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Bioavailability of dexmedetomidine after intranasal administration

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Conflict of Interest:

Dr Iirola, Dr Aantaa and Dr Olkkola have ongoing contract research relationships with Orion Corporation (Espoo, Finland), the original developer of dexmedetomidine.

Dr Iirola has received speaker fees from Orion Corporation (Espoo, Finland).

Dr Aantaa has been a paid consultant for Orion Corporation (Espoo, Finland) and Abbott Laboratories (Abbott Park, IL, USA), the original co-developers of dexmedetomidine, as well as for Hospira (Lake Forest, IL, USA). Hospira has a license agreement with Orion Corporation concerning dexmedetomidine (Precedex®).

Dr. Lahtinen has been engaged in contract research for Orion Corporation (Espoo, Finland).

The laboratory of Dr Scheinin has contract research relationships with Orion Corporation (Espoo, Finland) and Hospira (Lake Forest, IL, USA). Hospira has a license agreement with Orion Corporation concerning dexmedetomidine (Precedex®). Dr Scheinin has also received speaker fees and consulting fees from Orion Corporation.

Abstract

Purpose

The aim of this proof-of-concept study was to characterize the pharmacokinetics and pharmacodynamics of intranasal dexmedetomidine as compared to its intravenous administration in a small number of healthy volunteers.

Methods

Single doses of 84 µg of dexmedetomidine were given once intravenously and once intranasally to 7 healthy male subjects. Plasma dexmedetomidine concentrations were measured for 10 h and pharmacokinetic variables were calculated with standard noncompartmental methods. Heart rate, blood pressure, concentrations of adrenaline and noradrenaline in plasma, tiredness and subjective drug effects (with the Maddox wing, Bispectral Index and three visual analog scales) were monitored to assess the pharmacological effects of dexmedetomidine.

Results

Six subjects were included in the analyses. Following intranasal administration, peak plasma concentrations of dexmedetomidine were reached in 38 (15-60) min and its absolute bioavailability was 65 (35-93) % (medians and ranges). The pharmacological effects of dexmedetomidine were

similar with both routes of administration, but their onset was more rapid after intravenous administration.

Conclusions

Dexmedetomidine is rather rapidly and efficiently absorbed after intranasal administration.

Compared to intravenous administration, intranasal administration of dexmedetomidine may be a feasible alternative in patients requiring light sedation.

Keywords: Administration, Dexmedetomidine, Intranasal

Introduction

Dexmedetomidine is a highly selective and potent α_2 -adrenoceptor agonist indicated for perioperative and intensive care sedation. As well as offering sedation and anxiolysis, dexmedetomidine has analgesic qualities and it also reduces stress responses to surgical and intensive care procedures [1]. It has been shown that intranasally administered dexmedetomidine is efficacious and well tolerated in healthy volunteers [2] and that intranasally administered dexmedetomidine may be a useful alternative for oral midazolam as premedication in children [3]. The onset of sedation has been reported to occur at 45 min in healthy volunteers [2] and at 25 min in children [4]. However, information on the pharmacokinetics and bioavailability of dexmedetomidine after intranasal administration is lacking.

The aim of this proof-of-concept study was to compare the bioavailability and pharmacokinetics of intranasally and intravenously administered dexmedetomidine in healthy volunteers and to report the effects of intranasally and intravenously administered dexmedetomidine on plasma catecholamine levels, systemic blood pressure, heart rate and sedation.

Material and methods

The study (EudraCT 2008-008324-33, ClinicalTrials.gov identifier NCT00837187) was conducted according to the revised Declaration of Helsinki of the World Medical Association and ICH GCP guidelines for good clinical trial practice. The study underwent limited monitoring by a qualified representative of Turku Clinical Research Centre.

