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Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age

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Background. Information has been very limited on the pharmacokinetics of the selective α_2-adrenoceptor agonist dexmedetomidine in children, particularly in children <2 yr of age.

Methods. Eight children aged between 28 days and 23 months and eight children aged between 2 and 11 yr undergoing either elective bronchoscopy or nuclear magnetic resonance imaging were included in the study. Dexmedetomidine 1 $\mu g\ kg^{-1}$ was infused i.v. over 5 min. Blood samples for the measurement of plasma concentrations of dexmedetomidine were collected for 5 h after starting the infusion. Pharmacokinetic calculations were based on non-compartmental methods.

Results. In the two groups of paediatric patients, the median (range) values for total plasma clearance of dexmedetomidine were 17.4 (14.1–27.6) and 17.3 (9.3–22.5) ml $kg^{-1}\ min^{-1}$, for volume of distribution at steady state 3.8 (1.9–4.6) and 2.2 (1.3–2.8) litre kg^{-1} ($P<0.05$), and for elimination half-life 139 (90–198) and 96 (69–140) min ($P<0.05$), respectively. The volume of distribution at steady state was negatively associated with subject age ($r=-0.69$, $P<0.05$).

Conclusions. To reach a certain plasma concentration, children younger than 2 yr of age evidently need larger initial doses of dexmedetomidine than the older children, as young children have a larger volume of distribution of the drug than older children and adults. Since the total plasma clearance of dexmedetomidine is independent of age, similar rates of infusion can be used in younger and older children to maintain a steady-state concentration of dexmedetomidine in plasma.

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Dexmedetomidine is a potent, specific, and selective α_2-adrenoceptor agonist used as a sedative agent in intensive care of adult patients. It has many desirable properties for this use: its effects are not limited to sedation but also include anxiolysis, analgesia, and decreased activity of the sympathetic nervous system. In addition, dexmedetomidine does not depress respiratory drive.[1] These properties, associated with a unique type of pharmacological sedation that mimics natural sleep,[2] make dexmedetomidine a promising agent also for paediatric procedural and intensive care sedation.

Even if the only currently approved indication of dexmedetomidine is sedation of mechanically ventilated adult patients for <24 h, its off-label use for sedation of children is increasing.[3–9] Infants appear to require larger doses of dexmedetomidine compared with older children.[10] To ensure safe dosing of dexmedetomidine in children, we considered it important to evaluate the pharmacokinetics of dexmedetomidine in different paediatric age groups.

Methods

After appropriate approvals from the local ethics committee and the National Agency for Medicines, informed written consent was obtained from the parents to include

16 children in this pharmacokinetic study. The subjects' age range was from 28 days to 11 yr, all were ASA I–II, and were undergoing elective bronchoscopy or nuclear magnetic resonance imaging (NMRI). The use of enzyme inducing medication, for example, anticonvulsants, was an exclusion criterion. Two age groups of children were included. The first group consisted of eight children aged between 28 days and 23 months (children <2 yr) and the second group consisted of eight children aged between 2 and 11 yr (children >2 yr). These age groups are in agreement with current ICH guidelines.[11] The characteristics of the patients are summarized in Table 1. Premedication was not used, but EMLA® cream (Astra Zeneca Inc., Sweden) was applied topically before peripheral venous cannulation. After the insertion of an i.v. catheter, a control blood sample (1.0 ml) was drawn. Thereafter, a dose of 1 μg kg^{-1} of dexmedetomidine (Precedex®, Orion Pharma, Espoo, Finland) was administered over 5 min by continuous i.v. infusion. Another i.v. catheter was inserted in the opposite arm for drawing of blood samples once the patients had been anesthetized for bronchoscopy or NMRI, as described below.

After the loading dose of dexmedetomidine, the children undergoing bronchoscopy were anaesthetized with sevoflurane in a mixture of oxygen and air given via a face mask. The vaporizer was initially set to 8%. Upon loss of consciousness, the vaporizer setting was decreased to 4%. Bronchoscopy was performed with a flexible fibreoptic endoscope. The children were breathing spontaneously throughout the procedure. Heart rate and peripheral arteriolar oxygen saturation were monitored, and arterial pressure was recorded non-invasively every 5 min during the procedure and then every 15 min afterwards until the patient regained consciousness.

After the loading dose of dexmedetomidine, the children undergoing NMRI received i.v. midazolam 0.05 mg kg^{-1} or i.v. thiopentone 1 mg kg^{-1} to supplement the anaesthesia, if required. Heart rate and peripheral arteriolar oxygen saturation were monitored during the procedure and afterwards until the patient was awake. To avoid disturbance, arterial pressure was not measured.

Venous blood samples of 1.0 ml each were collected 5, 10, 20, 30, 60, 120, 180, 240, and 300 min after the end of the dexmedetomidine loading infusion. Blood samples were drawn into EDTA tubes and stored at +10°C. Plasma was separated within 2 h of blood collection, frozen, and stored at −20°C in polypropylene tubes for subsequent analysis.

