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Clinical Investigation

CLINICAL INVESTIGATION

Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine

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Abstract

Background: Intranasal dexmedetomidine produces safe, effective sedation in children and adults. It may be administered by drops from a syringe or by nasal mucosal atomization (MAD Nasal™).

Methods: This prospective, three-period, crossover, double-blind study compared the pharmacokinetic (PK) and pharmacodynamic (PD) profile of i.v. administration with these two different modes of administration. In each session each subject received 1 μg kg^{-1} dexmedetomidine, either i.v., intranasal with the atomizer or intranasal by drops. Dexmedetomidine plasma concentration and Ramsay sedation score were used for PK/PD modelling by NONMEM.

Results: The i.v. route had a significantly faster onset (15 min, 95% CI 15–20 min) compared to intranasal routes by atomizer (47.5 min, 95% CI 25–135 min), and by drops (60 min, 95%CI 30–75 min), ($P<0.001$). There was no significant difference in sedation duration across the three treatment groups ($P=0.88$) nor in the median onset time between the two modes of intranasal administration ($P=0.94$). A 2-compartment disposition model, with transit intranasal absorption and clearance driven by cardiac output using the well-stirred liver model, was the final PK model. Intranasal bioavailability was estimated to be 40.6% (95% CI 34.7–54.4%) and 40.7% (95% CI 36.5–53.2%) for atomization and drops respectively. Sedation score was modelled via a sigmoidal E_{max} model driven by an effect compartment. The effect compartment had an equilibration half time 3.3 (95% CI 1.8–4.7) min^{-1}, and the EC50 was estimated to be 903 (95% CI 450–2344) pg ml^{-1}.

Conclusions: There is no difference in bioavailability with atomization or nasal drops. A similar degree of sedation can be achieved by either method.

Clinical trial registration: HKUCTR-1617.

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Editor's key points

- Little is known about the pharmacokinetics of the α2 agonist dexmedetomidine when it is applied intranasally.
- Eight adults received 1 μg kg^{-1} dexmedetomidine on three separate occasions.
- Bioavailability was similar (~40%) for two methods of intranasal administration (drops or mucosal atomizer device).
- Degree and duration of sedation were similar for i.v. and intranasal administration.

Dexmedetomidine is a highly selective α2 adrenergic receptor antagonist that acts on the locus ceruleus[1] to produce dose-dependent sedation with no respiratory depression and only modest haemodynamic effects.[2,3] The i.v. formulation is also efficacious when administered by the intranasal route in both children[4–8] and adults.[9,10] Since this is not associated with any unpleasant sensation, there is increasing use for paediatric premedication and procedural sedation.[5,11]

There is one report on the bioavailability (65%) of intranasal dexmedetomidine in healthy volunteers,[12] performed with a special nasal pump and a highly concentrated veterinary formulation of dexmedetomidine (84 μg in 0.2 ml). Since neither the nasal pump nor the veterinary formulation are available for human use, these data cannot be applied to clinical practice where intranasal dexmedetomidine is usually administered by drops with a 1-ml tuberculin syringe or by using a nasal mucosal atomization device (MAD Nasal™, Wolfe Tory Medical Inc., Salt Lake City, UT, USA).

The aim of this study was to evaluate the pharmacokinetics and pharmacodynamics of dexmedetomidine with these two intranasal modes of administration in healthy volunteers and compare this with i.v. administration.

Methods

The study was approved by the Institutional Review Board of the University of Hong Kong (UW 12-373) and was registered with Hong Kong Clinical Trials Registry (HKCTR-1617). Written, informed consent was obtained from all participants before the study started. Healthy adults with ASA physical status class I were recruited. Exclusion criteria included BMI >30 kg m^{-2}, history of intolerance to the study drug or related compounds, concomitant drug therapy of any kind except paracetamol in the 14 days prior to the study, previous or present alcoholism, drug abuse, cigarette smoking, and abnormal ECG. All participants were requested to refrain from the use of any herbal medicine, any medications, and some natural products (including grapefruit products) for at least 14 days, and alcohol- and caffeine-containing products for at least 24 h.

This was a three-period, crossover study. Eight participants, seven males and one female, aged from 29 to 42 years with BMI ranging from 19.1 to 28.5 kg m^{-2} were recruited and attended three study sessions. The study was double-blind to avoid bias during assessment of sedation status by both participants and observers. All participants received i.v. drug/placebo and one mode of intranasal drug/placebo administration at the beginning of each study session. A crossover study design was used to reduce inter-individual variability (IIV). As there were three treatment periods for each participant and two possible routes of intranasal placebo whenever a participant received i.v. dexmedetomidine, the possible number of treatments with different assignment of intranasal placebo would be 12. However, whenever the intranasal route, be it placebo or active drug, were the same for the first two treatment periods, it would be possible for the participants and investigators to guess the route of active drug administration on the third study period. Therefore, eliminating those treatment and intranasal placebo combinations, the possible number of treatments was eight. All participants were randomly assigned to one of the eight possible treatment orders. Two independent anaesthesiologists who were not involved in data collection and drug administration were responsible for drug and placebo preparation during each study session. All syringes were labelled with the participants' name and identification number and were verified before drug administration during each study session. The study drugs were administered by investigators who were blinded to treatment allocation.

The order of drug administration was randomly assigned once the participant was recruited into the study with a washout period of at least 7 days. In each of these sessions each participant received 1 μg kg^{-1} dexmedetomidine either i.v., intranasal by atomizer or intranasal by drops. I.V. dexmedetomidine was prepared in 50 ml 0.9% saline and was administered via a 20G i.v. cannula over 10 min with a programmable syringe pump. When intranasal dexmedetomidine was administered by atomization or by drops, the parenteral formulation of undiluted dexmedetomidine (100 μg ml^{-1}) at 1 μg kg^{-1} was used and drawn up in tuberculin (1 ml) syringes. When atomization was used to deliver dexmedetomidine, the dead space of the atomizer was filled with dexmedetomidine before the drug was administered. An equal volume of drug was given via the two nostrils when the drug was administered intranasally. Atomization was performed with the participant sitting up with a slight backward head tilt as this allows optimal spread and absorption of atomized solutions.[5] When the intranasal drug was administered by drops, participants were asked to lie flat so that the solution could be dripped into the nostrils.

On the study day the participants were fasted from midnight until 3 h after the study drug administration. During this period water intake was allowed. Two 20G i.v. catheters, one on each upper limb, were inserted at the commencement of each session. One i.v. access was used for drug or placebo administration and the other for blood sampling. The study drug was administered after recording baseline pulse rate (PR), non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), oxygen saturation (SpO_2), and sedation status. SpO_2 and pulse rate were monitored continuously for the first