Study subjects

After receiving approval from the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency, written informed consent was obtained from eight voluntary healthy male subjects older than 18 years and weighing at least 60 kg. Subjects with a body mass index $> 30 \text{ kg/m}^2$, previous history of intolerance to the study drug or related compounds and additives, concomitant drug therapy of any kind except paracetamol in the 14 days prior to the study, existing or recent significant disease, history of any kind of drug allergy, previous or present alcoholism, drug abuse, psychological or other emotional problems, special diet or lifestyle or clinically significant abnormal findings in physical examination, ECG or laboratory screening were considered not eligible for the study. Additionally, donation of blood within six weeks prior to and during the study and participation in any other clinical study involving investigational or marketed drug products and smoking within one month prior to the entry into this study and during the study were prohibited.

It was defined in the protocol that six subjects must have undergone two treatment periods for study completion. Six of the eight subjects were initially allocated into the study group and two remained in reserve to replace subjects in case of a common cold or other condition jeopardizing the

reliability of the results after intranasal administration of dexmedetomidine or withdrawal of a subject for some other reason.

A two-period, cross-over design with balanced randomization was used. The subjects were given in a randomized order 84 µg bolus doses of dexmedetomidine, once intravenously and once intranasally. The wash-out period between the two administrations was at least seven days. The study protocol specified that at least six subjects had to undergo two evaluable treatment periods for study completion.

Prior to the study days, the subjects had to refrain from the use of any drugs known to cause enzyme induction or inhibition for 30 days, any medications and some natural products (including grapefruit products) for at least 14 days and alcohol and caffeine-containing products for at least 24 hours. On the study days, the subjects had to fast from midnight until 4 h after study drug administration. During this period, only water intake was allowed.

A venous catheter was inserted into a large forearm vein for administration of dexmedetomidine and other drugs potentially needed for the treatment of adverse events. An arterial catheter was inserted into the radial artery for blood sampling and blood pressure monitoring. ECG, invasive blood pressure and peripheral arteriolar oxygen saturation (SpO₂) were monitored continuously. The subjects were served standard meals 4 h and 8 h after dexmedetomidine administration.

Study treatments

A dose of 84 µg of dexmedetomidine (0.84 ml of dexmedetomidine hydrochloride 118 µg/ml, corresponding to dexmedetomidine base 100 µg/ml, Precedex®, Hospira, Lake Forest, IL, USA) was administered intravenously over 10 min at a constant rate using an infusion pump. Another

dose of 84 µg of a more concentrated veterinary formulation of dexmedetomidine (0.2 ml of dexmedetomidine hydrochloride 500 µg/ml, corresponding to dexmedetomidine base 420 µg/ml, Dexdomitor®, Orion Oyj, Espoo, Finland) was administered intranasally using a nasal spray application system (Spray Pump VP7/100S, 0.1 ml/dose, Valois Pharma, Le Vaudreuil, France) – one dose in each nostril.

Blood sampling

Arterial blood samples were collected immediately prior to administration of dexmedetomidine (baseline) and thereafter at 5, 10, 15, 20, 30 and 45 min and 1, 1.5, 2 and 3 h for determination of concentrations of dexmedetomidine, adrenaline and noradrenaline in plasma. Additional blood samples were collected at 4, 5, 6, 8 and 10 h after dexmedetomidine administration for determination of dexmedetomidine. EDTA was used as the anticoagulant.

Dexmedetomidine and catecholamine analysis

Dexmedetomidine concentrations in plasma were determined with a fully validated [5] method based on reversed-phase high-performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS; Shimadzu Prominence HPLC connected to an AB Sciex API4000 mass spectrometer). The method was based on a previously published method [6]. The mobile phase was 0.1 % formic acid in a mixture of 1:1:1 (v/v/v) methanol/acetonitrile/water. The lower limit of quantitation was 0.02 ng/ml. The within- and between-run precision of the assay (coefficient of variation) was within 8 % in the relevant concentration range. Concentrations of adrenaline and noradrenaline in plasma were measured using HPLC and coulometric electrochemical detection [7].