Concentrations of dexmedetomidine in plasma were determined using reversed-phase high-performance liquid chromatography with tandem mass spectrometric detection (PE Sciex API365 instrument; PE Sciex, Foster City, CA, USA) as described previously.[12] The lower limit of reliable quantitation of the assay was 0.1 ng ml^{-1}. The within- and between-run precision of the assay (coefficient of variation) was within 8% in the relevant concentration range.

The individual plasma dexmedetomidine concentrations were fitted to the following multiexponential function with the aid of a non-linear regression program (WinNonlin version 4.1, Pharsight Corporation, Mountain View, CA, USA), using iteratively reweighted least squares with reciprocal squared prediction weighting:

$$C(t) = \sum_{i=1}^{n} C_i \cdot e^{-\lambda_i \cdot t},$$

where $C(t)$ is the plasma concentration of dexmedetomidine at time t; C_i, a zero-time intercept; and λ_i, a disposition rate constant. The goodness of the fit was determined by Akaike's[13] information criterion, and by assessment of the randomness of the scatter of the actual data points about the fitted function. The values for the area under the plasma dexmedetomidine concentration *vs* time curve (AUC) were calculated from:

$$\mathrm{AUC} = \sum_{i=1}^{n} \frac{C_i}{\lambda_i}.$$

The plasma clearance (CL), steady-state volume of distribution (V_{ss}), and terminal elimination half-life ($t_{1/2,z}$) of dexmedetomidine were calculated according to the standard formulae.[14] In addition, we calculated the standardized values CL and V_{ss} for a body weight of 70 kg using an allometric model: standardized CL=CL/(weight/70)$^{0.75}$; standardized V_{ss}=V_{ss}/(weight/70).[15]

The Mann–Whitney *U*-test was used to compare the groups. Differences were regarded as statistically significant at $P<0.05$. The relationships of the pharmacokinetic parameters with age were analysed with Pearson's product moment correlation coefficient. The results are expressed as medians (range), except in Figure 1, where mean (SD) are given.

Results

The characteristics of the patients and the pharmacokinetic parameters are shown in Table 1. The pharmacokinetics of dexmedetomidine was best described by a bi-exponential function in all cases. Although the values for CL and standardized CL were similar in the two age groups, both V_{ss} and standardized V_{ss} were smaller ($P<0.05$) in children >2 yr of age than in the younger children (Fig. 1). Correspondingly, $t_{1/2,z}$ was shorter in the older group ($P<0.05$). Both V_{ss} and standardized V_{ss} were negatively associated with subject age ($r=-0.69$; $P<0.05$) (Fig. 2).

Dexmedetomidine was well tolerated. During the loading infusion of dexmedetomidine, all children fell asleep, but they were easily aroused when manipulated, for example, during insertion of an i.v. catheter or positioning for NMRI. During the NMRI procedure, five of eight children needed supplemental sedation with thiopentone. The median dose of thiopentone was 5.1 (3.6–8.0) mg kg^{-1}. Three patients,

Table 1 Patient characteristics and pharmacokinetic variables of dexmedetomidine in children given 1 μg kg^{-1} of i.v. dexmedetomidine in 5 min. Data are given as median (range), or mean (SD) for weight, or number. CL, total plasma clearance of dexmedetomidine; V_{ss}, steady-state volume of distribution; $t_{1/2,z}$, elimination half-life; AUC, area under the dexmedetomidine plasma concentration–time curve. *Significantly ($P<0.05$) different from children aged <2 yr

Variable	Children <2 yr	Children >2 yr
Age (yr)	0.6 (0.2–1.9)	4.2 (2.3–10.0)
Weight (kg)	8.7 (2.7)	20.4 (7.4)
Sex (M/F)	1/7	7/1
Type of procedure		
Bronchoscopy	4	4
NMRI	4	4
AUC (min ng ml^{-1})	57.4 (36.2–74.0)	57.9 (44.4–107.6)
CL (ml min^{-1} kg^{-1})	17.4 (13.5–27.6)	17.3 (9.3–22.5)
Standardized CL (ml min^{-1} 70^{-1} kg^{-1})	794 (515–1273)	854 (557–1048)
V_{ss} (litre kg^{-1})	3.8 (1.9–4.6)	2.2 (1.3–2.8)*
Standardized V_{ss} (litre 70^{-1} kg^{-1})	268 (134–322)	155 (89–199)*
$t_{\frac{1}{2},z}$ (min)	139 (90–198)	96 (69–140)*

