Eur J Pediatr (1991) 150:784–788
034061999100165Z

European Journal of
Pediatrics

Clinical experience with continuous intravenous sedation using midazolam and fentanyl in the paediatric intensive care unit*

S. Hartwig, B. Roth, and M. Theisohn*

Children's Hospital and Institute of Pharmacology*, University of Cologne, Joseph-Stelzmann-Strasse 9, W-5000 Cologne 41, Federal Republic of Germany

Received July 20, 1990 / Accepted March 7, 1991

Abstract. Twenty-four patients in a paediatric intensive care unit mostly undergoing cardiac surgery, received a midazolam dosage between 50–400 µg/kg per hour as a continuous intravenous infusion partly in combination with fentanyl [0,5–2,5 µg/kg per hour] for analgesia and sedation. The mean duration of midazolam infusion was 11.6 days (range 38 h–40 days). Blood samples for the HPLC assay of serum midazolam concentration were taken and the clearance estimated. The efficiency of sedation in correlation to the midazolam concentration was evaluated by a clinical sedation score. Serum midazolam concentrations between 100–400 µg/l were sufficient for sedation. Dosage had to be increased during therapy according to an increased midazolam clearance. The evaluation of the sedation score showed that sedation of artifically ventilated infants and young children can be established by continuous intravenous infusion of midazolam.

Key words: Midazolam – Intensive care units – Sedatives

Introduction

Sedation and analgesia are essential elements for the therapy of artificially ventilated paediatric patients, since such patients often experience pain, fear and anxiety. Until now, barbiturates, such as pheno- and pentobarbital and benzodiazepines such as diazepam, have been mostly used for sedation.

Initial studies exist on the use of midazolam in children [4, 15, 16, 23]. Given as an intravenous infusion, weaning from artifical ventilation is described to be successful [4, 16, 23, 24]. Furthermore, it has an antegrade amnesia effect, so that patients have little or no remembrance of unpleasant procedures [9] and in case of overdosing it can be antagonized very well by flumazenil. These properties and the rapid onset of sedation and quick elimination by the liver suggested that it could be used for continuous intravenous infusion to provide long-term sedation.

The purpose of the study was to investigate the following questions, not answered by previous studies:

1. Is there any relationship between midazolam dose and serum midazolam levels in children of different age?
2. Does midazolam clearance change during continuous intravenous administration?
3. Does the degreee of sedation correlate with serum midazolam levels?
4. Which dose of midazolam as the only sedative drug and in combination with low dose of fentanyl is necessary to allow artificial ventilation?

Patients and methods

Twenty-four artificially ventilated children, aged 26 days–5 years (17 infants younger than 1 year and 7 young children), received an intravenous midazolam infusion (Dormicum, Hoffmann-La-Roche, Grenzach-Wyhlen, FRG). The reason for artificial ventilation was mostly for respiratory support after cardiac surgery (16 patients), but other reasons were adult respiratory distress syndrome (ARDS, $n = 1$), brain damage with concomitant cerebral oedema ($n = 2$), epiglottitis ($n = 1$), bronchiolitis ($n = 1$), acute renal failure and pulmonary oedema ($n = 1$), aortoventropexia ($n = 1$) and submandibular abscess ($n = 1$). The study was approved by the Ethical Committee of the Medical Faculty, University of Cologne. The parents gave their informed consent to the study. All patients were undergoing continuous cardio-respiratory monitoring. Blood pressure was measured using an arterial canula or a Dinamap-device based on oscillometry (Dinamap Critikom GmbH, Norderstedt, FRG). The midazolam infusion was started at a rate of 100 µg/kg per hour after an i.v. bolus of 0.1–0.2 mg/kg given during 5 min. Fifteen of the 24 children received a combination of midazolam with fentanyl-chloride (Fentanyl, Janssen, Neuss, FRG) at a rate of 0.5–2 µg/kg per hour beginning directly after arrival at the intensive care unit after cardiac surgery. The mean duration of the fentanyl infusion was 64 h (range 20–188 h). After stopping the fentanyl infusion, the children were sedated with midazolam only.

