JPP Journal of Pharmacy and Pharmacology

JPP 2006, 58: 1311–1318

Received December 21, 2005
Accepted June 19, 2006
DOI 10.1211/jpp.58.10.0003
ISSN 0022-3573

Pain and Palliation Research Group, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, 7489 Trondheim, Norway

Ola Dale, Turid Nilsen, Pål Klepstad, Stein Kaasa

Department of Anaesthesia and Acute Medicine and Palliative Medicine Unit, Department of Oncology, St. Olavs University Hospital, Trondheim, Norway

Ola Dale, Pål Klepstad, Stein Kaasa

Department of Pharmacy, University of Oslo, Blindern, Norway

Hanne Hjorth Tønnesen

Department of Pharmacy, University of Iceland, Reykjavik, Iceland

Thorstein Loftsson

Gaustadalleen 21, 0349 Norway

Trond Holand, Per G, Djupesland

Correspondence: O. Dale, Pain and Palliation Research Group, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, 7489 Trondheim, Norway. E-mail: ola.dale@ntnu.no

Funding: This work was partially supported by a grant from Innovation, Norway.

Conflicts of interest: PGD and TH are founders and shareholders of OptiNose AS, a commercial company holding the rights to the patent describing the bi-directional nasal delivery concept. TL has a patent related to the nasal midazolam formulation used, but this is now in the possession of DeCode Genetics, Iceland, to whom TL now has no relation. OD, responsible for the project, has received economic support, from a grant from Innovation, Norway through Optinose A/S, to cover research related net expenses. TN, PK HTT and SK have no conflicts of interest.

Intranasal midazolam: a comparison of two delivery devices in human volunteers

Ola Dale, Turid Nilsen, Thorsteinn Loftsson, Hanne Hjorth Tønnesen, Pål Klepstad, Stein Kaasa, Trond Holand and Per G. Djupesland

Abstract

Bidirectional nasal drug delivery is a new administration principle with improved deposition pattern that may increase nasal drug uptake. Twelve healthy subjects were included in this open, non-randomized 3-way crossover study: midazolam (3.4 mg) intravenously (1 mg mL^{-1}), or nasally by bidirectional or traditional spray ($2 \times 100\,\mu L$ of a 17 mg mL^{-1} nasal midazolam formulation). The primary outcome was bioavailability. Blood samples were drawn for 6 h for determination (gas-chromatography–mass-spectrometry) of midazolam and 1-OH-midazolam. Pharmacokinetic calculations were based on non-compartmental modelling, sedation assessed by a subjective 0–10 NRS-scale, and nasal dimensions by non-invasive acoustic rhinometry. Mean bioavailabilities were 0.68–0.71, and Tmax 15 min for the sprays, which also were bioequivalent (ratio geometric means (90%) CI: 97.6% (90% CI 83.5; 113.9)). Sedation after bidirectional spray followed intravenous sedation closely, while sedation after the traditional spray was less pronounced. A negative correlation between C_{max} and smallest cross-sectional area was seen. Adverse effects such as local irritation did not differ significantly between the sprays. Apparently bidirectional delivery did not increase systemic bioavailability of midazolam. We cannot disregard that only the traditional spray caused less sedation than intravenous administration. This finding needs to be confirmed in trials designed for this purpose.

Introduction

In recent years a growing interest in alternative forms of drug administration has emerged. Nasal administration, with transmucosal absorption, may offer advantages such as ease of administration, rapid onset and patient control. It bypasses gastrointestinal and hepatic presystemic elimination, and is applicable in nauseated and vomiting patients who may have problems taking oral medication. Also, the rapid onset of action should make nasal administration of opioids an interesting tool for the management of breakthrough pain in cancer patients (Dale et al 2002).

