Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients

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Summary
The aim of this study was to determine the bioavailability and absorption kinetics of midazolam given as an intranasal (i.n.) spray. In addition, plasma concentrations of the active metabolite, 1-hydroxymidazolam, were measured to give an indication of enteral absorption. An i.v. and i.n. midazolam dose were given in a crossover study to 14 adult surgical patients. Individual uptake profiles of i.n. midazolam were estimated by numerical deconvolution. After an i.n. dose of 0.15 mg kg$^{-1}$, maximum arterial plasma concentrations were 192 (SD 48) mg litre$^{-1}$ at 14 (2) min. Uptake of midazolam was rapid and bioavailability was 83 (15) %. Formation of the 1-hydroxy metabolite after i.n. administration did not exceed that after the i.v. dose. This demonstrates that under optimal conditions absorption of midazolam via the nasal mucosa was virtually complete. In this case little midazolam was swallowed and subjected to first-pass metabolism in the liver and therefore pharmacologically important amounts of active metabolite were not produced. Routinely administering i.n. midazolam under the assumption that the bioavailability is approximately 50% (as reported previously in the literature) may lead to overdosing in some patients. (Br. J. Anaesth. 1997; 79: 575–580).

Key words Hypnotics benzodiazepine, midazolam. Pharmacokinetics, midazolam.

Midazolam given by the intranasal (i.n.) route provides a more rapid onset of effect than that after oral or rectal administration. Plasma concentrations of midazolam have been studied after i.n. administration to children. Mean bioavailability was estimated at 55% when plasma concentrations after i.n. or i.v. administration were compared in two separate groups of six children each.

In adults midazolam has also been used in adult patients to produce anxiolysis and sedation. The technique has been described for endoscopic procedures and dental treatment, and it might be particularly convenient for mentally retarded patients frightened of medical interventions such as venous cannulation.

Absorption through the nasal mucosa circumvents first-pass metabolism in the liver. If a mean bioavailability of 55% is found, what is the fate of the remaining 45%? In the cited studies, midazolam was administered as drops of aqueous solution which, unless expelled through the nostrils, are eventually swallowed. Some midazolam could therefore have been absorbed from the gastrointestinal tract. The mean bioavailability of oral midazolam in children has been estimated at 15–27%, depending on the dose. This low bioavailability is chiefly the result of extensive first-pass metabolism producing 1-hydroxymidazolam as the main metabolite.

This metabolite is almost equipotent with midazolam as a CNS depressant. Thus even if the mean bioavailability of unchanged midazolam after i.n. administration is only 55%, formation of active metabolite after intestinal absorption of the remaining dose could theoretically result in a total pharmacological effect approaching that after parenteral administration. Plasma concentrations of 1-hydroxymidazolam after i.n. administration of midazolam have not been measured.

The aim of this study was to determine the bioavailability of midazolam given as an i.n. spray. A complete crossover design allowing separate determination in each subject was possible in 14 adult surgical patients.

Patients and methods
After approval by the regional Ethics Committee and the Swedish Medical Products Agency, and after obtaining informed consent, we studied 14 patients (seven females and seven males), ASA I–II, undergoing elective breast or throat surgery. Mean age was 43 (range 28–55) yr, weight 79 (SD 12) kg and height 174 (10) cm. Patients receiving drugs with known metabolic interactions with midazolam and those with any liver dysfunction were excluded, as were patients with rhinitis or nasal obstruction.

All patients were premedicated orally with dixyrazine 25 mg. After an initial dose of fentanyl 0.1 mg, anaesthesia was induced with midazolam
0.15 mg/kg body weight given as an i.v. infusion of a 1 mg ml⁻¹ solution (Dormicum, Roche AB, Sweden) over 2 min. Anaesthesia was maintained with intermittent i.v. injections of fentanyl (total dose during surgery 0–0.15 mg), and inhalation of isoflurane (end-tidal concentration 0.54–1.1%) and 70% nitrous oxide in oxygen. Neuromuscular block was produced with vecuronium and antagonized at the end of surgery with glycopyrromine–neostigmine. Mean duration of anaesthesia was 1.4 (range 0.8–3.0) h and of surgery 1.0 (range 0.6–2.5) h. In the recovery ward, where all patients stayed for 24 h, morphine was given for pain relief. In the evening, patients were given i.n. midazolam 0.15 mg/kg body weight. The drug was administered as a standard injectable solution (Dormicum) of 5 mg ml⁻¹ with a spray bottle, with repeated sprayings alternating between nostrils. The spray bottle delivered a fine aerosol and the mean volume per activation was 0.09 (range 0.07–0.11) ml.

