An approach for dose finding of drugs in infants: sedation by midazolam studied using the continual reassessment method

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Aims No drug has been demonstrated to provide simultaneously appropriate sedation, safety and lack of disturbance of the measured parameters during cardiac catheterization in infants. The objective of this study was to estimate the dose of midazolam, administered rectally, that would provide a 90% probability of adequate sedation in infants during cardiac catheterization. A sedation score ≥ 4 (six-point scale) 30 to 60 min after dosing was rated as a success.

Methods A double-blind, continual reassessment method using a Bayesian approach has been used. Sixteen infants were administered a single midazolam dose, within a 0.1 to 0.6 mg kg⁻¹ dose range.

Results Consecutive failures led to allocation of the highest dose to 15 out of 16 patients. The final estimated probability of failure of the 0.6 mg kg⁻¹ dose was 81% (95% CI: 78.5 to 84%). The time to reach a score ≥ 4 was longer than expected and the median duration-time at score ≥ 4 was shorter (15 min) than expected.

Conclusions Delayed absorption and low rectal bioavailability may explain these data. Higher doses or different routes of administration may lead to the expected sedation, but the safety of doses higher than 0.6 mg kg⁻¹ administered rectally has not been evaluated. The therapeutic strategy for sedation of this category of infants in the hospital has now been changed based on the present results in that rectal midazolam has been abandoned in this indication.

Keywords: midazolam, sedation, infants, cardiac catheterization

Introduction

Sedation is required during cardiac catheterization, particularly in infants. Midazolam has been shown to provide an appropriate sedation in children using different routes of administration and dosages [1–14]. This drug is expected not to interfere with haemodynamic parameters [7, 10, 11], unlike some other drugs used for sedation in children. The rectal route is a non invasive route of administration that has been used at that age [1, 3–5, 10, 15]. The availability reported for rectal midazolam (18%) is similar to that for the oral drug (15 to 27%) [15]. In the development of midazolam as a sedative drug for cardiac catheterisation, the determination of the dosing regimen to be recommended for the effective and safe treatment of infants is a key issue and no adequate evaluation has previously been performed. It appeared appropriate to establish a relationship between dose and treatment effect, focusing on specified characteristics such as the minimal effective dose (MED), which elicits a prescribed lowest therapeutic response. However, in children, such dose-ranging studies meet with ethical, statistical and practical problems, that are not explicitly

addressed in the commonly used designs [16]. Alternative schemes have been developed recently [16], based on administering various doses to each included patient. However, their application requires chronic or stable diseases, so were inadequate in the framework of sedation. In this paper, a new approach, initially developed in the context of Phase I cancer clinical trials [17], is proposed for the conduct and analysis of a dose-ranging study of midazolam in the sedation of children for cardiac catheterization. The main objective of the present study was to determine the dose of midazolam, administered rectally, required to obtain appropriate sedation in 90% of patients during cardiac catheterization and to find a relationship between the level of sedation and plasma concentration.

Methods

Patients

Sixteen infants ranging in age from 1 to 21 months (mean 10.5 ± 6.7), and in weight from 3.8 to 9 kg (mean 6.8 ± 1.7), entered the study. They were scheduled for cardiac catheterization lasting no longer than 45 min. Those with mental retardation, respiratory depression, with

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tetralogy of Fallot, with hepatic or renal dysfunction and those who had received any drug known to interfere with the metabolism of midazolam, within the preceeding 4 weeks, or, a benzodiazepine within the preceeding 2 weeks, were not included. The protocol was approved by the Ethical Committee of Paris Cochin Hospital and written informed consent was obtained from all the parents.

