plasma midazolam and 1'-OH midazolam concentration data were fitted using the first-order conditional estimation with interaction (FOCE-I) estimation algorithm in NONMEM® (version 7.4; GloboMax LLC, Hanover, MD, USA). The 'tidyverse' package[14] (version 1.3.1.) in R® (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) was used to assess the goodness of fit of the fitted models graphically.

One-, two-, and three-compartment models with first-order absorption into and first-order elimination from the central compartment were fitted as a starting point for midazolam PK model development. To avoid over-parameterisation of the joint midazolam and 1'-OH midazolam PK model, we fixed the fraction metabolised (f_m) to 0.93, assuming that midazolam is 93% metabolised to 1'-OH midazolam.[15] One- and two-compartment models were evaluated for description of 1'-OH midazolam kinetics. In all models, we assumed a molar conversion ratio of 1'-OH midazolam to midazolam of 1.049.[16]

Inter-individual variability of the population parameters was assumed to be log-normally distributed. Residual unexplained variability was modelled using additive, proportional, or additive and proportional error models. Correlations between the residual variability for midazolam and 1'-OH midazolam that result from both compounds being measured from the same blood sample were accounted for by the L2 data item in NONMEM.[17]

Inclusion of covariates in the model was driven by graphical evaluation of the relationship between random effects (ETAs) and the covariates. Covariates evaluated for inclusion in the model were weight (kg), age (yr), height (m), sex, and formulation (i.v. or i.n.).

Population PD modelling

The 'individual PK parameter approach' was applied to develop the PD models.[18] In this approach, plasma concentration measurements from this study were used to derive individual *post hoc* PK parameters based on the final PK model, and these parameters were fixed for each individual and each period in the subsequent PD modelling process. The BIS, MAP, and SpO_2 data were fitted using the FOCE-I estimation algorithm, whereas the proportional odds logistic regression model for the MOAA/S was fitted using the LAPLACE-I algorithm in NONMEM (version 7.4; GloboMax LLC).

The development process for the structural PD models consisted of three consecutive steps. First, we tested different drug-effect models (linear, E_{max}, and sigmoid E_{max} models) to describe the observed PD response as a function of the plasma concentration in the central compartment or the concentration in a delayed effect compartment. Second, we tested whether the addition of inter-occasion variability of the parameters describing the drug effect (e.g. slope, C_{50}, etc.) improved the model. The identification of significant inter-occasion variability would indicate differences in the observed responses between the i.v. and i.n. administration periods. Third, the presence of a direct nose-to-brain effect[19] was tested in the model by fitting a proportional change in the drug-effect parameters (e.g. slope, C_{50}, E_{max}, etc.) for i.n. compared with i.v. administration (time-invariant approach), or by fitting a separate effect compartment model with a separate drug-effect model (linear, E_{max}, or sigmoid E_{max}) that described the direct nose-to-brain effect as a function of midazolam concentrations in the dosing compartment (the nose).

For BIS, E_{max} was not estimated from the data when using (sigmoid) E_{max} models but was fixed to 1. This approach was taken to ensure that the model would have reasonable extrapolation properties. BIS values <40 are largely determined by the burst suppression ratio, and burst suppression can occur with high benzodiazepine doses.[20,21]

Once the structural model was identified, covariates were screened for inclusion in the model. Covariates considered were weight (kg), age (yr), height (m), sex, and formulation (i.v. or i.n.).

Model building and evaluation

For model building, candidate models were compared with likelihood ratio testing based on the NONMEM objective function value (OFV) at the 1% level of significance with a ΔOFV <−3.84 considered significant for the addition of one parameter. Non-nested models were compared using the Akaike information criterion (AIC). Modifications to the models were accepted only if they resulted in a significant decrease in the OFV or a decrease in AIC, demonstrated improvements in the goodness-of-fit plots, and were estimable with acceptable numeric stability (i.e. condition number <500).

Internal model validation was based on goodness-of-fit plots based on normalised prediction distribution errors[17] and visual predictive checks.[22] For all model parameters, the maximum likelihood estimate and the associated 95% confidence interval (CI) derived from the NONMEM covariance matrix are reported. As a safeguard against model over-parameterisation during model building, we evaluated the condition number of the Fisher information matrix between candidate models.

