Scientific paper

A Study of Midazolam Plasma Concentrations in Patients Undergoing Conscious Sedation

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Abstract

We studied midazolam plasma concentrations in patients undergoing middle ear surgery (MES) in local anesthesia and sedation. This study was based on the clinical measurement of the level of sedation and determination of the sedation dose of midazolam. For optimal level of sedation for this type of surgery we suggest the midazolam plasma concentrations with median of 0.03 mg L^{-1} and range from 0.01–0.10 mg L^{-1}. This can be contrasted to the other studies where considerably higher plasma concentrations of midazolam (0.2 mg L^{-1}) were proposed (S. Michalk et al., Intens. Care Med. **1988**, *15*, 37–41). Despite low midazolam concentrations the level of sedation was adequate.

Keywords: Midazolam, sedation, adults, surgery: middle ear, chromatography, mass spectrometry

1. Introduction

Midazolam is a short-acting benzodiazepine, which is used as an oral or intravenous *(iv)* anxiolytic, sedative and hypnotic drug.[1] A sedative drug decreases activity, moderates excitement and calms the recipient, whereas a hypnotic drug produces drowsiness and facilitates the onset and maintenance of a state of sleep that resembles natural sleep in its electroencephalographic characterictics.[2] Benzodiazepines have sedative and hypnotic effect and cause a dose related depression of the central nervous system (CNS). Their effects range from mild daytime sedation to full general anaesthesia, depending on the dosage used and the preparation employed.[3]

Chemistry. The term benzodiazepine refers to the portion of the structure composed of a benzene ring fused to a seven-membered diazepine ring. Since all the important benzodiazepines contain a 5-aryl substituent and a 1,4-diazepine ring, the term has come to mean the 5-aryl-1,4-benzodiazepines.[2] Midazolam (8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a] [1,4] benzodiazepine) is an imidazobenzodiazepine derivative (Fig. 1). The nitrogen in the imidazole ring attached to positions 2 imparts to the molecule a higher basicity and hence water solubility, and the methyl group on position 1 to shorter duration of action than other injectable benzodiazepine drugs. Midazolam can be prepared as a water soluble salt with hydrochloric, maleic or lactic acid and is commercially available in a stable aqueous solution as the hydrochloride salt.[3]

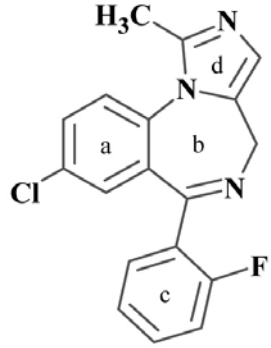

Figure 1. Structural formula of midazolam: (a) benzene ring, (b) 1,4-diazepine ring, (c) 5-aryl substituent, (d) fused imidazole ring

Pharmacological properties. Benzodiazepines are agonists of GABA (γ-amino acid butyric acid) receptor that is coupled to the chloride channel. By blocking the chloride channel neurons become hypopolarised, refractory and signal transduction is impaired. The most prominent effects of benzodiazepines actions on the CNS are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia and anticonvulsant activity.[2]

Middle ear surgery (MES) is a procedure where it is highly desirable to keep the patient conscious to such extent that they can collaborate with the surgeon. To reduce various discomforts during surgery under local anesthesia, adequate preparation for anesthesia and appropriate sedation are necessary.[4] Oral or *iv* sedation with midazolam is well established in clinical practice. Moreover, benzodiazepines have advantage of induction of anterograde amnesia.[5] Following oral administration of midazolam peak plasma concentrations are found after 60 min, while after *iv* administration the peak plasma concentration occurs after few minutes. The systemic bioavailability following oral administration has been shown to be between 35 and 44% after a 15 mg dose, although this is reduced with a dose of 7.5 mg.[6] Following *iv* injection there is rapid uptake of midazolam into the brain and other highly perfused organs which is followed by a phase of redistribution into tissues that are less well perfused, especially muscle and fat. The biological half life ($t_{1/2}\beta$) of midazolam is 2–2.4 h, and the apparent volume of distribution (V_D) at steady state is 1.1 L kg^{-1}. V_D is the theoretical volume of body fluids over which the total drug administered should have been distributed in order to achieve the concentration measured in the plasma.[7, 8] This indicates that midazolam is a highly lipophilic substance.

