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Midazolam Plasma Concentrations in Children after Anesthetic Premedication for Short Routine Cases - An Observational Study

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Abstract

Introduction: Midazolam is commonly used in pediatric patients as a sedative and anxiolytic before the induction of anesthesia. Little is known about clinically resulting plasma levels in the setting of short procedures. Aim of this study was to compare plasma levels of Midazolam at the end of intervention with the corresponding levels at the time point of anesthesia induction for short procedures. The hypothesis was that a certain percentage of patients have higher levels at the end of the procedure.

Method: Twenty pediatric patients between the age of 2 and 8 years, scheduled for short (< 30 minutes) surgical procedures requiring general anesthesia were prospectively enrolled. They all received 0.5 mg/kg Midazolam rectally (maximum dose 10 mg) 30 minutes before transport to the operating room. After induction of the general anesthetic, a first blood sample was obtained, and plasma midazolam levels were determined. A second sample was collected at the end of the procedure.

Results: Three patients had to be excluded from the study, because no midazolam plasma levels were detectable. Midazolam plasma levels were 0.38 ± 0.19 µmol/l in the first blood samples, and 0.2 ± 0.12 µ mol/l at the second time point. In three patients (17.6 %), the midazolam plasma level was higher at the end of the procedure than at the induction of anesthesia.

Conclusion: A considerable percentage of patients displayed a higher plasma level of Midazolam at the end of the procedure (compared to the moment of anesthesia induction). This may have implications for the post-operative period.

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Introduction

Midazolam is a standard drug for both adult and pediatric patients that is often used to achieve anxiolysis and sedation before general anesthesia[1,2]. The well-known drug has a multi-decade long track record and is also commonly used for sedation during procedures or in combination with regional anesthesia. Given as an adjunct before a general anesthetic, Midazolam reduces stress and anxiety, and facilitates better cooperation during the anesthesia induction for pediatric patients. At the very least, it helps reduce the children's resistance and decreases recall[1].

Midazolam is a very fat-soluble and consequently quick-acting, and also comparably short-acting benzodiazepine[3]. The standard dosage for premedication of children before general anesthesia is 0.5 mg/kg of midazolam either poor rectally, usually with a maximum dose between 10 and 20 mg[1,2]. An attempt is usually made, to administer it about 30 minutes

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before the patient is transported to the operating room. This routine clinical practice has proven to work mostly well on a daily basis. Surprisingly, there are only very few clinical studies that investigate achieved plasma levels of midazolam when the patients reach the OR in this setting[3-6]. Even less is known about the trajectory of plasma levels and their values at the end of the procedures. A potential issue arises from the fact that midazolam has an elimination half-life of 90 to 150 min with a corresponding duration of action. Especially for short interventions, the question arises, whether a prolonged post anesthesia care unit (PACU) stay may be secondary to elevated midazolam plasma levels.

In the present study, midazolam plasma levels were obtained from elective pediatric patients at the induction of anesthesia and at the end of the procedure. Our working hypothesis consisted of the prediction, that during short interventions, some individuals would have higher plasma levels of midazolam at the end of the surgery compared to the level at anesthesia introduction. The comparison of the midazolam plasma levels at these two time points was the primary endpoint of the study.

Methods

This study according to the Helsinki declaration was conducted prospectively with the approval of the local ethics committee (Ethikkomission des Kantons Thurgau, Münsterlingen, Switzerland, KEKTGAE 2014/16) and after registration with the German Clinical Trials Register (www.drks.de; DRKS00008736). The parents of the respective patients were informed before hand and gave their written consent.

Children (patients) who fulfilled the inclusion criteria (Table 1) received 0.5 mg per kilogram body weight of midazolam rectally (with a maximum dose of 10 mg; Dormicum® 1 mg/ml, Roche Pharma, Reinach BL, Switzerland) as an anesthetic premedication. The orders were triggered from the operating theater during the evolution of the daily program and at the discretion of the responsible anesthesia coordinator, who was blinded with regards to the study taking place. The order was carried out by the responsible nursing staff of the surgery center.

Table 1: Inclusion and exclusion criteria for including patients.

