Poster

[P27-3] P27-3: Anti-infective drugs (8): Antiviral

Chair: Birgit C. P. Koch, The Netherlands

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[P27-3-6] Population pharmacokinetics of ganciclovir in critically ill patients

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Background

Ganciclovir is a first-line antiviral agent for treatment of CMV infections. Currently, only limited data is available of ganciclovir pharmacokinetics in critically ill patients. Physiological changes in critically ill patients, specifically an increased volume of distribution (V) and alterations in renal clearance (CL), are likely to influence the pharmacokinetic profile of ganciclovir. This study aimed to characterize ganciclovir population pharmacokinetics and inter-individual variability (IIV) in critically ill patients. Secondary objectives were to identify patient characteristics that explain this IIV.

Methods

In this retrospective observational study, clinical data and serum ganciclovir levels were collected from all critically ill patients treated with intravenous ganciclovir at our intensive care unit between 1 October 2005 and 1 October 2015. Pharmacokinetic (PK) modeling was performed by non-linear mixed effect modeling (NONMEM). The final model was validated using bootstrap and visual predictive check.

Results

Included were 34 patients with a total of 128 ganciclovir measurements. Median CKD-EPI at start ganciclovir was 65 ml/min/1.73m^2 (Range: 9-166 ml/min/1.73m^2). Nineteen patients (55.9%) received continuous venovenous hemofiltration (CVVH) during a part of their treatment.

The best structural model for ganciclovir was a one-compartment model with first-order elimination. In the univariate analysis serum creatinine, CKD-EPI, CVVH (binary) and a history of kidney transplantation were associated with ganciclovir clearance ($p<0.05$), but only CKD-EPI was included after multivariate analysis ($p<0.001$). In the final model, the estimated CL and V were 2.3 L/h (RSE: 10%), and 42 L (RSE: 21%) respectively, for a patient with the median CKD-EPI of 65 ml/min/1.73m^2. For a patient with all median characteristics but a CKD-EPI of 20 ml/min/1.73m^2, CL was 0.98 L/h. This was 3.5 L/h when CKD-EPI was 120 ml/min/1.73m^2. Upon introduction of this association the residual variability changed from 0.56 to 0.43 and IIV for V from 114% to 80% and for CL from 43% to 47%.

Conclusions

In this study, a large variability was observed in ganciclovir pharmacokinetics during critical illness. CKD-EPI could explain part of the (residual) variability, however much variability remains unexplained. The authors are currently investigating this PK model for characterizing the relationship between ganciclovir exposure and viral eradication.