

Time-to-Event Modeling for Remimazolam for the Indication of Induction and Maintenance of General Anesthesia

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Lauren L. Lohmer, PhD¹, Frank Schippers, MD², Karl Uwe Petersen, MD², Thomas Stoehr, PhD², and Virginia D. Schmith, PhD¹

Abstract

Remimazolam is an ultra-short-acting benzodiazepine being investigated for induction and maintenance of general anesthesia and for procedural sedation. This dose-response analysis of 4 phase 2-3 studies evaluated covariates that may impact the pharmacodynamic profile (based on theoretical pharmacokinetic principles) and require dose adjustments in subpopulations, particularly elderly, and if remimazolam has cumulative properties. Covariates affecting the time to loss of consciousness and time to extubation were evaluated using Cox proportional hazards models. Factors affecting steady-state infusion rate required to produce adequate sedation were evaluated using linear regression. Variability in time to loss of consciousness was explained by induction dose, age, body mass index, and time from initiation of opioids to initiation of remimazolam. The steady-state infusion rate producing adequate sedation was higher in European than Japanese subjects due to differences in study design. American Society of Anesthesiologists physical status class 3 subjects had a 28% lower maintenance infusion rate than class 1 subjects. Other statistically significant covariates (American Society of Anesthesiologists class 2, estimated glomerular filtration rate, and sex) resulted in small ($\leq 14\%$), non-clinically relevant differences. Factors affecting time to extubation included the last infusion rate (ie, tapering), the bispectral index score at the end of infusion, and sex. The time to extubation after remimazolam did not increase with increased cumulative dose of remimazolam or duration of surgery. This evaluation of remimazolam's pharmacodynamic profile, in the absence of pharmacokinetic data, informed dosing recommendations and showed that remimazolam does not have cumulative properties in the general anesthesia setting.

Keywords

anesthesia, dose-response, remimazolam, sedation, time-to-event analysis

Remimazolam is an ultra-short-acting benzodiazepine being developed for induction and maintenance of anesthesia and for procedural sedation. The clinical studies conducted in general anesthesia include a phase 2 dose ranging trial including an elderly group (ONO-2745-03)¹ (also M. Doi et al, unpublished data, 2019), a phase 2b/3 efficacy and safety trial in American Society of Anesthesiologists (ASA) physical status class 1 or 2 subjects undergoing surgery (ONO-2745-05) (M. Doi et al, unpublished data, 2019), a phase 3 efficacy and safety trial in ASA class 3+ subjects undergoing surgery (ONO-2745-06) (M. Doi et al, unpublished data, 2019), and a phase 2 European study in cardiovascular surgery (CNS7056-010) (S. Probst et al, unpublished data, 2019). Additional studies have been conducted in healthy subjects and other populations but are not relevant to the current analysis.

Variability in the onset and offset profile of an anesthetic agent is likely due to factors affecting the pharmacokinetics and the relationship between plasma concentrations and the effect itself.² The onset (loss of consciousness [LoC]) is generally related to the volume of distribution given that these drugs are administered as an intravenous bolus or short infusion, potency (effective concentration producing 50% of the

maximum effect [EC₅₀], describing the sensitivity of an individual patient), and the rate of disequilibrium between plasma concentrations and the effect (keo, a measure of the rate of drug reaching the site of action, important in defining the drug onset).³ The steady-state infusion rate required to maintain an adequate level of sedation is related to the clearance of the drug and the EC₅₀ in the patient.³ The offset of drug effect is related to the clearance and volume of distribution of the drug and the EC₅₀ in the patient.³ Because sparse sampling was collected in the general anesthesia studies

¹Nuventra Pharma Sciences, Inc., Durham, North Carolina, USA

²Paion Deutschland GmbH, Aachen, Germany

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Corresponding Author:

Virginia D. Schmith, PhD, Nuventra Pharma Sciences, Inc., 2525 Meridian Parkway, Suite 200, Durham, NC 27713
Email: gschmith@nuventra.com

Virginia D. Schmith is a Fellow of the American College of Clinical Pharmacology.

of remimazolam, the estimation of keo was limited in this population; therefore, a unique approach was used to evaluate the effect of covariates that may theoretically impact pharmacokinetic/pharmacodynamic parameters (clearance, volume, EC₅₀, and keo) on the onset and offset profile of remimazolam using pharmacodynamic data only.

The objectives of the present analysis were to evaluate the effects of covariates on variability in the time to onset (time from beginning of remimazolam infusion to LoC), the steady-state infusion rate resulting in adequate sedation (bispectral index [BIS] or Narcotrend score ≤60), and the time to offset (time from ending of remimazolam infusion to extubation); to determine whether remimazolam has cumulative sedative effects; and to evaluate whether changes in dosage recommendations of remimazolam are required in special surgical populations, particularly elderly and ASA class 3 subjects.

Methods

Data Set

Each study protocol used in this analysis was reviewed by an investigational review board or research ethics committee. Data from 4 clinical trials in the induction and maintenance of general anesthesia were pooled for the analyses: ONO-2745-03,¹ ONO-2745-05 (M. Doi et al, unpublished data, 2019), ONO-2745-06 (M. Doi et al, unpublished data, 2019), and CNS7056-010 (S. Probst et al, unpublished data, 2019). The approving Research Ethics Committee(s) were ONO-2745-03, Institutional Review Board (IRB) of the Hamamatsu University School of Medicine, University Hospital; ONO-2745-05, 50 different IRBs; ONO-2745-06, 6 different IRBs; and CNS7056-010, Ethics Committee at the Medical Faculty of the University of Leipzig. Written informed consent was obtained prior to any study procedures. The trials were registered before patient enrollment in the Japanese registry for Studies ONO-2745-03 (JapicCTI-111495, Shigehito Sato, Hamamatsu University Hospital, May 12, 2011), ONO-2745-05 (JapicCTI-121973, Soushi Iwasaki, Sapporo Medical University Hospital, September 26, 2012) and ONO-2745-06 (JapicCTI-121977, Naoyuki Hirata, Sapporo Medical University Hospital, October 2, 2012) and in EudraCT for Study CNS7056-010 (2013-001113-32, Stefan Probst, Heart Center of the University Clinic Leipzig, April 26, 2013). All studies were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and good clinical practices. A brief description for each study is summarized in Table S1, along with which studies were included in each analysis. The numbers of subjects in each analysis are summarized in Table S2.