Inclusion criteria	Exclusion criteria
Elective surgery under general anesthesia	Allergy and / or hypersensitivity to benzodiazepines
Planned maximum procedure duration of 30 min	Severe respiratory insufficiency
Age 2 - 8 years	Myasthenia gravis
Preoperative Midazolam 0.5 mg/kg indicated as per the institution's guidelines (maximum dose 10 mg)	Sleep apnea syndrome
Written consent of the parents	Compromised renal and / or liver function
	Pre-existing psychiatric disease
	Long-term medication with antimycotics, virostatics, HIV protease inhibitors, macrolides, rifampicin, calcium antagonists, antihistamines, St John's wort.
	Consumption of grapefruit juice on the day of or the day before surgery
	Gastrointestinal disease with impairment of absorption
	Additional administration of midazolam before the second time point of blood sampling for midazolam level

The patients adhered to a fasting period of 6 hours for solid food and 2 hours for clear liquids before the start of the anesthetic. According to the standards for pediatric anesthetics at the Institute for Anesthesia and Intensive Care Medicine (IfAI) at our hospital (Kantonsspital Frauenfeld), the sedative premedication was administered 30 minutes before the patient was called to the operating room, and the time point was documented.

The patients were transported to the operating room at the discretion of the responsible anesthesiologist. The aim was to create the shortest possible waiting time for the patient in the operating theater, while also maintaining an efficient work flow with minimal operating room down time. The arrival of the patient to the operating room was routinely noted on the anesthesia record. Parents were not present during anesthesia induction.

For the purposes of the study, the sedation depth was assessed by means of a verbal analog scale (VAS 0-10; 0 = fully awake, 10 = not arousable) by one of the study coordinators and also by the responsible nurse from the surgery center at the time when the patient arrived in the operating room. The induction of anesthesia was performed via inhalation of sevoflurane in accordance with the standard procedures at the IfAI and under minimal monitoring with pulse oximetry. After the child was asleep, the other standard monitoring components (ECG, NIBP) were placed, initial values were recorded, before peripheral intravenous (PIV) access was obtained either on the back of the hand or the forearm. Via this PIV, 3 ml of the patient's blood were collected in a laboratory serum (EDTA) tube and the time point was recorded (blood sample 1, BS1).

The further course of the anesthetic and procedure was performed according to the institute's standard procedure, as a balanced anesthesia with sevoflurane and the supplementation of opioids. No regional blocks were performed, no further adjuncts given. At the end of the surgery, before emerging from the anesthetic, a second blood sample (3 ml, serum (EDTA) tube) was obtained (if possible via the existing PIV cannula, and if unsuccessful via a separate iv puncture). The time point of this blood sample was recorded as BS 2.

The two serum tubes were labelled with the patient study participation number and properly stored in the central laboratory of the Kantonsspital Frauenfeld. After completion of the study, all the samples were sent to the Institute of Clinical Chemistry of the University of Zurich (http://www.usz.ch) and midazolam as well as the midazolam metabolite 1-OH-midazolam plasma levels were determined by means of liquid chromatography-mass spectrometry (LC-MS). After addition of stable-isotope labeled internal standards, samples were centrifuged. Twenty micro liters of the clear supernatant was submitted to the analysis using a turbulent flow online extraction system. As extraction column, a Cyclone column (Thermo Fisher, Reinach, Switzerland; 50 × 0.5 mm) was used, as analytical column, an Uptisphere C18 (125 × 2 mm). The mobile phases consisted of 10

mM ammonium acetate in water+0.1% formic acid and 10 mM ammonium acetate in methanol/acetonitrile 50/50 (v/v)+0.1% formic acid. Calibration was done using an in-house prepared six point calibration curve. The method is validated and has an imprecision of less than 5.3%. The quantification limit is at 0.01 mcmol/l.

On the first day after the procedure, a study coordinator either visited the patient's parents in person or contacted them by phone in order to obtain their assessment of the sedation depth of their child and their own satisfaction with the preoperative sedation level on a verbal analogue scale (VAS; 0 - 10; 0 = completely awake, or absolutely dissatisfied respectively, 10 = not arousable, or completely satisfied respectively).

Statistics

All data on the midazolam plasma levels are presented in descriptive fashion. The correlation of the assessment of the degree of sedation was determined with a correlation Z-test ($p < 0.05$ as significance level). The relationships between the plasma level at the time of induction of the anesthetic with the degree of sedation and parent satisfaction were calculated by simple regression ($p < 0.05$ as significance level). The data were analyzed using Microsoft Excel 2010 (Microsoft, Redmond, USA) or Statview 5.0.1. (SAS Institute, Cary, USA).