* Dedicated to the 65th birthday of Prof. Dr. Erich Gladtke

Offprint requests to: B. Roth

	1	2	3	4	5
A. Motor response	No spontaneous movements	Spontaneous movements with pain	Spontaneous movements of extremities	Spontaneous global movements	Continous spontaneous movements, restless
B. Mimic	No reaction	Grimacing only with pain	Cries only when with pain, rapid return to rest	Cries even when without pain, but soon returns to rest	Cries, difficult to soothe
C. Eyes	Permanently closed	Opening only with pain	Opening when manipulated, quickly falls asleep again	Spontaneous opening, soon returns to sleep	Spontaneous opening, awake for long periods, sweating
D. Respiration			Easy, spontaneous breathing, fully synchronized	Mechanical respiration not disturbed by spontaneous breathing	Spontaneous breathing not synchronous with machine, tachypnoea
E. Aspiration		No reaction when aspirated	Grimacing only, no movements of extremities	Little coughing or retching	Strong opposition, intense coughing, straining

Fig. 1. Quality of sedation was assessed every 3 h with a clinical sedation score by the nursing staff, who quantified the following five criteria: motor function, mimic ability, eye opening, toleration of artificial ventilation and reactions to painful measures. One point was given for the highest, 5 points for the lowest rate of sedation

To determine the effect of sedation, we developed a sedation-score, to quantify the following five criteria: motor function, mimic ability, eye-opening, toleration of ventilation and reactions to painful measures, i.e. tracheal aspiration (Fig. 1).

Single values and sum of the the sedation score criteria were considered to reflect the whole amount of stress and painful measurements at the paediatric intensive care unit.

To evaluate each criterion 1 point was given for the highest degree of sedation and 5 points for the lowest, thus each patient could reach a total of between 8 and 25 points. Eight points indicated deepest sedation, no spontaneous movements, mimic-reactions or eye-opening were seen, whereas 25 points indicated insufficient sedation, patients were restless, sweating and not breathing synchronously with the respirator. Reliable sedation was achieved when a total of 15–18 points was reached. Patients were then asleep, well tolerating artificial ventilation and were yet able to show only a slight response to nursing procedures. Quality of sedation was assessed every 3 h by the nursing staff during routine treatment such as endotracheal suctioning. To evaluate the interrater deviation in assessment by the nurses, we compared the difference of the sum of sedation score points, given to four different patients by six nurses at the same time. The total sum of sedation score points showed a mean difference of 2,5 points (SD ± 1,3 points). The evaluation of the parameters motor response, mimic and respiration showed a mean difference of 1 point (SD ± 0 point) and a mean difference of 0.75 points (SD ± 0,5 points) for the parameters eye-opening and aspiration.

Table 1. Mean (± SD) serum concentrations, infusion rates and clearance data (absolute and in %) of midazolam estimated at a time period of 24–48 h and of 80–120 h after start of contiuous midazolam infusion in 11 patients

	24–48 h	80–120 h	
Infusion rate	131 (56)	195 (145)	µg/(kg × h)
Concentration	513 (327)	329 (353)[a]	µg/l
Clearance	5.8 (3.8)	13.5 (10.6)*	ml (kg × min)
Clearance	100	233	%

* Significant with $2P < 0.05$ according to the Wilcoxon, Mann and Whithney U-test for paired data

[a] Non significant

When the patient was still restless (sedation score > 18 points) the midazolam infusion was increased in steps of 50–100 µg/kg per hour. If there was no reaction to the handling of nursing staff (sedation score < 15 points), the rate of infusion was decreased in steps of 100 µg/kg per hour.

If a child became too restless despite an increase of continuous midazolam infusion, a bolus dose of 0,1 mg/kg midazolam or 3 mg/kg pentobarbital (Nembutal, Abbott Laboratories, North Chicago, USA) was given, additional. Sedation scores obtained up to 6 h after administration of pentobarbital were excluded from the study.

Blood samples for the assay of serum midazolam concentration were obtained in the morning between 6 a.m. and 8 a.m. Before each blood sampling, midazolam infusion was held constant for at least 3 h. Clearance rates (Cl) during continuous infusion for more than 12 h were estimated by the following formula:

$$\text{Cl} = \frac{\text{dose infused continuously}}{\text{serum concentration}} \quad [\text{ml/(kg per minute)}]$$

Serum was separated and stored at −30°C. The determination of midazolam was carried out by HPLC as follows: 200 µl serum after addition of 50 µl internal standard solution (Ro 7-9749 ,15 mg/l in CH_3OH, gift of Hoffmann-La-Roche, Grenzach-Wyhlen, FRG) and 500 µl $Na_2P_2O_7$ buffer (pH = 9) was extracted with diethyl ether. Extraction efficiency was 95% ($n = 15$, SD ± 12.0%). The organic phase was separated, evaporated and the residue reconstituted in 150 µl HPLC elution buffer. The HPLC elution buffer consisted of acetonitrile : methanol : 10% $Na_4CO_2NH_2$, pH 9.0 (33 : 5 : 62). 50 µl of this solution was injected onto the column. The column was a 125 mm × 4.0 mm LiCrospher RP select B (E. Merck, Darmstadt, FRG), flow rate was 1.5 ml/min and absorbance was measured at 230 nm. Chromatography was done with a Hewlett and Packard 1084 B system (Hewlett-Packard GmbH, Böblingen, FRG) with variable wavelength detector. Integration was computer assisted (Trivector 300, Trivector Systems International Ltd., Bedfordshire, England). The detection limit could be reduced to 10 µg/l in 200 µl serum. The inter-assay variation at 200 µg/l was 3%–5%.

