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Intranasal administration of midazolam in a cyclodextrin based formulation: bioavailability and clinical evaluation in humans

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Intranasal administration of midazolam has been of particular interest because of the rapid and reliable onset of action, predictable effects, and avoidance of injections. The available intravenous formulation (Dormicum® IV solution from Hoffmann-La Roche) is however less than optimal for intranasal administration due to low midazolam concentration and acidity of the formulation (pH 3.0–3.3). In this study midazolam was formulated in aqueous sulfobutylether-β-cyclodextrin buffer solution. The nasal spray was tested in 12 healthy volunteers and compared to intravenous midazolam in an open crossover trial. Clinical sedation effects, irritation, and serum drug levels were monitored. The absolute bioavailability of midazolam in the nasal formulation was determined to be 64 ± 19 % (mean ± standard deviation). The peak serum concentration from nasal application, 42 ± 11 ng ml^{-1}, was reached within 10–15 min following administration and clinical sedative effects were observed within 5 to 10 min and lasted for about 40 min. Intravenous administration gave clinical sedative effects within 3 to 4 min, which lasted for about 35 minutes. Mild to moderate, transient irritation of nasal and pharyngeal mucosa was reported. The nasal formulation approaches the intravenous form in speed of absorption, serum concentration and clinical sedation effect. No serious side effects were observed.

1. Introduction

Due to their well-defined anxiolytic properties, benzodiazepines are among the most popular sedatives for use before surgery and anaesthesia. Midazolam, a short-acting, water-soluble benzodiazepine, has been demonstrated to be a safe and effective preanesthetic anxiolytic agent [1] and its clinical efficacy is well documented after intravenous [2, 3], intramuscular [4], intranasal [5–7], oral [8, 9] and rectal [10] administration.

The available parental drug formulation (Dormicum® IV solution from Hoffmann-La Roche) is however less than optimal for intranasal use due to the low concentration of midazolam as well as the acidic pH (pH 3.3) of the formulation [11]. Nasal irritation [12], discomfort within the throat area as well as bitter taste are common complains following the intranasal administration. The large volume needed and accordingly extended administration time add to the unpleasant side effects from the available parenteral formulation when used for intranasal application.

By formulating midazolam in a solution containing sulfobutylether-β-cyclodextrin and hydroxypropyl methylcellulose, the solubility of midazolam (and therefore the midazolam concentration in the dosage form) was increased dramatically [13]. This enhanced solubility could be obtained at a higher pH (pH 4.3) than previously reported for the parenteral drug formulation used as intranasal midazolam dosage forms. Cyclodextrins and their derivatives have been extensively studied for their use as pharmaceutical excipients. Constructed of α-1,4 linked glucose units, they form cone shaped cylinders with hydrophilic exterior surface and a hydrophobic inner cavity. This allows cyclodextrins to form inclusion complexes with a lipophilic moiety of the midazolam molecule, increasing the aqueous solubility of midazolam dramatically without affecting the drug's pharmacological properties [13–15]. The addition of small amounts of water-soluble polymers, such as hydroxypropyl methylcellulose, to the solution further increases the solubility of midazolam in the aqueous cyclodextrin solution [16, 17]. The main objectives of the study of midazolam in the new midazolam nasal spray and to determine the clinical sedative effects in healthy volunteers.

2. Investigations and results

Mean midazolam serum concentration curves following both modes of administration are shown in the Fig. All values shown are the mean values ± the standard deviation of the mean. The maximum midazolam plasma concentration was 42.1 ± 11.2 ng ml^{-1} (range 29–72 ng ml^{-1}), 15.5 ± 7.9 min (range 5–30 min) following intranasal administration. Area under the curve divided by the dose (in mg) of midazolam administered (AUC/dose) was calculated to be 1981 ± 487 ng ml^{-1} min mg^{-1} following intravenous administration and 1209 ± 279 ng ml^{-1} min mg^{-1} following intranasal administration. The approximate 95% confidence interval was from 1705 to 2257 ng ml^{-1} min mg^{-1} dose and from 1052 to 1367 ng ml^{-1} min mg^{-1} dose for the AUC following intravenous and intranasal midazolam, respectively.