No data were excluded from the time-to-onset analysis. There were 12 steady-state infusion rates (2-3.2 mg/kg/h, <1.7% of the overall data set) in 12 different subjects excluded from infusion rate analysis because including these records led to significant nonnormality of the data (a violation of the assumption in linear regression). Each of these subjects had an additional 1 to 5 infusion rates that were continued for at least 21 minutes (3 times the longest reported half-life) that were assumed to be at steady state that remained in analysis. The model was rerun with and without exclusions without any changes to conclusions. Because administration of a neuromuscular blocking agent within 10 minutes of the end of the infusion could influence the time to extubation, there were 14 subjects who received rocuronium during this time period that were excluded; however, these records likely represent an inaccurate recording of the last dose of rocuronium because it is unlikely that the subjects could be extubated while on rocuronium, as these studies were conducted prior to the approval of sugammadex. For the subjects who received a reversal agent for benzodiazepines (eg, flumazenil; 44/345 or 12.8%), their time to extubation with remimazolam was censored (as per standard practice in time-to-event analysis) and set to the time between the end of the remimazolam infusion and administration of flumazenil.

Time-to-Event Analyses

Time-to-event data were analyzed using Kaplan-Meier plots to identify the shape of the survival function and whether the resulting curves in the subpopulations were proportional, implemented within SAS Version 9.4 using PROC LIFETEST (SAS Institute, Cary, North Carolina). Then, the times to events were analyzed using a semiparametric Cox proportional hazards model where the baseline hazard can take any form, but covariates enter the model linearly. The survival time of each member of a population is assumed to follow its own hazard function, as described in Equation 1:

$$\lambda_i(t) = \lambda_o(t) \exp^{Z_i^T \beta} \quad (1)$$

where $\lambda_o(t)$ is an arbitrary and unspecified baseline hazard function, Z_i^T is the vector of explanatory variables for the i th individual, and β is the vector of unknown regression parameters associated with the explanatory variables. The vector β is assumed to be the same for all individuals. The survivor function can be expressed as described in Equation 2:

$$S(t; Z_i) = S_o(t) \exp^{Z_i^T \beta} \quad (2)$$

where $S_o(t) = \exp(-\int_0^t \lambda_o(u) du)$ is the baseline survivor function. The partial likelihood function is used to estimate β , which eliminates the unknown baseline

hazard $\lambda_o(t)$ and accounts for censored survival times. These equations were implemented within SAS Version 9.4 using the PROC PHREG procedure.

Covariates (Table 1) were then added to the Cox proportional hazards model stepwise one at a time, until no further covariates produced a statistically significant change in the -2 -log likelihood ($P < .05$). When the -2 -log likelihood was statistically significant, the hazard ratio (HR) was also evaluated, and an HR that did not overlap with 1 was considered a stronger model. For each set of colinear covariates, the covariate with the highest individual magnitude of effect and/or statistical significance was chosen to be used in the development of the model. For example, sex, body mass index, body weight, and smoking were all correlated, and ASA class, estimated glomerular filtration rate (eGFR), creatinine clearance (CrCL), and age were colinear. After univariate assessment of each covariate within a group of colinear covariates was assessed, the best model from each group was chosen for progression. Then, a forward addition process was followed until there were no more statistically significant effects identified. Finally, the assumptions of the Cox proportional hazard model were assessed by using a plot of the deviance residuals (transformed Martingale residual to achieve a more symmetric distribution) vs linear predictor.

Infusion Rate Analysis

Factors affecting the steady-state infusion rate of remimazolam required to maintain adequate sedation were determined by linear regression using PROC REG with the automated stepwise function (SELECTION = STEPWISE, SLENTRY = 0.05, STSTAY = 0.05) within SAS Version 9.4. Colinear covariates were evaluated independently as for other analyses (Table 1), and one from each group of colinear covariates was used for model development. Evaluation of Q-Q plots uncovered nonnormality. Therefore, residuals >3 also meeting at least one more criterion for being an outlier (Cook's D influence statistic or DFFITS [standard influence of observation on the predicted value]) were excluded (see Data Set section), and the model was rerun and demonstrated adequate normality. Because the goodness-of-fit plots (residual vs predicted value) showed some bias at lower and higher infusion rates and the condition estimates for age and sex remained high (>10), backward elimination was conducted that resulted in the reduced infusion rate model.

Results

Time to LoC

The time-to-LoC analysis included 456 subjects (one observation/subject) receiving remimazolam with a wide range of ages (including 199 subjects ≥ 65 years of

age receiving remimazolam), body weights, body mass indices (BMIs; including 21 obese subjects), eGFR, and CrCL values (including 71 subjects with moderate to severe renal impairment [CrCL <60 mL/min]; Table 2).

Kaplan-Meier plots for categorical covariates for subjects receiving remimazolam did not indicate any relationship between covariates (eg, age [Figure 1], sex, ASA class, renal impairment, or smoking history) and time to LoC after remimazolam. Subjects with a cardiac index <3 L/min/m² and those with ≥ 3 L/min/m² looked different, but the survival curves crossed, indicating that the hazards were not proportional.

