Plasma concentrations and sedation scores after nebulized and intranasal midazolam in healthy volunteers

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Background. An efficacious, reliable, and non-invasive route of administration for midazolam, a drug used for sedation and pre-anaesthetic medication, would have obvious advantages. This study compares two potential methods of administering midazolam by the nasal and nebulized routes.

Methods. Midazolam (0.2 mg kg⁻¹) was given by both nebulizer and nasally by liquid instillation to 10 healthy volunteers in a randomized, double-blind crossover study. Plasma concentrations of midazolam, Ramsay sedation scores, visual analogue scores, critical flicker fusion frequency, and parameters of cardiovascular and respiratory function were measured over 60 min and summarized using ‘area under the curve’.

Results. Nasal instillation caused more sedation than nebulized administration. This was demonstrated by higher Ramsay sedation scores (P=0.005), lower visual analogue scores (P<0.001), and lower critical flicker fusion frequency (P<0.02). Nasal instillation was associated with higher plasma concentrations of midazolam (P<0.001). Unpleasant symptoms were recorded by six volunteers in the intranasal and one in the nebulized group (P=0.06).

Conclusions. There was some evidence that midazolam caused less discomfort when given by nebulizer compared with intranasally. Comparative bioavailability of midazolam, estimated by the ratio (nebulized:nasal) of area under the 60 min plasma concentration curve, was 1:2.9. A higher dose may need to be administered for adequate pre-anaesthetic medication when midazolam is given by nebulizer.

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Midazolam is a water-soluble drug, which is the shortest acting in relation to other benzodiazepines and is often used as an i.v. sedative. Various other routes of administration have been investigated, for example, oral, rectal, i.m., sublingual, and nasal, but slow and unreliable onset of action and low bioavailability have been described via the oral route.1 Wilton and colleagues2 first described intranasal administration of midazolam as a pre-anaesthetic sedative for children. Its successful use has since been described for sedating pre-school children before suture of lacerations in the emergency department,3 as a premedicant in young children undergoing short surgical procedures,4 for the rapid sedation of an adult patient in whom i.v. access was not possible5 and for the emergency treatment of seizures.6 Although intranasal midazolam is safe and effective in reducing anxiety and stress in children,3 it may cause nasal burning, irritation, and lacrimation during instillation.7 Nebulized midazolam may offer a more comfortable and easy to use route of administration.

This study was designed to compare the plasma concentrations and sedative effects of intranasal and nebulized midazolam in healthy adult volunteers.
Methods

The study was approved by Southampton University NHS Trust Ethics Committee. Ten healthy adult volunteers aged 26–38 yr (seven men and three women) were recruited and informed consent was obtained. Volunteers were excluded if they had active respiratory disease, including asthma, atopy, or were taking other prescribed medication. None of the volunteers was smokers. After recording their weight, each volunteer was randomized into two groups of equal size. Group A received instillation of normal saline into the nasal passage followed by nebulized midazolam during the first session and instillation of midazolam solution into the nasal passage followed by nebulized normal saline during the second session. Group B received instillation of midazolam into the nasal passage followed by nebulized normal saline during the first session and instillation of normal saline into the nasal passage followed by nebulized midazolam during the second session. Volunteers were initially unaware as to the route through which the active drug was being administered. The dose of midazolam given at each session was 0.2 mg kg$^{-1}$. Subjects breathed room air before and after the nebulized solution. Sessions were spaced at least 5 days apart (median 12, range 5–15 days).

Physiological measurements

Baseline measurements of heart rate, arterial pressure, and oxygen saturation were taken and a self-assessed visual analogue score for sedation using a 100 mm line (0=asleep, 100=awake) was completed by the volunteer. A baseline Ramsay sedation score$^8$ was recorded by the observer using a six-point scale. Critical flicker fusion frequency was measured according to Turner’s method$^9$ once the subject was familiarized with the test, with the exception that adaptation to intermittent light before measurement of critical flicker fusion frequency was not used. The omission of light adaptation had previously been shown to give more reproducible results.$^{10}$ The mean of two ascending and two descending trials was taken after ensuring that ambient light and distance of the device from the subject remained constant.

