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Population pharmacokinetics of ketamine in children with heart disease

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ABSTRACT

This study aims at developing a population pharmacokinetic model for ketamine in children with cardiac diseases in order to rationalize an effective 2-h anesthetic medication, personalized based on cardiac function and age. Twenty-one children (6 months to 18 years old) were enrolled in this prospective, open label study. Ketamine 2 mg/kg IV was administered and blood samples were then collected over 8 h for ketamine assay. Pharmacokinetic data analysis using NONMEM, was undertaken. Ketamine pharmacokinetics was adequately described by a two-compartment linear disposition model. Typical population parameters were: total clearance: $60.6 \times (\text{weight}/70)^{0.75}$ L/h, intercompartmental clearance: $73.2 \times (\text{weight}/70)^{0.75}$ L/h, central distribution volume: $57.3 \times (\text{weight}/70)$ L, and peripheral distribution volume: $152 \times (\text{weight}/70)$ L. Ketamine clearance in children with pre-existing congenital heart disease was comparable to values reported in healthy subjects. Computer simulations indicated that an initial loading dose of ketamine 2 mg/kg IV over 1 min followed by a constant rate infusion of 6.3 mg/kg/h for 29 min, 4.5 mg/kg/h from 30 to 80 min, and 3.9 mg/kg/h from 80 to 120 min achieves and maintains anesthetic plasma level for 2 h in children 1 year or older (weight $\geq$10 kg).

1. Introduction

Ketamine differs from most anesthetic agents in that it stimulates the sympathetic nervous system, often resulting in increased systemic vascular resistance, cardiac output, and blood pressure (Haas and Harper, 1992). Accordingly, ketamine has been a popular agent for induction of anesthesia in young children with pre-existing congenital heart disease (Greeley et al., 2001). Ketamine was reported to be a safe alternative for anesthesia maintenance in children with both cyanotic (Tugrul et al., 2000), and non-cyanotic structural heart disease (Ulke et al., 2008). Ketamine has been used to provide anesthesia during pediatric cardiac catheterization procedures (Oklu et al., 2003), and to achieve sedation in children after cardiac surgery (Hartvig et al., 1993; Tobias et al., 1990).

Ketamine is a highly lipid soluble drug (Cohen and Trevor, 1974), that is associated with large steady-state volume of distribution (1.5–3.7 L/kg) and rapid clearance (0.7–2 L/h/kg). (Brunette et al., 2011; Clements and Nimmo, 1981; Clements et al., 1982; Domino et al., 1984, 1982; Geisslinger et al., 1993; Grant et al., 1983; Hartvig et al., 1993; Herd and Anderson, 2007; Herd et al., 2007; Hijazi et al., 2003; Malinovsky et al., 1996). Ketamine is eliminated by hepatic metabolism through *N*-demethylation to Nor-ketamine via CYP 3A4, CYP 2B6, and CYP 2C9 enzyme systems (Hijazi and Boulieu, 2002). However, CYP 3A4 has been shown to be the major contributor to ketamine metabolism (Hijazi and Boulieu, 2002). The high ketamine clearance rate suggests that its elimination is susceptible to factors affecting hepatic blood flow (Brunette et al., 2011; Hartvig et al., 1993; Malinovsky et al., 1996).

Despite the common use of ketamine in children with cardiac disease, pharmacokinetic (PK) data in this population are sparse. To the best of our knowledge, there is only one study that investigated ketamine disposition from long-term infusions in children after cardiac surgery (Hartvig et al., 1993). The current study was undertaken to better define the PK of ketamine in children with

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pre-existing congenital heart disease following a single dose of ketamine in order to rationalize an effective 2-h anesthetic medication, personalized based on cardiac function and age.

2. Material and methods

2.1. Patients, ketamine dosing and monitoring

Following approval of the Institutional Review Board (IRB), twenty-one children between the ages of 6 months and 18 years were enrolled in this prospective, open label study, after informed written consent of their parents. All patients were fasted prior to surgery and received premedication according to institutional guidelines. Upon arrival in the operating room, following standard monitoring and inhalational induction of anesthesia with sevoflurane, an IV catheter was inserted and a neuromuscular blocking agent was administered. The trachea was intubated, then arterial and central venous catheters were inserted as per institutional protocol.

A baseline (T_0) venous blood sample was obtained, following which ketamine 2 mg/kg IV was administered as a zero order infusion over 5 min using a Baxter AS50 infusion pump (Baxter Inc., Deerfield, IL, USA). Venous blood samples were drawn at 1, 5, 10, 15, 20, 30, 45, 60 min; then at 2, 3, 4, 5, 6 and 8 h later. The blood samples were drawn into EDTA tubes that were gently mixed to mix EDTA with blood and put on ice. Samples were immediately centrifuged following collection at 1500 *g* for 10 min at 4 °C and plasma was separated into propylene tubes that were frozen for batched assay.