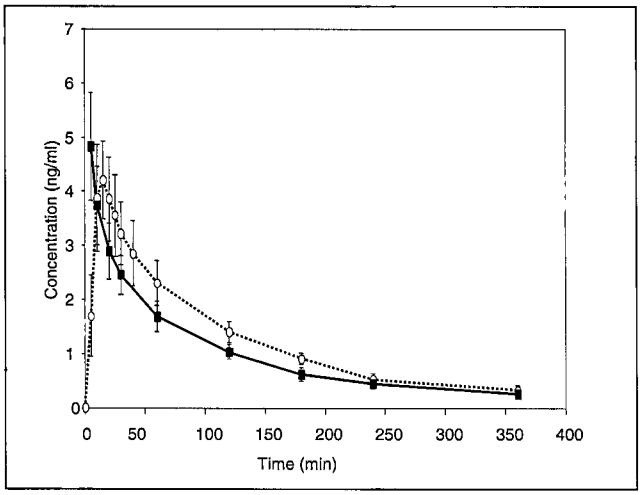

Fig: Serum concentration-time profiles following administration of mida-

Table 1: Distribution of sedative scores after intravenous and intranasal midazolam administration (n = 12)

	Sedation score	Contr.	Admin.			Time in minutes after administration													
		−5	0	1	2	3!	4!	5	8	10	15	20	25	30	35	40!	45!!	50!!	55	60	65
IV-Values	1																				
	2																				
	3																				
	4					1	3	3	3	3	3	2	2	2							
	5			1	3	4	2	2	2	2	2	3	3	3	5	4	1				
	6	12	12	11	9	7	7	7	7	7	7	7	7	7	7	8	11	12	12	12	12
						*	*	*	*	*	*	*	*	*	*	*					
IN-Values	1																				
	2																				
	3										1	3	4	4	4	4	3	2	1		
	4									1	2	1					2	1	1	1	
	5							1	4	5	4	3	3	3	3	3	2	3	2	2	1
	6	12	12	12	12	12	12	11	8	6	5	5	5	5	5	5	6	6	8	9	11
									*	*	*	*	*	*	*	*	*	*			

* Comparison of distribution of sedation scores between control (5 min before adm.) and post-administration using Wilcoxon's test (*P < 0.05)
! Comparison of distribution of sedation scores between groups IV vs. IN using Mann-Whitney test (!P < 0.05, !!P < 0.01)

This gave a mean intranasal midazolam bioavailability of 64 ±19%. Mean terminal half-life ($t_{1/2}$) following intravenous midazolam administration was 107.8 ± 30.9 min and 128.8 ± 54.0 min following intranasal midazolam administration. The approximate 95% confidence interval was 90 min to 125 min and 98 min to 159 min for the $t_{1/2}$ values following intravenous and intranasal midazolam administration, respectively. In one half of the group of twelve participants the initial sedative effect was seen within 5–10 min, and for one additional participant within 15 min, following intranasal drug administration. Maximal sedative effects were attained from 15–20 min and these continued until 55–60 min after administration. Five of the above mentioned participants showed initial sedative effect within 2–3 min following intravenous drug administration and approximate maximal sedative effects were attained from 3–4 min until 35–40 min after administration. The other members of the group, namely five participants, experienced minor or no sedative effects following either intranasal or intravenous drug administration. Comparison of distribution of sedative scores between control and post administration midazolam using Wilcoxson's test, revealed statistically significant differences ($p < 0.05$) from baseline from 8 min through 50 min post administration for the intranasal group. Similarly, there were statistically significant differences ($p < 0.05$) in sedation from baseline from 3 min through 40 min post administration in the intravenous group. Comparison of difference of sedative effects between the intranasal and intravenous groups using Mann-Whitney test, revealed statistically significant differences ($p < 0.05$) from 3 to 4 min and from 40 to 50 min post administration (Table 1).