Monitoring during surgery and in the recovery ward included indirect arterial pressure, heart rate and arterial oxygen saturation (SpO₂) by pulse oximetry. Blood samples for drug assays were obtained from an arterial cannula inserted before induction of anaesthesia and kept patent with the aid of a continuous saline infusion (3 ml h⁻¹). Sampling was performed before and at 2, 4, 6, 9, 12, 15, 20 and 30 min and 1, 1.5, 2, 3, 4, 6, 8 and 10 h after the start of the i.v. infusion. Another sample was obtained before i.n. administration, 2–3.8 h later. Blood sampling in the first five patients, blood sampling started after completion of spraying. As this was found to take several minutes, sampling in the remaining patients was scheduled from the beginning of administration and time to completion was noted. Consequently, the total time of each study was 22–24 h, and any deviation from the scheduled sampling time was noted and the true time used in data processing. Total blood sampling volume was 260 ml. Mean peroperative blood loss was 160 (range 25–350) ml.

Blood samples were kept on ice for a maximum of 2 h until centrifuged. Plasma was stored at −20 °C until assay within 8–12 weeks. The syringes and spray bottles were weighed before and after administration of their contents, and samples of the solutions were saved for assay.

Plasma samples were assayed for midazolam by gas–liquid chromatography (GLC) with electron capture detection after addition of diazepam as internal standard and extraction with diethyl ether. The within–day coefficient of variation (CV) was 4.6% at 7.5 μg litre⁻¹ (3 ng sample⁻¹), 3.0% at 75 μg litre⁻¹ and 3.1% at 750 μg litre⁻¹ (n = 8). The limit of detection was approximately 1 μg litre⁻¹, and the between–day CV was 11% at 60 μg litre⁻¹ (n = 8). For each patient, samples from i.v. and i.n. administrations were assayed on the same day.

Plasma samples from eight patients were also assayed for 1-hydroxymidazolam by high pressure liquid chromatography (HPLC). The within–day CV was 11% at 4 μg litre⁻¹ and 3.1% at 10 μg litre⁻¹, and the limit of detection was approximately 2 μg litre⁻¹.

Concentrations of midazolam in the i.v. and i.n. solutions were determined by HPLC using the same standards as for the plasma assay, and each actual dose was calculated from the weight of administered solution and its measured concentration of midazolam. Conventional compartmental models with elimination from the central compartment were fitted to the plasma concentration data from the i.v. administration, using PCNONLIN software (Scientific Consulting Inc., Apex, NC, USA). The final choice of model and weighting was three compartments and concentration⁻¹. The set of variables obtained included clearance (Cl), volume of distribution at steady state (Vss), mean residence time (MRT) and terminal half-life (T½).

The contribution from the i.v. injection to the plasma concentration of midazolam after i.n. administration was subtracted from all measured concentrations, as shown in figure 1. The area under the concentration curves after i.v. and i.n. administration (AUC i.v. and AUC i.n.) were calculated by the logarithmic trapezoidal method. In both cases, extrapolation to infinite time was based on the terminal hybrid rate constant obtained from the PCNONLIN fit to the i.v. data. The bioavailability based on the AUC (F AUC i.n.) of i.n. midazolam was then calculated using the standard formula:

\[ F_{AUC} = \frac{\text{AUC}_{i.n.} \times \text{dose}_{i.n.}}{\text{AUC}_{i.v.} \times \text{dose}_{i.v.}} \] (1)

The absorption profile of i.n. midazolam was estimated by numerical deconvolution (fig. 2). The PCNONLIN fit provided the theoretical disposition function of midazolam after instantaneous injection (as opposed to actual 2-min infusions), calculated by analytical deconvolution. This equation was divided by the dose (in μg) to give the unit disposition function (UDF), that is the triexponential function that would describe the plasma concentration curve of midazolam after instantaneous injection of one dose unit (here, 1 μg). Numerical deconvolution...
Pharmacokinetics of intranasal midazolam

Integration of the input function gives the total absorbed amount of midazolam as a function of time. Bioavailability based on input \( F_{\text{inp}} \) was therefore calculated as:

\[
F_{\text{inp}} = \frac{I_{\text{cum}}}{\text{dose}_{\text{i.n.}}}
\]

where \( I_{\text{cum}} \) = cumulated input, that is absorbed midazolam at 10 h after dosing. This gives a cross-validation of the results.