The statistical analysis of the data shown in Table 1 was carried out by the Wilcoxon-U-test for paired data. To prove the significance of the difference between midazolam infusion rate in combination with fentnyl and midazolam infusion rate as the only sedative drug, we used the Wilcoxon-Mann-Whitney U test for unpaired data. A linear regression analysis was used to evaluate correlation between midazolam clearance and time (Fig. 2) and between midazolam serum concentration and sedation score (Fig. 3). Statistical significance was considered at a level of $2P < 0.05$.

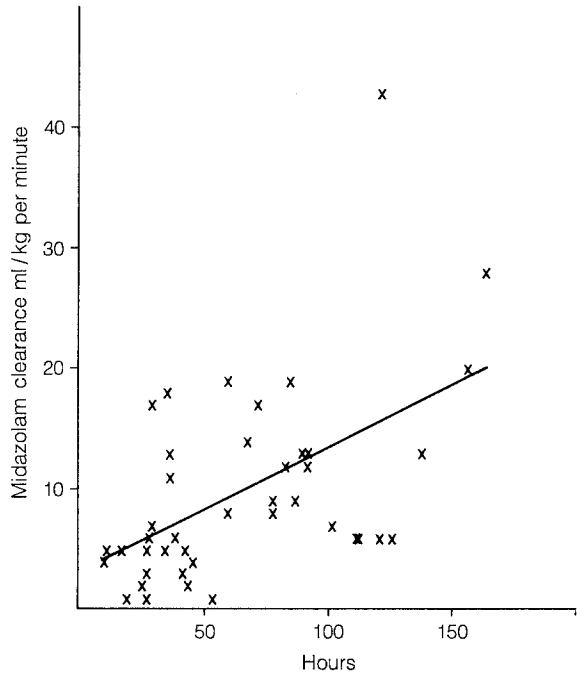

Fig. 2. A significant increase of midazolam clearance ($r = 0.544$, $2P < 0.01$) is shown in all patients during continuous midazolam infusion over 6–7 days. One point corresponds to one estimated data of midazolam clearance. Midazolam clearance was estimated with all steady state serum concentrations measured (3–6 per patient)

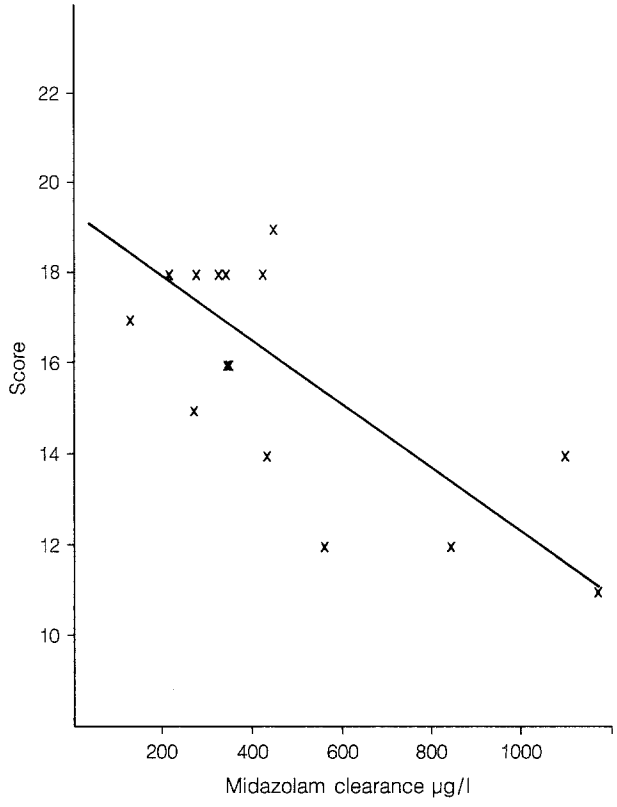

Fig. 3. A significant correlation between serum midazolam concentration and sedation score during 24–72 h ($r = 0.759$, $2P < 0.001$) could be detected. One point of the sedation score indicates the mean of 5 score values, assessed every 3 h by the nursing staff

Results

All 24 patients received a continuous midazolam infusion with various duration ranging from 38 h to 40 days (mean duration 11.6 days), which was started at a rate of 100 µg/kg per hour. In all these patients we saw no adverse cardiovascular or respiratory effects attributable to midazolam.

