

ORIGINAL ARTICLE

Minimum effective dose of midazolam for sedation of mechanically ventilated neonates

J.-M. Treluyer* MD PhD, S. Zohar† PhD, E. Rey* Pharm D, P. Hubert‡ MD, F. Iserin‡ MD, M. Jugie§ MD, R. Lenclen§ MD, S. Chevret† MD PhD and G. Pons* MD PhD

*Pharmacologie, Hôpital Cochin-Saint-Vincent de Paul, AP-HP, Université Paris V, Paris, †Département de Biostatistique et Informatique Médicale, Hôpital Saint-Louis, AP-HP, Université Paris VII, U717 INSERM, Paris, ‡Réanimation Pédiatrique, Cardiologie Hôpital Necker Enfants malades, AP-HP, Université Paris V, Paris and §Réanimation, Hôpital de Poissy-Saint Germain, France

SUMMARY

Objective: To determine the minimal effective dose (MED) of intravenous midazolam, required for appropriate sedation in 95% of patients, 1 h after drug administration.

Methods: A double-blind dose-finding study using the continual reassessment method, a Bayesian sequential design. Twenty-three newborn infants hospitalized in intensive care unit participated. Inclusion criteria were: (i) post-natal age <28 days, (ii) gestational age >33 weeks, (iii) intubation and ventilatory support required for respiratory distress syndrome, (iv) need for sedation (i.e. one of the six following criteria: agitation or grimacing or crying facial expression before tracheal suctioning, agitation or grimacing or crying facial expression during tracheal suctioning). Each neonate was allocated to a loading dose, ranging from 75 to 200 µg/kg, and a maintenance dose ranging from 37.5 to 100 µg/kg/h.

Results: The primary endpoint was the level of sedation 1 h after the onset of infusion. The sedation procedure was classified as a success if all the following clinical criteria were met: no agitation, no grimacing and no crying facial expression before as well as during tracheal suctioning. Based on the 23 patients, the final

estimated probability of success was 76.9% (95% credibility interval: 56.6–91.4%) for the 200 µg/kg loading dose. No significant adverse effect was observed.

Conclusions: Continual reassessment is a new approach, suitable for dose-finding study in neonates. This method overcomes some of the ethical, statistical and practical problems associated with this population. Using this method, the MED was estimated to be the 200 µg/kg loading dose of midazolam.

Keywords: continual reassessment method, dose-finding study, midazolam, neonates, stopping rules for decision making

INTRODUCTION

Proper sedation of patients is part of good clinical practice in intensive care units (ICU) in children as well as in adults. The main goal of sedation is to increase patients' comfort by decreasing stress and anxiety (1). Moreover, adequate sedation during mechanical ventilation may facilitate effective ventilation so that complications such as pneumothorax and intraventricular haemorrhage may be prevented (2, 3). Benzodiazepines, such as midazolam and lorazepam, are frequently chosen for sedation in the neonatal ICU. Intravenous midazolam differs from other benzodiazepines by its water solubility, short elimination half-life, and generally short duration of action. Many authors have studied the pharmacokinetic properties and clinical efficacy of midazolam in ventilated neonates. However, the dosage used to initiate and

Received 18 March 2005, Accepted 5 July 2005

Correspondence: Jean-Marc Treluyer, Pharmacologie Clinique, Hôpital Saint-Vincent de Paul, 82 avenue Denfert Rochereau, 75645 Paris cedex 14, France.

Tel.: 33/1 40 48 82 09; fax: 33/1 40 48 83 28;