Simulation

Simulations of the concentrations and clinical responses that would result from additional midazolam boluses were performed with software developed in-house by author PC. To enable others interested in this topic to perform their own simulations, the software and the final models were subsequently implemented in a cloud-based application using the following packages: shiny,[23] RxODE,[24] and gridExtra[25] in RStudio (version 1.4.1106).[26]

Results

Twelve participants were enrolled in the study and completed all study actions; their characteristics are listed in Table 1. Of 288 planned blood samples, one sample was lost (participant 004; sample IN-MDZ 00:05:00) because blood could not be drawn from the i.v. cannula at that time point. Before starting PK modelling, we decided to exclude the results of four 1'-OH midazolam samples taken at the 5-min time point, as the results were below the limit of quantification (0.1 ng ml^{-1}). Data are shown in Supplementary Figure 1.

Population PK model for midazolam and 1'-OH midazolam after intravenous and intranasal administration

A three-compartment model best described the midazolam PK following intravenous administration. Intranasal absorption of midazolam was best described by a first-order absorption rate constant (k_a) and a lag time (ALAG). The bioavailability of midazolam after intranasal administration was introduced as an additional parameter in the model (F_{abs}).

The formation of 1'-OH midazolam was described by a first-order formation rate of 0.93 times the estimated elimination rate of midazolam. To remedy over-prediction of 1'-OH midazolam concentrations at the early time points, a series of transit compartments was added to the model to describe the delay in 1'-OH midazolam formation relative to the decrease in midazolam concentrations. The disposition kinetics of 1'-OH midazolam were best described by a two-compartment model with linear elimination from the central compartment (Cl_m).

Between-participant variability in PK was described by implementing a log-normal distribution for midazolam clearance (Cl), absorption rate constant (k_a), 1'-OH midazolam clearance (Cl_m), mean transit time (MTT) for 1'-OH midazolam formation, and intranasal absorption time-lag (ALAG). Covariate analysis showed that age was the only significant covariate of PK with absorption rate constant (k_a) decreasing with increasing age.

During model building, we found that the bioavailability of intranasally administered midazolam was lower compared with intravenous administration (F_{abs} 95%; 95% CI: 89–100%), and that there was a significant lag time for intranasal absorption (2.1 min; 95% CI: 1.3–2.9 min). We also found that there is a significant delay in 1'-OH midazolam formation relative to disappearance of midazolam from the central compartment (MTT for a five transit compartment model of 7.6 min).

The structure of the final PK model is shown in Supplementary Figure 2, with parameter estimates shown in Table 2. All parameters were estimated with good precision. A

Table 1 Characteristics of study participants.

Participant number	Age (yr)	Sex	Weight (kg)	Height (cm)	ASA physical status
1	67	Male	80	179	1
2	72	Female	79	170	1
3	68	Female	75	162	1
4	80	Female	58	153	1
5	74	Male	82	186	1
6	73	Female	64	159	1
7	74	Female	59	152	1
8	78	Female	56	153	1
9	69	Male	86	179	1
10	73	Male	69	159	1
11	71	Male	75	165	1
12	66	Male	79	186	1

Table 2 Pharmacokinetic and pharmacodynamic parameter estimates. BIS, bispectral index; CI, confidence interval; Cl, midazolam clearance; Cl_m, 1'-OH midazolam clearance; C_{50}, concentration achieving half-maximum effect; E_{max}, maximum effect; F_{abs}, absolute bioavailability; k_a, absorption rate constant; k_{e0}, rate constant for effect-site equilibration; lag time, absorption lag time; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; MTT, mean transit time for the five transit compartments describing 1'-OH midazolam formation; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation; TVD, time-varying difference; V_1, volume of distribution of the central midazolam compartment; V_2, volume of distribution of the fast peripheral midazolam compartment; V_3, volume of distribution of the slow peripheral midazolam compartment; V_4, volume of distribution of the central 1'-OH midazolam compartment; V_5, volume of distribution of the peripheral 1'-OH midazolam compartment; γ, steepness of the concentration–effect relationship. *CV(%) is calculated according to $\sqrt{\omega^2}$*100%, where ω^2 is the estimated variance in NONMEM. †SD is calculated as the square root of the estimated variance in NONMEM.