The final model for remimazolam showed that induction dose (for a unit of 6 mg/kg/h; HR, 1.801; 95% confidence interval [CI], 1.569-2.067), age (for a unit of 25 years; HR, 1.238; 95%CI, 1.064-1.44), BMI category (for underweight/normal vs obese: HR, 0.283; 95%CI, 0.175-0.456; for underweight/normal vs overweight: HR, 0.934; 95%CI, 0.753-1.159; for overweight vs obese: HR, 0.303; 95%CI, 0.184-0.500), and time from initiation of opioids to initiation of remimazolam (for a unit of 60 seconds; HR, 1.082; 95%CI, 1.040-1.125) were all statistically significant covariates ($P \leq .006$) explaining variability in the time to LoC. The linear predictor vs deviance residuals of the final model showed little to no bias. Plots of the covariates by the deviance residuals also showed no bias. Predictions were conducted to evaluate the clinical relevance of these findings (Figure 2) and showed that:

- A remimazolam induction dose of 12 mg/kg/h had 15- to 20-second faster onset compared to 6 mg/kg/h (Figure 2A).
- A 75-year-old had a 5- to 10-second faster time to LoC than a 30-year-old at a remimazolam induction dose of 6 mg/kg/h (Figure 2A).
- Administration of opioids 10 minutes prior to remimazolam 6 mg/kg/h had a 20-second faster time to LoC than if opioids were started 2 minutes prior to remimazolam (Figure 2B). There is very little difference (~ 5 seconds faster) when opioids are administered within 4 minutes of remimazolam 6 mg/kg/hr, compared to when opioids are administered 2 minutes prior to remimazolam 6 mg/kg/h. The difference becomes more pronounced (~ 15 seconds faster) when opioids are administered 8 minutes prior to remimazolam 6 mg/kg/h, compared to when opioids are administered 2 minutes prior to remimazolam 6 mg/kg/h.
- Obese subjects had a 20-second faster time to LoC than nonobese subjects receiving remimazolam 6 mg/kg/hr (Figure 2C).

Table 1. Summary of Covariates Evaluated for the Time to Offset, Infusion Rate, and Time to Onset Analyses

Covariate	Time to Onset Analysis	Infusion Rate Analysis	Time to Offset Analysis
Age (age as a continuous variable), age categorical 1 (>65 yr vs <65 yr), and age categorical 2 (<30 years vs 30 to 65 years vs >65 years)	X	X	X
Creatinine clearance (CrCL) and estimated glomerular filtration rate (as continuous variables), renal impairment categorical (normal renal function [CrCL ≥90 mL/min], mild renal impairment [CrCL ≥60 and <90 mL/min], moderate renal impairment [CrCL ≥30 and <60 mL/min], or severe renal impairment [CrCL <30mL/min]), or renal impairment categorical 2 (normal, mild, or moderate/severe)	X	X	X
Weight and body mass index (BMI; as continuous variables), BMI categorical 1 (underweight [$<18 \text{ kg/m}^2$] and normal [≥ 18 to $<25 \text{ kg/m}^2$] vs overweight [≥ 25 to $<30 \text{ kg/m}^2$] vs obese [$\geq 30 \text{ kg/m}^2$]), or BMI categorical 2 (underweight and normal vs overweight vs obese)	X	X	X
Smoking history	X	X	X
Sex	X	X	X
Race White in Study CNS7054-010 and Japanese in Studies ONO-2745-03, ONO-2745-05, and ONO-2745-06	X	X	X
ASA Classification	X	X	X
BIS score at baseline	X		
BIS score at end of remimazolam infusion			X
Treatment (remimazolam vs propofol)	X		
BIS or Narcotrend score of <60 at end of each steady-state infusion rate		X	
BIS or Narcotrend score of <60 at end of the last infusion rate			X
Total dose (mg/kg) from the beginning of remimazolam infusion to LoC (dose of remimazolam during the induction phase)	X		
Number of steady-state infusion rates that were changed		X	
Extracorporeal circulation		X	X
Duration of surgery	X	X	X
Opioid before LoC: Remifentanyl (Studies ONO-2745-03, ONO-2745-05, and ONO-2745-06), or both (Study CNS-7056-010)	X		
Body temperature		X	X
Rate for first dose of remifentanyl at induction (0.25-0.5 mcg/kg/min for Studies ONO-2745-03, ONO-2745-05, and ONO-2745-06)	X		
Total duration of remimazolam infusion		X	
Total dose of remimazolam administered			X
Total dose of remifentanyl (mcg/kg) between time of starting remifentanyl and the time of starting remimazolam or propofol	X		
Total dose of remimazolam administered during the two hours prior to extubation			X
Dose of fentanyl at induction	X		
Average infusion rate of remimazolam			X
Time between start of remifentanyl or fentanyl and start of the remimazolam	X		
Last infusion rate prior to discontinuing remimazolam			X
Remimazolam dose 4, 6, 12, 21, or 30 mg/kg/hr	X		
Number of minutes between end of last opioid dose and extubation			X
Last cardiac index before beginning remimazolam or propofol	X		
Time since the last dose of rocuronium			X

ASA, American Society of Anesthesiologists; BIS, bispectral index; BMI, body mass index; CrCL, creatinine clearance; LoC, loss of consciousness.

To understand the effect of obesity and because this effect may be due to a larger initial amount of drug distributed in the small volume of the central compartment (ie, blood volume), the induction dose was converted to doses in milligrams per kilogram based on ideal and adjusted body weight. A small number of subjects (<10%) who received 6 mg/kg/h based on actual body weight as an induction dose did receive 8 to 10 mg/kg/h based on ideal body weight and 7 to 8 mg/kg/h based on adjusted body weight. The same trend was observed for 12 mg/kg/h. The final time-to-onset model was then rerun using the doses calculated for ideal and adjusted body weight. BMI

category remained a statistically significant covariate, regardless of whether dosing was based on ideal or adjusted body weight, and therefore, the final model retained dosing based on actual body weight.