Pharmacokinetic analysis

The peak drug concentrations in plasma (C_{\max}) and the corresponding time points (t_{\max}) were

directly determined from the data. Areas under the dexmedetomidine plasma concentration–time curves were estimated using the trapezoidal rule with extrapolation to infinity ($AUC_{0-\infty}$). We used the linear trapezoidal rule when successive concentration values were increasing and the logarithmic trapezoidal rule when successive concentration values were decreasing after the peak concentration. For each subject, the terminal log-linear phase of the dexmedetomidine plasma concentration-time curve was visually identified, and the elimination rate constant (k_e) was determined by regression analysis. The elimination half-life ($t_{1/2}$) was then calculated from the following equation: $t_{1/2} = \ln 2 / k_e$.

After intravenous administration of dexmedetomidine, plasma clearance (CL) and steady-state volume of distribution (V_{ss}) of dexmedetomidine were calculated with noncompartmental methods based on statistical moment theory. The bioavailability of intranasally administered dexmedetomidine (F) was calculated as follows: $F = AUC_{0-\infty \text{ intranasal}} / AUC_{0-\infty \text{ intravenous}}$. The pharmacokinetic data were analyzed with the WinNonlin pharmacokinetic program (version 4.1; Pharsight, Mountain View, CA, USA).

Pharmacodynamic measurements

Heart rate, systolic and diastolic blood pressure and adrenaline and noradrenaline concentrations in plasma were measured to assess the sympatholytic effects of dexmedetomidine. The Maddox wing test was used to measure the effect of dexmedetomidine on the coordination of the extraocular muscles [8], and the Bispectral Index (BIS) was used to monitor the level of sedation [9]. Subjective effects were recorded with 100-mm horizontal visual analog scales (VAS) with opposite qualities at each end (no effects of the drug/very strong effects of the drug, excellent performance/poor performance, alert/drowsy) [10]. For adrenaline and noradrenaline concentrations and each pharmacodynamic variable, the area under the concentration-time curve (AUC) or response-time

curve (AUEC) was determined by use of the trapezoidal rule in fractions of 0 to 0.5, 0 to 3 or 0 to 10 hours, depending on the duration of recording of each variable.

Assessment of local tolerability

The tolerability of intranasally administered dexmedetomidine was assessed with visual analog scales by the study subjects and by visual inspection by the investigator immediately prior to administration of dexmedetomidine (baseline) and thereafter at 1, 5 and 10 h. Subjective effects (no irritation/strong irritation, no obstruction/total obstruction, no numbness/total numbness, no rhinorrhea/strong rhinorrhea) were recorded using VAS as described above. In the visual inspection by the investigator, possible local mucosal irritation, inflammation, bleeding and ulcerations were recorded. For each VAS value, the area under the response-time curve (AUEC) was determined using the trapezoidal rule for 10 hours.

Statistical analysis

The results are expressed as medians (range). The Wilcoxon signed rank test was used, and differences were regarded as significant at $P < 0.05$. All data were analyzed using PASW Statistics 18.0 for Mac (SPSS Inc, Chicago, IL, USA).

The primary outcome variables in this study were the observed dexmedetomidine concentrations in plasma and the calculated pharmacokinetic parameters of dexmedetomidine. Secondary variables were heart rate, blood pressure, plasma adrenaline and noradrenaline concentrations, sedative effects of dexmedetomidine and possible local effects of intranasally administered dexmedetomidine.

Results

One subject informed in the morning of the second study day that he had caught a common cold, and he was replaced in that study session by a reserve subject. Once the subject with the flu had recovered, a third study session was arranged for him and the replacing subject. Therefore, seven subjects participated in both treatment periods. Intranasal administration of dexmedetomidine failed in one subject because of a handling error of the nasal application system. This study subject was excluded from the analysis. Thus, seven study subjects participated in the study but only six successfully completed the study and were included in the analyses.