No clinically significant symptoms of a midazolam overdose like respiratory depression or cardiovascular depression were seen in any of the volunteers. No volunteer complained of nausea or vomiting but approximately one half of the subjects reported mild to moderate discomfort and/or pain within either the nasal passage or throat area following intranasal midazolam-cyclodextrin administration. Comparison of distribution of nose and throat discomfort scores during and after study-drug administration using Wilcoxson's test, revealed ($p < 0.05$) significant differences the first 4 min after administration in the nasal passage and the first 15 min in the throat area respectively (Table 2). No clinically relevant changes in arterial oxygen saturation, heart rate and blood pressure and following both intravenous and intranasal midazolam administrations were demonstrated. In both groups, all subjects had recov-

Table 2: Distribution of nose and throat discomfort scores after intranasal midazolam administration (n = 12)

	Discom. score	Contr.	Admin.	Time in minutes after administration										
		−5	0	1	2	3	4	5	8	10	15	20	25	30
NOSE -Values	4													
	3		1	1										
	2		3	3	4	3	2	1						
	1		3	2	2	2	3	2	3					
	0	12	5	6	6	7	7	9	9	12	12	12	12	12
			*	*	*	*	*							
THROAT -Values	4													
	3		5	3	4	3	3	2						
	2			2	2	4	4	7	9	6				
	1							2	2	3	7			
	0	12	7	7	6	5	5	1	1	3	4	12	12	12
			*	*	*	*	*	*	*	*	*			

ered from sedation and were fully awake and alert within 150–180 min of the initial drug administration.

3. Discussion

The nose is a unique route of drug delivery into the body. The nasal cavity is highly accessible to sprays and drops, there is a large surface area (approximately 160 cm^2) [18] through which absorption can occur. Intranasal midazolam is absorbed through the highly vascularized nasal mucosa [19, 20] directly into the systemic circulation, thus bypassing first pass hepatic metabolism. This results in a faster peak plasma concentration and a higher bioavailability than can be achieved after oral or rectal administrations [21, 22].

The intranasal route has been extensively described and the successful use of intranasal midazolam, although still unlicensed via this route, has been reported in children undergoing dental procedures [7], anaesthesia induction [5, 22–25], and minor surgery [9, 26]. In adult patients, intranasal midazolam has been used for the management of claustrophobia during magnetic resonance imaging [27], for endoscopic procedures [28] for dental surgery [6, 29] and this administration looks promising for short-term management of seizures [30, 31].

This study demonstrates that it is possible to achieve effective intranasal delivery of midazolam using a drug delivery system based on cyclodextrin complexation with a bioavailability of the midazolam-cyclodextrin-nasal spray of 64 ± 19%. In a previous study in six healthy volunteers the bioavailability of the nasal spray was determined to be 73 ± 7% [13]. There are some indications that the absolute bioavailability of midazolam from the nasal cavity is dose dependent, i.e. that the bioavailability increases somewhat with increasing dose but this study was the first clinical trial for this nasal-spray formulation and therefore the dose was kept at a minimum (0.06 mg/kg). Comparative pharmacokinetic studies in adults demonstrate that bioavailability after oral administration is from 44% to 68% [32, 33] (depending on dose given) and a single report of pharmacokinetic data following buccal administration of 5 mg midazolam in adults shows a bioavailability of 74.5% [34]. Another single report of pharmacokinetic data following intranasal administration of midazolam (0.15 mg/kg body weight) in adults demonstrates that under optimal conditions absorption of midazolam via the nasal mucosa can be virtually complete, with a bioavailability of 83% [35] but more often a combined nasal/gastrointestinal absorption occurs, following intranasal midazolam administration, due to the large volume used, with a bioavailability quoted between 50 and 57% [24, 36].