Results

Twenty patients were enrolled in the study. Three patients had to be excluded from the statistical evaluation, since neither midazolam itself nor the midazolam metabolite 1-OH-midazolam was detectable in either of the two tested blood samples, which indicates that the rectal premedication was not successful in these patients. The demographic data of the patients are summarized in Table 2. The average rectally administered dose of Midazolam was 9.2 ± 1.0 mg. The average time from the midazolam application to the time point of the first blood sample (BS 1) at anesthesia induction was 39 ± 12 min, the surgical procedure lasted 30 ± 13 min, the average time from the midazolam application to the second blood sampling (BS 2) at the end of the procedure was 68 ± 17 min.

Table 2: Demographic data (mean ± standard deviation).

Gender	**F - M**	**8-9**
Age	years	5.5 ± 1.5
Size	cm	110 ± 10
Weight	kg	20.7 ± 5.7

The sedation level of the patients before anesthesia induction as indicated by the investigator was 6.3 ± 1.6, while the responsible RN in the surgery center scored it at 6.4 ± 1.4, and of the parents at 5.4 ± 2.5. These values all correlated well (correlation coefficients 0.8 or higher) and statistically significant ($p = 0.019$ or lower) with each other. In the first blood sample (BS1), the midazolam plasma levels were 0.38 ± 0.19 µmol/l, and at the time point 2 (BS2) at the end of the procedure were 0.2 ± 0.12 µmol/l. In three patients (17.6%), the midazolam plasma level was higher at the end of the operation than at the induction of anesthesia (Figure 1).

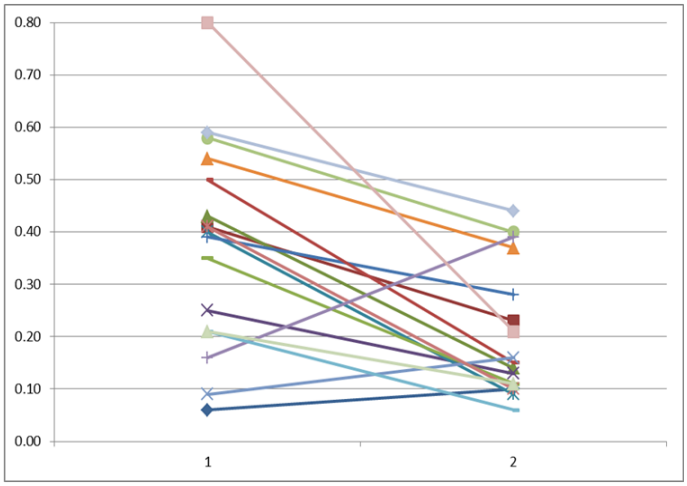

Figure 1: Midazolam plasma concentrations (µmol / l). 1 = anesthesia introduction, 2 = end of surgery.

Parent satisfaction with midazolam premedication was weakly ($r^2 = 0.472$), but statistically significant ($p = 0.0195$) associated with the plasma levels at the time BS 1.

Discussion

In this study, we compared midazolam plasma levels of children undergoing short elective surgical procedures at the time of anesthesia induction with the levels at the end of the surgical procedure. The children routinely received a standard dose of midazolam rectally roughly 30 minutes before their procedure in the surgery center. The primary outcome of our study was the finding, that a significant number of patients displayed midazolam plasma levels at the end of the procedure that were higher than their respective levels at anesthesia induction.

Some studies have shown mixed results when midazolam as a preoperative sedative was compared to alternatives such as alpha-2 agonists, ketamine, or melatonin[7-9]. While that has led to some authors questioning the role of Midazolam as a preoperative anxiolytic, both history and current practice clearly indicate that midazolam is still the drug of choice in this setting for children, adolescents and adults alike[1,2]. In adults, the standard doses usually range between 7.5 and 15 mg po, while children receive comparatively high doses (0.5 mg/kg, up to 20 mg total)[1,2,10].