e-mail: jm.treluyer@svp.ap-hop-paris.fr

maintain sedation show dramatic differences. Most reports to date have been case series of midazolam used in patients of diverse age groups (from 3 days to 18 years of age), with doses ranging from 25 to 300 $\mu\text{g}/\text{kg}$ administered as a bolus injection, and 24–400 $\mu\text{g}/\text{kg}/\text{h}$ administered as a continuous infusion (4–8). In a multicentre pilot study, Anand *et al.* (9), administered midazolam with 200 $\mu\text{g}/\text{kg}$ loading dose followed by an infusion of 20, 40, or 60 $\mu\text{g}/\text{kg}/\text{h}$ for infants of gestational ages 24–26, 27–29, or 30–33 weeks respectively. Jacqz-Aigrain *et al.* (10), administered midazolam as a 60 $\mu\text{g}/\text{kg}/\text{h}$ infusion for up to 5 days in infants >33 week gestation, or 60 $\mu\text{g}/\text{kg}/\text{h}$ for 1 day followed by 30 $\mu\text{g}/\text{kg}/\text{h}$ for up to a total of 5 days in infants \leq 33 week gestation without any loading dose. As with many drugs used in children, little is known about midazolam in neonates. In using midazolam as a sedative in ventilated neonates, the dosing regimen for effective and safe treatment is a key issue and no adequate evaluation has been reported. However, in this patient group such a dose-finding study meets with distinct ethical, statistical and practical problems. A new approach proposed and used previously by us for dose-finding of ibuprofen in patent ductus arteriosus (12) is proposed for dose-finding of midazolam for sedation of ventilated neonates, to overcome some of the ethical and recruitment issues. The main objective was to determine the dose of intravenous midazolam, required to obtain appropriate sedation in 95% of ventilated neonates within 1 h of administration.

MATERIALS AND METHODS

The study was approved by the local ethics committee (Cochin Hospital, Paris) and written informed consent was obtained from the parents. Inclusion criteria were: (i) post-natal age <28 days, (ii) gestational age >33 weeks, (iii) intubation and ventilatory support required for respiratory distress syndrome, (iv) need for sedation (i.e. one of the six following criteria: agitation or grimacing or crying facial expression before tracheal suctioning, agitation or grimacing or crying facial expression during tracheal suctioning). We excluded babies if they or their mother had previously received benzodiazepines or opioids during the 15 days before the time of inclusion. The other exclusion criteria

were abnormalities of renal, hepatic, neurologic or haemodynamic functions.

Midazolam was administered intravenously at a 0.6 mL/kg loading dose over 1 h, followed by an infusion of 0.3 mL/kg/h over 47 h using the same infusion rate for all the dose levels. Only the concentration of the solution was modified. The concentrations of the solution ranged from 6.2 to 16.7 mg/50 mL. Each neonate was double-blindly allocated to a loading dose of 75–200 $\mu\text{g}/\text{kg}$ and a maintenance dose of 37.5–100 $\mu\text{g}/\text{kg}/\text{h}$. Six dose regimens were tested: 75, 100, 125, 150, 175, 200 and 37.5, 50, 62.5, 75, 87.5, 100 $\mu\text{g}/\text{kg}$ for loading doses and maintenance doses respectively. Physicians, nurses and all NICU staff were blind to the dose of midazolam administered.

The primary endpoint was the level of sedation 1 h after the onset of the infusion (H1). The sedation procedure was classified as a success if all the following clinical criteria were absent: agitation, grimacing and crying facial expression before as well as during tracheal suctioning. The following secondary endpoints were also studied: level of sedation at H4, H12, H18, H24, H48 using the same criteria used at H1, heart rate, blood pressure, oxygen saturation measured by pulse oximetry, oxygenation index, and triggering of ventilator breathing by the patients at H0, H1, H4, H12, H18, H24 and H48.

Additional midazolam bolus doses or increases in the rate of infusion were not allowed. Sedative drugs that may interact with the assessment of sedation (benzodiazepines, opioids, muscle relaxants) were not allowed. Infusion was continued for as long as clinically necessary but no longer than 48 h. At completion of the study, depending on the level of sedation achieved, physicians were allowed to prescribe midazolam or another sedative drug according to their own practice. After the assessment of the primary endpoint, the treatment could be stopped before the end of the study if the level of sedation was considered insufficient by the physicians. Midazolam was also stopped after H1 if respiratory distress rapidly improved and extubation of the child was considered.

Dose-finding statistical analysis

The continual reassessment method (CRM) (11), a Bayesian sequential design, was used in order to

determine the minimal effective dose (MED) of midazolam for the sedation of 95% of newborn infants. The CRM is an iterative Bayesian method based on a one-parameter model, which aims at estimating the percentile of among k distinct dose levels d_i ($i = 1, \dots, k$). Each of the six dose levels was arbitrarily chosen by the investigator (according to his/her personal experience and literature data) with the following prior estimated success probability, p_i ($i = 1, \dots, 6$), that is 0.3, 0.5, 0.7, 0.9, 0.95 and 1.0 for the 75, 100, 125, 150, 175 and 200 $\mu\text{g}/\text{kg}$ loading dose respectively. Then, a one-parameter logistic model (the scale parameter was fixed at 3) was used to fit the dose-response curve, with a unit exponential distribution for the model parameter. The posterior response probability of each dose level was re-estimated after each new patient's inclusion. The dose allocated to each new patient was the dose level with the updated posterior response probability closest to 0.95.