Several techniques and devices for intranasal drug administration have been developed; however, the use of manually actuated spray pumps dominate. The Norwegian company OptiNose has patented a new concept for nasal delivery of drugs and vaccines based on bi-directional airflow between the two nasal passages connected in series (Djupesland et al 2004). The device has both a mouth and a nosepiece connected to the patient. When the patient exhales through the nosepiece, the soft palate closes to establish the bi-directional airflow entering one nostril and exiting through the other. The dose is released from a spray pump pre-charged by a spring and actuated by the airflow through the device. Gamma-scintigraphy deposition studies shown significantly improved deposition pattern of bi-directional administration compared with traditional nasal spray (Djupesland et al 2006), which possibly may improve drug bioavailability or clinical effects.

Recent experiences in human subjects with a midazolam formulation designed for nasal use displayed maximum serum concentrations at 15 min, and a bioavailability of 64%. A sedative effect was recorded within 5–10 min and maximal effect about 10 min later. It follows that this may serve as a model drug in volunteers, not least since a clinically relevant outcome, sedation, may be determined in volunteers (Gudmundsdottir et al 2001; Loftsson et al 2001).

In the above study the majority of the subjects reported mild to moderate irritation within the nasal cavity passages or the throat (Gudmundsdottiret al 2001; Loftsson et al 2001)). Subjective symptoms, such as irritation and discomfort, are frequently associated with congestion of the nasal mucosa, thus changes in the nasal airway dimensions may be an objective correlate to subjective reporting. Acoustic rhinometry (AR) is a reliable and sensitive method for fast, non-invasive assessment of changes in the nasal airway dimensions of clinical significance in small groups of individuals (Djupesland 1999; Hilberg 2002; Djupesland et al 2001). Previous studies suggest a correlation between nasal dimensions and nasal deposition/filtering efficiency (Kesavanathan & Swift 1998; Djupesland et al 2004). Nasal airway dimensions may also correlate with bioavailability and other outcome measures.

The primary objective of this study was to compare pharmacokinetics and pharmacodynamics of a standard nasal spray pump (Traditional) with the new nasal delivery device (OptiMist) from OptiNose in human subjects, and with intravenous (IV) administration. The anticipation was that the OptiMist may increase bioavailability and result in more profound sedation.

Materials and Methods

Ethical and regulatory aspects

This study was conducted according to the principles of the Helsinki declaration and approved by the Regional Committee for Medical Research Ethics, Central Norway. Written, informed consent was obtained from subjects before inclusion. The study was also approved by the Norwegian Medicines Agency, The Norwegian Data Directorate/Norwegian Social Science Data Service and the Ministry of Health.

Inclusion and exclusion criteria

Male and female, 18- to 45-year-old, healthy subjects were eligible. Subjects with a history of liver disease, taking any medications metabolized by or affecting CYP3A, having any local nasal disease, any history of drug allergies or a history of drug abuse or professional access to drugs of abuse were excluded from the study. Pregnant women were also excluded. Before inclusion the following pre-study clinical chemical tests were evaluated: haemoglobin, creatinine, ALAT, albumin.

Design

Subjects received 3.4 mg midazolam intravenously (IV) or nasally (one actuation delivered 100 μL (mean particle size of 43 μm) in each nostril) by a standard (Traditional) multi-dose spray pump (Ing. Erich Pfeiffer, Radolfsee, GmHb) or the OptiNose device (OptiMist, containing an identical Pfeiffer spray pump), in an open, non-randomized three-way cross-over study (Djupesland et al 2006). The study was open as blinding with a double-dummy technique would have changed the absorption conditions by doubling spray volume.

Each study session consisted of a 6-h stay in the research facilities. The sessions were separated by at least one week. For practical reasons to reduce travelling (PGD, TH), the sequence of sessions was not randomized. Sedation level and local symptoms (nose and pharynx) were recorded systematically, and subjects were requested to report all adverse events. Since PGD or TH were always present for acoustic rhinometry and delivery of the Optimist spray, observer blinding was not possible.

