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Evaluation of the estimation of midazolam concentrations and pharmacokinetic parameters in intensive care patients using a bayesian pharmacokinetic software (PKS) according to sparse sampling approach

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Abstract

The aim of the study was to assess the performance of a bayesian program (PKS System, Abbott) for predicting midazolam concentrations and pharmacokinetic parameters in intensive care patients by comparing the pharmacokinetic parameters estimated by PKS to those calculated according to rich data. The study involved 42 patients receiving midazolam infusion for two hours or for several days. The program was used to predict plasma midazolam concentrations after feedback of 1, 2 or 3 concentrations. High correlation between observed and estimated concentrations was shown ($r^2 > 0.992$). Mean prediction error, mean absolute prediction error and root mean squared error were low for the patients of the reference and validation groups. From two or three feedback concentrations, midazolam pharmacokinetic parameters estimated by PKS were statistically comparable with those obtained using a rich pharmacokinetic analysis ($P > 0.05$ paired Wilcoxon test). Thus, PKS is useful for predicting midazolam concentrations and pharmacokinetic parameters when at least two feedback concentrations are known. This software seems to be appropriate for providing significant help to the clinician for midazolam dosage adjustment, according to midazolam concentrations and clinical sedation.

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Introduction

Midazolam is a benzodiazepine widely used as a sedative drug in mechanically ventilated patients (Dundee et al 1984). However, dosage adjustment to obtain an optimal degree of sedation is complicated due to a wide variability of midazolam pharmacokinetic parameters and the variability in clinical response and delay in waking, particularly in intensive care patients. Furthermore, prolonged sedation due to an accumulation of midazolam is often described in the literature (Shelly et al 1987, 1991; Vree et al 1989; Power et al 1993). So, a midazolam dosage adjustment according to the individual pharmacokinetic parameters appears necessary for midazolam monitoring in critically ill patients. To estimate the pharmacokinetic parameters in intensive care patients, sparse sampling approach is recommended due to ethical and practical considerations. The use of a bayesian method to estimate midazolam concentration and predict individual dosage requirements in critically ill patients is of particular interest. Bayesian studies on midazolam have been previously reported in the literature, but have been focused on the paediatric population (Burtin et al 1994; Lee et al 1999). A study has been performed in adult intensive care patients during midazolam short-term infusion (Zomorodi et al 1998), but no data are available following long-term midazolam infusion.

The bayesian pharmacokinetic software PKS (Abbott) has previously been used for the estimation of concentrations of several drugs, such as vancomycin, carbamazepine and ciclosporin, and these studies have shown that the use of PKS led to effective concentration predictions (Wu et al 1995; Gaulier et al 1997; Polard et al 1999).

According to midazolam pharmacokinetic and pharmacodynamic variability in intensive care patients, an individual dosage adjustment is essential for long-term sedation, to quickly reach optimal pharmacodynamic effect. Thus, we propose to investigate the performance of a bayesian pharmacokinetic software (PKS) used in clinical practice for the prediction of midazolam concentrations and pharmacokinetic parameters in intensive care patients.

Materials and Methods

Patients

After approval of the study by the University-Hospital Ethics committee and with informed consent, 42 intensive care patients were included. Seventeen patients were issued from the postoperative intensive care unit of the Neurologic Hospital of Lyon and received midazolam intravenously as follows: a bolus dose of $0.2\,mg\,kg^{-1}$ and an infusion of $0.1\,mg\,kg^{-1}\,h^{-1}$ for 2 h. Twenty-five patients from the intensive care unit of the Cardiologic Hospital of Lyon were included and received midazolam as follows: a bolus dose of $0.1\,mg\,kg^{-1}$ and an infusion of $0.05\,mg\,kg^{-1}\,h^{-1}$ for more than four days. The midazolam dosage was then adapted empirically according to the level of sedation and midazolam concentrations.

The bayesian pharmacokinetic study was divided into two steps. In the first step, a bayesian pharmacokinetic study was performed retrospectively on 30 patients (12 from the Neurologic Hospital, 18 from the Cardiologic hospital). In a second step, 12 patients (5 from the Neurologic Hospital, 7 from the Cardiologic Hospital) were enrolled for the bayesian software validation. The principal characteristics of the two populations of patients (reference and validation groups) are summarised in Table 1.

Blood sampling

Blood samples were withdrawn from the arterial line and collected in heparinized tubes. For the neurologic population, samples were drawn before the midazolam infusion and at 5, 15 and 30 min and 1, 2, 2.5, 3, 4, 5, 6, 8, 12 and 24 h after the end of the infusion. For the cardiologic population, samples were drawn once a day during the midazolam infusion, at the end of the infusion and at 5, 10, 15 and 30 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 20, 24 and 48 h after the end of the infusion. Blood samples were immediately centrifuged and stored at $-20\,^{\circ}C$ until analysis.