Experimental design

The design of this phase II, double-blind, study was chosen in order to assess the dose-effect relationship of midazolam in the sedation during catheterization, using a Bayesian sequential method previously developed in phase I cancer trials [17]. The so-called Continual Reassessment Method (CRM), which aims to estimate any percentile of response for a given dose, is a sequential Bayesian approach in the sense that the estimation of dose-response relationship is iteratively performed, modifying the recommended dose for the next patient; d_i , $i=1, \dots, k$, the k dose levels for experimentation, that could be either equally or unequally spaced. These levels are chosen initially by the investigator through an implicit idea of the dose-response relationship, based either on historical data, pilot experiments, literature findings, or toxicological studies. To estimate the dose level ED_{90} , necessary to achieve a positive response in 90% of the treated patients when administered with fixed dose level and schedule, the investigator arbitrarily chose six dose levels of midazolam, namely 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 mg kg⁻¹, denoted d_1 , d_2 , d_3 , d_4 , d_5 , and d_6 , respectively. Each of these dose levels was associated by the investigator with the following estimated failure probabilities, p_i ($i=1 \dots, 6$), eg 0.70, 0.60, 0.40, 0.20, 0.10, 0.01, respectively. A logistic model was then chosen, allowing mathematical fitting of the dose-response relationship, assuming the higher the dose, the higher (or the lower) the response. Allowing a range of possible values for its parameter expressed via a (prior) exponential density enabled us to represent the large initial uncertainties about this hypothesized dose-efficacy relationship.

Let x_i , denote the dose administered to the i th patient; $i=1, \dots, n$. Experimentation began at any arbitrary level (d_s , $1 < s < 6$). In the present study, the first patient was administered blindly the fourth dose level (i.e., 4 mg kg⁻¹). Subsequent patients were assigned a dose depending on the updated curve, that is after incorporating the outcome of the previous patients at the administered doses. This means administering the dose d_4 to the first patient, and then observing response to treatment (success or failure). This observed response was combined with the prior information to update, applying the Bayes theorem, the hypothesized dose-response distribution, so that the next allocation could be based on these updated (posterior) response probabilities as if they were the prior. This process was iterated until a scheduled total sample size (20 patients) was completed. The conduct was blind to the administered dose, although the statistician was aware of the current estimated dose-response relationship.

The main disadvantage of the method is the finite number of doses to be tested, necessarily fixed before the onset of the trial. Since a wrong choice in the dose range to be

tested would not allow determination of the true effective dose, it was planned that the repeated observation of failures at the highest dose level would lead to consultation of an expert board to decide upon the early stopping of the trial.

The children received midazolam (0.12 ml kg⁻¹) rectally, at t_0 , by means of a rectal adaptor (Roche). The drug was kindly supplied by Produits Roche, France. The cardiac catheterization performed through of the femoral vein began at t_{15} . Intra-cardiac procedures begun at t_{30} were planned to end at t_{60} .

Sedation was measured on a six point scale, previously described in the literature (1- Awake, anxious, crying or agitated; 2- Awake, alert, normal; 3- Awake, calm, motionless; 4- Drowsy, reduced reactivity; 5- Asleep, easily arousable; 6- Asleep, not easily arousable), immediately before and 15, 30, 45, 60, 75, 90, 105, 120, 180, 240 min after drug administration [3, 5]. Midazolam effect was rated as a failure if the level of sedation was lower than 4 between T_{30} and T_{60} . A rescue treatment (25 to 50 mg kg⁻¹ of sodium gamma hydroxy butyrate, i.v., Gamma-OH) was allowed if sedation at t_{30} was lower than 4. Heart rate, arterial blood pressure, oxygen saturation were recorded by a Dinamap Oxytrack before and 15, 30, 45, 60, 120, 180, 240 min after drug administration (Johnson and Johnson Medical Corporation).

Blood samples (1 ml) were collected prior and 15, 30, 45, 60, 120, 180 and 240 min after dosing. Plasma was stored at -20°C until analysis.