Pharmacokinetics

The calculated pharmacokinetic parameters are shown in Table 1 and the median (range) plasma concentrations of dexmedetomidine are shown in Figure 1. The values of C_{\max} were 0.34 (0.23-0.70) and 3.48 (2.70-3.72) ng/ml after intranasal and intravenous administration, respectively. The median value for t_{\max} was 38 (15-60) min after intranasal administration. The corresponding values for $t_{1/2}$ were 114 (107-151) and 115 (99-145) min and for dexmedetomidine $AUC_{0-\infty}$ 74.1 (45.7-114.4) and 123.6 (92.2-138.4) min·ng/ml. The number of subjects having dexmedetomidine concentrations below the lower limit of quantitation was one at 8 h and five at 10 h following intravenous dexmedetomidine. Following intranasal dexmedetomidine, the corresponding numbers were two at 8 h and four at 10 h, respectively. Dexmedetomidine concentrations could be quantitated in all other samples drawn after the administration of dexmedetomidine. The median absolute bioavailability of intranasal dexmedetomidine was 65 %, although the individual values had notable variation, ranging from 35 to 93 %.

Pharmacodynamics

Heart rate and systolic and diastolic blood pressure were monitored until 10 hours to assess the effects of dexmedetomidine (Fig. 2). Based on the values for AUEC, heart rate was significantly ($P = 0.046$) lower during the initial 0-30 min period after intravenous than intranasal administration, but there was no statistically significant difference over the 0-10 hour period. Systolic and diastolic blood pressure were similar regardless of the administration route and no statistically significant differences between the treatments were noted.

There were no differences in plasma adrenaline concentrations based on $AUC_{0-30 \text{ min}}$ or $AUC_{0-3 \text{ h}}$. Plasma noradrenaline $AUC_{0-30 \text{ min}}$ was significantly lower ($P = 0.028$) after intravenous administration than after intranasal administration, but the values for $AUC_{0-3 \text{ h}}$ did not differ (Fig. 3).

Subjective effects (drug effect, performance and drowsiness) and BIS results are shown in Figure 4. After intravenous administration of dexmedetomidine, drug effects became apparent sooner compared to intranasal application: $AUEC_{0-30 \text{ min}}$ values of subjective effects, BIS and the Maddox wing test were significantly ($P < 0.05$) different after intranasal and intravenous administration but there were no differences in the $AUEC_{0-3 \text{ h}}$ values.

Local tolerability

There were no visual signs of local mucosal irritation, inflammation, bleeding or ulceration of the nasal mucosa. In addition, no subjective adverse events were reported.

Discussion

Bioavailability of dexmedetomidine after oral and buccal administration has been described previously [11], but the bioavailability after intranasal administration has remained undetermined. However, intranasal dexmedetomidine has been used successfully as premedication in children [3, 4], and the current study confirms that the bioavailability of intranasal dexmedetomidine is sufficient to warrant further investigation of this route of administration. The large interindividual variation observed in our study subjects attests to the need to develop and document an improved drug delivery system compared to the one used by us, if intranasal application is to be clinically applicable.

The effects of intranasal dexmedetomidine were similar to those of intravenous dexmedetomidine judged by the areas under the effect curves, but – as expected - the onset of the effects was more rapid after intravenous administration. The onset of the effects of intranasal dexmedetomidine was at 30 - 45 min after administration, which is in line with the observed C_{\max} of intranasal dexmedetomidine and previous experience in clinical paediatric patients [4] and adult volunteers [2]. If used for premedication before surgery or other invasive procedures, intranasal dexmedetomidine should optimally be administered 45-60 min before the start of the procedure.

The study subjects reported no numbness, irritation, bleeding, bad taste or any other subjective effects after intranasally administered dexmedetomidine. Neither was any local irritation of the nasal mucosa observed by the investigators. These findings suggest that the intranasal administration route might be a safe method to administer dexmedetomidine. However, this aspect has to be confirmed in a larger number of study subjects and also in real-life patients.