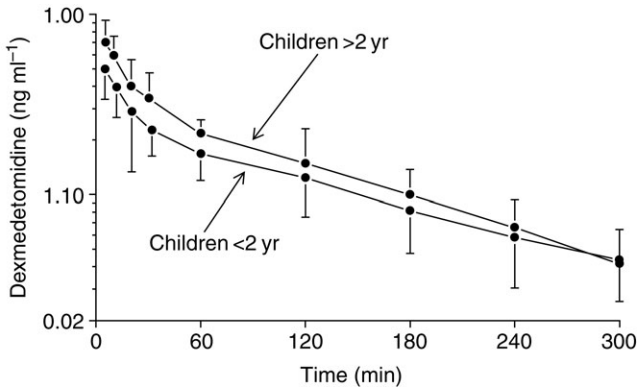

Fig 1 Mean (SD) plasma concentrations of dexmedetomidine after an i.v. dose of 1 μg kg^{-1} in children younger or older than 2 yr of age.

including one patient already given thiopentone, were given midazolam 0.15 (0.05–0.22) mg kg^{-1}. There were no clinically significant decreases in peripheral arteriolar oxygen saturation. None of the patients experienced nausea or vomiting, and no adverse effects were reported during the study.

Discussion

The pharmacokinetics of dexmedetomidine were clearly dependent on subject age in the present study. Total plasma clearance was similar in younger and older children, but the volume of distribution (V_{ss}) and consequently also the terminal elimination half-life ($t_{1/2,z}$) were greater in children younger than 2 yr of age compared with older children. There was, however, quite marked inter-individual variation in the pharmacokinetic parameters, especially in the younger age group.

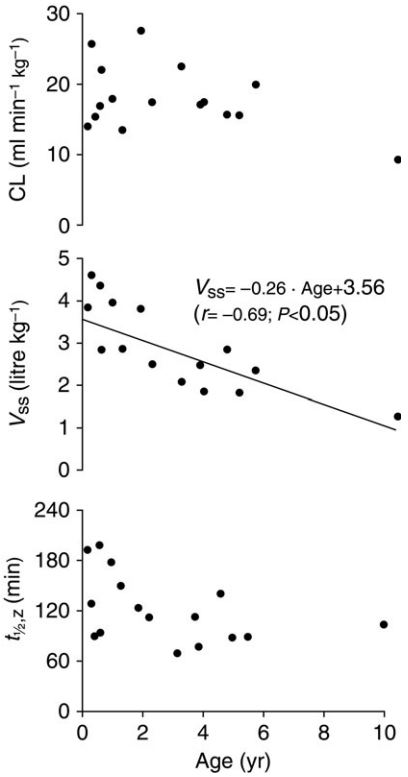

Fig 2 Total plasma clearance (CL), volume of distribution at steady state (V_{ss}), and elimination half-life ($t_{1/2,z}$) of dexmedetomidine related to age. The line describes the linear regression equation between V_{ss} and subject age.

Information on the pharmacokinetics of dexmedetomidine in the paediatric population is very limited, especially in children younger than 2 yr of age. To our knowledge, there are only two published reports on the pharmacokinetics of dexmedetomidine in children. Díaz and colleagues[16] studied 10 paediatric postoperative patients aged between 0.3 and 7.9 yr who were mechanically ventilated in the paediatric intensive care unit. Nine patients had had cardiac surgery and one had had craniofacial surgery. The patients received a loading dose of dexmedetomidine 1 μg kg^{-1} over 10 min and were then given a constant-rate infusion of 0.2–0.7 μg kg^{-1} h^{-1} of dexmedetomidine as clinically indicated. In that patient population, the values for CL, V_{ss}, and $t_{1/2,z}$ of dexmedetomidine were approximately 9.5 ml kg^{-1} min^{-1}, 1.5 litre kg^{-1}, and 100 min, respectively. In another study, a population pharmacokinetic approach was used.[17] Altogether 24 children undergoing major surgery completed the pharmacokinetic part of the study. Their ages ranged from 2 to 12 yr. Typical values in that study for systemic CL and $t_{1/2,z}$ were 13 ml min^{-1} kg^{-1} and 110 min, respectively.

Compared with the two previous paediatric studies, the total plasma clearance of dexmedetomidine appeared to be somewhat greater in our subjects than what has been earlier observed in children.[16 17] Our subjects were in good general health and not deeply anaesthetized, which

might explain this difference. Our subjects also had somewhat greater clearance of dexmedetomidine than has been reported for adult subjects.[18–20] The allometric scaling procedure, however, brought the observed clearance values rather close to those previously reported for adults. Thus, by using allometric scaling, the CL of dexmedetomidine and consequently also the steady-state requirements could have been predicted rather well with the pharmacokinetic data collected from adults. Regarding V_{ss} and standardized V_{ss}, it is obvious that allometric scaling does not predict the volume of distribution in children younger than 2 yr of age. V_{ss} and consequently also $t_{1/2,z}$ was greater in children younger than 2 yr of age, compared with the older children and adults. This pharmacokinetic age-related difference causes younger children to need larger initial doses of dexmedetomidine than older children and adults in order to reach similar steady-state plasma levels, but the maintenance doses are similar. In the clinic, this is a well-known phenomenon.[10] However, the characterization of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children is still far from complete, and further studies addressing both pharmacokinetic and pharmacodynamic issues at young age are warranted.

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