PK parameters	Estimate (95% CI)		
F_{abs} (%)	$\begin{cases} IV = 100\% \\ IN = \theta_1 \bullet 100\% \end{cases}$	V_4 (L)	36.5 (30.2; 42.8)
θ_1	0.95 (0.89; 1.01)	V_5 (L)	151 (101; 200)
Lag time (min)		Cl_m (L min^{-1})	2.39 (2.11; 2.67)
θ_2	2.09 (1.28; 2.90)	Q_5 (L min^{-1})	1.21 (0.77; 1.65)
k_a (min^{-1})	$\theta_3\ e^{(\theta_4[age\{yr\}-70])}$	Between-participant variability (CV%*)	
θ_3	0.081 (0.059; 0.102)	k_a	26.2 (15.7; 33.6)
θ_4	−0.07 (−0.11; −0.03)	Cl	20.8 (14.6; 25.6)
V_1 (L)	4.42 (2.63; 6.20)	Lag time	40.2 (13.9; 55.2)
V_2 (L)	22.6 (19.1; 26.1)	Cl_m	18.2 (8.8; 24.2)
V_3 (L)	49.4 (43.4; 55.4)	MTT	14.7 (9.8; 18.4)
Cl (L min^{-1})	0.31 (0.27; 0.35)	Residual unexplained variability (SD)†	
Q_2 (L min^{-1})	1.93 (1.48; 2.38)	Proportional error: midazolam	0.17 (0.15; 0.20)
Q_3 (L min^{-1})	0.30 (0.25; 0.35)	Proportional error: 1'-OH midazolam	0.17 (0.15; 0.20)
MTT (min)	7.56 (6.54; 8.58)	Additive error: 1'-OH midazolam	0.24 (0.12; 0.37)
		Correlation	0.58 (0.45; 0.70)

Estimate (95% CI) PD parameters	BIS	MOAA/S	MAP	SpO_2
k_{e0} (min^{-1})	0.06 (0.05; 0.07)	0.09 (0.07; 0.11)	0.05 (0.03; 0.07)	0.07 (0.05; 0.09)
Baseline	95.5 (93.6; 97.3)		87.8 (82.5; 93.1)	$\theta_1 \bullet e^{(\theta_2 \bullet (age\ (yr)-70))}$
θ_1				98.4 (98.0; 98.8)
θ_2				−0.002 (−0.001; −0.003)
E_{max}	$e^{(\theta_3[age\ \{yr\}-70])}$			
θ_3	−0.05 (−0.06; −0.03)			
C_{50} (ng ml^{-1})	200 (154; 246)			
γ	1.71 (1.12; 2.30)			
k_{e0}_TVD (min^{-1})	0.03 (0.02; 0.05)			0.06 (0.04; 0.08)
E_{max}_TVD	$\theta_4\ e^{(\theta_3[age\ \{yr\}-70])}$			
θ_4	0.18 (0.11; 0.24)			
Logit (MOAA/S ≤1)		−12.9 (−15.5; −10.2)		
Logit (1< MOAA/S ≤2)		2.64 (1.67; 3.61)		
Logit (2< MOAA/S ≤3)		1.63 (0.73; 2.53)		
Logit (3< MOAA/S ≤4)		3.45 (2.62; 4.28)		
Slope		$\begin{cases} IV = \theta_5 \\ IN = \theta_5 + \theta_6 \end{cases}$	0.001 (0.001; 0.002)	0.03 (0.02; 0.04)
θ_5		0.06 (0.05; 0.08)		
θ_6		0.02 (0.01; 0.03)		
Slope_TVD				0.007 (0.005; 0.009)
Between-participant variability (CV%*)				
Base			11.4 (7.75; 14.1)	0.91 (0.54; 1.16)
Slope		23.4 (0.01; 35.9)	53.3 (0.01; 93.4)	
Between-occasion variability (CV%*)				
C_{50}	5.63 (3.05; 7.35)			
Slope		7.74 (0.01; 11.8)	21.9 (6.32; 30.2)	36.5 (0.01; 54.3)
Residual unexplained variability (SD)†				
Additive error	6.00 (5.07; 6.79)		4.82 (4.32; 5.27)	1.54 (1.29; 1.76)

visual predictive check for the final model and additional goodness-of-fit graphs (Fig. 1; Supplementary Figs 3–7) show that the final model describes the observed data well.