Subjects also received a post-trial questionnaire to report aspects of sedation; was there a difference between treatments? If so, which gave the deepest sedation? Was there a difference between the nasal sessions? In that case, which gave the deepest sedation? How significant was this difference?

Drug doses and administration

Commercial midazolam HCl (Alpharma, 1 mg mL^{-1} (free base) 3.4 mg was administered at the intravenous sessions, while a nasal midazolam formulation was employed for the two nasal session (Gudmundsdottir et al 2001; Loftsson et al 2001). The 3.4-mg midazolam (free base; Sifa, Shannon, Ireland) doses given were within the range previously published for similar studies with midazolam (Gudmundsdottir et al 2001), and were censored by the volume one can administer nasally, and by the midazolam concentration in this formulation. It was expected that this dose would induce sedation in a majority of subjects, with a minimal risk for over-sedation.

The nasal formulation (midazolam free base 17 mg mL^{-1}) was produced by our Hospital Pharmacy as described previously (Loftsson et al 2001). Briefly, the nasal formulation was an aqueous solution containing midazolam base (1.7% w/v), sulfobutylether-β-cyclodextrin sodium salt with molar substitution of 6.2 (Captisol, 14% w/v), which was donated by CyDex Inc. (Kansas City, KS), hydroxypropyl methylcellulose (0.1% w/v), benzalkonium chloride (0.02% w/v), ethylenediaminetetraacetic acid (0.1% w/v) and phosphoric acid (0.73% w/v). The formulation was adjusted to pH 4.20–4.35 with sodium hydroxide. The purity and content of midazolam was determined by the Department of Clinical Pharmacology at St Olavs University Hospital, Trondheim, Norway.

Procedures

Subjects were asked not to take alcohol, grapefruit, grapefruit juice, caffeine or medications for 12 h before, and during, each study period (6 days). Subjects were asked to abstain from food and liquids after midnight the day before study days. A washout period of at least one week was employed for each subject. Two subjects were studied on each study day over a period of 5 weeks. Before administration of midazolam, one or two (two for the intravenous sessions) peripheral intravenous catheters were inserted in a hand or arm vein for drug administration and blood sampling. Subjects were monitored for 2 h (blood pressure, ECG, respiratory rate and oxygen saturation). Oxygen was administered if oxygen saturation decreased below 94. Venous blood samples (9 mL) were drawn just before and at 2, 5, 10, 15, 20, 25, 30, 35, 45, 60, 90, 120, 240 and 360 min after drug administration.

Subjects were fed a standard breakfast 2 h after midazolam administration, and had free access to food thereafter.

Assessments

Subjective sedation was scored by a numeric rating scale (NRS) 0–10 where 0 is awake and 10 is falling asleep (or as tired as you can imagine) at 0, 2, 5, 10, 15, 20, 25, 30, 35, 45, 60, 90, 120 and 360 min. Sedation was also rated by the Observers Assessment Sedation/Scale (OAS/S)(Chernik et al 1990) ranging from 9 (deep sedation) to 20 (no sedation).

Subjective nasal discomfort, discharge, bad taste and throat discomfort were recorded by a verbal rating scale (0–3 where: 0 = none, 1 = mild, 2 = moderate, 3 = severe) at 0, 2, 5, 10, 15, 20, 25, 30, 120 and 360 min. Subjects were instructed about the procedures for the subjective ratings before the start of each study day. Subjects were asked by study personnel who recorded their ratings.

Nasal cavity dimensions were measured by acoustic rhinometry (Rhin2100; RhinoMetrics AS, Lynge, Denmark) in the seated position, using a handheld sound wave tube and an anatomic nasal adapter. The mean of three independent measurements with a CV% < 5% were used for calculations (Hilberg 2002). Nasal volumes (VOL) and cross-sectional areas (CSA) were calculated as the sum of both nasal cavities, to minimize bias due to the nasal cycle. The smallest total CSA and total volumes of 0–5cm, 0–7 cm and 2–5 cm from the nostril were determined. Measurements were performed before administration of the nasal midazolam, after the last blood sample and 15 min after nasal administration of a standard dose of a topical decongestant (xymetazoline, Otrivin). The degree of mucosal swelling was estimated from the decongestive effect (Taverner et al 1999).