Infusion Rate Analysis

There were 707 individual steady-state infusion rate observations (>60% of which were equal to 1 mg/kg/h; Figure S1) from 333 subjects in this analysis with a wide range of age, body weight, BMI, CrCL, and eGFR, including 158 elderly subjects (≥ 65 years) and 54 subjects with CrCL <60 mL/min (Table 2).

Table 2. Summary of Demographics and Covariates

Covariate	Time to LoC-Remimazolam	Infusion Rate	Time to Extubation
	Mean \pm SD (Min-Max) Number per Category	Mean \pm SD (Min-Max) Number per Category	Mean \pm SD (Min-Max) Number per Category
Age (y)	59.2 \pm 15.2 (20-93)	60.5 \pm 14.7 (20-93)	58.7 \pm 15.6 (20-93)
Age category (<30 y/30-65 y/ \geq 65 y)	23/234/199	15/160/158	20/174/151
Weight (kg)	62.4 \pm 13.2 (33.6-111)	63.3 \pm 13.6 (33.6-108)	59.9 \pm 11.3 (33.6-98)
BMI (m ²)	23.7 \pm 3.6 (14.4-43.8)	23.8 \pm 3.5 (14.4-33.5)	23.1 \pm 3.3 (14.4-35.3)
BMI (underweight/normal/overweight/obese)	16/303/116/21		14/244/81/6
Renal function category (normal renal function/mild renal impairment/moderate renal impairment/severe renal impairment)	208/177/64/7	143/136/47/7	159/131/48/7
Duration of surgery (min)	155.8 \pm 90.2 (15-554)	158.0 \pm 86.6 (15-554)	155.8 \pm 90.2 (15-554)
ASA class (1/2/3)	173/201/81	118/145/70	143/147/55
Sex (male/female)	249/207	199/134	180/165
Dose of remifentanyl (mg)	2.83 \pm 2.10 (0.13-13.68)		2.83 \pm 2.10 (0.13-13.68)
BIS score at end of infusion			60.3 \pm 11.8 (34.0-93.0)
Time since the last dose of rocuronium (min)	85.1 \pm 67.8 (10.1-376.0)		85.1 \pm 67.8 (10.1-376.0)
Last remimazolam infusion rate (mg/kg/h)	0.73 \pm 0.42 (0.04-2.00)		0.73 \pm 0.42 (0.04-2.00)
Smoking category (never/history/present)	173/123/49		173/123/49
Level of sedation category (BIS or Narcotrend score \leq 60/ $>$ 60)	178/167		178/167
Cardiac index category (\geq 3 L/min/m ² / $<$ 3 L/min/m ²)	22/33		
Remimazolam induction dose (mg/kg)	9.35 \pm 3.95 (4-30)		
Remimazolam induction dose based on ideal body weight (mg/kg)	9.91 \pm 4.57 (4-45.2)		
Remimazolam induction dose based on adjusted body weight (mg/kg)	9.63 \pm 4.14 (4-30.9)		
Time between start of remifentanyl or fentanyl and start of the remimazolam or propofol (sec)	217 \pm 145 (0-1435)		
BIS score at baseline	92.7 \pm 7.47 (48-98)		

ASA, American Society of Anesthesiologists; BIS, bispectral index; BMI, body mass index; SD, standard deviation.

The initial regression model suggested that the infusion rate required to produce adequate sedation may be related to number of changes in the steady-state infusion rates, race, ASA class, eGFR, extracorporeal circulation, sex, and age. Since some of these covariates were colinear; the condition index was high (>10) for sex and age; and there was nonnormality of the data, the final reduced infusion rate regression model was generated after removal of 12 infusion records from 12 subjects (see Data Set section) and backward elimination of covariates was conducted until the model had less bias in the residual vs predicted plots. Removal of extracorporeal circulation as a covariate improved fit by decreasing of bias and removal of age decreased the condition number and improved the lack of bias.

The final model showed that the variability in the infusion rate required to produce adequate sedation can be explained by race (44% lower in Japanese than Europeans), ASA class (14% lower with class 2 and 28% lower with class 3 compared to class 1), eGFR (7% lower in someone with eGFR of 60 mL/min/1.73 m² and 12% lower in someone with an eGFR of 40 mL/min/1.73 m², compared to someone with an eGFR of 90 mL/min/1.73 m²), and sex (5% higher in women than in men).

Plots showed that the race effect appeared to be an artifact of study conduct. All subjects in Japanese studies started with an infusion rate of 1 mg/kg/h after LoC, but $>95\%$ of subjects in the European study (a study in cardiac surgery that may require