PK/PD model for BIS, MOAA/S, MAP, and SpO_2

An overview of the PD model-building process is shown in Supplementary Table 1. For MOAA/S, MAP, and SpO_2, linear models relating the effect compartment concentrations to the PD outcome best described the data. For BIS, a sigmoid E_{max} model linking changes in BIS to the predicted effect-site concentration outperformed a linear model. Inter-occasion variability of the drug-effect parameters (slope or C_{50}) was significant in all models. For the MAP model, there was no significant difference in the slope between intranasal and intravenous administration (P=0.08).

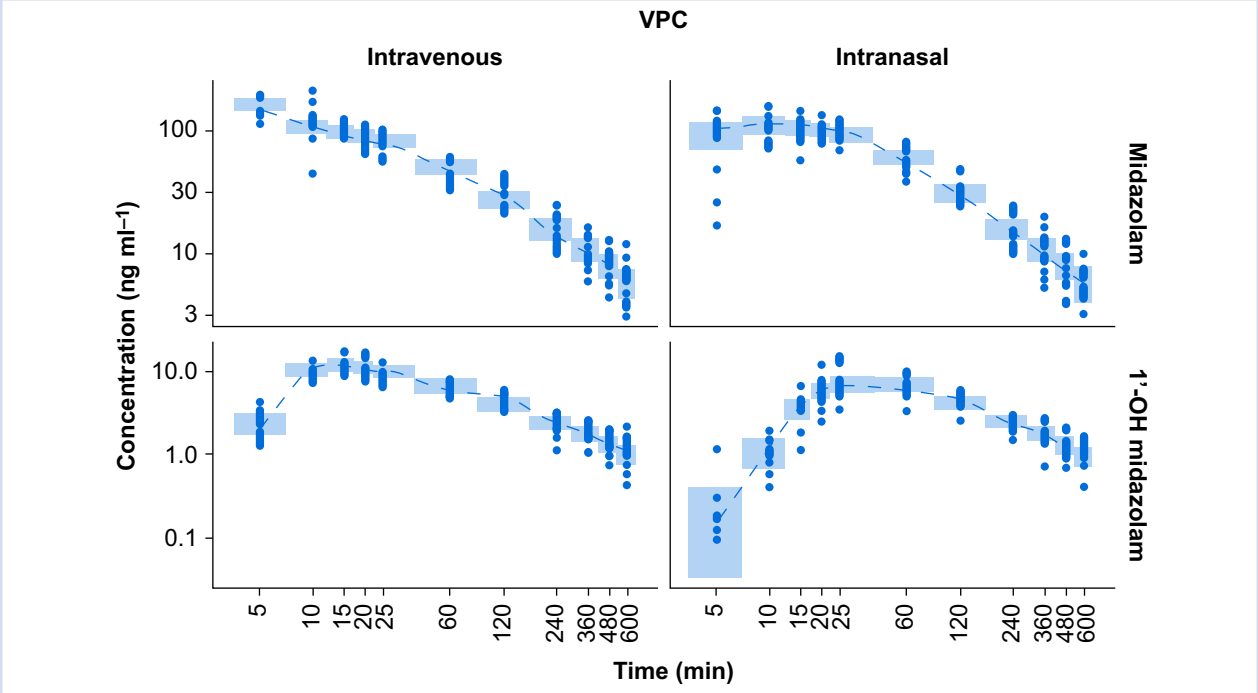

Fig 1. Visual predictive checks for the final model and goodness of fit.

For the MOAA/S model, the slope was significantly greater for intranasal compared with intravenous administration (0.08 *vs* 0.06 logits ng ml^{-1}). For BIS and SpO_2, the E_{max} and slope were greater for intranasal administration, and a separate effect compartment linked to the dose compartment best described this observed time-varying difference in drug effect between IN-MDZ and IV-MDZ.

Covariate analysis revealed that the drug effect on BIS (E_{max}), the magnitude of this time-varying difference in drug effect between IN-MDZ and IV-MDZ on BIS (E_{max}TVD), and baseline SpO_2 decreased with increasing age. Changes in other covariates were not significant.

