Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol18Issue1abst175P.pdf

A population pharmacokinetic analysis of paracetamol in a u.k population

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Introduction: Paracetamol (APAP) overdose is a major medical problem in the UK and leading cause of drug induced liver injury and acute liver failure [1]. Mechanistic biomarkers have been demonstrated to provide added value for the early prediction of APAP-induced hepatotoxicity. The objective of this study was to develop a predictive model of liver injury risk representative of a British APAP overdose population.
Method: Subjects were selected from the BIOPAR NHS portfolio prospective study from 10 independent UK centres between 2010-2014 [2]. The pharmacokinetic model was developed by using Pirana integrated with NONMEM 7.3 with first order conditional estimation method (FOCE). Model evaluation was based on objective function (OFV) and diagnostic plots. Visual predictive check plots and bootstrapping 1000 replicates indicated that the proposed model was adequate and robust. Performance of the model was also assessed when patients were stratified by liver injury biomarkers as a covariate on clearance (CL).

Results: 94 patients out of 202 were included into the analysis, (51%female and 49%male), median weight 66.68kg (range 35-171.4), median age 29years (range 18-81), the median ingestion of APAP was 32g (range 8-140), 225 samples and the median APAP plasma concentration at first presentation was 33mg/L (range 2-500). A one compartment (first order absorption kinetics) with exponential error model was chosen as the most appropriate model for the data. The effects of the covariates (weight, age, gender and liver injury biomarkers) were evaluated in the final model, as a results no covariate warranted inclusion into the final model. The mean population estimation of CL and volume distribution (Vd) were 10.2L/h and 133L, respectively. Between occasion variability of CL was 43%. To aid model fit, the absorption constant (Ka) was fixed at $4.57h^{-1}$ after a sensitivity analysis using parameter values found in literature.

Conclusions: The pharmacokinetics of APAP overdose in this population have slightly decrease in CL and increase in Vd compared with therapeutic dose. Future work will utilise further data in APAP overdose cohorts by using a Bayesian method to investigate the effect of biomarkers in CL.

References

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2. Dear, J., et al., *Sensitive and specific risk stratification after paracetamol overdose using mechanistic biomarkers.* Lancet Gastroenterology, 2017.