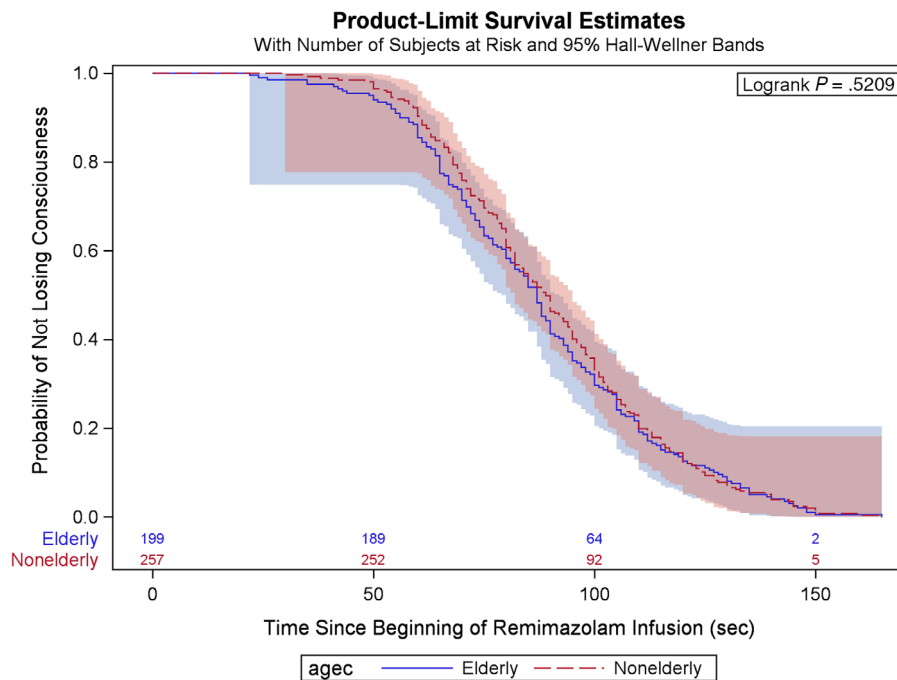


Figure 1. Kaplan-Meier plot of the observed probability of not losing consciousness from the beginning of remimazolam infusion (seconds) by age group. The blue line is elderly (≥ 65 y), and the red line is nonelderly (< 65 y). The boxes represent 95% confidence intervals.

deeper sedation) received >2 mg/kg/h and $>25\%$ received 3 mg/kg/h as their first maintenance infusion. The steady-state infusion rates remained constant for Japanese studies, but were reduced over time for the European study. While Narcotrend and BIS scores are not completely correlated,⁴ it appears that subjects receiving a steady-state remimazolam infusion of 1 mg/kg/h were more sedated in the European study (mean Narcotrend score, 30.4) than in Japanese studies (mean BIS score, 52.9-58.2, depending on study) (Figure S2). Thus, this race effect was an artifact, and Japanese subjects are not likely to be more sensitive to remimazolam.

While extracorporeal circulation was not statistically significant in the final model, the mean observed infusion rate was 34% higher when subjects were on extracorporeal circulation than when not on extracorporeal circulation ($n = 118$ individual steady-state infusion rate records occurring when the subjects were not on extracorporeal circulation and $n = 45$ individual infusion rate records while these same subjects were on extracorporeal circulation), and the full infusion rate model (including the nonnormal data) predicted an 18% higher infusion rate while on extracorporeal circulation.

Time-to-Extubation Analysis

There were 345 subjects (one observation/subject) included in the time-to-extubation analysis (Figure S3) with a wide range of ages, body weights, BMIs, CrCL, and eGFR values, including 151 elderly subjects

(≥ 65 years) and 55 subjects with CrCL < 60 mL/min (Table 2).

Kaplan-Meier plots showed no relationship between age (Figure 3), BMI, or ASA class and time to extubation. The final Cox proportional hazard model included the last remimazolam infusion rate (for a unit of 0.5 mg/kg/h; HR, 0.665, 95%CI, 0.572-0.773), the BIS score at the end of remimazolam infusion (for a unit of 20; HR, 1.341; 95% CI, 1.093-1.644), and sex (for women; HR, 0.651, 95%CI, 0.516-0.821) as statistically significant covariates ($P < .005$). Age and ASA class did not reach statistical significance and were not included in the model. The data met the criteria for the assumptions of the Cox proportional model.

To understand the clinical relevance of this model, predictions were conducted for last infusion rates of remimazolam of 0.5, 1, and 1.5 mg/kg/h; BIS score at the end of infusion as 40 or 60; and both sexes. As illustrated in Figure 4, the model predicted that:

- Changes in the last infusion rate of remimazolam from 1 to 0.5 mg/kg/hr (eg, 21 minutes before discontinuation, the time to reach steady state) resulted in a ~ 5 -minute faster time to extubation (Figure 4A).
- Changes in the BIS score at the end of infusion from 40 to 60 (ie, the subject was more alert) resulted in a ~ 3 - to 5-minute faster time to extubation (Figure 4B).
- Women had a ~ 3 - to 5-minute faster time to extubation than men (Figure 4C).