In the present study, the first patient received a loading dose of 175 $\mu\text{g}/\text{kg}$ with the prior success probability closest to the target (0.95). The MED was defined as the dose level among the six chosen doses that had a final response probability closest to the target. The decision to end the study was based on stopping criteria, in order to detect whether all doses were likely to be inefficient, or a suitable estimation of the MED has been obtained (13).

RESULTS

Description of the population

Twenty-three newborns entered the study. The demographic and clinical variables for the neonates are presented in Table 1. Twenty-one (91.3%) children stopped the study before H48, seven (30.4%) because the level of sedation was considered insufficient by the physicians and 14 (60.9%) because the respiratory distress rapidly improved and children were extubated. The median observation time period was 12 h (1–60).

Dose-finding analysis

The estimated success probability, updated after each patient, was <95% for all dose level, and led to allocation of the maximum loading dose

Table 1. Demographic and clinical variables of the neonates at inclusion

Patients	N (%) / Median (range)
Sex (male)	16 (69.6)
Post-natal age (days)	0 (0–4)
Gestational age >33 weeks	23 (100)
Weight (g)	2650 (1335–3960)
FiO ₂ (%)	45 (21–80)
Serum creatinine ($\mu\text{mol}/\text{l}$)	86.5 (50–122)
Prothrombin time (%)	59 (20–79)
Plasma fibrine (g/l)	1.9 (0.2–5.5)
Blood platelets ($10^3/\text{mm}^3$)	198 (100–418)

(200 $\mu\text{g}/\text{kg}$) from the fifth patient to the 23rd patient (Table 2). The final estimated probability of success of that dose level was 76.9% (95% credibility interval: 56.6–91.4%) after 23 infants had been included (Fig. 1). The posterior success probability for the six doses 75, 100, 125, 150, 175 and 200 $\mu\text{g}/\text{kg}$ corresponded to 27.7%, 32.7%, 38.1%, 47.3%, 52.5% and 76.9% respectively (Table 2). Because the target was fixed at 95%, the MED was selected to be 200 $\mu\text{g}/\text{kg}$. Failures were recorded in five (25%) of 20 patients receiving a 200 $\mu\text{g}/\text{kg}$ midazolam loading dose. Among these patients, the failure was assessed on 6, 4, 3, 3, 1 of the 6 failure criteria. Classification as a failure was the result of agitation ($n = 2$), grimacing ($n = 3$) and crying facial expression ($n = 3$) before tracheal suctioning, agitation ($n = 3$), grimacing ($n = 4$) and crying facial expression ($n = 3$) during tracheal suctioning.

The stopping decision has been made after the analysis of the stopping criteria. The first decision was based on the probability that the posterior estimated response probability of success of either dose was lower than the targeted response probability. This probability was higher than 95% after the inclusion of the 14th patient. The second stopping decision was associated with four stopping criteria, based on the predictive mean and the maximum gain from further patient inclusions on the response probability and the width of the associated credibility interval. These stopping criteria (3 from 4) were lower than 5%, after the 20th patient with a success probability at 78.7% (95% credibility interval: 57.6–93.3%). The response probability associated with the 200 $\mu\text{g}/\text{kg}$ dose level would have changed for <5%, even if more

Table 2. Posterior estimated probabilities of success of the five tested doses, updated after each newly included patient