Nevertheless, the volume, formulation and site of intranasal spray application may be of crucial importance when any drug is administered via this route. Indeed, we failed in the intranasal application in one subject, although we had practised the use of the application system. In the clinical situation, dosing with nasal spray administration may be even more difficult to accomplish than in an experimental setting, especially in children. Development of an optimized formulation and nasal delivery system is clearly required for this route to be clinically applicable. Nevertheless, it likely makes no great difference for absorption if part of the dexmedetomidine dose ends up in the pharynx and mouth, because dexmedetomidine is also readily absorbed from the oral mucosa [11]. Still, if the applied volume is too large, part of the administered drug will be swallowed, causing impaired bioavailability because of first-pass metabolism, and diminished efficacy.

According to the literature [4], intranasal dexmedetomidine has mainly been used as premedication in paediatric patients. The intranasal route is an efficacious and rather comfortable way to administer dexmedetomidine particularly in children afraid of needles, and this route could be favoured over intravenous or intramuscular administration. The intranasal route could also be a convenient and safe means to provide dexmedetomidine sedation and analgesia for terminally ill patients.

This study has several limitations. The study involved a rather small number of healthy volunteers. However, it was not intended to be a formal bioequivalence study, but its aim was to characterize the pharmacokinetics and pharmacodynamics of intranasally administered dexmedetomidine as compared to its intravenous administration. The absolute dose of intranasally administered dexmedetomidine remains uncertain even though we had practiced administration and the commercial application system we used was specifically designed for this purpose - the manufacturer of the nasal application system guarantees that the volume administered is $0.1 \text{ ml} \pm 10 \%$, which was verified by us with weighing experiments performed in the laboratory (results not

shown). It is possible that part of the intranasal drug solution ran from the nasal cavity to the pharynx and was swallowed, even though the volume of the administered dexmedetomidine solution was small (0.1 ml / nostril) and the administration was synchronized with the inspiration to maximize the spread of the aerosol within the nasal cavity. This inaccuracy in dosing probably caused part of the large variation in nasal bioavailability between the subjects. Even if the range of individual nasal bioavailability estimates was broad (35-93 %), five of the six individual estimates of bioavailability exceeded 50 %. Such variability in bioavailability is not unusual when unmodified intravenous preparations are used for intranasal drug administration [12]. An optimized delivery system for the intranasal route would most likely improve the bioavailability and reduce its interindividual variability.

In conclusion, the bioavailability of intranasal dexmedetomidine is good. Intranasal administration of dexmedetomidine is efficacious and seems to be well tolerated, making it suitable for clinical situations requiring light sedation. According to the current study, intranasal dexmedetomidine should be administered 45-60 min prior to the desired moment of maximal effect.

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Figure legends

Fig. 1 Dexmedetomidine concentrations in plasma (median (range)) after administration of 84 µg of dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers. The concentrations are shown both on arithmetic and logarithmic scales (inset).

Fig. 2 Heart rate and blood pressure (median (range)) after administration of 84 µg of dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers. *SAP*, systolic arterial pressure; *DAP*, diastolic arterial pressure.

Fig. 3 Adrenaline and noradrenaline concentrations in plasma (median (range)) after administration of 84 µg of dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers.

Fig. 4 Results (median (range)) of recordings of subjective effects (drug effect, performance, drowsiness) from visual analog scales (VAS) and Bispectral Index after administration of 84 µg of

dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers.