After drug administration, Ramsay sedation scores, self-assessed visual analogue scores, and critical flicker fusion frequency were measured before nasal installation, then at 5, 15, 30, 45, and 60 min, from the time at which nebulization commenced. Non-invasive systolic and diastolic arterial pressure and heart rate were measured before nasal installation, then at 1, 3, 5, 10, 15, 30, 45, and 60 min, from the time at which nebulization commenced. Heart rate and oxygen saturation were observed continually and recorded at the same time intervals as for arterial pressure and heart rate. Adverse symptoms volunteered by the subjects were noted. The observer responsible for recording psychomotor scores was blind to the route of midazolam administered.

Blood sampling

A pre-treatment 10 ml sample of blood was obtained into a lithium heparin tube from a 22 gauge cannula sited peripherally in the subject’s arm. After drug administration, further 10 ml blood samples were collected at 1, 3, 5, 10, 15, 30, and 60 min, from the time at which nebulization commenced. All samples were then centrifuged within 30 min of collection of the final sample at room temperature (2500 rpm for 10 min) and the plasma transferred to another tube before freezing (−20°C) to await analysis.

Drug administration

For both routes of administration, 0.2 mg kg$^{-1}$ midazolam (as hydrochloride) was given as the standard 5 mg ml$^{-1}$ solution supplied for i.v. use (HYPNOVEL, Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK). For intranasal administration, the required quantity of either saline or midazolam solution was introduced into whichever nostril was more patent, using a needleless 5 ml syringe rapidly in an upwards direction keeping the head in a neutral position. This was followed immediately by nebulized administration, for which saline or midazolam was given via a compressed air operated jet nebulizer (PARI LC PLUS, PARI Medical Ltd). The required volume of solution was placed in the nebulizer bottom and the nebulizer top was reconnected. The device was held vertically during drug administration. A mouthpiece with an expiratory valve was attached and oxygen via a connecting hose was administered at 6 litre min$^{-1}$ for 5 min. The volumes given for each route of administration were identical.

Assay of midazolam in plasma

Samples were analysed by the high-performance liquid chromatography method described by Lehmann and Boulié$^{11}$ with the minor modification that methyl t-butyl ether was used to extract the drug from plasma. The assay has a lower limit of quantification of 3 μg litre$^{-1}$ and a coefficient of variance of 6–9% within and between batches at 20 μg litre$^{-1}$.

Data analysis

Plots of log plasma concentration vs time were prepared, to calculate the AUC 0–60 min (Microsoft Excel).

Statistical analysis

With 10 participants, the study had 80% power to detect a ‘within subjects’ effect size of 1 so, using the paired t-test with a 5% significance level. Multiple measurements on each individual were converted to a summary score using the area under the curve (AUC) over the 60 min measurement period. Where there were missing data for plasma concentration, visual analogue, and Ramsay sedation
scores, this was dealt with by imputing values from measurements from either side of the missing value or carrying over values if the missing value was the final measurement made (three nebulized and four nasal). Missing values in the critical flicker fusion frequency test due to over-sedation and inability to complete the test were scored as zero (three nebulized and 14 nasal). Mean AUC scores, age, and weight were compared between nebulized and nasal drug using the paired $t$-test with a two-sided 5% significance level.

Graphs show mean sedation scores, critical flicker fusion frequency, oxygen saturation, arterial pressure, heart rate, and plasma concentrations together with 95% confidence intervals for the means. Only actual measurements were used with no substitutions for missing data. The number of participants experiencing unpleasant symptoms was compared between the phases using McNemar’s test with exact probability.

**Results**

Groups A and B were comparable with respect to age, weight, and BMI (Table 1). There were five male volunteers in group A and two male and three female volunteers in group B. In all cases, there was no evidence of solution left in the nebulizer at the end of the 5 min nebulization period.

The intranasal route was associated with significantly more sedation, as shown by Ramsay sedation scores and visual analogue scores (Figs 1 and 2). Owing to excessive sedation, it was not possible to perform critical flicker fusion frequency tests on 17% of occasions (6% in the nebulized and 28% in the nasal group) (Fig. 3). Maximal average sedation tended to occur between 15 and 30 min for both routes.