The infusion rate was increased or decreased in steps of 50–100 µg/kg per hour depending on the level of sedation. The mean infusion rate for the whole period of sedation was 184 µg/kg per hour [range 50–500, SD ± 106]. While the patients were being sedated with midazolam and fentanylchloride, the mean midazolam infusion rate was 142 µg/kg per hour [range 50–250, SD ± 55].

With midazolam as the only sedative drug a significantly higher mean infusion rate of 209 µg/kg per hour [range 100–500, SD ± 114] was necessary to reach a reliable sedation ($2P < 0.05$).

In 17 patients the infusion rate was held constant over 96.3 h (range 24–243 h). During the period of constant infusion 13 of these patients showed a decrease in serum midazolam concentration up to 52% (SD ± 22%) in relation to the initial serum midazolam level measured about 12 h after onset of treatment, 2 patients showed an increase of serum midazolam concentration and in 2 patients the level remained unaltered.

In order to achieve paired data of pharmacokinetic parameters at the beginning and after a longer period of continuous midazolam infusion we measured serum midazolam concentrations between 24–48 h as well as after 4–5 days after the beginning of a continuous midazolam infusion in 11 of the patients (Table 1).

There was no significant correlation between the serum midazolam concentration and the midazolam infusion rate with respect to all data ($r = 0.354$). However, splitting the data into two groups (0–72 h and > 72 h) correlation was significant: early group $r = 0.423$, $2P < 0.05$; late group $r = 0.458$, $2P < 0.01$.

Average infusion rate was increased from 132 µg/kg per hour [SD ± 56] at beginning of treatment to 196 µg/kg per hour [SD ± 146] after 4–5 days. Mean serum concentration decreased from 513 µg/l (range 124 µg/l–1093 µg/l, SD ± 327 µg/l) to 330 µg/l (range 58 µg/l–1240 µg/l, SD ± 353 µg/l). Midazolam clearance increased in relation to the duration of midazolam therapy ($r = 0.544$, $2P < 0.01$) (Fig. 2).

This increase could also be demonstrated comparing the intrapatient variation of midazolam clearance between the first 24–48 h and the clearance at 80–120 h of midazolam therapy (Table 1). In the early phase of midazolam therapy the clearance was 5.8 ml/kg per minute [SD ± 3.8] and increased significantly by 133% to 13.6 ml/kg per minute [SD ± 10.6] in the late phase ($2P < 0.05$).

During the first 24–72 h of midazolam therapy the sedation score was significantly correlated to the serum midazolam concentration ($r = 0.76$; $P < 0.001$) (Fig. 3).

The desirable sedation score of 15–18 points could be achieved during this time period at a serum concentration between 100–500 µg/l with an infusion rate of 100–400 µg/kg per hour.

Beyond 72 h there was no longer a correlation between the sedation-score and serum midazolam concentration ($r = 0.09$). During weaning from the ventilator the midazolam infusion was reduced in steps of 100 µg/kg per hour. Eleven of the 24 patients were extubated whilst still receiving midazolam infusion at a mean rate of 173.5 µg/kg per hour [range 50–300]. At the time of extubation serum concentrations ranged between 195 µg/l and 384 µg/l at a mean sedation score of 16.3 points (SD ± 1.5 points). No respiratory complications (i.e. apnoea) occurred. One patient showed a higher serum concentration of 772 µg/l at an infusion rate of 200 µg/kg per hour. He, too, had no respiratory problems after extubation.

Discussion

To maintain low levels of stress, pain and fear, artificially ventilated paediatric patients need special requirements of the nursing staff and parents [18], but additional pharmacological treatment is also necessary [4, 7, 11, 24]. Especially post-operative infants and children need reliable analgesia and sedation for better recovery [1, 14, 25].

The new water-soluble 1,4-benzodiazepine, midazolam, seems to guarantee reliable sedation and anxiolytic action. Studies in adults and children have shown that midazolam given by continuous infusion causes no significant changes in blood pressure, heart and respiration rate [3, 5, 8, 13, 21, 24]. Only rapid intravenous administration of midazolam can induce a considerable drop in blood pressure. It has anxiolytic and sleep-inductive effects. As a continuous intravenous infusion it can be easily adjusted because of it's short half-life of 1.5–2.5 h [9, 22].