The main advantage of *iv* application of midazolam is rapid titrability to the desired level of sedation and avoidance of the hepatic first-pass effect. However, the use of oral midazolam for premedication before the procedure, is important to induce anterograde amnesia.[9]

It was demonstrated that measuring midazolam plasma concentrations during sedation has been explored in only few clinical trials,[10,11] and up to our knowledge none of them evaluated the plasma concentrations of midazolam during MES under local anesthesia and sedation. The aim of this study was to determine plasma concentrations of midazolam during moderate (conscious) sedation during MES under local anesthesia and to investigate the relationship between the additional dose of midazolam and measured plasma concentration of midazolam after that. We analysed also the relationship between measured plasma concentrations of midazolam and clinical measurements of the depth of sedation.

Organisation of this article is as follows. Section 2 describes clinical protocol and applied analytical technique, section 3 contains results, while discussion is in section 4.

2. Materials and Methods

2. 1. Patients

Thirty one patients with American Society of Anesthesiologists[12] (ASA) physical status score of 1 or 2 who were scheduled to undergo elective MES were included in a prospective trial of sedation during local anesthesia. ASA score 1 or 2 refers to relatively healthy patients. The study was approved by the national ethics committee and informed consent was obtained from all patients. Elective MES procedures were performed at the Department of Otorhinolaryngology and Cervicofacial Surgery in University Medical Centre Ljubljana (characteristics of the patients are presented in Table 1).

The patients' mean age was 45 years (range 16–70); they had otosclerosis or chronic otitis media and were scheduled to undergo stapes surgery or tympanoplasty. Exclusion criteria for the study were: a history of chronic use of analgesic or sedative agents or both; a history of alcohol abuse; language barrier or mental disorder; allergy to any of the study medications; and obstructive sleep apnoea.

Table 1: Characteristics and surgical data of the patients included in the study*.

Parameter	Midazolam group (n = 31)
Age (yr)	45 ± 10
Weight (kg)	74 ± 16
Height (cm)	167 ± 9
Sex (Female/Male) (n)	20 / 11
ASA[a] physical status (1/2) (n)	19 / 12
Operation: tympanoplasty (n)	10
Operation: stapes surgery (n)	21
Fentanyl dose (10/20 μg) (n)	30 / 1
Surgery time (min)	53 ± 22
Sedation time (min)	63 ± 21

* Values are mean ± standard deviation or number (n).
[a] ASA = American Society of Anesthesiologists.

2. 2. Study Protocol

Standard formulation of midazolam hydrochloride in aqueous solution (Midazolam Torrex 1 mg mL^{-1}) was administered intravenously (as a slow *iv* injection over 15 s into a venous cannula inserted into the peripheral vein of the lower arm), with a starting dose of 0.02 to 0.05 mg kg^{-1} and a maintenance dose of 0.01 to 0.02 mg kg^{-1}. To evaluate the level of sedation, the bispectral index score[13] (BIS) and the Ramsay sedation score[14] (RSS) were used. BIS is integrated electroencephalogram estimated level of sedation in the range from 0 (no brain activity) to 100 (fully awake patient). RSS is clinically estimated level of sedation where at level 1 the patient is just anxious and at level 6 there is no response. The doses of midazolam were

titrated to the level of conscious sedation (BIS 70 to 80, RSS 3 to 4). Sedation was discontinued just before the end of surgery.

Blood samples (5 ml) were collected from a forearm vein in Vacutainer tubes (without additives). Blood was collected 10 and 20 min after application. Plasma samples were stored frozen at –20 °C until assayed.

Patient's preparation for the operation, local anesthesia, operative protocol with monitoring of vital signs and BIS, and postoperative recovery was the same for all the patients included in the study.[15, 16]

2. 3. Gas Chromatograph-Mass Spectrometry (GC-MS) Analysis of Midazolam

Standard compounds midazolam maleate and prazepam were purchased from Sigma-Aldrich (Steinheim, Germany), phosphate buffer was prepared by dissolving 400g K_2HPO_4 p.a. Merck (Darmstadt, Germany) in one L of deionized water, 1-chlorobutane was from Merck (Hohenbrunn, Germany).