The Student's \( t \) test was used to evaluate the statistical significance of the differences between the bioavailability of midazolam and 100% (unpaired test) and of drug-induced changes in arterial pressure (paired test). The level of significance was set at \( P<0.05 \) in one-tailed tests.

Results

The plasma concentration curves of midazolam for all patients are shown in figure 3 and the main pharmacokinetic variables in table 1. The absorption profiles of midazolam after i.n. administration are shown in figure 4. Bioavailability was generally high, with an excellent correlation \( (r^2 = 0.965) \) between \( F_{\text{AUC}} \) and \( F_{\text{inp}} \). Mean values of \( F_{\text{AUC}} \) and \( F_{\text{inp}} \) were, however, both significantly different from 100%.
Uptake from the nasal mucosa was rapid and close to completion within 1–2 h (fig. 4). Dose-normalized AUC after i.n. administration varied 2.2-fold, from 1.13 to 2.47 min litre$^{-1}$, compared with 1.5-fold (1.62–2.41 min litre$^{-1}$) after i.v. infusion. The contribution from i.v. infusion to the total AUC after i.n. administration was 3.7 (2.7) %, and the error caused by subtraction would be a fraction of this percentage.

The concentration curves of 1-hydroxymidazolam in eight of the patients are included in figure 3. After i.v. infusion of midazolam, the \( C_P^\text{max} \) of the metabolite was 28–104 µg litre$^{-1}$ at 12–20 min. After i.n. administration of midazolam, \( C_P^\text{max} \) for 1-hydroxymidazolam ranged from undetectable to 24 µg litre$^{-1}$ at 15–26 min after the beginning of administration.

The i.v. dose of midazolam induced hypnosis in all patients within 4 min. Cardiovascular variables were stable with an initial mean arterial pressure (MAP) of 105 (11) mm Hg and with a maximum reduction (ns) to 96 (10) mm Hg within 15 min of induction of
anaesthesia. The same dose administered i.n. had a less profound effect and a slower onset. After 6–14 min, that is a few minutes before mean \( t_{C_{\text{Pmax}}} \) values, all patients fell asleep but were rousable. Some patients found the solution slightly irritating or tickling, but all found the procedure acceptable. Cardiovascular variables were stable, MAP decreasing from 108 (12) to 105 (9) mm Hg (ns) when patients fell asleep. During anaesthesia \( S_{\text{PVO}_2} \) remained greater than 95% in all patients, but after i.n. midazolam administration desaturations occurred in five patients necessitating extra oxygen (5 litre min\(^{-1}\) by face mask) to achieve \( S_{\text{PVO}_2} > 95\% \).

**Discussion**

This study had demonstrated that under optimal conditions absorption of midazolam via the nasal mucosa can be rapid and virtually complete. Routinely using an i.n. dose of midazolam that is twice the i.v. dose under the assumption that bioavailability is approximately 50% may lead to overdosing in some patients. The earlier study in children\(^3\) was not a crossover study and calculation of the rate of uptake of midazolam from the nasal mucosa was not attempted. In addition, administration of midazolam as i.n. drops may cause loss of solution either as sneezing,\(^1\) spilling\(^4\) or swallowing,\(^5\) all of which result in underestimation of bioavailability. As midazolam is not available in solutions higher than 5 mg ml\(^{-1}\), large volumes must be given (at least 2 ml in normal adults).\(^7\)–\(^10\) Some of this solution is probably swallowed. We minimized spilling and swallowing by slow and careful spraying of approximately 0.1-ml aliquots. This proved time-consuming. However, in a 15-kg child three sprayings in each nostril would be sufficient to give a recommended\(^1\) \( 0.2 \text{ mg kg}^{-1} \) dose of midazolam.

