Poster

[P27-5] P27-5: Cardiovascular drugs (2)

Chair: David A. Joyce, Australia

Wed. Sep 27, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Wed. Sep 27, 2017 12:30 PM - 1:30 PM Annex Hall)

[P27-5-6] Population pharmacokinetics of milrinone in newborns and infants after cardiac surgery

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Keywords: Pharmacometirics, Neonates and infants, Developmental Pharmacokinetics, Acute Kidney Injury, Phosphodiesterase 3 inhibitor

Background

Milrinone is an inotropic agent used in the treatment of ventricular dysfunction after pediatric cardiac surgery. Milrinone is mainly eliminated by the kidney and previous data suggested that an association exists between pediatric patients with renal dysfunction and decreased clearance [Gist KM et al. Ther Drug Monit. 2015]. However, there is limited information on developmental changes in milrinone clearance in newborns and infants who also experience acute kidney injury (AKI). The aim of this study was to develop a milrinone PK model using prospectively collected data in patients with or without AKI following cardiac surgery.

Methods

PK data were obtained from 94 infants aged 6 days to 12 months in the prospective clinical study (NCT01966237). Two patients were excluded from the PK modeling because of milrinone treatment initiated before surgery. Milrinone was administered by continuous infusion at a rate of 0.25-1.2 g/kg/min intra- or post-operatively with or without a loading dose. Blood samples were collected at specific time intervals after termination of cardiopulmonary bypass (CPB), and at each dose change and at multiple times (3-4) after termination of milrinone. Milrinone concentration was determined by validated LC-MS/MS assay. AKI status was determined based on the KDIGO clinical Practice Guideline within the first 3 post-operative days. Population PK analysis was performed using NONMEM. The final model was used in a simulation analysis to characterize developmental changes in clearance.

Results

A total of 1088 milrinone concentrations were available for population PK modeling. A 2-compartment model was found to most adequately describe the PK data. Inclusion of allometrically-scaled body weight and age-dependent maturation described by a sigmoidal Emax model significantly improved the model fit ($P < 0.001$). AKI status was identified as a significant covariate on milrinone clearance. Simulated age-dependent milrinone clearance values were in good agreement with observed estimates.

Conclusions

This study provides a population PK model for milrinone in newborns and infants which captures the developmental changes in clearance. The developed PK model will facilitate model-informed precision dosing of milrinone in patients with or without AKI. Further studies including older children are warranted.