An 0.5 mL aliquot of patient's serum was spiked with prazepam (internal standard, final concentration was 0.5 mg L^{-1}), alkalinized by adding an equal volume of phosphate buffer and extracted with 4 mL of 1-chlorobutane. 3 mL of organic solvent were evaporized with nitrogen and the residue dissolved in 50 µL of methanol before analysis.

Gas chromatograph HP 6890 and mass selective detector (MSD) 5973 from Hewlett Packard were used for quantitative analyses (Palo Alto, CA, USA). The compounds were separated on 30 m HP-5MS ((5%-Phenyl)-methylpolysiloxane) fused-silica capillary column (0.25 mm i.d., 0.25 µm film thickness). The temperature programme was: 60 °C (2.30 min), ramped 100 °C min^{-1} to temperature 260 °C, second ramp was 8 °C min^{-1} to final temperature 300 °C (2.20 min). Temperatures of injector, transfer line, ion source and quadrupole were 275 °C, 280 °C, 230 °C and 150 °C, respectively. The flow rate of helium was 1 mL min^{-1}. One µL of sample was injected in splitless mode.

During development of method mass spectrometer was used in electron impact scan mode enabling comparison of mass spectra obtained from standards with Pfleger-Maurer-Weber library of Mass Spectral and GC Data of Drugs, Poisons, Pesticides, Pollutants and their metabolites (Pmw_TOX3).

Quantitation was performed in selective ion monitoring mode (SIM). Original method was developed for analysis of bupivacaine in blood plasma of young children and as then only small volumes of samples were available, to obtain better sensitivity only two *m/z* values were used, molecular ion and one fragment ion. Later the method was extended to three other compounds, propofol, midazolam and fentanyl and due to their behaviour and dosage the use of two *m/z* values remained. For midazolam m/z values 325 (M^+, 47) and 310 (100) at retention time 8.5 min were used, retention time of internal standard was 8.8 min and *m/z* values were 91 (47), 296 (100). The instrument was calibrated with blank drug-free serum and standards of midazolam prepared by spiking drug-free serum and treated afterwards in the same way as the patients' samples. Eleven standards in the range from 0.01 to 0.50 mg L^{-1} were injected five times, patients´samples were measured in duplicate. The calibration curve was linear, correlation coefficient was 0.993, while RSD was in the range of 2 to 19 %. The lower limit of quantification was set to 0.01 mg L^{-1} based on common criteria for biological samples, that the method should satisfy the 20% demands on precision and accuracy at the lowest relevant concentration.

2. 4. Statistical Analysis

All statistical procedures were performed with the SPSS statistical software, version 10.0 for Windows. Data were presented as means and standard deviations (SD).

3. Results

3. 1. Vital Parameters and the Depth of Sedation

Vital physiological parameters (heart rate, systolic blood pressure and oxygen saturation), end-tidal carbon dioxide, and respiratory rates during the induction and

Table 2: Intraoperative vital parameters during sedation with midazolam*.

Parameter	Midazolam group (n = 31)
HR (beats min^{-1}) at 1 min[a]	85 ± 9
HR at 10 min	84 ± 10
HR at 20 min	83 ± 11
HR at 30 min	83 ± 11
SBP (mmHg) at 1 min[b]	135 ± 14
SBP at 10 min	128 ± 13
SBP at 20 min	124 ± 11
SBP at 30 min	125 ± 12
O_2 saturation (%) at 1 min	99 ± 1
O_2 saturation at 10 min	99 ± 1
O_2 saturation at 20 min	99 ± 1
ET CO_2 (kPa) at 1 min[c]	4.1 ± 0.6
ET CO_2 at 10 min	4.1 ± 0.8
ET CO_2 at 20 min	4.3 ± 0.6
RR (breaths min^{-1}) at 1 min[d]	20 ± 4
RR at 10 min	20 ± 5

* Values are mean ± standard deviation.
[a] HR = heart rate
[b] SBP = systolic blood pressure, 1 mmHg = 0.133 kPa
[c] ET = end-tidal
[d] RR = respiratory rate.

Table 3: BIS values, RSS, side effects and postoperative data during sedation with midazolam*.