There was no significant difference in oxygen saturation between the intranasal and nebulized phases. Mean oxygen saturation decreased with time and in both groups was at its lowest 15 min after administration (Fig. 4). There were 16 episodes of desaturation to 95% or below in the nebulized group and 13 episodes in the intranasal group. The lowest reading in both groups was 93% (two patients on one occasion each at 15 and 30 min in the nebulized group and one patient on two occasions at 10 and 30 min in the intranasal group). Supplementary oxygen was not given.

Mean heart rate and diastolic arterial pressure were both significantly higher in the intranasal phase of the trial, with a trend also towards higher systolic pressure (Figs 5–7). These findings may reflect the discomfort caused by this route of administration.

**Table 1** Demographic data [mean (range) or mean (SD)]

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.2 (28–38)</td>
<td>29.6 (26–33)</td>
<td>0.17</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.7 (9.1)</td>
<td>72.4 (10.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.3 (2.41)</td>
<td>25.3 (2.17)</td>
<td>0.53</td>
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significance ($P=0.06$). Six volunteers in the intranasal group complained of nasal stinging or irritation, as well as streaming eyes, hiccups, dyspnoea, and excessive nasal and oral secretions.

One of these volunteers also complained of feeling slightly wheezy both 5 min and 4 h after nebulized midazolam and admitted a history of childhood asthma at the end of the study. Compared with nebulized administration, plasma concentrations of midazolam were significantly higher in the intranasal group, although maximum concentrations occurred at 10 min by both routes (Fig. 8).

Discussion
When midazolam is nebulized at a dose of 0.2 mg kg$^{-1}$, it produces less sedation than the same dose given intranasally. To our knowledge, this is the first comparison of intranasal and nebulized midazolam in adults, although the intranasal route has been extensively studied in the paediatric population.

The bioavailability of intranasal midazolam in children has been estimated at 55$,^{12}$ but using a concentrated nasal spray it may reach 83%.$^{13}$ These values compare with between 36% and 50% for the oral route in adults$^{14}$ and 87%, 18%, 27%, respectively, for the i.m., rectal, and oral routes in children.$^{15}$ Bioavailability by the buccal route of 74.5% has also been reported in healthy volunteers.$^{16}$

Orally administered midazolam is extensively metabolized by the CYP3A system and extensive first-pass metabolism occurs in both the small intestine and the
Nebulized and nasal administration of midazolam

liver, which may account for the large inter-individual variability in disposition after oral administration. It is likely that the mucosal route avoids the first-pass effect. This has been confirmed in a study showing that 1-hydroxymidazolam levels were no higher in patients given midazolam intranasally than i.v., indicating that absorption via the nasal mucosa is almost complete.\(^{18}\)

The efficacy of nasal midazolam, in doses of 0.2 and 0.3 mg kg\(^{-1}\), has been compared with normal saline in 45 children undergoing routine surgery.\(^{2}\) Sixty per cent of patients receiving intranasal normal saline became agitated, compared with only 3% who received midazolam. Both doses of midazolam were effectively anxiolytic and sedative between 5 and 10 min after administration, with no adverse effects. In another trial, a group of 88 patients aged 10–36 months received either intranasal midazolam or normal saline before myringotomy and tube insertion; patients receiving midazolam demonstrated significantly easier parental separation and anaesthetic induction than those receiving saline.\(^{19}\) Sufentanil and midazolam, both given intranasally, have been shown to be effective pre-anaesthetic agents in children.\(^{20}\) However, midazolam (0.2 mg kg\(^{-1}\)) was less variable in its effect on parental separation and produced a lower incidence of desaturation and difficulty in ventilating the lungs than sufentanil (2 \(\mu g\) kg\(^{-1}\)). The incidence and duration of crying after administration was higher in the midazolam group, perhaps due to discomfort caused by the preparation.\(^{20}\) In the present study, the unpleasant irritant effect of intranasal midazolam was suggested by higher systolic and diastolic arterial pressures in the volunteers, compared with the nebulized route. Although comments as to the discomfort produced by each of the routes were noted, ideally this effect should have been quantified immediately after drug administration, as the intranasal route in particular was commonly associated with anterograde amnesia.