Subject	Dose ($\mu\text{g}/\text{kg}$)	Clinical response	Midazolam loading dose ($\mu\text{g}/\text{kg}$)					
			75	100	125	150	175	200
			Prior estimated probability of success (%)					
			30.0	50.0	70.0	90.0	95.0*	100
			Posterior estimated probability of success (%)					
1	175	Success	30.8	55.8	78.2	95.0	98.0	100
2	150	Success	31.4	60.8	84.0	97.3	99.1	100
3	150	Failure	28.5	38.6	49.7	67.1	75.3	96.2
4	200	Failure	27.5	30.9	34.6	40.9	44.5	63.6
5	200	Success	27.6	32.0	36.7	44.7	49.3	72.1
6	200	Success	27.8	33.0	38.6	48.3	53.7	78.6
7	200	Success	27.9	33.8	40.3	51.2	57.3	83.1
8	200	Success	28.0	34.5	41.6	53.6	60.2	86.2
9	200	Failure	27.7	32.1	36.9	45.2	49.8	73.0
10	200	Success	27.7	32.7	38.0	47.1	55.3	76.6
11	200	Success	27.8	33.1	38.9	48.8	54.4	79.5
12	200	Success	27.9	33.5	39.8	50.3	56.2	81.8
13	200	Success	27.9	33.9	40.5	51.6	57.7	83.6
14	200	Failure	27.7	32.6	37.9	46.8	51.9	76.1
15	200	Success	27.8	32.9	38.5	48.0	53.3	78.1
16	200	Success	27.8	33.2	39.0	49.0	54.6	79.8
17	200	Success	27.8	33.4	39.6	49.9	55.7	81.3
18	200	Success	27.9	33.7	40.0	50.8	56.8	82.5
19	200	Success	27.9	33.9	40.5	51.6	57.7	83.6
20	200	Failure	27.8	33.0	38.7	48.3	53.8	78.5
21	200	Success	27.8	33.2	39.1	49.1	54.7	79.9
22	200	Success	27.8	33.4	39.5	49.7	55.5	81.0
23	200	Failure	27.7	32.7	38.1	47.3	52.5	76.9

*Targeted probability of success.

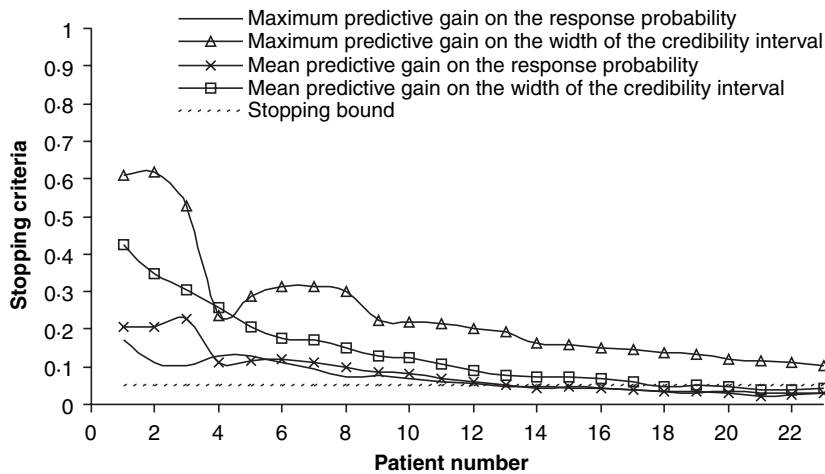
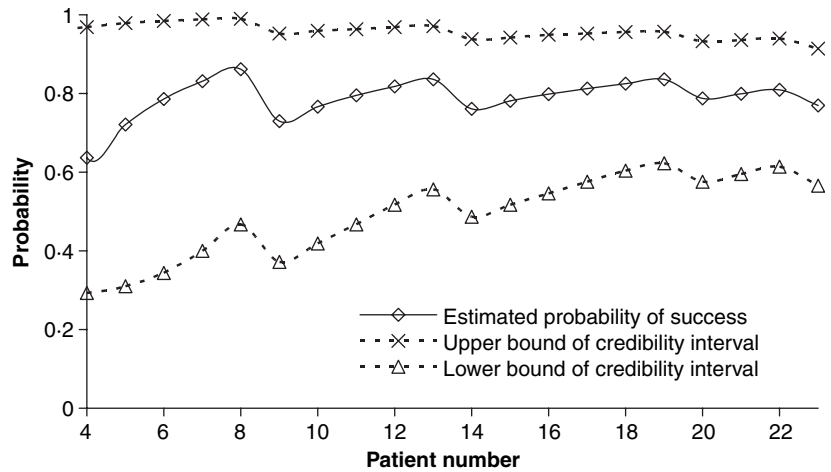


Fig. 1. Estimated posterior probability of success of the 200 $\mu\text{g}/\text{kg}$ midazolam dose and associated 95% credibility interval along the trial. This dose level was administered from the fourth patient up to the last patient.

Fig. 2. Stopping criteria based on the predicted gain from further patient inclusions on the response probability (mean and maximum) and on the width of its credibility interval (mean and maximum). Three criteria out of the four were lower than 5% from the 20th patient.



patients were included (Fig. 2). No significant effect of sedation on pulse oximetry, oxygenation index or triggering of ventilator breathing was evidenced after the onset of midazolam administration.