Midazolam assay

Plasma midazolam in 200 μl samples was measured by h.p.l.c., using prazepam as the internal standard. The drug was extracted with 6 ml diethyl ether, in an alkaline medium (200 μl NaOH 0.5N). After centrifugation, the organic phase was evaporated to dryness under a stream of nitrogen at 37°C . The residue was dissolved in 100 μl of the following mobile phase: acetonitrile (35%), KH-2PO₄ (64%) and triethylamine (1%). The chromatographic conditions used, were: column octyl 4,6 $\times$ 75 mm (Beckman), C8; automatic injector (Wisp 712: Waters); spectrophotometer at 242 nm (Spectra 100: Spectra Physics). The calibration curve was linear between 10 and 1000 $\mu\text{g l}^{-1}$. The limit of detection was 10 $\mu\text{g l}^{-1}$. The coefficient of variation was 11.2% ($n=17$) at a plasma concentration of 40 $\mu\text{g l}^{-1}$.

Dose-effect statistical analysis

A posteriori probabilities of failure were calculated sequentially for each patient recruited using the Bayesian approach [18]. At the end of the study, the time to obtain a level of sedation higher than or equal to 4 and the duration of sedation at level 4 were estimated by the Kaplan-Meier method using SAS software package.

Pharmacokinetic calculations

Pharmacokinetic analysis was performed using the Triomphe program [19]. A non-compartmental method was used to determine the pharmacokinetic parameters of midazolam after rectal administration. Half life of elimination ($t_{1/2}$) and

the area under the concentration–time curve (AUC 0, t and AUC 0, ∞), were calculated by standard kinetic procedures [20].

Relationship between sedation and midazolam plasma concentration

Sedation score was plotted as a function of the midazolam plasma concentration at the corresponding time.

Results

Dose-effect study

Sixteen of the 20 planned infants entered the study. The early stopping of the patients' accrual was decided by an expert committee upon the observation of 13 out of 15 failures at the highest dose level (Table 1). On average, cardiac catheterization lasted longer than scheduled (mean duration 61 ± 24.5 min instead of 45 min).

The expected sedation was obtained as required for both score and duration in only two patients: patients 3 and 13 (Table 1). Failures were recorded in the fourteen remaining patients. Eight of these (patients 5, 6, 7, 10, 11, 12, 15, 16) received a rescue treatment (Table 1). One (patient 10) received 3 mg kg^{-1} diazepam i.v. instead of Gamma-OH and constituted a protocol violation. In the other six patients who did not receive a rescue treatment, the cardiac catheterization was completed, although the patients did not meet the sedation criterion required for the midazolam treatment to be considered as a success. Due to the large number of failures in achieving the expected sedation, the estimate failure probabilities of each of the six doses, updated after each patient recruited, remained high throughout the trial, and led us to allocate the maximum dose (0.6 mg kg^{-1}) in the chosen dose range in infants 2

to 16 (Table 2). The estimated probability of failure for the maximum dose remained very much higher than the *a priori* set value (1%), and was equal to 81% (95% confidence interval: 78.5–84%), after the sixteenth infant has been included (Table 2). The 95% confidence interval of the probability of failure in the 0.6 mg kg^{-1} group narrowed as the number of patients included increased (Figure 1).

The calculation of the time to score 4 of sedation and of the time-duration at a sedation score ≥ 4 , were based on data obtained from only 11 infants (patients 2, 3, 4, 8, 9, 10 and 12 to 16). Indeed, patients who received a rescue treatment without reaching score 4 30 min after dosing, were not taken into account in this calculation (patients 5, 6, 7, 11); 31% and 70% of these infants reached a sedation score equal to 4, respectively 30 and 45 min after drug administration (Figure 2). Median time-duration of sedation

Figure 1 Probability of failure for the 0.6 mg kg^{-1} midazolam dose and 95% confidence interval ◆ estimated, □ lower CI, △ upper CI.

Table 1 Sedation score at the different evaluation-times after dosing.