Parameter estimates for the final PD models are shown in Table 2. All parameters were estimated with good precision, as judged by the 95% CIs.

Visual predictive checks showing only the predicted median responses for all PD endpoints are shown in Supplementary Figure 3 and demonstrate that the final models describe the observed data well. The only exception is that the BIS and MOAA/S models under- and over-predict the drug effect, respectively, resulting in an over-prediction of BIS and an over-prediction of the occurrence of an MOAA/S 2 at the early time points (<8 min) after intravenous administration.

Table 3 shows the calculated peak effect, time-to-peak effect, and time required for attenuation of the peak effect by 90% for all participants based on *post hoc* estimates for the final PK/PD models. The online simulation tool was developed under the auspices of the Department of Anaesthesiology, University Medical Center Groningen, and is freely accessible at https://umcgresearch.org/w/anaesthesiology. The results of a simulation of a single bolus of midazolam 5 mg intravenously and intranasally can be found in Figure 2.

Safety monitoring

Heart rate remained relatively unchanged in all participants. Cardiac rhythm and ECG morphology remained unchanged for

Table 3 Maximum predicted effects (nadir), time to maximum effect, and time to 90% attenuation of effect. BIS, bispectral index; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; SD, standard deviation; SpO_2, peripheral oxygen saturation; T_{att}, time to 90% attenuation of effect; T_{nadir}, time to maximum effect.

	Intravenous	Intranasal
SpO_2		
Nadir (%) (SD)	93.2 (1.9)	92.9 (1.9)
T_{nadir} (min) (SD)	6.9 (0.3)	23.1 (3.0)
T_{att} (min) (SD)	154 (29.4)	139 (19.6)
MAP		
Nadir (mm Hg) (SD)	76.2 (9.3)	77 (8.7)
T_{nadir} (min) (SD)	14.8 (1.7)	41 (7.6)
T_{att} (min) (SD)	208 (44)	264 (66)
BIS		
Nadir, mean (SD)	72 (5)	70.5 (5.31)
T_{nadir} (min) (SD)	8.8 (0.7)	31.9 (6.2)
T_{att} (min) (SD)	105 (14)	119 (17)
MOAA/S		
5	0.05 (0.90)	0.11 (0.13)
4	0.38 (0.21)	0.49 (0.23)
3	0.26 (0.14)	0.19 (0.1)
2	0.19 (0.14)	0.16 (0.20)
1	0.12 (0.27)	0.03 (0.05)
T_{peak} (min) (SD)	5.74 (0.19)	30.4 (6.73)
T_{att} (min) (SD)	61.3 (13.6)	102 (19.2)