Adverse events

No serious adverse event was reported during the study. Pneumothorax was reported in two children who had received a 200 $\mu\text{g}/\text{kg}$ initial loading dose, and were classified as 'success' for sedation. However, the sedation study was stopped after the diagnosis of pneumothorax to administer morphine for prevention of pain.

Relative median variations between H0 and H1 of systolic, diastolic and mean blood pressure were -2% (-18% ; 27%), -7% (-43% ; 19%), -6% (-40% ; 15%), respectively, but none was found different from 0. A decrease of more than 30% for systolic, diastolic and mean blood pressure was observed during the study inclusion in none, two (8.7%) and one (4.3%) children respectively (all received the 200 $\mu\text{g}/\text{kg}$ loading dose level). However, this event was very transient and no haemodynamic support was required. Relative variation of heart rate was -4% (-22% ; 16%) between H0 and H1.

DISCUSSION

Midazolam is suitable for sedation of neonates as it is a short-acting benzodiazepine with a high clearance and a short elimination half-life. However, consequent to immature hepatic cytochrome

P450 activity, midazolam clearance is reduced, and half-life and time to reach steady-state increased in neonates compared with children and adults (14–20). Consequently, a specific phase II study was conducted to determine the optimal dose for sedation of ventilated neonates. A CRM was chosen for this study because of the potential advantages of such an approach in paediatric patients: small number of patients required (25 or less), no placebo group necessary and ethical suitability as each subject takes advantage of the previous inclusions to receive the current estimated MED.

As our objective was to obtain an optimal sedation 1 h after the onset of midazolam administration, a loading dose was used. The final estimated probability of success of the highest dose (i.e. 200 $\mu\text{g}/\text{kg}$ for the loading dose and 100 $\mu\text{g}/\text{kg}/\text{h}$ for the maintenance dose) was 76.9% (95% credibility interval: 56.6–91.4%). Based upon the estimated probabilities of success, the optimal dose to obtain 95% of success (the initial objective of our study) appears to be higher than the maximum dose used in this study. One can wonder if the criteria used to define sedation were too stringent. There is a paucity of tools to measure the level of sedation in preterm neonates and those who require mechanical ventilation. The scoring systems used in previous studies concerning use of midazolam for sedation in neonates were not validated and were not assessed during clinical care. We used a behavioural scale adapted from the scoring system by Barrier *et al.* (21) and Jacqz-Aigrain *et al.* (10). We modified these scores as we chose to assess sedation before but also during tracheal

suctioning. As tracheal suction is an acute and repetitively stressful in mechanically ventilated neonates, and as the main objective of sedation is to decrease the deleterious effects of clinical care for the patients, we assessed sedation during tracheal suction. The other difference in the design of our study compared with previously published studies is that sedation was assessed as early as 1 h after the onset of midazolam infusion to obtain an effective and very rapid sedation. This may explain the highest dose of midazolam being selected at the end of the study.

The aim of this study was to improve management of non-painful stress (anxiety). Analgesics were administered only if painful procedures were anticipated. However, concomitant use of opioids and benzodiazepines necessitates a decrease in the total dose of opioids and benzodiazepines (22). Consequently, results of the present study are applicable only when midazolam is used singly.

No severe side-effect was observed. Transient hypotension was noticed in two children. In the study by Jacqz-Aigrain *et al.* (10) the number of infants with haemodynamic instability was not significantly different between the two midazolam and the placebo groups, although blood pressure was significantly decreased in the midazolam group. In most cases, hypotension observed with midazolam occurred only during concomitant use of opioids (23, 24). Transient neurologic effects have been associated with the use of midazolam, but no such side-effect was noticed in the present study (22).

In conclusion, the probability of success for sedation in ventilated neonates, even during tracheal suctioning, using a 200 µg/kg loading dose of midazolam during 1 h followed by a 100 µg/kg/h maintenance dose, was estimated to be 76.9% in the absence of analgesics. Given the small number of children included, tolerability of this dose schedule needs to be confirmed in a larger group of neonates.