Nasal irritation appears to be a major disadvantage of instilling midazolam into the nasal passageway and this unpleasant side-effect is well documented in children. During a study of 93 children aged 6 months to 10 yr, 71% cried in response to nasal instillation of midazolam, compared with 18% after sublingual application of the same dose.\(^{21}\) Prior instillation of 4% lidocaine nasally has been advocated in order to reduce the irritation produced by intranasal midazolam.\(^{7}\) Administration by nebulizer would overcome these problems.

In the present study, plasma concentrations (together with AUC\(_{0–60min}\)) were lower and sedative effects less with nebulized midazolam compared with nasal instillation. The decreased bioavailability of the nebulized route may be in part due to inefficiency of the jet nebulizer system. Nebulizer efficiency depends on several factors: (a) the proportion of respirable particles produced during nebulization; (b) the proportion of aerosol released during inhalation; and (c) minimizing the residual ‘dead volume’ of drug remaining in the nebulizer, which may be as much as 66% of the original solution.\(^{22}\) Increasing the driving gas flow increases drug delivery to the lungs, whereas decreasing the concentration of the solution will prolong delivery and increase dead volume in the nebulizer.\(^{23}\) The PARI LC PLUS nebulizer takes 2.54 min to nebulize 2.5 ml solution, with 52% of particles in the respirable range and a mean particle diameter of 4.38 \(\mu m\). Tests on volunteers using radioactively labelled aerosols have revealed that only 27% of the dose is deposited in the body by the PARI LC PLUS used in the continuous mode, with 57% being retained in the nebulizer.\(^{24}\) However, there was considerable inter-subject variability, which may reflect differences in airway anatomy and airflow patterns between subjects. Drug delivery by other nebulizer systems may well be markedly different from the PARI LC PLUS.

The bioavailability of nebulized midazolam has not previously been compared with the intranasal route in humans. Jaimovich and colleagues\(^{25}\) administered midazolam (0.1 mg kg\(^{-1}\)) via an endotracheal catheter in the lamb model and compared plasma concentrations with the i.v. route. Absolute bioavailability was not calculated, but results indicated that the mean plasma concentration after endotracheal administration was 30% (range 24–54%) of that obtained i.v. Increasing the dose to 0.2 mg kg\(^{-1}\) produced a mean plasma concentration which was 59% (range 45–91%) of that via the i.v. route. The absolute bioavailability of nebulized midazolam was not determined in the present study, but these results indicate that it is about 34% of that by nasal instillation. This would account for the diminished sedative effect of nebulized midazolam compared with nasal instillation. A previous study showed that at midazolam concentrations of 150–200 ng ml\(^{-1}\), adult patients were asleep but rousable, sedation and amnesia being pronounced until the concentration decreased below 75–100 ng ml\(^{-1}\).\(^{26}\) Since these units are equivalent to those obtained in our study (in \(\mu g\) litre\(^{-1}\)), a direct comparison is possible. The mean peak concentration in our intranasal group decreased within the sedation/amnesia band, three volunteers having peak concentrations in the asleep/rousable band. The mean peak concentration in the nebulized group was below the threshold for sedation/amnesia and only three volunteers achieved peak concentrations above the 75 \(\mu g\) litre\(^{-1}\) level.

A criticism of the analysis of critical flicker fusion frequency test was that missing values were replaced by the value zero when participants were too sedated to take the test. The critical flicker fusion frequency test can be used as a measurement of sedative effect of drugs and so this seems appropriate. However, if we used the same imputation method as for the other outcomes, the statistical significance was reduced (\(P=0.16\)).

It was interesting that one of the volunteers became wheezy after nebulized midazolam and bronchospasm may be a potential problem in susceptible individuals, such as those with a history of obstructive airways disease.
Reductions in FEV1/FVC of greater than 12% after nebulized midazolam but not after nasal administration have previously been reported in humans.27 A significant increase in peak airway pressure was found in lambs after 0.1 mg kg

either by improving nebulizer delivery or by increasing administration of midazolam, but requires further evaluation.

We observed a decrease in oxygen saturation which was similar in both groups in our study, despite the increased sedative effect of the intranasal route. One possible explanation is that asymptomatic airway constriction led to desaturation in the nebulized group, whereas in the intranasal group it was caused by sedation.

The nebulized route may offer an alternative mode of administration of midazolam, but requires further evaluation of the dose required to produce a sedative effect, either by improving nebulizer delivery or by increasing the dose administered.

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