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Does intranasal dexmedetomidine provide adequate plasma concentrations for sedation in children: a pharmacokinetic study

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Abstract

Background: Atomised intranasal dexmedetomidine administration is an attractive option when sedation is required for paediatric diagnostic procedures, as vascular access is not required. The risk of haemodynamic instability caused by dexmedetomidine necessitates better understanding of its pharmacokinetics in young children. To date, intranasal dexmedetomidine pharmacokinetics has only been studied in adults.

Methods: Eighteen paediatric patients received dexmedetomidine 1 or 2 μg kg^{-1} intranasally or 1 μg kg^{-1} i.v. Plasma concentrations were determined by liquid chromatography/mass spectrometry. Non-compartmental analysis provided estimates of C_{max} and T_{max}. Volume of distribution, clearance, and bioavailability were estimated by simultaneous population PK analysis of data after intranasal and i.v. administration. Dexmedetomidine plasma concentration-time profiles were evaluated by simulation for intranasal and i.v. administration.

Results: An average peak plasma concentration of 199 pg ml^{-1} was achieved 46 min after 1 μg kg^{-1} dosing and 355 pg ml^{-1} was achieved 47 min after 2 μg kg^{-1} dosing. A two-compartment pharmacokinetic model, with allometrically scaled parameters, adequately described the data. Typical bioavailability was 83.8% (95% confidence interval 69.5–98.1%).

Conclusion: Mean arterial plasma concentrations of dexmedetomidine in infants and toddlers approached 100 pg ml^{-1}, the low end reported for sedative efficacy, within 20 min of an atomised intranasal administration of 1 μg kg^{-1}. Doubling the dose to 2 μg kg^{-1} reached this plasma concentration within 10 min and achieved almost twice the peak concentration. Peak plasma concentrations with both doses were reached within 47 min of intranasal administration, with an overall bioavailability of 84%.

Keywords: anaesthesia; dexmedetomidine; intranasal; paediatrics; pharmacokinetics

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Editor's key points

- Dexmedetomidine is a highly selective α2 adrenergic agonist with anxiolytic, sedative, and mild analgesic properties.
- Although intranasal use is well-described in children, little is known of its pharmacokinetics in this setting.
- The pharmacokinetics of intranasal and i.v. dexmedetomidine was studied in 18 children.
- After intranasal administration, peak plasma concentrations occurred at 46 min, and bioavailability was >80%.

Intranasal dexmedetomidine is an attractive needle-free sedative for paediatric use where i.v. access is unnecessary or may be deferred until sedation is achieved. Dexmedetomidine has been widely used for paediatric sedation for non-painful procedures.[1] It has a short half-life, promotes a calm emergence, and is associated with maintenance of airway stability and spontaneous ventilation.[2–4] Dexmedetomidine is effective and painless when administered by the nasal route.[5] Pharmacodynamic studies of intranasal dexmedetomidine onset, efficacy, and adverse effects have been reported in children.[6–10]

To minimise side effects and instruct clinical dosing, it is imperative to gather pharmacokinetic information on dexmedetomidine in paediatric patients. The pharmacokinetics of i.v. dexmedetomidine have been studied in children, including premature infants.[11–13] However, while one pharmacokinetic study of intranasal bolus dosing of dexmedetomidine has been performed in adult humans,[14] no such data exist in children. This represents a substantial lack of information, as rapid administration of dexmedetomidine is associated with hemodynamic alterations, such as bradycardia, arterial hypotension, and hypertension.[15] The margin of safety with intranasal dosing is currently unknown.

Accordingly, this represents the first pharmacokinetic study of atomised intranasal dexmedetomidine in children. Cardiac surgery patients were selected for this study because of the availability of intra-arterial access for repeated blood sampling, routine use of dexmedetomidine as part of our anaesthetic plan, and our previously published pharmacodynamic data with intranasal dexmedetomidine in a similar patient population.[7,10] The aim of the study was to characterise the peak drug concentration in plasma for two different doses of intranasal dexmedetomidine and to determine bioavailability compared with i.v. dosing. Based on prior adult pharmacokinetic and paediatric pharmacodynamic data, we hypothesised that intranasal atomised dexmedetomidine would reach plasma concentrations associated with sedation in approximately 20 min, with peak plasma concentrations within 60 min of administration.[7,14]

Methods

This prospective pharmacokinetic study in a single quaternary paediatric referral centre was registered at clinicaltrials.gov on January 8, 2016 (NCT02836431) with principal investigator: J.W.M. Dexmedetomidine is not approved by the US Food and Drug Administration (FDA) for use in paediatric patients; accordingly, this study was conducted under an Investigational New Drug (IND # 76-346) application. After FDA review, the Institutional Review Board of Cincinnati Children's Hospital Medical Center approved this trial on December 1, 2015. This manuscript adheres to the applicable Equator guidelines.[16]

Study population

The enrolment period was from January 2016 to December 2016. Paediatric patients for elective cardiac surgery aged 6–48 months were eligible for this study. All patients were scheduled to receive postoperative sedation with i.v. dexmedetomidine infusions. Written, informed consent was obtained from a parent or legal guardian. Eighteen children were sequentially assigned to three treatment groups, each containing six children. With no prior available paediatric data and given funding constraints, we chose six patients per group and eight to nine bioassay samples per patient. Terminal elimination was not studied because of the confounding effects of hemodilution with initiation of cardiopulmonary bypass (CPB) within 2 h of drug administration.

Exclusion criteria were: patients admitted to the hospital before surgery, patients with a history of cardiac conduction system disease (e.g. sinus node disease, first or second degree atrioventricular block) or formally diagnosed channelopathy (e.g. "long QT syndrome"), current treatment with digoxin, alpha-adrenergic or beta-adrenergic agonists or antagonists, clonidine, anti-arrhythmic medications, anticonvulsants, presence of life-threatening medical conditions (ASA Physical Status 4 or 5), previous exposure to dexmedetomidine within 1 week, or unrepaired coarctation of the aorta. Patients with acute nasal or respiratory symptoms on the day of the study were excluded because of potential interference with intranasal absorption.

Clinical protocol

All subjects received an inhalation induction of anaesthesia with sevoflurane followed by i.v. and intra-arterial cannula placement and tracheal intubation. Medications administered before surgery and during the study period were recorded. Standard monitoring per ASA guidelines was fully instituted before dexmedetomidine administration. Patients were in the supine position with their head positioned in the midline. The first six patients received undiluted intranasal dexmedetomidine (Mylan Pharmaceuticals, Canonsburg, PA, USA; 100 μg ml^{-1}), 1 μg kg^{-1}, by atomiser (Teleflex MAD Nasal; Research Triangle Park, NC, USA) in one naris as a rapid spray from a 1 ml syringe containing the dexmedetomidine and 0.2 ml air as a 'chaser' to ensure complete expulsion of the medication.[17] The second six patients received 2 μg kg^{-1} intranasal dexmedetomidine in one naris in identical fashion. The maximum volume administered was 0.29 ml. The syringe was oriented approximately 30 degrees from horizontal in supine patients to direct the atomised medication cephalad toward the upper third of the nasal cavity.[18] All nasal dexmedetomidine administration was performed by a single physician (J.W.M.) with extensive experience using the atomiser. To determine bioavailability, the final six patients received 1 μg kg^{-1} i.v. dexmedetomidine (Mylan Pharmaceuticals; 4 μg ml^{-1}) over 10 min by infusion pump into a peripheral i.v. cannula.

Supplemental anaesthetic drugs were reduced by the anaesthesia team in anticipation of the co-anaesthetic effects of the administered dexmedetomidine. The patients each