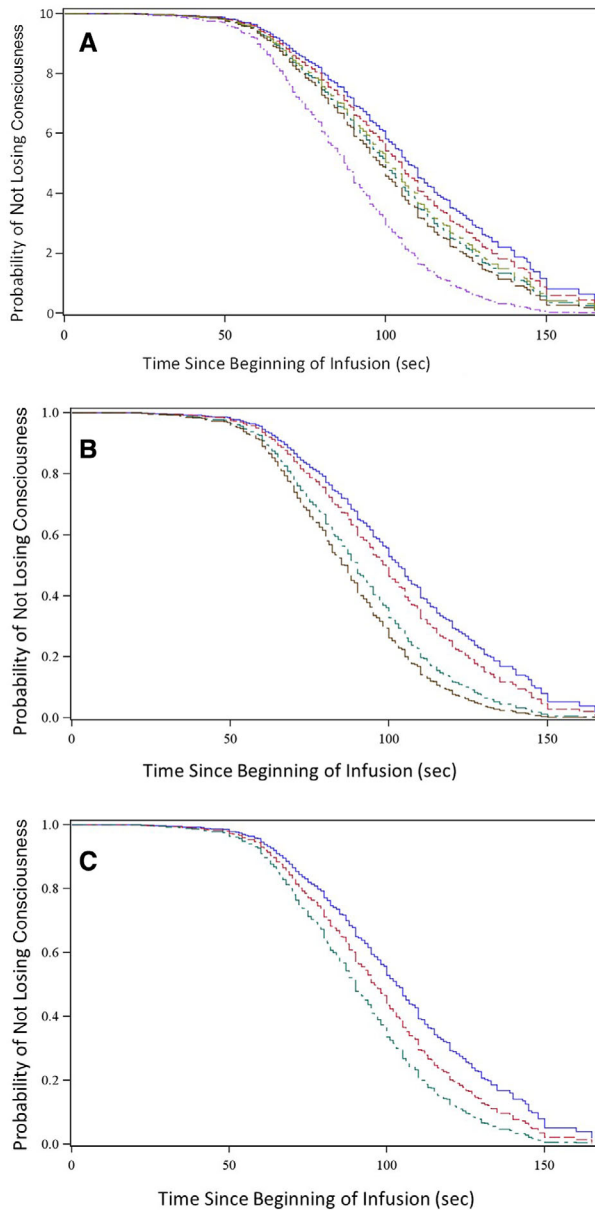


Figure 2. Predicted probability of not losing consciousness over time (seconds) for remimazolam by (A) dose and age, (B) time between administration of opioids and remimazolam in seconds, and (C) body mass index (BMI) category. (A) The leftmost line represents induction dose = 12 mg/kg/h and age = 59 y (purple); the next line represents induction dose = 6 mg/kg/h and age = 75 y (brown); the next line represents induction dose = 6 mg/kg/h and age = 65 y (dark green); the next line represents induction dose = 6 mg/kg/h and age = 59 y (pea green); the next line represents induction dose = 6 mg/kg/h and age = 45 y (red); and the rightmost line represents induction dose = 6 mg/kg/h and age = 30 y (blue). (B) Induction dose is kept at 6 mg/kg/h and age = 50 y. The leftmost line represents a time between opioid and remimazolam administration of 600 sec (10 min, brown); the next line represents a time of 480 sec (8 min, green); the next line represents a time of 240 sec (4 min, red); and the rightmost line represents a time of 120 sec (2 min, blue). (C) Induction dose is kept at 6 mg/kg/h, and time between opioid and remimazolam is kept at 120 sec. The leftmost line represents obese subjects (green; BMI ≥ 30 kg/m²); the next line represents overweight subjects (red; BMI ≥ 25 to < 30 kg/m²); and the rightmost line represents normal weight subjects (blue; BMI < 25 kg/m²).

Notably, the time to extubation was not affected by duration of surgery (mean, 156 minutes; range, 15-554 minutes; HR, 1.001; 95%CI, 1.000-1.003), total dose of remimazolam (mean, 195 mg; range, 30.5-782 mg; HR, 0.999; 95%CI, 0.998-1.000), or total dose of remimazolam within the 2 hours prior to extubation (mean, 88.0 mg; range, 9.8-234 mg; HR, 1.000; 95%CI, 0.997-1.003), providing strong evidence that there were no cumulative sedative effects of remimazolam.

Discussion

Factors affecting variability in remimazolam's time to LoC, steady-state infusion rate producing adequate sedation, and time to extubation were evaluated by combining data across studies in the induction and maintenance of general anesthesia. Covariates that may affect the pharmacokinetics or pharmacodynamics of benzodiazepines in general and remimazolam in particular were considered for inclusion to determine whether dosage adjustments are required in subpopulations, particularly the elderly and ASA class 3, and whether remimazolam has cumulative sedative effects with increased duration of administration in the general anesthesia setting. This evaluation of remimazolam's pharmacodynamic profile (influencing both efficacy and safety), in the absence of pharmacokinetic data, informed dosing recommendations.

Dose

Remimazolam's induction dose had an effect on the time to LoC (with a 15- to 20-second faster onset with 12 mg/kg/h remimazolam when compared to 6 mg/kg/h), as expected. Although both doses are adequate, the higher dose is recommended in situations where a particularly rapid LoC is required. Once the dose is adjusted to maintain adequate sedation, the time to extubation was related to the subject's infusion rate and sedation level at the end of surgery. These results indicate that tapering of the dose as the surgical procedure is ending will result in faster recovery.

Lack of Cumulative Properties

A key objective of this analysis was to evaluate whether increased duration of surgery or cumulative remimazolam dose delayed the rate of recovery. The HRs of ~ 1 with narrow 95%CIs demonstrated that there was no effect of duration of surgery or total remimazolam dose on time to extubation. Thus, there were no cumulative sedative effects of remimazolam when administered for up to ~ 9 hours during general anesthesia.

Elderly

Study ONO-2745-03, which included 55 nonelderly and 30 elderly subjects, showed that time to LoC was

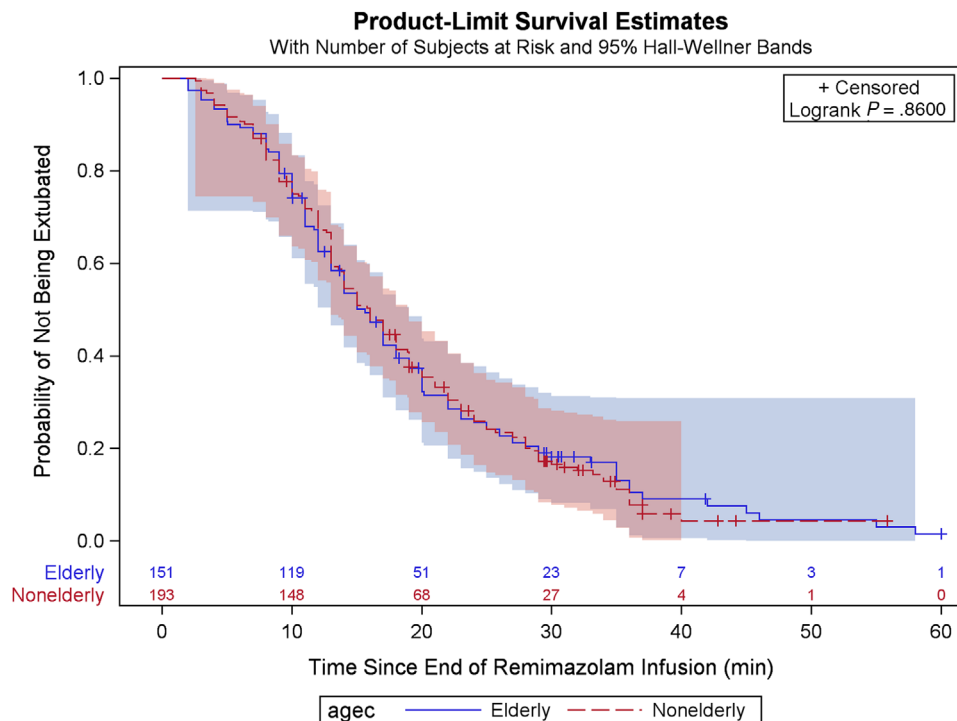


Figure 3. Kaplan-Meier plot of the observed probability of not being extubated over time from end of remimazolam infusion (min) by age group. The blue line is elderly (≥ 65 y), and the red line is nonelderly (< 65 y). The boxes represent 95% confidence intervals.