Drug analysis and pharmacokinetics

The plasma concentration of midazolam and 1-hydroxymidazolam were determined according to Martens & Banditt (1997). Plasma spiked with diazepam and temazepam as internal standard (IS) was alkalinized and extracted by toluene containing 0.1% amyl alcohol. The organic phase was evaporated and the residue was derivatised with TBDMSTFA (*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide with 1% *tert*-butyldimethylsilyllchloride) at 60°C. After the excess of TBDMSTFA was evaporated, the residue was dissolved in ethyl acetate and analysed on a gas chromatograph (Hewlett Packard HP 5890) with a mass-spectrometry detector (Hewlett Packard HP 5972). Midazolam and diazepam (IS) were quantified by the mass ions 310 and 256, respectively, and 1-hydroxymidazolam and temazepam (IS) were quantified by the mass ions 398 and 357, respectively. The same procedure was applied to samples of unknown concentration, calibrators (CALs) and quality controls (QCs). The standard curves were linear in the range 0.25–250 ng mL^{-1} for both midazolam and 1-hydroxymidazolam ($r^2 = 0.9994$, CV = 0.07% and $r^2 = 0.9987$, CV = 0.11%, respectively (n = 13)). The limit of quantification (LOQ) for both midazolam and 1-hydroxymidazolam was 0.25 ng mL^{-1}. The precision (CV) for LOQ was 11.0% and 9.8% and the inaccuracy was 7.3% and –7.2% for midazolam and 1-hydroxymidazolam, respectively (n = 12). Quality controls for both midazolam and 1-hydroxymidazolam were prepared at 0.75, 25.0, 50.0 and 200 ng mL^{-1}. As assessed by QC samples, the overall inter-assay precision (CV) was 8.4% for midazolam and 9.7% for 1-hydroxymidazolam, and the overall inaccuracy was −1.3% for both midazolam and 1-hydroxymidazolam.

Plasma concentration data was analysed by noncompartmental techniques. Midazolam clearance, volume of distribution, elimination rate, C_{max} (maximum serum concentration), T_{max} (time maximum serum concentration) and area under the curve AUC (linear trapezoidal rule) were calculated by computerized curve fitting using the Win-Nonlin Standard 4.1 (Pharsight Corporation, USA). Systemic clearance $(Cl) = dose/AUC_{iv}$, apparent nasal clearances $(Cl_n) = dose/AUC_n$, and the respective bioavailabilities $(F_x) = (AUC_x/dose_y)/(AUC_y/dose_x)$ were determined. Bioequivalence was described as the ratios (%) of the geometric means of the AUC_{last} test administration (OptiMist)/reference administration (Traditional) with its 90% confidence interval. The power was also calculated.

Outcome measures

The primary objective of this study was to compare bioavailability of a Traditional nasal spray pump with OptiMist in human subjects. The anticipation was that OptiMist increased bioavailability. Secondary aims were comparison of time to maximum concentrations and the maximum concentration levels and finally comparison of onset times by means of sedation. Additional objectives were to compare the subjective evaluation of irritation and discomfort and potential corresponding objective changes in nasal airway dimensions as determined by acoustic rhinometry.

Statistics

Sample size was not calculated for this explorative pilot study. Data are given as median (range). Friedmans test was used for multiple, related comparisons. Wilcoxon signed ranks test was used for group comparisons. No corrections were made for multiple comparisons. Bivariate correlation (Pearson) was used to determine associations between variables. A linear mixed model, allowing correlation between repeated observations, was employed with the median sedation as the outcome variable. This model assumes that each individual patient possesses a random intercept (i.e. an individual offset), in addition to being affected by the different treatments. Model parameters were estimated by the method of restricted maximum likelihood (REML) using the linear mixed models. The SPSS 12 for Windows was used for the statistical calculations.