Drug analysis

Plasma concentrations of midazolam were analysed by HPLC on a Spherisorb CN, 5-μm column with methanol-2-propanol (75:25, v/v) containing 0.015% perchloric acid as mobile phase. The detection wavelength was 215 nm. Inter-day coefficient of variation ranged from 2.7 to 6.5% and the quantification limit was $5\,ng\,mL^{-1}$ for a plasma volume of 500 μL (Lehmann & Boulieu 1995). The coefficient of variation (10%) and the sensitivity ($5\,ng\,mL^{-1}$) were implemented in PKS, to allow it to calculate in the estimation process the standard deviation of the concentration. The formula used was:

$$SD = (C \times CV_{assay}) + S_{assay} \quad (1)$$

where SD is the standard deviation ($ng\,mL^{-1}$), C is the concentration ($ng\,mL^{-1}$), CV_{assay} is the coefficient of variation of the assay and S_{assay} is the sensitivity of the assay.

Pharmacokinetic analysis

First, for the 42 patients, midazolam pharmacokinetic parameters were estimated using the Siphar Win or PKFit software, according to a compartmental analysis. Individual data were fitted independently and the quality of the fitted model was assessed by a random scatter of residuals, a minimum value for the Akaike and Schwarz criteria, and by the coefficient of variation of the estimated pharmacokinetic variables (CV < 20%). According to these criteria, a two-compartmental model and a weighing factor of $1/Y^2$ (predicted) was the most appropriate for all patients. The parameters of the 30 patients of the reference group were used to calculate the mean and variation coefficient of the parameters to constitute the pharmacokinetic values of the reference population.

Secondly, the midazolam concentration predictions were performed for the patients of the reference group using a bayesian regression analysis program (PKS System, Abbott). No database concerning the pharmacokinetic parameters of midazolam was available in the

Table 1 Principal characteristics of the population.

	Reference	Validation	*P* value (Mann Whitney test)
No. of patients	30	12	
No. female (%)	20	17	
Age (years)	55 ± 14	62 ± 11	0.1682
Weight (kg)	68 ± 12	74 ± 7	0.1157
Height (cm)	170 ± 8	173 ± 7	0.1644
TP (%)	75 ± 12	64 ± 19	0.1400
Serum creatinine ($\mu mol\,L^{-1}$)	162 ± 128	208 ± 134	0.2259
Creatinine clearance ($mL\,min^{-1}\,kg^{-1}$)	0.954 ± 0.712	0.564 ± 0.364	0.1770
Total bilirubinaemia ($\mu mol\,L^{-1}$)	39 ± 47	50 ± 40	0.2952

program package. For a two-compartment linear model, central volume (Vc), clearance (CL), transfer constants and coefficient of variation of each parameter are required to compute midazolam concentration predictions. Mean values of midazolam model pharmacokinetic parameters are given in Table 2.

Third, the PKS software validation was performed. The estimation of midazolam concentrations and pharmacokinetic parameters was performed for the 12 patients of the validation group.

The following patient data: age, sex, weight, height, serum creatinine, creatinine clearance (estimated using Cockroft and Gault formula), total bilirubin, transaminases, albuminaemia and prothrombin level were collected for information. The concomitant administration of inhibitor (erythromycin, fluconazole, amiodarone) or inducer (carbamazepine) drugs was also noted. PKS was not able to take into account these covariates for the calculation. However, in a previous study in adult intensive care patients with multiorgan failure (not published), we showed that covariates such as creatinine clearance have no influence on midazolam pharmacokinetic parameters.

The performance of the bayesian pharmacokinetic program (PKS) for predicting midazolam concentrations and pharmacokinetic parameters from 1, 2 and 3 feedback concentrations was evaluated. The sampling times were as follows: at the end of midazolam infusion, 4 or 6 h after the end of infusion, 12 h after the end of infusion or the last time for which midazolam concentration was superior to the quantification limit, corresponding to the C1, C2 and C3 concentrations respectively. The following time-point combinations were evaluated: one-point approaches (C1 or C2 or C3), two-point approaches (C1 and C2, C1 and C3 or C2 and C3), and three-point approaches (C1 and C2 and C3).

Fourth, the bayesian software was used to estimate midazolam concentration from one steady-state feedback concentration. According to the administration schedule, steady-state concentrations were obtained for only 15 patients (11 were issued from the model population, 4 from the validation population).