REFERENCES

1. Quinn MW, Wild J, Dean HG, Hartley R, Rushforth JA, Puntis JW, Levene MI (1993) Randomised double-blind controlled trial of effect of morphine on catecholamine concentrations in ventilated pre-term babies. *Lancet*, **342**, 324–327.
2. Greenough A, Morley C, Davis J (1983) Interaction of spontaneous respiration with artificial ventilation in preterm babies. *Journal of Pediatrics*, **103**, 769–773.
3. Perlman JM, Goodman S, Kreuzer KL, Volpe JJ (1985) Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. *New England Journal of Medicine*, **312**, 1353–1357.
4. Hartwig S, Roth B, Theisohn M (1991) Clinical experience with continuous intravenous sedation using midazolam and fentanyl in the paediatric intensive care unit. *European Journal of Pediatrics*, **150**, 784–788.
5. Pellier I, Monrigal JP, Le Moine P, Rod B, Riolland X, Granry JC (1999) Use of intravenous ketamine-midazolam association for pain procedures in children with cancer. A prospective study. *Paediatric Anaesthesia*, **9**, 61–68.
6. Rosen DA, Rosen KR (1991) Midazolam for sedation in the paediatric intensive care unit. *Intensive Care Medicine*, **17** (Suppl. 1), S15–S19.
7. Hogberg L, Nordvall M, Tjellstrom B, Stenhammar L (1995) Intranasal versus intravenous administration of midazolam to children undergoing small bowel biopsy. *Acta Paediatrica*, **84**, 1429–1431.
8. Ng E, Taddio A, Ohlsson A (2000) Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database of Systematic Review*, CD002052.
9. Anand KJS, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R (1999) Analgesia and sedation in preterm neonates who require ventilatory support – results from the NOPAIN trial. *Archives of Pediatrics and Adolescent Medicine*, **153**, 331–338.
10. Jacqz-Aigrain E, Daoud P, Burtin P, Desplanques L, Beaufilet F (1994) Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies [see comments]. *Lancet*, **344**, 646–650.
11. Desfrere L, Zohar S, Morville P *et al.* (2003) Dose-finding study of ibuprofen in patent ductus arteriosus using the continual assessment method. *Journal of Clinical Pharmacy and Therapeutics*, **30**, 121–132.
12. O'Quigley J, Pepe M, Fisher L (1990) Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics*, **46**, 33–48.
13. Zohar S, Chevret S (2001) The continual reassessment method: comparison of Bayesian stopping rules for dose-ranging studies. *Statistics in Medicine*, **20**, 2827–2843.
14. de Wildt SN, Kearns GL, Hop WC, Murry DJ, Abdel-Rahman SM, van den Anker JN (2001) Pharmacokinetics and metabolism of intravenous midazolam in

- preterm infants. *Clinical Pharmacology and Therapeutics*, **70**, 525–531.
15. Nahara MC, McMorrow J, Jones PR, Anglin D, Rosenberg R (2000) Pharmacokinetics of midazolam in critically ill pediatric patients. *European Journal of Drug Metabolism and Pharmacokinetics*, **25**, 219–221.
 16. Jacqz-Aigrain E, Daoud P, Burtin P, Maherzi S, Beaufils F (1992) Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. *European Journal of Clinical Pharmacology*, **42**, 329–332.
 17. Jacqz-Aigrain E, Wood C, Robieux I (1990) Pharmacokinetics of midazolam in critically ill neonates. *European Journal of Clinical Pharmacology*, **39**, 191–192.
 18. Burtin P, Jacqz-Aigrain E, Girard P *et al.* (1994) Population pharmacokinetics of midazolam in neonates. *Clinical Pharmacology and Therapeutics*, **56**, 615–625.
 19. Lee TC, Charles BG, Harte GJ, Gray PH, Steer PA, Flenady VJ (1999) Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics. *Anesthesiology*, **90**, 451–457.
 20. Harte GJ, Gray PH, Lee TC, Steer PA, Charles BG (1997) Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *Journal of Paediatrics and Child Health*, **33**, 335–338.
 21. Barrier G, Attia J, Mayer MN, Amiel-Tison C, Shnider SM (1989) Measurement of post-operative pain and narcotic administration in infants using a new clinical scoring system. *Intensive Care Medicine*, **15** (Suppl. 1), S37–S39.
 22. Fetus and Newborn Committee (2000) Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. *Pediatrics*, **105**, 454–461.
 23. Van den Anker J, Sauer P. (1992) The use of midazolam in the preterm neonate. *European Journal of Pediatrics*, **151**, 152.
 24. Burtin P, Daoud P, Jacqz-Aigrain E, Mussat P, Moriette G (1991) Hypotension with midazolam and fentanyl in the newborn. *Lancet*, **337**, 1545–1546.