Dexmedetomidine Pharmacology in Neonates and Infants After Open Heart Surgery.

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Abstract

BACKGROUND:

Dexmedetomidine is a highly selective α2-agonist with hypnotic, analgesic, and anxiolytic properties. Despite off-label administration, dexmedetomidine has found a niche in critically ill neonates and infants with congenital heart disease because of its minimal effects on respiratory function at sedative doses, facilitating early extubation and fast-track postoperative care. There are little pharmacokinetic data regarding newborns who have immature drug metabolizing capacity and who are at risk for reduced dexmedetomidine clearance and drug toxicity. The aim of this study was to determine the pharmacokinetics of dexmedetomidine in neonates and infants after open heart surgery. This study included 23 evaluable neonates (age, 1 day-1 month) and 36 evaluable infants (age, 1 month-24 months) after open heart surgery.

METHODS:

Full-term neonates and infants requiring mechanical ventilation after open heart surgery received dexmedetomidine in a dose-escalation study. Dexmedetomidine was administered as a loading dose over 10 minutes followed by a continuous IV infusion up to 24 hours. Cohorts of 12 infants were enrolled sequentially to receive 0.35, 0.7, or 1 μg/kg dexmedetomidine followed by 0.25, 0.5, or 0.75 μg/kg/h dexmedetomidine, respectively. Cohorts of 9 neonates received 0.25, 0.35, or 0.5 μg/kg dexmedetomidine followed by 0.2, 0.3, or 0.4 μg/kg/h dexmedetomidine, respectively. Plasma dexmedetomidine concentrations were determined using a validated high-performance liquid chromatography-tandem mass spectrometry assay. A population nonlinear mixed effects modeling approach was used to characterize dexmedetomidine pharmacokinetics.

RESULTS:

Pharmacokinetic parameters of dexmedetomidine were estimated using a 2-compartment disposition model with weight allometrically scaled as a covariate on drug clearance, intercompartmental clearance, central and peripheral volume of distributions and age, total bypass time, and intracardiac shunting on clearance. Dexmedetomidine demonstrated a plasma drug clearance of 657 × (weight/70) mL/min, intercompartmental clearance of 6780 × (weight/70) mL/min, central volume of distribution of 88 × (weight/70) L and peripheral volume of distribution of 112 × (weight/70) L for a typical subject with age >1 month with a cardiopulmonary bypass time of 60 minutes and without right-to-left intracardiac shunt. Dexmedetomidine pharmacokinetics may be influenced by age during the neonatal period, weight, total bypass time, and presence of intracardiac shunt.

CONCLUSIONS:

Dexmedetomidine clearance is significantly diminished in full-term newborns and increases rapidly in the first few weeks of life. The dependence of clearance on age during the first few weeks of life reflects the relative immaturity of metabolic processes during the newborn period. Continuous infusions of up to 0.3 μg/kg/h in neonates and 0.75 μg/kg/h in infants were well tolerated after open heart surgery.

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