Subject	Dose (mg kg ⁻¹)	Time (min)											Clinical response
		0	15	30†	45‡	60‡	75	90	105	120	180	240	
1	0.4	1	3	1	1	1	1	★	★	★	★	★	Failure
2	0.6	1	3	3	6‡	6‡	6‡	6‡	2	1	1	1	Failure
3	0.6	1	1	6‡	6‡	5‡	6‡	6‡	6‡	6‡	1	1	Success
4	0.6	1	1	1	4‡	4‡	1	1	1	1	5‡	4‡	Failure
5	0.6	1	3	3	RT								Failure
6	0.6	1	3	3	RT								Failure
7	0.6	1	3	3	RT								Failure
8	0.6	2	3	3	3	3	2	3	2	2	5‡	5‡	Failure
9	0.6	2	3	3	6‡	6‡	4‡	1	1	3	3	4‡	Failure
10	0.6	1	6‡	6‡	RT								Failure
11	0.6	1	3	3	RT								Failure
12	0.6	2	4‡	2	1	RT							Failure
13	0.6	1	1	4‡	5‡	6‡	5‡	4‡	3	2	2	4‡	Success
14	0.6	2	5‡	4‡	3	4‡	3	3	4‡	3	3	3	Failure
15	0.6	1	3	1	4‡	5‡	4‡	3	1	RT			Failure
16	0.6	3	3	3	1	3	3	1	5‡	RT			Failure

RT: rescue treatment.

*: missing data.

†Time (T) of desired sedation score ≥ 4 .

‡Sedation score ≥ 4 .

Table 2 *A posteriori* estimated probabilities of failure of the six tested doses, updated after each included patient.

Subject	Administered dose (mg kg ⁻¹)	Clinical response	Midazolam dose range studied (mg kg ⁻¹)					
			0.1	0.2	0.3	0.4	0.5	0.6
			A priori probabilities of failure (%)					
			70	60	40	20	10	1
			A posteriori estimated probabilities of failure (%)					
1	0.4	Failure	89	87	83	76	70	46
2	0.6	Failure	92	91	89	86	84	73
3	0.6	Success	90	89	86	81	76	58
4	0.6	Failure	92	91	89	86	83	71
5	0.6	Failure	92	91	90	87	85	76
6	0.6	Failure	93	92	90	88	86	79
7	0.6	Failure	93	92	91	89	87	80
8	0.6	Failure	93	92	91	89	87	80
9	0.6	Failure	93	92	91	89	87	81
10	0.6	Failure	93	92	91	89	87	81
11	0.6	Failure	93	92	91	89	88	81
12	0.6	Failure	93	92	91	89	88	81
13	0.6	Success	93	92	91	89	87	81
14	0.6	Failure	93	92	91	89	88	81
15	0.6	Failure	93	92	91	89	88	81
16	0.6	Failure	93	92	91	89	88	81

Figure 2 Cumulated percentage of subjects with a sedation score ≥ 4 as a function of time elapsed after dosing.

at score ≥ 4 was 15 min (range: 0–90 min). At t_{15} and t_{30} median scores were equal to 3 (range: 1–5) and 3 (range: 1–6) respectively.

Pharmacokinetic results

All patients included in the study received 0.6 mg kg⁻¹ midazolam except patient 1 who received 0.4 mg kg⁻¹, and whose results are not presented here. Due to technical problems, several blood samples were missing in patients 3, 10 and 14, and the kinetic study could not be performed.

Maximum concentration ($C_{\max}$) was calculated in the remaining twelve patients, except in patient 13 whose t_{15} sample was missing, and was equal to $147 \pm 58 \mu\text{g l}^{-1}$ ($n = 11$). Median $t_{\max}$ in these patients was 31.5 min (range: 18–38 min). The half-life, calculated only in patients whose percentage of extrapolation from AUC (0, t) to AUC (0, ∞) was lower than 30%, was 1.3 ± 0.3 h ($n = 4$). The midazolam concentration-time curve is presented for one representative subject (Figure 3). The others were similar.

