UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY
CENTER FOR TRANSLATIONAL MEDICINE

POPULATION PHARMACOKINETICS OF ACETAMINOPHEN IN ACUTE OVERDOSED PATIENTS TO DERIVE A NEW RISK METRIC FOR ANTIDOTE ADMINISTRATION

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Background & Objective

Interpretation of acetaminophen (APAP) plasma concentrations is the standard risk-stratification method used to determine the risk of hepatotoxicity in acute acetaminophen overdose and the need for the administration of the antidote.

The purpose of this study is to examine whether a better metric, such as time of maximum plasma APAP concentration (PAC) or area under the curve, can be used as tools to identify those at greatest risk of liver injury in whom antidotal therapy is required using population pharmacokinetic modeling.

Specific objectives of this presentation:
- To explore the acute overdosed patients data
- To develop a population pharmacokinetic (PK) model of APAP in acute overdosed patients.

Methods

Data from Maryland Poison Center
- 561 patients
- Acute APAP overdose
- Between 2 and 6 PAC
- 7 Product Categories
- Some dose information missing

→ Exploration of data by product categories

→ PK Model with APAP only data
- Structural PK Model
- Between-Subject Random Effects
- Residual Error Terms

Missing doses were estimated using linear regression of C_{max} vs dose

The between subject variability (BSV) on the fraction of drug absorbed (F) and lag time (Tlag) represents uncertainty in patient reported dose and time of dose. [1]

→ PK Models by Product Categories

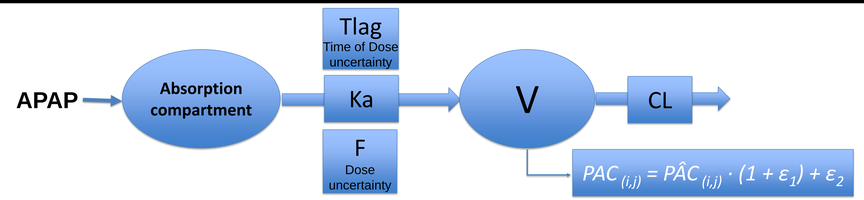
→ PK Model all data = Base PK Model

→ Adequacy of Structural and Residual error model was determined with goodness of fit plots

The analyses were performed using R and Phoenix 6.4 NLME 1.3

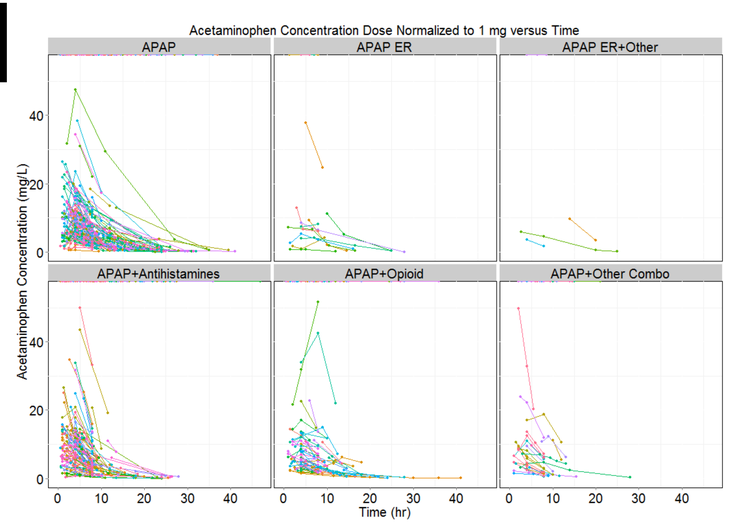
Results

One-Compartment 1st Order Input and Elimination With Proportional + additive residual error structure

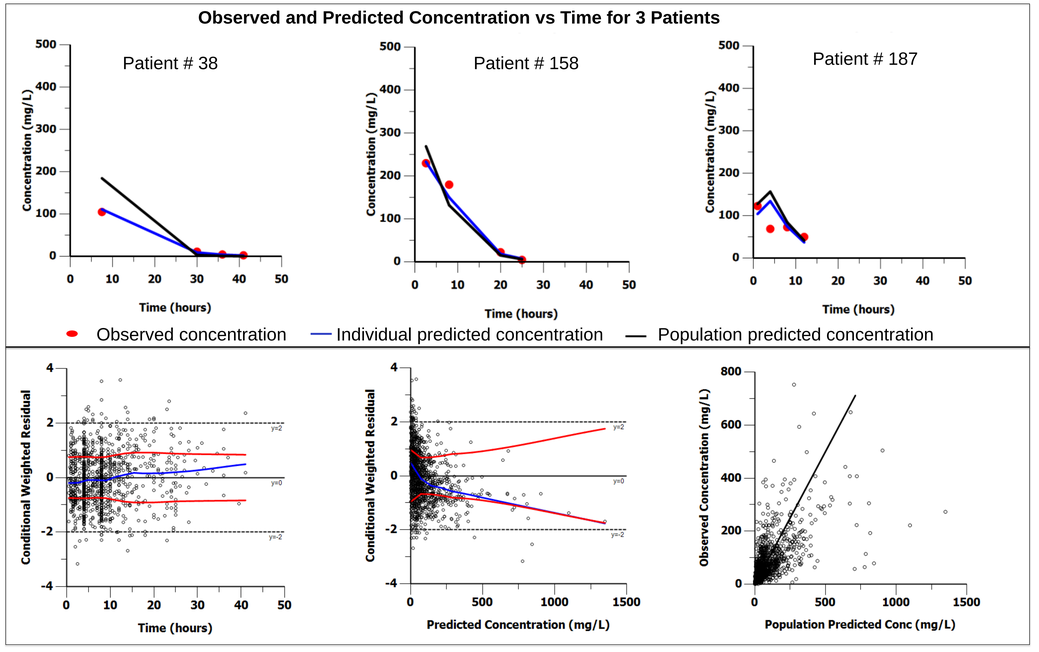


Parameter	Estimate	SE	BSV (%)	RSE (%)
V (L)	91.20	0.63	1.44	13.75
CL (L/hr)	16.52	0.07	6.78	11.62
Ka (1/hr)	0.724	0.001	98.51	2.83
F	1	-	69.78	5.36
Tlag (hr)	0	-	4.42	5.03
Residual error				
Additive (mg/L)	1.76	0.01		
Proportional (%)	27.33	0.08		

Dosing Information



Goodness of Fit Diagnostics



Discussion/Conclusions

- Exploratory plots of dose normalized concentration profile by product showed no major trend between products.
- For the PK model build by product the parameter estimates were similar between each other. Thus all data were modeled together.
- The parameter estimates are similar to that reported for therapeutic levels.[2,3]
- The base model adequately predict the individual concentrations.
- The model still need to be improved by evaluation of covariates, before to be used to identify a better metric to determine should and when an antidote be administered.

References

1.Cooper J.M., Duffull S.B., Saiao A.S., Isbister G.K. **The pharmacokinetics of sertraline in overdose and the effect of activated charcoal**. *Br J Clin Pharmacol*. 2015 Feb;79(2):307-15
2. McNeil's background package on acetaminophen http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882B1_13_McNeil-Acetaminophen.htm
3.Allegaert K., Olkkola K.T., Owens K.H., Van de Velde M., de Maat M.M., and Anderson B.J, **Covariates of intravenous paracetamol pharmacokinetics in adults**. *BMC Anesthesiology* 2014, 14:77