Results

Fourteen subjects met for screening, one was excluded (subject 11) due to allergy, one was a potential substitute. Twelve healthy male (n = 4; age 21–24 years, height 179–192 cm, weight 71–80 kg) and female subjects (n = 8; age 20–25 years,

height 165–182 cm, weight 52–68 kg) completed the study. There were no clinically relevant changes apparent in clinical laboratory parameters or vital signs. One case report form (subject 13) disappeared and data on sedation, adverse effect and safety were lost, although demographic data, acoustic rhinometry, post-study postal survey and blood samples for pharmacokinetics were available. Traditional spray was given at the first session for two subjects and at the third session for 10 subjects. Intravenous treatment was given to 4 subjects at the first session, six subjects at the second session and to two subjects at the third session. The corresponding numbers for bidirectional spray (Optimist) were 6, 6 and 0, respectively.

Figure 1 shows the time course (360 min) of serum concentrations of midazolam after the three administrations of 3.4 mg. The curves of the two nasal administrations did not differ; however, intravenous midazolam always displayed higher, although parallel, time–concentrations curves. The curves did not seem to be log-linear, indicating that a true elimination phase was not reached within 6 h.

Table 1 shows the pharmacokinetic characteristics of midazolam for the three administrations. As can be seen, the two nasal administrations displayed similar pharmacokinetics, including rapid mean T_{max} of 15 min. IV had a shorter T_{max}, and a significantly larger area under the curve. The absolute bioavailabilities for the nasal administrations were 0.68 (0.55) and 0.71 (0.59) for OptiMist and Traditional spray (median (range)), respectively. The ratio (Optimist/Traditional) between the geometric means of AUC_{last} was 97.6% (90% CI 83.5; 113.9) with a power of 0.77.

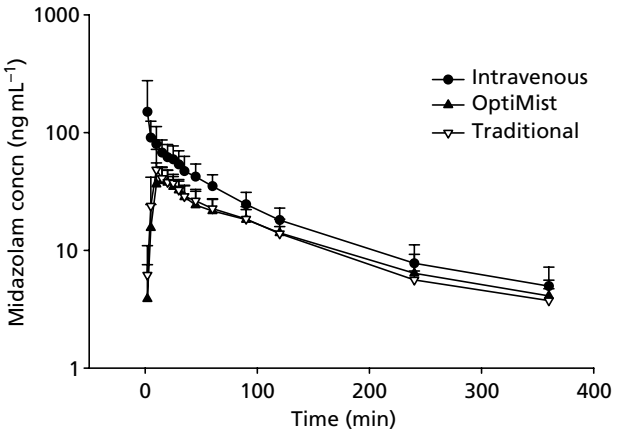

Figure 1 The time course (0–6 h) of serum concentrations of midazolam (mean ± s.d.) in 12 healthy subjects after intravenous and two nasal administrations (OptiMist and Traditional spray) of 3.4 mg midazolam (three-way crossover design). Pharmacokinetic calculations are shown in Table 1.

Figure 2 shows the time course of the formation of midazolam metabolite 1-OH midazolam. Somewhat lower serum concentrations were seen for the nasal administrations than for the intravenous over the first 90 min. The nasal sessions displayed similar pharmacokinetic characteristics (Table 2). However, T_{max} was shorter after IV. The AUC ratios for the nasal administrations differed significantly ($P = 0.017$: IV vs Optimist ($P = 0.023$); IV versus Traditional ($P = 0.012$)).