Evaluation of predictive performance

The estimated midazolam concentrations were compared with the observed concentrations measured using the determination of prediction error (Pe) corresponding to the difference between predicted concentrations and measured concentrations.

Predictive performances of PKS were assessed for each set of estimates by measurement of the prediction bias (mean prediction error, ME), the precision (mean absolute prediction error, MAE) and a composite of bias and precision (root mean squared error, RMSE) (Sheiner & Beal 1981).

Confidence intervals were determined for each parameter. The significance probability level chosen was $P = 0.05$.

Statistical analysis

The statistical analysis was done using Instat software. The Kruskal–Wallis nonparametric test was used for multiple comparison of bias and precision. A paired Wilcoxon test was used for the comparison between pharmacokinetic parameters.

Table 2 Population pharmacokinetic parameters of midazolam of the reference group.

Pharmacokinetic parameters	Values
Central volume ($L\,kg^{-1}$)	0.402 ± 0.324
Clearance ($L\,h^{-1}\,kg^{-1}$)	0.460 ± 0.452
k_{12} (h^{-1})	0.990 ± 0.584
k_{21} (h^{-1})	0.271 ± 0.204

k_{12} and k_{21}, transfer constants. Values are presented as mean ± s.d. (n = 30).

Results

The clinical and demographic characteristics of the patients did not differ between reference and validation patients (Table 1).

Figure 1 shows the relation between observed concentrations and estimated concentrations from three midazolam concentration data in 30 intensive care patients. The predictive performance of each estimation sets for the reference and validation groups are summarised in Tables 3 and 4, respectively. High correlation between the observed and estimated concentrations was shown whatever the number of concentrations used by PKS ($r^2 = 0.992$ to 0.999).

No statistical difference was found for the pooled population between each set of estimates for ME values ($P = 0.4276$, Kruskal–Wallis nonparametric test). On the contrary, the values of MAE were significantly greater when three feedback concentrations were used ($P < 0.05$

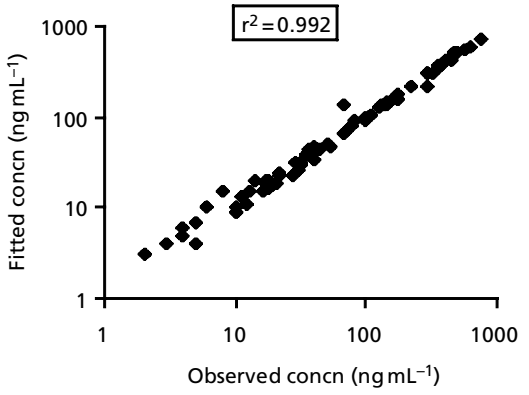

Figure 1 Relation between observed concentrations and fitted concentrations from three midazolam concentration data using the PKS program in 30 intensive care patients (n = 90). r^2, coefficient of correlation.

Table 3 Predictive performance of each set of estimates for the reference group.

Feedback concn	r^2	ME (ng mL^{-1})	MAE (ng mL^{-1})	RMSE (ng mL^{-1})
C1 + C2 + C3	0.992	0.09 (−3.30; 3.48)	7.50 (4.55; 10.45)	15.17 (8.81; 21.54)
C1 + C2	0.9988	−1.13 (−2.86; 0.59)	3.70 (2.23; 5.17)	6.85 (3.92; 9.78)
C1 + C3	0.9995	−1.90 (−3.47; −0.34)	3.44 (2.09; 4.79)	6.01 (3.28; 8.74)
C2 + C3	0.9938	−1.10 (−4.19; 1.99)	5.98 (3.35; 8.62)	11.31 (5.46; 17.17)
C1	0.9998	−2.53 (−4.54; −0.53)	3.20 (1.32; 5.08)	6.07 (2.61; 9.54)
C2	0.9998	−1.27 (−2.72; 0.19)	2.13 (0.82; 3.44)	4.19 (1.42; 6.95)
C3	0.9998	−1.19 (−2.45; 0.06)	1.65 (0.48; 2.82)	3.41 (1.02; 5.80)

C1, concentration at the end of midazolam infusion; C2, concentration 4 or 6 h after the end of infusion; C3, concentration 12 h after the end of infusion or last concentration, superior to the quantification limit. ME, mean prediction error; MAE, mean absolute prediction error; RMSE, root mean squared error. r^2, coefficient of correlation between observed and estimated concentrations (95% confidence interval; n = 30 patients).