References

- 1 Hayashi Y, Maze M (1993) Alpha 2 adrenoceptor agonists and anaesthesia. *Br J Anaesth* 71 (1): 108-118
- 2 Yuen VM, Irwin MG, Hui TW, Yuen MK, Lee LH (2007) A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. *Anesth Analg* 105 (2): 374-380
- 3 Yuen VM, Hui TW, Irwin MG, Yuen MK (2008) A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. *Anesth Analg* 106 (6): 1715-1721
- 4 Yuen VM, Hui TW, Irwin MG, Yao TJ, Wong GL, Yuen MK (2010) Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. *Anaesthesia* 65(9): 922-929
- 5 FDA Guidance for Industry, Bioanalytical Method Validation, May 2001.
- 6 Ji QC, Zhou JY, Gonzales RJ, Gage EM, El-Shourbagy TA (2004) Simultaneous quantitation of dexmedetomidine and glucuronide metabolites (G-Dex-1 and G-Dex-2) in human plasma utilizing liquid chromatography with tandem mass spectrometric detection. *Rapid Commun Mass Spectrom* 18 (15): 1753-1760
- 7 Scheinin M, Karhuvaara S, Ojala-Karlsson P, Kallio A, Koulu M (1991) Plasma 3,4-dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG) are insensitive indicators of alpha 2-adrenoceptor mediated regulation of norepinephrine release in healthy human volunteers. *Life Sci* 49 (1): 75-84
- 8 Hannington-Kiff JG (1970) Measurement of recovery from outpatient general anaesthesia with a simple ocular test. *Br Med J* 3 (5715): 132-135
- 9 Sigl JC, Chamoun NG (1994) An introduction to bispectral analysis for the electroencephalogram. *J Clin Monit* 10 (6): 392-404
- 10 Bond A, Lader MH (1974) The use of visual analogue scales in rating subjective feelings. *Br J Med Psychol* 1974 (47): 211-218
- 11 Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H (2003) Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. *Br J Clin Pharmacol* 56 (6): 691-693
- 12 Takala A, Kaasalainen V, Seppälä T, Kalso E, Olkkola KT (1997) Pharmacokinetic comparison of intravenous and intranasal administration of oxycodone. *Acta Anaesthesiol Scand* 41 (2): 309-312

Table 1 Pharmacokinetic parameters after 84 µg of dexmedetomidine administered intravenously and intranasally in six healthy male volunteers.

No	Body mass index (kg/m ²)	Intravenous route						Intranasal route					
		C _{max} (ng/ml)	t _{1/2} (min)	AUC _{0-∞} (ng·min/ml)	Fraction of AUC _{0-∞} extrapolated (%)	CL (l/h)	V _{ss} (l)	C _{max} (ng/ml)	T _{max} (min)	t _{1/2} (min)	AUC _{0-∞} (ng·min/ml)	Fraction of AUC _{0-∞} extrapolated (%)	F (%)
1	22.8	3.26	103	129.3	3.5	39.0	73.2	0.23	15	109	45.7	10.6	35.3
2	24.8	3.72	126	135.5	5.7	37.2	87.2	0.28	60	151	71.8	7.2	53.0
3	26.5	3.69	131	138.4	3.2	36.4	86.1	0.70	60	118	114.4	3.5	82.6
4	25.9	2.70	145	110.3	8.0	45.7	120.2	0.37	45	109	76.3	5.4	69.2
5	25.9	3.36	99	92.2	6.0	54.7	94.7	0.31	30	107	56.7	8.9	61.5
6	19.6	3.60	104	118.0	2.7	42.7	80.1	0.46	20	141	110.1	10.6	93.3
Median	25.3	3.48	115	123.6	4.6	40.9	86.6	0.34	38	114	74.1	8.1	65.4
Range	19.6-26.5	2.70-3.72	99-145	92.2-138.4	2.7-8.0	36.4-54.7	73.2-120.2	0.23 – 0.70	15-60	107-151	45.7-114.4	3.5-10.6	35.3-93.3

The results are given as median and range.

C_{max}, peak plasma concentration; t_{max}, time corresponding to C_{max}; AUC_{0-∞}, area under dexmedetomidine plasma concentration–time curve; CL, plasma clearance; V_{ss}, steady-state volume of distribution; F, bioavailability.

Dexmedetomidine (ng/ml)