The bioavailability of i.n. midazolam given by spray was greater than after oral administration in adults, with reported mean values in various groups of subjects of 46–68% (depending on dose),\(^12\) 44%\(^23\) or 36–50%.\(^24\) As very little i.n. midazolam was apparently absorbed by the gastrointestinal route, the formation of 1-hydroxymidazolam did not exceed that after a parenteral dose of midazolam.

The deconvolution analysis revealed rapid uptake of midazolam, presumably chiefly from the nasal mucosa, in most patients. A more prolonged uptake, as in patient Nos 7, 10 and 13 (fig. 4), could to some extent be by gastrointestinal absorption. The \( t_{C_{\text{Pmax}}} \) of midazolam was, however, highly reproducible at 14 (range 10–16) min after the beginning of spraying, and \( C_{\text{Pmax}} \) reasonably so at 192 (range 124–267) \( \mu \text{g litre}^{-1} \). Similar mean \( t_{C_{\text{Pmax}}} \) values of 13 min,\(^2\) 10 min,\(^4\) 12 min\(^5\) or 12–16 min (with different doses)\(^6\) were found after rapid instillation of i.n. midazolam solution in children. This suggests that absorption from the nasal mucosa is rate limiting and the time taken to administer the spray is relatively unimportant. Inter-individual variation in \( C_{\text{Pmax}} \) was similar\(^3\) or tended to be greater\(^2\) in the earlier studies compared with ours.

Midazolam was used as an i.v. induction agent before surgery and then as a hypnotic in the evening. Thus a crossover design was achieved with valid medical indications for both doses. This implied however that the i.v. dose was invariably given in the morning and the i.n. dose in the evening. As there is no apparent circadian variation in the clearance of midazolam,\(^25\) we feel that this design was justified. We also avoided major (intra-abdominal) surgery which may influence the pharmacokinetics of midazolam.\(^26\)–\(^28\) Minor surgery\(^27\) or administration of volatile anaesthetics\(^29\) have not been found to significantly affect the disposition of midazolam. Putative interactions of anaesthesia, other medications and surgery would tend to lower clearance, that is increase the \( \text{AUC}_{\text{iv}} \) of midazolam. As the \( \text{AUC}_{\text{iv}} \) is in the denominator in equation (1), this would cause underestimation of \( F_{\text{AUC}} \) (and influence \( F_{\text{exp}} \) in a similar manner). The “true” \( F \) values would in this case be higher than we calculated.

The pharmacokinetic variables of midazolam after i.v. administration were also in good agreement with earlier findings in young to middle-aged healthy volunteers or patients undergoing minor surgery.\(^12\)\(^14\)\(^24\)\(^26\)\(^27\)\(^30\)–\(^34\) In studies using 12–24 h blood sampling, the mean terminal \( T_{1/2} \) of midazolam was normally estimated at 2.1–3.3 h.\(^12\)\(^24\)\(^26\)\(^27\)\(^31\)–\(^33\) In approximately 6% of the population a considerably longer terminal \( T_{1/2} \) was found,\(^27\)\(^33\) and in our study this occurred in one of 14 subjects.

The observation that all patients were asleep but rousable a few minutes before a \( C_{\text{Pmax}} \) of 192 (48) \( \mu \text{g litre}^{-1} \) was reached is in good agreement with previous findings\(^30\) at midazolam plasma concentrations of 150–200 \( \mu \text{g litre}^{-1} \). In a later study in volunteers\(^34\) a midazolam concentration of 131 (14) \( \mu \text{g litre}^{-1} \) at awakening was observed. In all studies, however, effects were recorded during non-steady state conditions, ignoring any effect of hysteresis\(^14\) of midazolam. All patients had stable haemodynamic variables and minor oxygen desaturation was seen in only five patients, which is in good agreement with earlier findings on i.n. midazolam.\(^12\)\(^6\)\(^8\)\(^9\)

In conclusion, this study has shown that the bioavailability of midazolam administered via the nasal mucosa was high and that active metabolite was not formed in pharmacologically important amounts. However, to achieve this, it is important to optimize nasal delivery by slow and careful spraying of the drug solution to avoid losses or swallowing. A good technique for doing this also in small children should be developed in order to fully exploit the advantageous pharmacokinetic and pharmacodynamic properties of midazolam.

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**References**