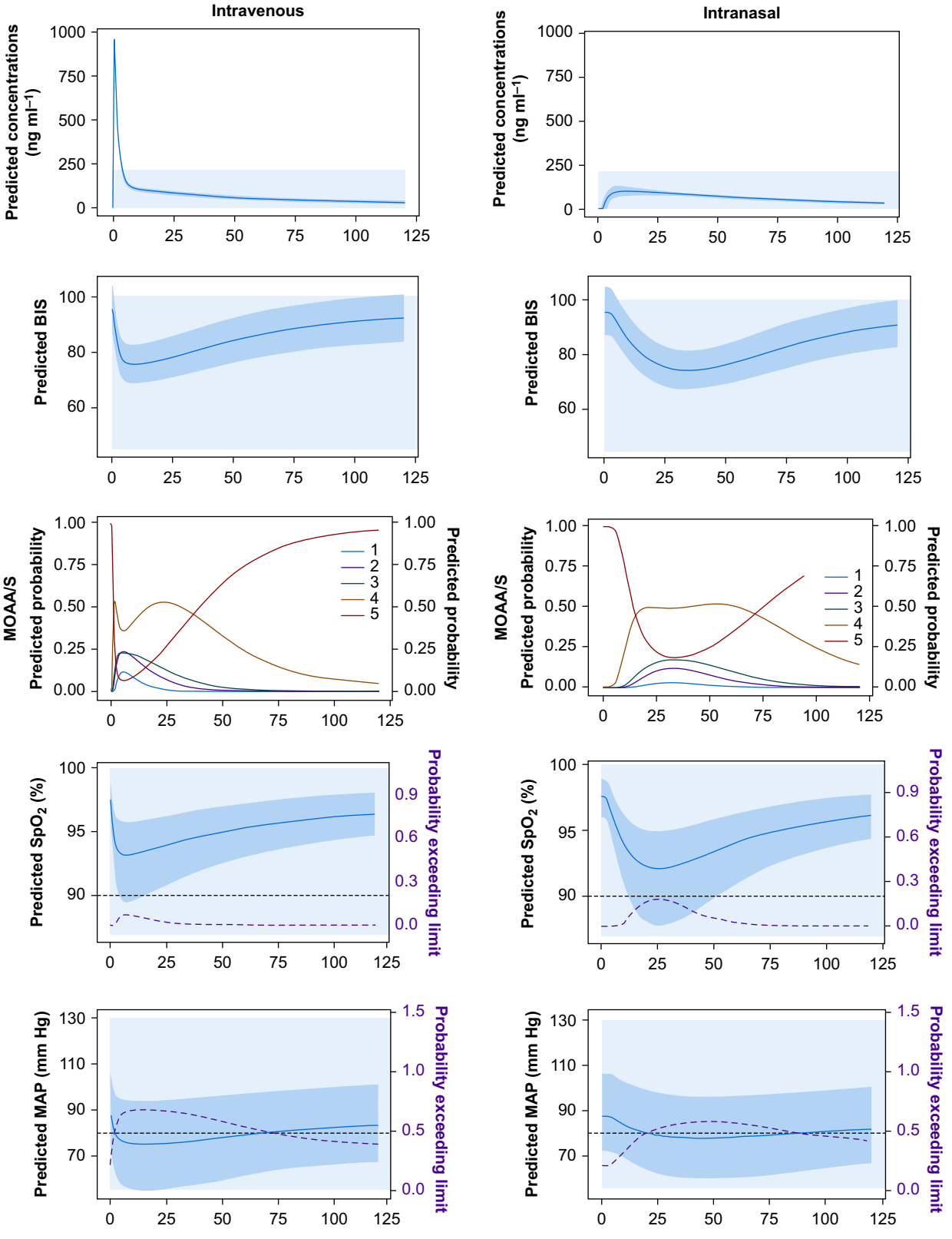

Fig 2. Simulation of administration of midazolam 5 mg intravenously or intranasally. BIS, bispectral index; MOAA/S, Modified Observer's Assessment of Alertness/Sedation.

all participants. No participants required vasopressor support or intravenous fluid boluses after either IV-MDZ or IN-MDZ. One participant was placed in 10–15% Trendelenburg position when her systolic BP dropped below 90 mm Hg (MAP 60 mm Hg; MOAA/S 5–4; BIS 68). Although her normal resting systolic BP was 105 mm Hg and she remained asymptomatic, we considered this intervention to be prudent, and the effect was satisfactory with a return of her systolic BP to >90 mm Hg.

No participants required airway manoeuvres or mechanical ventilation, and no apnoea, central or obstructive, was observed. One participant required additional O_2 (3 L min^{-1} via nasal prongs for SpO_2 <90% for >3 min. (The ventilatory frequency was 24 bpm and $etCO_2$ was 4.3 kPa.) She recovered without problems and reported no respiratory complaints.

Intranasal midazolam led to onset of sedation (MOAA/S <5) after 14 (4.5) min compared with 6 (4) min after i.v. administration. Two participants reached MOAA/S 1 (one i.v. and one i.n.).

Table 4 shows the results of the simulation of peak effect for administration of 5 mg i.n. midazolam to a 75-yr-old, 70 kg individual and the results of additional administration of 2.5, 5, and 7.5 mg of i.n. midazolam to the same individual 15 and 30 min after the initial bolus.

Recovery and follow-up

All participants recovered uneventfully, and none needed flumazenil. No paradoxical reactions occurred. Time to FR was mainly determined by the time to FA. APRS for motor activity, respiration, BP, and oxygenation did not determine the time to FR. The overall time until the participants were FA was 70 (21) (range: 40–120) min. For IN-MDZ, this was 78 (18) min; for IV-MDZ, time to FA was 63 (20) min.