Subjective reporting of median sedation scores is displayed in Figure 3. IV showed the most rapid onset and offset of sedation, OptiMist did not differ significantly from the IV curve, while sedation for the Traditional spray was slower and less pronounced than after IV ($P = 0.033$, linear mixed model comparing medians). The objective sedation score (OAS/S) did not show any differences between the groups, as very few observations with sedation scores below 17 were observed. The subjects evaluated (n = 12) the treatments with respect to sedation after the study was completed as follows: eleven of the subjects reported differences in sedation; one person rated them to be equal. Eight subjects reported the strongest sedation with the IV, two with OptiMist, while none rated Traditional spray to cause the strongest sedation. One person rated IV and OptiMist to be equal. Nine subjects reported difference between OptiMist and Traditional, eight of these expressed that OptiMist gave the strongest sedation. Four reported that the difference was minor, while five reported a moderate difference between the nasal sessions. No subject reported that the difference was significant.

Two subjects reported short periods with nausea that recovered spontaneously without any intervention. One person (subject 4) apparently showed signs of experiencing hallucinations at 2 h for a brief period when she was waking up. During this episode she displayed tachycardia (heart rate about 120 beats/min). Midazolam was administered by the OptiMist device at this session. The subject was kept in-house for an extra 2-h period. The subject explained that she had slept little the night before the study as she had been travelling by bus from her home during the preceding night.

Table 3 displays the reporting of nasal and pharyngeal discomfort. Individual subjects (n = 12) reported moderate or strong nasal discomfort (n = 3), discharge (n = 0), congestion (n = 0) or throat discomfort (n = 9) at any time after

Table 1 Pharmacokinetic variables after intravenous (IV), OptiMist and Traditional nasal administration of midazolam (3.4 mg) in 12 human subjects studied in a crossover fashion

Route	T_{max} (min)	C_{max} (ng mL^{-1})	t½ (min)	AUClast (min ng mL^{-1})	AUCinf (min ng mL^{-1})	Vz[a] (obs) (mL)	Cl[a] (obs) (mL min^{-1})
IV	2 (3)*	125 (484)	109 (88)	7022 (7589)	7559 (9225)	64206 (58066)	450 (426)
OptiMist	15 (15)	41 (52)	108 (114)	4632 (3736)	5507 (4615)	111551 (160243)	590 (1166)
Traditional	15 (15)	51 (78)	103 (92)	4660 (2012)	5489 (2273)	92758 (162824)	605 (883)

Data are expressed as median (range). [a]Calculations for OptiMist and Traditional are not corrected for F (bioavailability). *$P = 0.000$, Friedman test, Wilcoxon signed rank test 0.02.

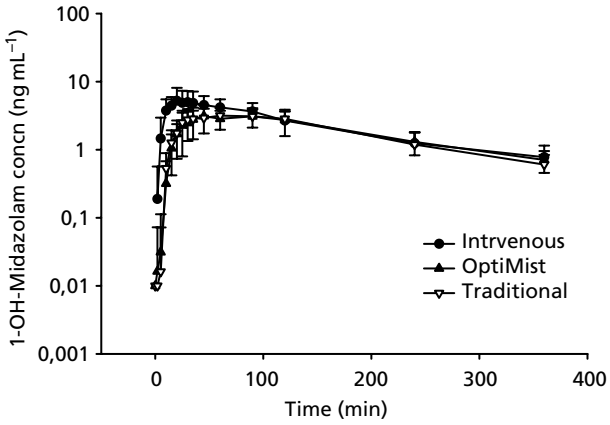

Figure 2 The time course (0–6 h) of serum concentrations of 1-OH-midazolam (mean ± s.d.) in 12 healthy subjects after intravenous and two nasal administrations (OptiMist and Traditional spray) of 3.4 mg midazolam (three-way crossover design). Pharmacokinetic calculations are shown in Table 1.

OptiMist. Subjects reported moderate or strong nasal discomfort (n = 5), discharge (n = 2), congestion (n = 0) or throat discomfort (n = 5) at any time after Traditional spray. With few exceptions, moderate and strong symptoms appeared within 2 min and resolved after 5 min.