After a 6:1 (acetonitrile:plasma) protein precipitation, plasma samples were measured by iC42 clinical research (Aurora, CO) using a Waters Acquity UPLC-MS/MS system. The injection volume was 10 μL of supernatant. The analytical column was an Acquity UPLC HSS T3 1.8 μm 2.1 × 100 mm. The assay had a lower limit of quantitation (LLQ) of 0.003 μg/mL and the range of reliable response was from 0.003 to 2.5 μg/mL ($r^2 > 0.999$), inter-day accuracy was ±2.5% and inter-day precision was ±3.4%. Intra-day accuracy was ±4.2% and intra-day precision was ±1.1%. The analytical run time was 2.5 min.

2.2. Population PK modeling

Ketamine plasma concentration–time data were analyzed using the non-linear mixed effects modeling software program NONMEM (version VII; Icon Development Solutions, Ellicott City, MD). A two-compartment linear disposition model parameterized in terms of total clearance (CL), inter-compartmental clearance (Q), central (VC) and peripheral (VP) volume of distribution was used as the structural PK model. The model was specified using PREDPP subroutines ADVAN3 TRANS4. The first-order conditional estimation (FOCE) with η–ε interaction was used for the estimation of the model parameters.

Under the assumption that the PK parameters are log-normally distributed, the inter-individual variability was described by an exponential variance model (Eq. (1)):

$$P_i = \theta \times \exp(\eta_I) \tag{1}$$

where P_i is the value of the respective PK parameter in the *i*th individual, θ is the typical (population) value of the parameter, and η_I is the random (unexplained) difference between θ and P_i. Values of η_I are assumed to follow a multivariate normal distribution with mean zero and variance–covariance matrix, Ω. Covariance was permitted between each of the pharmacokinetic parameters.

Proportional (Eq. (2)) and combined additive and proportional (Eq. (3)) models of residual (intra-individual) variability for PK observations were evaluated:

$$Y_{ij} = F_{ij} \times (1 + \varepsilon_{ij}) \tag{2}$$

$$Y_{ij} = F_{ij} \times (1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \tag{3}$$

where Y_{ij} is the *j*th observed ketamine concentration in the *i*th subject, F_{ij} is the model-predicted concentration, and ε is the residual error assumed to be independently and normally distributed with mean zero and variance σ^2.

In addition to the two compartment model, one-compartment model (ADVAN1 TRANS2) and three-compartment model (ADVAN6 TOL5) were initially evaluated as structural models. Selection between the competing models was based on (1) the Akaike information criterion (AIC) (Beal et al., 1994), computed as two times the number of model estimated parameters added to the NONMEM minimum objective function (−2 log likelihood) value (OFV); (2) the basic goodness-of-fit plots, including observed *versus* predicted concentrations and conditional weighted residuals *versus* population predictions; and (3) the precision of parameter estimates, expressed as the relative standard error (% SE) and calculated as the percentage of the standard error provided by NONMEM $COVARIANCE step to the parameter estimate.

After selecting the best structural model, likelihood ratio testing under the assumption of χ^2-distributed difference in the NONMEM OFV (Sheiner and Ludden, 1992), was used to discriminate between several hierarchical models (*e.g.*, diagonal/non-diagonal Ω, proportional/mixed ε,*etc.*). The significance level (α) was set to 0.01, which means that a decrease in the OFV of ≥6.63 was necessary to consider model improvement due to an added parameter (1 degree of freedom). When more than one parameter was added, a decrease in OFV of ≥9.21, 11.35, or 13.28 was needed for 2, 3, and 4 degrees of freedom, respectively.

Following principles of pediatric clinical pharmacology and previous population PK models in infants and children for ketamine (Brunette et al., 2011; Herd and Anderson, 2007; Herd et al., 2007), an allometric body weight (WT)-based model scaled to a 70 kg adult (Anderson and Meakin, 2002; Holford, 1996) was first implemented to account for the influence of body size on the PK parameters:

$$P_{\mathrm{i}} = P_{\mathrm{std}} \times \left(\frac{\mathrm{WT}_i}{70\mathrm{kg}}\right)^{\mathrm{PWR}} \tag{4}$$

where P_{std} is the parameter value in an individual weighting 70-kg. The exponent PWR was fixed to 0.75 for clearances and 1.0 for volumes. The allometrically scaled model was the base model for further covariate model building.

Besides weight, other covariates evaluated were post-natal age (AGE), gender, hypoxia, and patient physical status (ASA scores <3 and ≥3). Relationship between a continuous covariate and a PK parameter was modeled as linear (Eq. (5)), exponential (Eq. (6)), or power (Eq. (7)) functions:

$$\theta = \theta_0 \times [1 + \theta_{\mathrm{COVAR}} \times (\mathrm{COVAR} - \mathrm{mean\ COVAR})] \tag{5}$$

$$\theta = \theta_0 \times \exp[\theta_{\mathrm{COVAR}} \times (\mathrm{COVAR} - \mathrm{mean\ COVAR})] \tag{6}$$

$$\theta = \theta_0 \times \left[\frac{\mathrm{COVAR}}{\mathrm{mean\ COVAR}}\right]^{\theta_{\mathrm{COVAR}}} \tag{7}$$

where θ_0 is the typical value of θ for a subject with mean covariate value and θ_{COVAR} is the estimated effect for the covariate on parameter value. For categorical covariates, the following model was used (Eq. (8)):