At discharge, all participants were lucid and fit to go home (APRS 10). In the telephone follow-up, none of the participants reported any of the symptoms listed in the questionnaire (dizziness, nausea, loss of concentration, excessive sleepiness, or nasal irritation), neither on the study day after discharge or during the following day. More than two-thirds of participants reported a more than satisfactory night's sleep after the study day compared with usual.

Discussion

The current study evaluated and modelled the PK and PD properties of intranasally administered midazolam in older participants. Previous models of IN-MDZ were developed from data from children or younger adults.[1 27 28] Frailty in older patients and increased sensitivity to sedatives, such as midazolam, necessitate specific evaluation in this population. Our results inform on the use of intranasally administered midazolam for procedural sedation in older patients.

We identified both similarities and differences between the PK of older compared with younger participants. The only available study of the PK/PD of i.n. midazolam in older participants[29] used USL261, a chitosan-based midazolam formulation different from the water-based formulation we used. We found T_{max} of 10.4 min, whereas in other studies T_{max} ranged between 8 and 20 min.[27–30] The area under the curve (AUC) after IV-MDZ in the present study (13.0 [3.0] mg L^{-1} min^{-1}) is similar to that reported by Knoester and colleagues[2] (13.0 [4.7 mg L^{-1} min^{-1}]). The same holds for the AUC of 1'–OH–midazolam in both studies (1.8 [0.6] *vs* 1.7 [0.3] mg L^{-1} min^{-1}, respectively).[2] This indicates that clearance of midazolam in both populations is similar, a finding corroborated by a previous study by Albrecht and colleagues.[11] However, in the current study, the AUC after IN-MDZ was ~30% higher (10.2 [3.3] *vs* 13.8 [3.1] mg L^{-1} min^{-1}), and C_{max} was almost 100% higher (71 [25] *vs* 118 [28] mg ml^{-1}.[2] The only other study of IN-MDZ with older participants reported a C_{max} of 55.8 ng ml^{-1}.[29] Possible explanations for the difference include the following. Firstly, a difference in the formulations used. Knoester and colleagues[2] used a formulation of midazolam 2.5 mg in 90 μl, whereas we used a formulation of 2.5 mg in 75 μl of spray, and Berg and colleagues[29] used a chitosan-based formulation. Secondly, the absorption characteristics of midazolam might be different in younger adults compared with older adults, although a physiological mechanism for this explanation is currently lacking. Thirdly, the volume of distribution in our population is smaller than the volume of distribution in other populations. This is difficult to ascertain because of the different methods used to determine volume of distribution. Other possible explanations could be our use of two doses of 2.5 mg delivered to each nostril, a difference in concentration (see above), and differences in the delivery devices used.

None of our participants experienced discomfort during or after IN-MDZ administration. In contrast, Berg and colleagues[29] reported that up to 89% of geriatric participants experienced one or more adverse effects, such as increased lacrimation, nasal irritation, cough, and rhinorrhoea. Although such adverse side-effects might not be of particular importance in emergent situations, they are reasonable

Table 4 Simulation of the effect of additional boluses of intranasal midazolam at different times after the original 5 mg dose. Boluses given either after 15 min or after 30 min to a 75-yr-old, 70 kg individual. Values median [inter-quartile range]. BIS, bispectral index; MAP, mean arterial pressure; SpO_2, peripheral oxygen saturation.

Intranasal midazolam (mg)	Simulated peak effect		
	BIS	SpO_2 (%)	MAP (mm Hg)
5	71.8 [61.9; 81.1]	92.2 [87; 95.6]	77.4 [55.9; 98.4]
Additional bolus given after 15 min			
2.5	63.5 [56.4; 70.9]	89.2 [82.4; 94.2]	72.8 [47; 97.3]
5	54.2 [46.9; 62.5]	86.5 [76.7; 92.9]	67.9 [32.2; 92.5]
7.5	46.5 [40.3; 54.1]	83.8 [70.6; 91.8]	62.4 [15.5; 92.3]
Additional bolus given after 30 min			
2.5	65.8 [58; 73.2]	90.3 [84.2; 94.5]	73.4 [46.4; 98.7]
5	56.3 [48.8; 64]	87.6 [77.9; 93.2]	68.2 [36.4; 94.4]
7.5	48.1 [41.4; 55.8]	84.7 [73.7; 92.1]	63.1 [28.1; 89.2]

concerns when the objective is to provide comfort to frail older patients.