This new, more concentrated (17 mg/ml) nasal spray formulation made it possible to obtain clinically sedative effect in adult patients using only 200–300 µl (based on body weight) compared with 2–3 ml, using the conventional intravenous (5 mg/ml) solution [29, 36, 37]. The sedation levels in our study were evaluated under ideal circumstances with no adverse stimuli and the clinical effect documented based on the individual sedation assessed by the participants. Approximately 10–15 min following administration of the nasal spray seven out of twelve participants demonstrated satisfactory sedation status where as the other participants experienced minor or no sedative effects throughout the study, so clearly the individual responses to midazolam plasma concentration differ, according to our study. The same subgroup of participants had a clinical sedative effect from both intranasal and intravenous dative effect from every formulation, which indicates the individual difference in people's response to midazolam. Additionally a relationship between plasma midazolam concentration and clinical effects could not been clearly established, following either intranasal or intravenous administration, but some researchers suggest that sedation may be associated with plasma midazolam concentrations greater than 30–100 ng/ml [38, 39].

The administration time for this new nasal-spray-formulation was less than 1 min. The majority of the participants reported mild to moderate irritation within the nasal passage and/or throat area following nasal-spray administration. The irritation is most likely due to the bitterness of midazolam. Based on a preliminary double blind/randomised study six volunteers could not differentiate between saline and the vehicle administered intranasally by a Pfeiffer, "unit dose" device. Evaluation of subjective irritation is always difficult but discomfort level in our study was scored mild to moderate that is not as severe as previously reported [9, 12, 40]. No other side effects were observed in the nose and local symptoms such as sneezing and coughing were not observed in this study.

In conclusion, the pharmacokinetic data presented in our study demonstrate that the midazolam-cyclodextrin nasal spray formulation approaches the intravenous form in speed of absorption and serum concentration. By formulating midazolam in a solution containing sulfobutylether-β-cyclodextrin and hydroxypropyl methylcellulose, the solubility is increased dramatically at a higher pH (pH 4.3) and this unique property, as well as the ease of administration, offers significant advantages over currently used treatment modalities for sedation.

4. Experimental

4.1 Materials and methods

Sulfobutylether-β-cyclodextrin was kindly donated by CyDex Inc. (USA), hydroxypropyl methylcellulose 4000 was obtained from Mecobenzon (Denmark) and midazolam from Sifa (Ireland). All other chemicals used were of pharmaceutical grade (European Pharmacopeia, 3rd Edition, 1997). The midazolam nasal spray was formulated in a sulfobutylether-β-cyclodextrin-hydroxypropyl methylcellulose aqueous solution. Midazolam base (1.7 g) was added to 100 ml of an aqueous solution containing 14 g sulfobutylether-β-cyclodextrin, 0.1 g hydroxypropyl methylcellulose, 0.02 g benzalkonium chloride, 0.1 g ethylenediaminetetraacetic acid and 0.73 g phosphoric acid. The pH of the formulation was adjusted to pH 4.20–4.35 with sodium hydroxide. The solution was heated in an autoclave at 121 °C for 40 min to promote the complexation [13, 16]. The resulting solution was then filtered through a 0.45 µm membrane and aseptically divided into amber crimp cap vials. Finally, the vials and their contents were sterilised in an autoclave at 121 °C for 20 min. The nasal spray was prepared at the facilities of Icelandic Pharmaceuticals (Iceland).

4.2. Study protocol

The protocol was an open crossover trial, approved by the local ethics committee of the National University Hospital and the State Committee on Pharmaceuticals in Iceland. Before enrolment, all volunteers gave written informed consent. Twelve healthy volunteers were chosen among 18 Caucasian students who applied for participation, on the basis of normal liver and kidney function, as reflected in normal creatinine and bilirubin blood values and no history or signs of a cold within the two weeks prior to the first experimental day. They were prohibited from using any drugs with known metabolic interactions with midazolam such as tranquilizers or alcohol 2 days prior to and during the study. The mean age of the volunteers was 25.8 years (range 19–37 years) and the mean weight was 73.0 kg (range 55–92 kg). Five female and seven male volunteers were included in this study. Volunteers reported to the study unit at 10:00 AM each study day after an 8-hour fasting period. They continued to fast until 2 h after administration of the study drug. Electrocardiography and blood oxygenation monitors were affixed and an intravenous cannula inserted into a forearm vein for collection of blood samples. Baseline blood samples were obtained 5 min prior to administration of the study medication, according

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