Figure 3 Midazolam plasma concentration-time curve in patient 2.

Relationship between sedation and midazolam plasma concentration

Sedative effect related to plasma concentration curves were obtained in the four infants who did not receive a rescue treatment and who had no missing blood samples (patients 2, 4, 9, 14). They showed counterclockwise hysteresis after the observation-time points were connected in time sequence. The data are displayed for one representative subject (Figure 4). The other three had similar hysteresis.

Tolerability

Tolerability was good. Haemodynamic parameters were stable during the course of catheterization. Hiccups was noted at 5 min, 10 min and 21 min after dosing in patients 3, 6 and 9 respectively, lasting 60, 25 and 20 min respectively.

Figure 4 Sedation score as a function of the midazolam plasma concentration in patient 2.

and resolving spontaneously. Vomiting occurred in patient 11, 3 h after dosing.

Discussion

A continual reassessment method [16, 17] was preferred to a parallel group design because of the potential advantages of such a design in pediatric trials: the small number of patients required (20 to 25); no placebo group necessary; the dose allocated to each subsequent patient is supposedly closer to the optimal dose. Due to the failure of the doses of midazolam lower than 0.6 mg kg^{-1} to achieve the required sedation, the maximum dose (0.6 mg kg^{-1}) in the chosen dose-range was assigned 15 times out of 16, suggesting an initial underestimation of the required dose range. The optimal dose may therefore be higher than 0.6 mg kg^{-1} , but there is no data available on the tolerance of such high doses in infants with spontaneous ventilation.

Only 16 infants entered the study, while 20 were planned, because the estimated high probability of failure remained stable after the 10th patient, and for ethical reasons. A calculation was performed for four additional simulated patients: the probability of failure for the 0.6 mg kg^{-1} dose would not have decreased further than 77% even if 4 consecutive successes were observed at that dose.

The catheterization was completed in six patients whose treatments were rated as failures although they were not administered a rescue treatment. This might be related to the additional methods of sedation that were used by the nursing staff, starting at t_{30} , such as the use of a dummy, the sound of the voice and fondling.

The analysis of the secondary endpoints helps in understanding the failure of the midazolam treatment to fulfill the required main criterion within the studied dose-range. The time to reach sedation score 4 was longer than the expected 30 min time-interval: only 31.5% of the infants reached this score within 30 min after dosing, and 70% within 45 min (Figure 2). This lag-time was not expected from the previous reported studies since they were mostly performed before surgery and the evaluation was discontinued at the time of induction of anesthesia precluding evidence of a lag-time to be [1–9]. If a sedation score ≥ 4 was required between t_{45} and t_{75} , instead of between t_{30} and t_{60} , the treatment in five infants out of 16 (31.25%) instead of 2 out of 16 (12.5%) would have been rated as a success. Therefore, the

high rate of failure that we observed cannot be explained solely by the delay in obtaining the appropriate sedation. A short median time-duration of sedation at score 4 (15 min instead of 30 min) also explains in part our results. A sedation score ≥ 3 was reached in 81% of the infants within 15 min of dosing. Furthermore, the median time-duration of sedation at score ≥ 3 was 45 min (range: 15–225 min). These results are consistent with previous studies: 0.3 and 0.4 mg kg^{-1} of midazolam administered rectally in infants induced 75% of sedation at score 3 within 20 min of dosing [1]. It can be concluded that a 0.6 mg kg^{-1} midazolam dose administered rectally induces sedation, but at a lower level (score 3) and with a longer lag time (45 min) than desired (score ≥ 4 ; duration 30 min). This emphasises the importance of selection of the main criterion in the CRM.