Parameter	Midazolam group (n = 31)
BIS – before induction [a]	97 ± 2
BIS – 1 min after induction	93 ± 6
BIS – 5 min after induction	80 ± 6
BIS – 10 min after induction	77 ± 6
BIS – 15 min after induction	78 ± 4
BIS – Responds to simple commands	92 ± 5
BIS – Oriented as to person and place	94 ± 3
RSS 3 (n), *t*: 5, 10, 15 (min) [b]	15, 14, 25
RSS 4 (n), *t*: 5, 10, 15 (min)	15, 15, 6
Intraoperative apnoea (n)	0
Intraoperative movement (n)	2 (6.4%)
Postoperative nausea (n)	2 (6.4%)
Vertigo	2 (6.4%)
VAS > 3 (n) [c]	11 (35.4%)

* Values are mean ± standard deviation
[a] BIS = bispectral index
[b] RSS = Ramsay sedation score
[c] VAS = visual analog scale

maintenance periods of sedation with midazolam were within normal values (Table 2). Mean values of BIS during the perioperative period were from 97 ± 2 (before induction of sedation) to 77 ± 6 (10 min after induction of sedation). During the period of sedation the majority of patients reached the RSS 3 and 4. BIS values, the RSS, and the most frequent side effects are presented in Table 3.

3. 2. Midazolam Plasma Concentrations

The median value of midazolam plasma concentration was 0.03 mg L^{-1} (range from 0.01 to 0.10 mg L^{-1}). The mean value of midazolam *iv* dose was 6.7 ± 2.1 mg. For nine patients concentrations were higher 20 min after induction of sedation than 10 min after the induction. For twelve patients the opposite was true, while for ten patients concentrations at both times were equal. The midazolam plasma concentrations and the doses of midazolam are collected in Table 4.

4. Discussion

We studied midazolam plasma concentrations of thirty one patients undergoing middle ear surgery. Adverse effects for applied concentration range of 0.02–0.05 mg kg^{-1} were minor. For two patients the procedure was associated with vertigo. In two cases post operative nausea and vomiting was recorded. The results of this study have shown, that midazolam can be safely used for sedation in patients undergoing middle ear surgery (MES) in local anesthesia. In this study the mean midazolam plasma concentration of 0.03 mg L^{-1} correlates with bispectral index (BIS) values of 70 to 80 and the Ramsay sedation score (RSS) of 3 to 4. The determined midazolam plasma concentrations during conscious sedation in MES are a valuable aid in the determination of the midazolam dose used for conscious sedation.

The values of measured midazolam plasma concentrations in the present study has shown, that they are lower as in the previously published studies. Despite lower midazolam plasma concentrations the level of sedation was adequate. In the study of Michalk et al.[10] the measured midazolam plasma concentrations were 0.21 ± 0.06 mg L^{-1} (initial dose: 0.33 mg kg^{-1}; maintenance dose: 0.06 mg kg^{-1}). In the study of Oldenhof et al.[17] they found that midazolam plasma concentration of 0.2–0.3 mg kg^{-1} correlates with clinical evaluation of the depth of sedation with RSS value of 2–4. A midazolam plasma concentration higher than 0.1 mg L^{-1} induces an hypnotic effect in adults.[18] This higher values of midazolam plasma concentration can be explained with higher initial dose of midazolam.

Up to our best knowledge this is the first reported study of midazolam plasma concentrations for sedation in the context of middle ear surgery. The other reported studies (Michalk et al[10], Oldenhof et al[17]) refer to sedation of intensive care patients, where considerably higher concentrations were reported. It should be stressed that the intensive care patients need deeper level of sedation because of invasive threatment and consequently higher doses of midazolam.

From Table 4 it is evident that concentrations vary considerably from patient to patient. This can be attributed to individual differences of the rate of midazolam metabolism, midazolam dose and oral midazolam premedication (midazolam 7.5 mg before the operation) and amount of adipose tissue. After oral administration to adults, midazolam has been reported to be subject to saturable first-pass metabolism, with reported bioavailabilities in the range of 0.24–0.5.[19] Furthermore, after oral administration to volunteers, the formation of active metabolite significantly contributes to the sedative effect.[20] In the present study the midazolam active metabolite 1-hydroxymidazolam was not measured.