The pediatric patients in our study received a moderate dose of 0.5 mg per kilogram body weight rectally (with a maximum dose of 10 mg). As a result, the sedative effects that we recorded pre-operatively were in the moderate range. The sedative effects of midazolam also appear to taper as the patients get older, and are remarkably low (and/or more difficult to objectify) in older children or adults when they arrive in the operating room, or immediately before anesthesia induction. For example, Brosius and Bannister reported an initial BIS score of 92 in adolescents pre-medicated with 20 mg Midazolam po and only 40% of the patients demonstrated a measurable sedation effect according to the OAA/S scale immediately before anesthesia induction. 4 One possible explanation could be that the level of awareness and attentiveness was secondary to the fact that the transport to the operating theater in conjunction with the start of the anesthesia procedure with placement of monitoring electrodes and devices probably resulted in a great amount of mental

stimulation and nervousness. In the quieter and less stimulating atmosphere of a pharmacodynamics study, Misaka et al. used quantification of eye movements and VAS to demonstrate sedative effects even at sub-therapeutic doses of midazolam[3]. Despite this, the parents in our study reported an adequate success for the sedative effect of midazolam preoperatively. The extent, to which varying expectations for the effects of the sedative and anxiolytic medication play a role in this, remains unanswered.

In addition to the desired preoperative anxiety suppression, midazolam has the potential to also influence the patient's response to anesthetic drugs during the procedure, and possibly delay the emergence from anesthesia at the end of the operation. Brosius and Bannister, however, found no evidence of either in their study; They concluded that their anesthetic management (sevoflurane-based) did not lead to a prolonged emergence in the midazolam group compared to a placebo group[4]. Despite this, many anesthesiologists are likely to wonder whether the preoperative midazolam application could play at least a partial role in cases of unexpected, prolonged awakening of their patient at the end of a short intervention. This question cannot be conclusively assessed from our data, because we did not fully standardize the intraoperative anesthetic management and consequently also did not quantify the emergence temporally.

Nevertheless, the not insignificant percentage of patients in which the midazolam plasma levels increased during the short procedure, would support the above-mentioned notion. The proportion of patients in our cohort with a higher midazolam plasma level at the end of the operation is similar to the one described by Steiner, et al[11]. They investigated 22 adult patientsthat underwent short gynecological procedures (approximately 20 minutes), and found in 5 patients (27%), plasma levels to be higher at the end of the operation than during the anesthesia induction. This was in contrast to the 24 patients that underwent longer surgical procedures (approximately 80 minutes), in which none displayed higher midazolam levels at the end of the surgery. The cases, where the midazolam levels rose during the procedure, indicate that the absorption of the drug was not completed at anesthesia induction. In the setting of an oral application, this could at least partially be attributed to delay gastric emptying due to stress. We are not aware of any corresponding data for the rectal application and absorption.

The large fluctuations of the measured plasma levels amongst individual patients could also be caused by the rectal administration of the drug. Rectally administered drugs are usually very effectively absorbed, partially bypassing the liver and avoiding a first-pass effect. This can be explained by the rectal venous blood supply: the upper part of the rectum drains into the portal system, whereby the lower part flows into the systemic circulation[12]. Otherwise, it is difficult to prevent, let alone quantify that a portion of the medication is passed without absorption. Lastly, there appear to be marked inter individual differences in the rate of metabolism of midazolam. Additionally, a comparative study with participants from five different ethnic Chinese tribes, showed vastinter-tribal differences in metabolism of midazolam[13].

In accordance with these aspects, our study demonstrated a fairly low objective sedation effect, while the subjective satisfaction of the sedative effects was deemed adequate by the parents. The optimal timing for the administration of midazolam preoperatively remains unclear and might be individually different. We routinely met our target for the administration of Midazolam 30 minutes before the transport to the operating room. The midazolam plasma levels displayed a large variance and hardly allowed conclusions as to when exactly the maximum level was reached. We demonstrated that for short interventions, the plasma level at the end of the procedure may be higher than the one measured at the time of anesthesia induction. This is remarkable for a drug that is solely used to achieve an effect in the preoperative phase. It may also confound the anesthesiologist's concept and judgement, because for the given patient it is not really predictable. A substance such as remimazolam with a significantly shorter half-life could alleviate the issue and produce a temporally more predictive sedation trajectory[14].

There are limitations to our study setup. In our institution, midazolam is usually given via the oral route. For this study, the patients received the drug rectally, because despite the common practice of applying the intravenous formulation orally, it is an off-label indication in Switzerland. The fact that neither midazolam nor its metabolite could be detected in the blood of 3 patients can be an indication that the rectally administered drug was immediately pushed out. The extent to which rectal application route affected the satisfaction of the parents was not specifically recorded. The number of patients in our study and the fact that we draw blood only at two clinically relevant time points did not allow to further quantify the inter subject variability of our findings nor any pharmacokinetic modeling. Furthermore, it would have been interesting to correlate the midazolam plasma level with time it took from the end of surgery to fully awaken and emerge from the anesthetic. For this purpose, however, we would have had to fully standardize and protocolize the intra-operative anesthetic management.