The effects of IN-MDZ administration were more pronounced than expected from the plasma concentrations: 5 mg of IN-MDZ led to light sedation (MOAA/S 4–3) in six participants and deep sedation (MOAA/S 2–1) in another six participants), whereas intravenous administration led to light and deep sedation in eight and four participants, respectively. This effect is not explained by PK differences because our analysis takes PK differences into account. Our pharmacological analyses further indicate that absorption from the nasal cavity in older patients is protracted and delayed (T_{max} for IV-MDZ 0.5 min *vs* T_{max} for IN-MDZ 11.5 min), and that the slope of the E_{max} curve was steeper after IN-MDZ ($P<0.01$). In addition to this, we observed a time-varying difference in drug effects between IN-MDZ and IV-MDZ by linking a separate effect compartment to the dose compartment. These observations and identification of such a separate effect compartment model for BIS and SpO_2 suggest that the reported differences are not a chance finding, but rather suggest that another absorption route to the CNS exists for midazolam: direct nose-to-brain transport. Several physiological mechanisms of direct nose-to-brain transport have been proposed, amongst them midazolam diffusion into perineural spaces, crossing the cribriform plate to enter the cerebrospinal fluid, and intracellular transport through olfactory sensory neurones.[31] Such drug transport is enhanced for lipophilic and small (<1000 g mol^{-1}) drugs.[32] Midazolam is lipophilic at a pH of >4.0, the pH of the solution used in our study, and has a molecular weight of 325 g mol^{-1}. These findings suggest that for the formulation used, midazolam is likely reaching the CNS not only by the vascular system, but also by direct nose-to-brain transport. This phenomenon has been suggested previously in a study in dogs.[33]

Simulations performed using the PK/PD model developed from our data can help inform decisions about dosing of midazolam in older persons. They suggest that a single 5 mg bolus of midazolam administered intranasally (2.5 mg in each nostril) in older persons is likely to lead to clinical sedation after ~30 min with little cardiorespiratory compromise. Additional boluses will deepen sedation but will likely also lead to reduced oxygen saturation. When planning to administer an additional bolus to increase sedation depth, it is advisable to wait at least until the time to peak sedative effect has passed, when the peak effect on oxygen saturation can also be evaluated, before administering additional drug.

Limitations

Although we used a crossover design with an adequate washout period, our participants did not receive a placebo administration on either study day, nor did we use blinding. An important limitation is that outcome measures, such as the MOAA/S score and the nasal irritation score, might have been influenced by these factors. Our primary outcome parameters plasma midazolam concentrations and BIS score, however, are unlikely to have been influenced by lack of blinding. Secondly, participants were all healthy, the maximum age was 80 yr, and the population from which we developed this model had a limited variation in weight and height. This might explain why these covariates were not significant factors in the model. Lastly, the simulation tool can only be used with some caveats; the study did not examine the linearity of the PK system through the intranasal route, and the effect of multiple dosing was simulated but was not examined in the study.

We have developed a PK/PD model to estimate plasma and effect-site midazolam concentrations after IN-MDZ administration in older persons. To our knowledge, this is the only such model available. In our model, age is the only covariate of midazolam PK. A unique feature of the PD aspect of the model is that it can also be used to estimate sedation scores, BIS values, BP, and oxygen saturation for both single-dose administrations and a timed additional bolus. Further research on administration of midazolam in older people with poor health or dementia is needed to further improve the PK/PD model, but such studies are likely to suffer ethical hurdles. The model we developed for intranasal administration of midazolam 5 mg in healthy older persons and the online simulation tool provide further insights into the PK and PD of midazolam in older people.

Authors' contributions

Study design: all authors
Data acquisition: CB, AA, MD, AV
Data analysis: CB, AA, PC
Data interpretation: CB, AA, IdD, MD, PC
Drafting of paper: all authors
Critical revision of paper: all authors
All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix A. Supplementary data

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