After midazolam i.v. administration, the time to reach deep sedation depends on the dose and on the administration rate. Klienlen *et al.* [21] suggested that midazolam brain concentrations should be above a threshold in order to reach a target sedation level. Therefore, the slow absorption ($t_{\text{max}} = 30 \pm 14.3 \text{ min}$) and the low availability (18%) obtained after rectal midazolam administration in children [15], may delay the time to reach this minimum concentration threshold. Consistent with this, four children developed a secondary response, i.e., a sedation score value equal to or greater than 4 (two were actually asleep), after having spent about 1.5 h awake. It is unlikely that this represented data errors or unreliability of the scale, owing to the careful checking of the data and the ease in discriminating between drowsy or asleep children and awake children. A pharmacokinetic phenomenon is possible but there was no secondary increase in the midazolam plasma concentration and an effect of the active metabolite (1-hydroxymethyl-midazolam derivative) is unlikely since it has been shown that the C_{max} for the metabolite and the parent compound occurs only few minutes apart after oral administration in adults: 48.5 min and 44.5 min respectively [22]. Whether a pharmacodynamic phenomenon could be responsible remains an open issue. One may however hypothesize that at the end of the observation period the patients had less stimuli, were tired by the procedure and the sedation score was therefore more likely to be rated 3 or 4.

Doses higher than 0.6 mg kg^{-1} may shorten the time to reach the expected sedation and expand the duration of sedation. The large inter-individual variability in plasma concentrations obtained in this study suggest that at higher doses, some patients may be exposed to a greater risk of side effects, or excessive effects. Another route of administration with a more rapid absorption may be more appropriate in achieving the appropriate level of sedation during cardiac catheterization. Deep sedation seems to be better suited than conscious sedation for some intracardiac procedures since investigators require the patient to be motionless during stimulation and not only to be relieved of anxiety. The nasal route seems to be painful in many patients and the i.v. route would require the presence of an anesthesiologist.

The percentage of extrapolation from $\text{AUC}(0, t)$ to $\text{AUC}(0, \infty)$ was higher than 30% in all but four patients due to sampling for too short a time after dosing. This sampling interval was planned according to the expected

duration of the cardiac catheterization and to cover 3 times the midazolam half-life reported in children. The midazolam half-life has not been reported previously in infants. The high number of patients excluded from the calculation due to a high percentage of extrapolation suggests that these patients had a half-life longer than that calculated in the remaining four patients.

The counterclockwise hysteresis observed in the four patients whose plots could be drawn suggests that the equilibrium between the plasma and the site of effect was not achieved rapidly. Such a relationship could also be explained by the production of the active metabolite of midazolam. However, the 1-hydroxymethyl-midazolam and unchanged midazolam maximum plasma concentrations are separated by only a few minutes [22]. These data are not consistent with the latter hypothesis.

A midazolam plasma concentration higher than $100 \mu\text{g l}^{-1}$ induces an hypnotic effect in adults [23], whereas a concentration above $250 \mu\text{g l}^{-1}$ is necessary in children between 8 months and 8 years [24]. Maximum plasma concentration in most of our patients ranged between 100 and $268 \mu\text{g l}^{-1}$, with deep sedation in only one.

Hiccups have been reported in children as a frequent side-effect after midazolam administration either as 0.04 to 0.25 mg kg^{-1} intravenously [25, 26, 28], 0.15 mg kg^{-1} intramuscularly [5], 0.4 mg kg^{-1} orally [27] or as 0.5 mg kg^{-1} rectally [5]. After i.v. administration, hiccups occurred after a shorter lag-time (2, 5 to 15 min) than observed in the present study (5 to 21 min), and did not last as long (1 to 8 min instead of 20 to 60 min) [26]. Hiccups have also been described after diazepam [29] and flunitrazepam [30].

Rectal midazolam at doses equal to or lower than 0.6 mg kg^{-1} does not provide an appropriate sedation during cardiac catheterization in infants. The present data might be related to delayed absorption and low rectal bioavailability of midazolam. Higher doses or different routes of administration may shorten the time to reach the expected sedation and expand the duration of sedation but the safety of doses higher than 0.6 mg kg^{-1} administered rectally has not been evaluated.

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