The rectal application of midazolam prior to transport to the operating room in pediatric patients for short surgical procedure, can result in higher concentrations at the end of the operation than before anesthesia induction. This needs to be factored into the clinical decision-making process. A more reliable, short-acting anxiolytic agent would be desirable.

Ethical approval: This study was conducted prospectively with the approval of the local ethics committee (Ethikkomission des Kantons Thurgau, Münsterlingen, Switzerland, KEKTGAE 2014/16) and after registration with the German Clinical Trials Register (www.drks.de; DRKS00008736). The parents of the prospective patients were informed beforehand and gave their written consent.

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Conflicts of interest: No conflicts of interest declared.

References

1. Johr, M. Midazolam for premedication in pediatric patients: pros and cons debate. (2013) Anaesthesist 62: 171.
Pubmed | Crossref | Others
2. Rosenbaum, A., Cain, Z.N., Larsson, P., et al. The place of premedication in pediatric practice. (2009) Pediatr Anesth 19(9): 817-828.
Pubmed | Crossref | Others
3. Misaka, S., Uchida, S., Imai, H., et al. Pharmacokinetics and pharmacodynamics of low doses of midazolam administered intravenously and orally to healthy volunteers. (2010) Clin Exp Pharmacol Physiol 37(3): 290-295.
Pubmed | Crossref | Others
4. Brosius, K.K., Bannister, C.F. Midazolam premedication in children: a Comparison of two oral dosage formulations on sedation score and plasma midazolam levels. (2003) Anesth Analg 96(2): 392-395.
Pubmed | Crossref | Others
5. Malinovsky, J.M., Populaire, C., Cozian, A., et al. Premedication with midazolam in children. Effect of intranasal, rectal and orally routes on plasma midazolam concentrations. (1995) Anesthesia 50(4): 351-354.
Pubmed | Crossref | Others
6. Schwagmeier, R., Alincic, S., Striebel, H.W. Midazolam pharmacokinetics following intravenous and buccal administration. (1998) Br J Clin Pharmacol 46(3): 203-206.
Pubmed | Crossref | Others
7. Bozkurt, P. Premedication of the pediatric patient - anesthesia for the uncooperative child. (2007) Curr Opin Anaesthesiol 20: 211-215.
Pubmed | Crossref | Others
8. Impellizzeri, P., Vinci, E., Gugliandolo, M.C., et al. Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients. (2017) Eur JPediatr 176: 947-953.
Pubmed | Crossref | Others
9. Kumari, S., Agrawal, N., Usha, G., et al. Comparison of Oral Clonidine, Oral Dexmedetomidine, and Oral Midazolam for Premedication in Pediatric Patients Undergoing Elective Surgery. (2017) Anesth Essays Res 11(1): 185-191.
Pubmed | Crossref | Others
10. Storm, S. Preoperative evaluation, premedication, and induction of anesthesia in infants and children. (2012) Curr Opin Anaesth 25(3): 321-325.
Pubmed | Crossref | Others
11. Steiner, C., Steurer, M.P., Mueller, D., et al. Midazolam plasma concentration after anesthesia premedication in clinical routine - an observational study: Midazolam plasma concentration after anesthesia premedication. (2016) BMC Anesthesiol 16(1): 105.
Pubmed | Crossref | Others
12. de Boer, A.G., Moolenaar, F., de Leede, L.G., et al. Rectal drug administration: clinical pharmacokinetic considerations. (1982) Clinical Pharmacokinet 7(4): 285-311.
Pubmed | Crossref | Others
13. Guo, T., Mao, G.F., Xia, D.Y., et al. Pharmacokinetics of midazolam tablet in different Chinese ethnic groups. (2011) J Clin Pharm Ther 36(3): 406-411.
Pubmed | Crossref | Others
14. Wesolowski, A.M., Zaccagnino, M.P., Malapero, R.J., et al. Remimazolam: Pharmacologic Considerations and Clinical Role in Anesthesiology. (2016) Pharmacotherapy 36(9): 1021-1027.
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