The level of sedation is a critical element of surgery in local and regional anesthesia. It remains a challenge to optimize the dosing of various sedative agents for various procedures. We believe that such studies will contribute to clinical and pharmacological aspects of sedation.

5. Conclusions

A clinical study of midazolam plasma concentrations of patients undergoing middle ear surgery revealed that for this type of procedure an optimal level was 0.03 mg L^{-1} and range 0.01–0.10 mg L^{-1}. This can be contrasted with other clinical studies, where much higher dose of 0.2 mg L^{-1} was recommended. Despite significantly lo-

Table 4: The administered doses of midazolam and corresponding midazolam plasma concentrations at 10 and 20 min after the induction of sedation.

Patient number (n)	Midazolam-initial dose (mg, mg/ kg^{-1}) [a]	Midazolam-maintenance dose (mg, mg/ kg^{-1})	Midazolam concentration (mg L^{-1}) at t = 10 min	Midazolam concentration (mg L^{-1}) at t = 20 min
1	6.0 / 0.06	1.0 / 0.01	0.03	0.04
2	4.0 / 0.07	0 / 0	0.04	0.05
3	3.0 / 0.05	2.0 / 0.03	0.02	0.03
4	4.0 / 0.05	1.0 / 0.01	0.01	0.02
5	5.0 / 0.06	3.0 / 0.04	0.06	0.07
6	3.0 / 0.05	1.0 / 0.01	0.03	0.04
7	2.0 / 0.02	3.0 / 0.04	0.03	0.04
8	3.0 / 0.03	4.0 / 0.04	0.02	0.03
9	4.0 / 0.06	1.0 / 0.01	0.02	0.04
10	8.0 / 0.10	2.0 / 0.02	0.04	0.04
11	5.0 / 0.08	1.5 / 0.02	0.03	0.03
12	3.0 / 0.05	1.0 / 0.01	0.02	0.02
13	2.0 / 0.02	3.0 / 0.03	0.04	0.04
14	3.0 / 0.04	1.0 / 0.01	0.03	0.03
15	3.0 / 0.03	1.0 / 0.01	0.02	0.02
16	3.0 / 0.03	1.0 / 0.01	0.02	0.02
17	4.0 / 0.04	2.0 / 0.02	0.02	0.02
18	2.0 / 0.02	2.0 / 0.02	0.02	0.02
19	3.0 / 0.05	2.0 / 0.03	0.03	0.03
20	5.0 / 0.08	3.0 / 0.05	0.03	0.02
21	5.0 / 0.09	1.0 / 0.01	0.07	0.06
22	5.0 / 0.06	1.0 / 0.01	0.10	0.07
23	6.5 / 0.07	5.0 / 0.05	0.07	0.06
24	7.0 / 0.07	1.5 / 0.01	0.05	0.03
25	2.0 / 0.02	0 / 0	0.04	0.02
26	3.0 / 0.03	2.0 / 0.02	0.03	0.01
27	5.0 / 0.04	2.0 / 0.01	0.04	0.03
28	3.0 / 0.05	1.0 / 0.01	0.04	0.03
29	3.0 / 0.02	2.0 / 0.01	0.04	0.03
30	4.0 / 0.07	2.0 / 0.03	0.05	0.04
31	4.0 / 0.05	4.0 / 0.05	0.04	0.02

[a] Initial dose is given in mg followed by dose per weight unit (mg kg^{-1}).

wer midazolam plasma concentrations relative to the other studies the level of sedation was adequate.

6. References

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Povzetek

Proučevali smo plazemske koncentracije midazolama pri bolnikih, ki so dobili za operacijo srednjega ušesa lokalno anestezijo z dodajanjem pomirjeval. Raziskava je temeljila na kliničnem vrednotenju učinkov uporabljenega midazolama. Najboljši učinek sedacije smo ugotovili pri mediani vrednosti midazolama 0.03 mg L^{-1}, v območju 0.01–0.10 mg L^{-1}. Ugotovitve se razlikujejo od podatkov iz literature, kjer so navajali večje plazemske koncentracije (0.2 mg L^{-1}, S. Michalk et al., Intens. Care Med. **1988**, *15*, 37–41). Kljub manjšim plazemskim koncentracijam je bila stopnja sedacije v naši raziskavi zadostna.