Until recently, midazolam was used in children mostly for premedication and induction of anaesthesia [5, 11, 23], and as a basic sedative and amnesic drug before painful investigations [21]. In 1986, Booker et al. [4] first described the administration of midazolam as a continuous intravenous infusion in the paediatric intensive care unit. They found that an intravenous infusion of midazolam provides effective sedation which is superior to that provided by sedative regimens based upon intermittent administration. Our aim was to establish a treatment, which promises a good basic sedation for the intensive care unit, partly in combination with fentanyl analgesia, without considerable side-effects.

The evaluation of the sedation-score showed that reliable sedation can be achieved at a midazolam infusion rate of 100–400 µg/kg per hour and at a serum midazolam concentration between 100–500 µg/l. We found a weak correlation between infusion rate and serum midazolam concentration, so that the dosage of midazolam should be adjusted by the clinical aspects of the child. Lloyd-Thomas and Booker [16] took blood samples during 24 h treatment of midazolam infusion in eight children after cardiac surgery and found a high correlation ($r = 0.87$), probably due to the short period of treatment. In combination with fentanyl the midazolam infusion rate could be held at a lower level. Fifteen patients received a combination of midazolam as a sedative and fentanyl as an analgesic drug. These patients were suffering from pain after cardiac surgery and needed effective analgesic treatment, because pain is intimately associated with a potentially dangerous stress response [25]. Controlled studies have demonstrated reduced morbidity and mortality rates in adults and during childhood when adequate analgesia is provided [1, 9, 14]. Continuous intravenous fentanyl infusion had been shown to provide satisfactory analgesia [9, 25, 26]. Our patients received a fentanyl infusion for a mean of 76 h (range 30–188 h). Under continuous analgo-sedation their condition became stable and sedation could be continued with midazolam infusion alone.

Being sedated with midazolam alone the infusion rate had to be raised up to 200% during 120 h to hold a constant serum midazolam level due to an increasing midazolam clearance. Changing of the total body clearance in children during long-term sedation has not been previously described. In contrast, Michalk et al. [19] described nearly constant serum concentrations of midazolam in adults during 72 h of intravenous infusion: at the beginning of treatment 215 µg/l (SD ± 61 µg/l) and at the end 199 µg/l (SD ± 93 µg/l). The mean total body clearance was 7.12 ml/kg per minute.

The reason for the increase of midazolam clearance may be either an increase of the distribution volume or an increase of the hepatic clearance due to an enzyme induction by midazolam or by increasing hepatic blood flow during a treatment over a longer period.

Patients with impaired liver function have to be treated carefully. The impaired hepatic metabolism is responsible for high serum midazolam concentrations and a reduced midazolam clearance. Lloyd-Thomas and Booker [16] reported on two patients with impaired hepatic metabolism with serum midazolam concentrations of 3000 µg/l. These extremely high serum concentrations obviously did not induce a deeper sedation.

In 1988 Fahnenstich et al. [10] reported on four cases of cerebral convulsions after intravenous midazolam administration. They injected a high dose of midazolam (0.29–0.4 mg/kg) to premature babys, who all had cerebral complications. One other case of convulsions in children after intravenous injection is reported in literature [20]. This full-term baby received 0.3 mg/kg midazolam as an intravenous bolus injection. All these patients received a higher dose than recommended and they all had also cerebral complications.

If children receive a single bolus injection of midazolam, 0.2 mg/kg should not be exceeded and the intravenous injection has to be given over a period of some minutes. Patients with cerebral complications should not receive more than 0.1 mg/kg as a bolus injection [2].

Our patients were older than those reported by Fahnenstich et al. [10] and v. Mühlendahl [20]. Diament and Stanley [6], Halloway et al. [11] and Otte et al. [21] also reported on the intravenous bolus application of high midazolam dosages (0.3–0.4 mg/kg) in children between 7 days and 18 years but observed no complications. They found that the intravenous application of midazolam is

safe as long as the medication is injected over 1–3 min period and the patient is monitored carefully.

It is of utmost importance to point out that midazolam is not an analgesic drug [22]. If children are suffering from pain after surgery or undergoing painful investigations, a combination with an analgesic drug is necessary and must be provided [17, 18, 25]. v. Mühlendahl [20] and Otte et al. [21] used midazolam in combination with local anaesthesia, but they both described motor restlessness, indicating insufficient analgesia.

In conclusion, this study shows that reliable sedation of artificially ventilated infants and children can be established by continuous intravenous infusion of midazolam. Combination with fentanyl provides satisfactory analgesia if necessary. The midazolam infusion rate has to be increased during therapy according to an increase in midazolam clearance. Caution should be exercised in patients with impaired liver function.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft, Grant No. Ro-799/1-1

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