Dunn's multiple comparison test). The value of MAE was significantly lower when the C3 feedback concentration was used compared with 2 feedback concentrations ($P < 0.05$, Dunn's multiple comparison test). For each set of estimates, the ME values obtained for the model, validation and pooled patients were not statistically different ($P > 0.05$, Kruskal–Wallis nonparametric test). Likewise, no statistical differences were found for the MAE values. Biases were negative for each set of estimates for the validation group, indicating that PKS underpredicted midazolam concentrations. As confidence intervals included zero in all cases, biases were not significantly different from zero.

Table 5 shows the mean midazolam pharmacokinetic parameters obtained from reference and validation groups using rich pharmacokinetics and bayesian approach. The Wilcoxon paired test was used to compare the values obtained for each set of estimates.

The estimation of midazolam concentrations from one steady-state feedback concentration obtained from 15 patients gave the following data of ME, MAE and RMSE (confidence interval 95%): −4.87 (−7.66; 2.07),

Table 4 Predictive performance of each set of estimates for the validation group.

Feedback concn	r^2	ME (ng mL^{-1})	MAE (ng mL^{-1})	RMSE (ng mL^{-1})
C1 + C2 + C3	0.9989	−1.78 (−4.15; 0.60)	5.56 (3.94; 7.17)	7.39 (4.45; 10.33)
C1 + C2	0.9989	−3.13 (−6.63; 0.38)	4.79 (1.62; 7.97)	9.13 (2.96; 15.30)
C1 + C3	0.9991	−3.00 (−6.38; 0.38)	4.42 (1.30; 7.53)	8.81 (2.60; 15.02)
C2 + C3	0.9990	−1.42 (−4.16; 1.32)	4.33 (2.16; 6.50)	6.86 (2.74; 10.98)
C1	0.9998	−3.83 (−7.90; 0.23)	4.17 (0.22; 8.11)	7.87 (0.31; 15.44)
C2	0.9999	−2.33 (−6.05; 1.38)	2.67 (−0.97; 6.30)	6.71 (−0.28; 13.69)
C3	0.9999	−2.17 (−5.74; 1.40)	2.50 (−0.99; 5.99)	6.42 (−0.27; 13.10)

C1, concentration at the end of midazolam infusion; C2, concentration 4 or 6 h after the end of infusion; C3, concentration 12 h after the end of infusion or last concentration, superior to the quantification limit. ME, mean prediction error; MAE, mean absolute prediction error; RMSE, root mean squared error. r^2, coefficient of correlation between observed and estimated concentrations (95% confidence interval; n = 12 patients).

Table 5 Comparison of midazolam pharmacokinetic parameters obtained using rich pharmacokinetics and bayesian approach (PKS) for the patients of the reference and validation groups (Wilcoxon paired test).

	Elimination half-life (h)				**Central volume ($L\,kg^{-1}$)**				**Clearance ($L\,h^{-1}\,kg^{-1}$)**			
	Reference		Validation		Reference		Validation		Reference		Validation	
	Mean (s.d.)	*P*	Mean (s.d.)	*P*	Mean (s.d.)	*P*	Mean (s.d.)	*P*	Mean (s.d.)	*P*	Mean (s.d.)	*P*
Rich PK	7.5 (7.6)		13.1 (15.3)		0.402 (0.324)		0.320 (0.156)		0.460 (0.452)		0.276 (0.275)	
C1 + C2 + C3	9.1 (7.9)	0.0780	11.2 (12.7)	0.7334	0.370 (0.247)	0.2229	0.315 (0.170)	0.7334	0.386 (0.342)	0.9191	0.299 (0.251)	0.1763
C1 + C2	8.6 (7.6)	0.0688	10.7 (12.1)	0.5186	0.375 (0.187)	0.7971	0.298 (0.139)	0.9697	0.528 (0.708)	0.8370	0.294 (0.246)	0.3013
C1 + C3	8.9 (7.8)	0.1124	11.3 (12.7)	0.7334	0.361 (0.239)	0.2531	0.311 (0.164)	0.7910	0.393 (0.342)	0.5091	0.303 (0.261)	0.3804
C2 + C3	9.1 (7.7)	0.1374	13.0 (12.6)	0.6377	0.372 (0.141)	0.7995	0.452 (0.224)	0.0425	0.384 (0.309)	0.7800	0.328 (0.243)	0.0425
C1	8.2 (5.7)	0.1333	13.7 (11.3)	0.3013	0.401 (0.060)	0.1443	0.414 (0.078)	0.0522	0.531 (0.708)	0.5104	0.286 (0.241)	0.5186
C2	8.9 (7.5)	0.0166	12.8 (12.2)	0.9697	0.400 (0.082)	0.1196	0.439 (0.090)	0.0640	0.452 (0.331)	0.7734	0.328 (0.235)	0.0771
C3	9.7 (8.5)	0.0435	13.1 (12.9)	0.6772	0.418 (0.088)	0.1550	0.448 (0.110)	0.0522	0.405 (0.285)	0.2862	0.353 (0.265)	0.0049

The *P* values test the hypothesis of the median change for rich pharmacokinetics to PKS equal 0.