72.1 seconds in nonelderly and 57.6 seconds in elderly subjects receiving remimazolam 12 mg/kg/h.¹ Maintenance infusion rates were between 0.8 to 2 mg/kg/h and 0.4 to 1 mg/kg/h for nonelderly and elderly subjects, respectively.¹ The current analysis was more extensive, with 199, 158, and 151 elderly subjects in the time to LoC, infusion rate, and time to extubation analyses, respectively, and showed that a 75-year-old had a 5- to 10-second faster time to LoC than a 30-year-old after 6 mg/kg/h. Advanced age did not affect the time to extubation or the steady-state infusion rate required to produce adequate sedation. In general, there are no changes in benzodiazepine pharmacokinetics with age⁵; however, the slightly faster time to LoC in elderly patients receiving remimazolam was consistent with increased sensitivity in the elderly to the sedative effects reported for other benzodiazepines.⁵⁻⁷ While the age effects are not likely clinically relevant in most patients, lower remimazolam doses may be warranted for some fragile elderly patients, as for other anesthetics.

ASA Class

ASA class was not a significant factor in the time-to-LoC or time-to-offset analyses. ASA class had an effect on steady-state infusion rate, producing adequate sedation in which the rate was 14% lower in class 2 and 28% lower in class 3 compared to class 1. In general, ASA class effects are not likely clinically relevant.

However, lower remimazolam infusion rates may be warranted for some fragile ASA class 3 patients, as for other anesthetics.

Interaction Between Opioids and Benzodiazepines

There is a well-known synergistic relationship between opioids and benzodiazepines.^{8,9} Patients in Japanese studies¹ (also M. Doi et al, unpublished data, 2019) had remifentanyl infusions started 2 to 10 minutes prior to remimazolam administration, and the analysis showed that the time between the initiation of opioids and the initiation of remimazolam influenced the time to LoC. The time to LoC was ~ 15 seconds faster when opioids are administered 8 minutes prior to remimazolam 6 mg/kg/h, compared to when opioids are administered 2 minutes prior to remimazolam 6 mg/kg/h. There is very little difference (~ 5 seconds faster) when opioids are administered within 4 minutes of remimazolam 6 mg/kg/h, compared to when opioids are administered 2 minutes prior to remimazolam 6 mg/kg/h. The reason for this difference is not fully explained by their synergistic relationship, as the rate of remifentanyl was kept constant and remifentanyl does not have cumulative properties.

Other Populations

Time to LoC was 20 seconds faster in obese subjects than in nonobese subjects. This difference is partially