Acoustic rhinometry data are displayed in Table 4. There was no significant difference between the rhinometric measurements at the start of the two nasal sessions. The sums of the volumes (S 0–7) were reduced by approximately 25% ($P < 0.005$) of recumbence (Cole & Haight 1984) as described previously (Taverner et al 1999). Nasal mucosa decongestion with Otrivin significantly increased all volumes. Volumes returned to pre-study levels after 8 h.

Correlation analysis, adjusting for difference in volume 0–7 and minimum cross-sectional area (MCA) between OptiMist and Traditional spray showed no significant difference between the treatments with respect to AUC and C_{max}. Except for the correlation between the sum of the cross-sectional areas (SMCA) and maximum serum concentrations (C_{max}), no other correlations between acoustic rhinometry data measured before start and pharmacokinetic variables were found. For Traditional spray there was a significant correlation between C_{max} and SMCA (–0.61, $P = 0.036$), while the corresponding calculations for OptiMist showed a trend (–0.6, $P = 0.068$). By pooling the data for both sessions the correlation was the same (–0.61), but statistically much stronger ($P = 0.003$) than for the separate observations.

Discussion

Some other studies have recently examined the pharmacology of nasal formulations of midazolam. Knoester et al (2002) found a bioavailability of 0.83 after 5 mg midazolam, which was higher than the 0.64 reported by Gudmundsdottir et al (2001) and Loftsson et al (2001) and that of about 0.7 found in our study. This is probably due to the fact that Knoester et al studied a different formulation. However, all studies report T_{max} of about 15 min. By and large, our study confirmed the pharmacokinetic observations made previously with the same nasal formulation (Gudmundsdottir et al 2001; Loftsson et al 2001).

The formation of the major midazolam metabolite 1-OH midazolam also displayed a striking similarity between OptiMist and Traditional spray. Knoester et al (2002) reported a relationship between AUCs for the metabolite and midazolam of about 0.12–0.13, but no difference in metabolite formation for intravenous and nasal administration. The ratios AUClast (1-OH midazolam)/AUClast (midazolam) in our study were statistically lower for the intravenous administration (0.11) than for the two nasal administrations (0.13–0.14), indicating some signs of presystemic elimination of midazolam. Since the t_{max} for the metabolite after the nasal administrations was significantly longer than that of intravenous administration, one may assume that oral absorption has taken place. This may explain the lower bioavailability than reported by Knoester et al (2002).

The hypothesis that OptiMist, compared with a traditional spray pump device, would increase bioavailability and C_{max} together with a decreased T_{max} was not confirmed. On the contrary, the administrations met the criteria for bioequivalence. The basis for this assumption was previous observations that OptiMist gave more extensive nasal distribution than Traditional spray, as measured by scintigraphy after nasal administration of ^{99m}Tc aerosols (Djupesland et al 2006). Although venous sampling is commonly used in pharmacokinetic studies, venous samples may display much lower concentrations than those of arterial blood in the early distribution phase (Chiou 1989a, b). For diazepam, a fat soluble drug, the initial arterio-venous difference in man after

Table 2 Pharmacokinetic variables for 1-OH-midazolam after IV, OptiMist and Traditional nasal administration of midazolam (3.4 mg) in 12 human subjects studied in a crossover design

Route	T_{max} (min)	C_{max} (ng mL^{-1})	t½ (h)	AUClast (min ng/ml)	Ratio AUClast (1-OH Midaz/Midazolam)
IV	28 (45)#	5 (11)	120 (129)	822 (1159)	0.11 (0.7)*
OptiMist	90 (110)	3 (5)	115 (113)	627 (719)	0.13 (0.17)
Traditional	60 (66)	4 (3)	112 (49)	628 (644)	0.14 (0.13)

Data are expressed as median (range). *$P = 0.017$ (Friedman test). IV vs OptiMist 0.023, IV vs Traditional 0.012 (Wilcoxon signed rank test); #$P = 0.006$ (Friedman test), IV versus OptiMist: 0.01, IV versus Traditional 0.006, (Wilcoxon signed rank test).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.