5.00 (2.27; 7.73), 7.22 (2.34; 12.11), respectively. A high correlation was shown between observed and estimated concentration ($r^2 = 0.9999$).

Discussion

Patients included in the reference group had similar characteristics to patients enrolled in the validation group with regard to demographic and biological factors (Table 1).

The mean total clearance value of the reference group was close to those reported in the literature in intensive care patients (Michalk et al 1988; Malacrida et al 1992).

Tables 3 and 4 showed the acceptable performance of PKS for estimating midazolam concentrations. The ME, MAE and RMSE values were very low for each set of estimates for the reference and validation groups. According to ME, MAE and RMSE values, acceptable predictions of midazolam concentrations were obtained when at least one feedback concentration was used.

According to Table 5, no statistical difference between midazolam pharmacokinetic parameters calculated using rich pharmacokinetics or estimated by PKS was found for the reference and validation group when the following set of estimates were used: C1 + C2 + C3, C1 + C2, C1 + C3, C1.

Although the reference and validation populations have similar demographic and biological data, midazolam elimination of the validation population was slower. Likewise, mean central volume and clearance of the validation group were inferior to those obtained in the reference group. However, the estimation of midazolam pharmacokinetic parameters of the validation group was as effective as the reference group.

Different authors reported that two sampling times are needed for an efficient estimation of clearance and distribution volume. The first sample should be taken as early as possible after the maximum drug concentration, and the second as late as possible (Kinowski et al 1995; Bressolle et al 1996). According to our results obtained with the reference, validation or pooled population (not shown), the estimation of pharmacokinetic parameters was better when two feedback concentrations were used corresponding to sampling times at the end of the midazolam infusion and 4–6 h after the end of infusion.

Prediction errors were generally more important for high midazolam concentrations (300–700 ng mL^{-1}). Important prediction error observed could be explained in some cases by drug interactions, particularly interaction between midazolam and enzymatic inhibitor or activator drugs, which modify metabolism and elimination of midazolam. This point could not be taken into account by PKS and leads to over- or underestimated concentrations.

Few pharmacokinetic studies on midazolam in adult intensive care patients have been reported in the literature. Zomorodi et al (1998) used the NONMEM software for a population pharmacokinetic study of midazolam administered by target-controlled infusion for short-term sedation. A third compartment model was chosen to improve the objective function. Zomorodi et al (1998) did not confirm the large variability of midazolam pharmacokinetic parameters usually reported in midazolam pharmacokinetic studies from rich data (Michalk et al 1988; Malacrida et al 1992).

The bayesian software was used to estimate midazolam concentration from one steady-state feedback concentration in 15 patients. Indeed, the main interest of predicting pharmacokinetic profiles with a bayesian approach is to perform in-course dose adjustment. Furthermore, it seems important for clinicians to estimate midazolam concentrations and pharmacokinetic parameters to adapt the midazolam regimen during the infusion. According to the values of ME, MAE and RMSE, although a negative bias was found, these results showed that PKS was able to predict midazolam steady-state concentrations. No statistical difference was shown between mean central volume and midazolam clearance estimated by PKS or measured by rich pharmacokinetics. The mean elimination half-life estimated by PKS (11.4 ± 5.0 h) was statistically superior to those calculated by a rich pharmacokinetics (8.0 ± 5.6 h) ($P = 0.0067$ Wilcoxon paired test), but this statistical difference should not have significant consequence in clinical practice. The estimation of both midazolam concentrations and pharmacokinetic parameters during the infusion could allow adjustment of the midazolam regimen to enable the optimal sedative effect quickly in intensive care patients. As these preliminary investigations were done in only a few patients, these results should be confirmed.

Following this study, the bayesian approach was used to adjust midazolam dosing in patients with low or excessive sedation. This point shows that the dosage regimen could be adjusted according to a target level of sedation corresponding to a target midazolam concentration.

Conclusions

These preliminary results showed the acceptable performance of the PKS program in estimating midazolam concentrations from two feedback concentrations in intensive care patients. Moreover, the use of two feedback concentrations corresponding to the sampling times at the end of midazolam infusion and 4 or 6 h after midazolam infusion could be suggested to obtain the best predictions of midazolam pharmacokinetic parameters. This software seemed to be appropriate for providing significant help to the clinician for midazolam monitoring in intensive care patients.

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