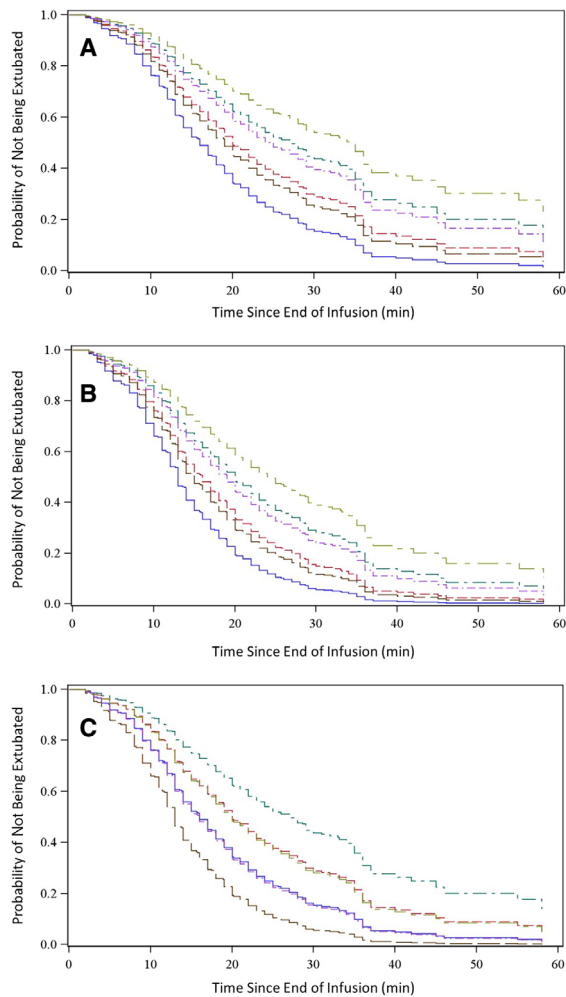


Figure 4. Predicted probability of not being extubated over time from end of remimazolam infusion (min) by (A) last remimazolam infusion rate (mg/kg/h) and bispectral index (BIS) score at the end of infusion for men, (B) last remimazolam infusion rate and BIS score at the end of infusion for women, and (C) last remimazolam infusion rate and sex at BIS score of 60 at the end of infusion. (A) Effect of infusion rate and BIS score in men, where the leftmost line represents men with infusion rate = 0.5 mg/kg/h and BIS = 60 (blue); then men with infusion rate = 0.5 mg/kg/h and BIS = 40 (brown); then men with infusion rate = 1 mg/kg/h and BIS = 60 (red); then males with infusion rate = 1 and BIS = 40 (pink); then men with infusion rate = 1.5 mg/kg/h and BIS = 60 (green); and men with infusion rate = 1.5 mg/kg/h and BIS = 40 (pea green). (B) Effect of infusion rate and BIS score in women, where the leftmost line represents women with infusion rate = 0.5 mg/kg/h and BIS = 60 (blue); then women with infusion rate = 0.5 mg/kg/h and BIS = 40 (brown); then women with infusion rate = 1 mg/kg/h and BIS = 60 (red); then women with infusion rate = 1 and BIS = 40 (pink); then women with infusion rate = 1.5 mg/kg/h and BIS = 60 (green); and women with infusion rate = 1.5 mg/kg/h and BIS = 40 (pea green). (C) Effect of sex and infusion rate when BIS score is constant, where (from left to right) the leftmost line represents women with infusion rate = 0.5 mg/kg/h and BIS = 60 (brown); the next line represents overlapping lines for both men with infusion rate = 0.5 mg/kg/h and BIS = 60 (blue) and women with infusion rate = 1 mg/kg/h and BIS = 60 (pink); the next line represents overlapping lines for men with infusion rate = 1 mg/kg/h and BIS = 60 (red) and women with infusion rate = 1.5 mg/kg/h and BIS = 60 (pea green); and the rightmost line represents men with infusion rate = 1.5 mg/kg/h and BIS = 60 (green).

explained by the higher body weight-adjusted dose in obese subjects distributed into the same central volume as a nonobese subject and is likely not related to sensitivity differences as reported for other benzodiazepines.

The race effect on steady-state infusion rates required to produce adequate sedation was artifactual because the European study was conducted in cardiac surgery and investigators used a higher infusion rate at the beginning of surgery, assuming these subjects would have higher remimazolam requirements due to the magnitude of surgical stress. However, these investigators reduced the infusion rates in the European subjects to maintain an adequate Narcotrend score, eventually reaching to 1 mg/kg/h. In the Japanese studies, subjects having elective surgeries received remimazolam 1 mg/kg/h over time, with very few changes in their infusion rates due to inadequate or excessive sedation. Thus, Japanese subjects were not more sensitive to the sedating effects of remimazolam.

The effects in women and in renal impairment on infusion rates were tiny (<12%) and not clinically relevant. Women also had a slightly faster (~3-5 minute) time to extubation than men, but this effect was not clinically relevant.

Limitations

Modeling of exposure-response data using complete plasma concentration-time profiles can be more informative than the current approach; however, there is a need to balance the amount of information gained from a small group of subjects with both pharmacokinetic and pharmacodynamic assessments in healthy volunteers compared to that from a much larger group of subjects with only pharmacodynamic assessments. The objective was to evaluate whether dose adjustments are needed in subpopulations, using a much richer data set by combining pharmacodynamic assessments across all of the general anesthesia studies.

The time-to-event (ie, onset or offset) models are limited only by the need for the hazards to be proportional; this assumption was met for both analyses. The infusion rate analysis was limited by the large number of subjects receiving 1 mg/kg/h, the colinearity of covariates, and the fact that there was >1 observation per subject. Even with these limitations, the analyses provided useful insights into factors affecting variability in the infusion rate required to produce adequate sedation.

Conclusions

The current analyses support a remimazolam induction dose of 6 to 12 mg/kg/h, followed by a maintenance infusion at ~1 mg/kg/h adjusted to the patient's sedation level. Remimazolam does not have cumulative sedative effects with increased duration of dosing up to

~9 hours in the general anesthesia population. As with other anesthetics, tapering of remimazolam infusion rate leads to a faster time to extubation, and lower remimazolam doses may be warranted for some fragile elderly or ASA class 3+ patients, even though the effects of age and ASA class are small and not clinically relevant for the majority of patients.

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Conflicts of Interest

F.S., K.U.P., and T.S. are employees of Paion GmbH. V.S. and L.L. are paid consultants for Paion GmbH.

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Data Accessibility

The data are not available in a repository, but requests can be directed to t.stoehr@paion.com.

References

1. Doi M. Remimazolam. *Journal of Japan Society for Clinical Anesthesia*. 2014;34(7):860-866.
2. Holford NH, Sheiner LB. Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. *Clin Pharmacokinet*. 1981;6(6):429-453.
3. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clin Pharmacol Ther*. 1979;25(3):358-371.
4. Kreuer S, Bruhn J, Larsen R, Bialas P, Wilhelm W. Comparability of Narcotrend index and bispectral index during propofol anaesthesia. *Br J Anaesth*. 2004;93(2):235-240.
5. Platten HP, Schweizer E, Dilger K, Mikus G, Klotz U. Pharmacokinetics and the pharmacodynamic action of midazolam in young and elderly patients undergoing tooth extraction. *Clin Pharmacol Ther*. 1998;63(5):552-560.
6. Ihmsen H, Albrecht S, Hering W, Schuttler J, Schwilden H. Modelling acute tolerance to the EEG effect of two benzodiazepines. *Br J Clin Pharmacol*. 2004;57(2):153-161.
7. Bertz RJ, Kroboth PD, Kroboth FJ, et al. Alprazolam in young and elderly men: sensitivity and tolerance to psychomotor, sedative and memory effects. *J Pharmacol Exp Ther*. 1997;281(3):1317-1329.
8. Vinik HR, Bradley EL, Jr., Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg*. 1989;69(2):213-217.
9. Loscalzo LM, Wasowski C, Paladini AC, Marder M. Opioid receptors are involved in the sedative and antinociceptive effects of hesperidin as well as in its potentiation with benzodiazepines. *Eur J Pharmacol*. 2008;580(3):306-313.

Supplemental Information

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