PK of acetaminophen and its metabolites in preterm and term neonates using relevant external background information in a Bayesian approach with Stan

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Objectives

- Optimize IV dosing of acetaminophen (APAP) in neonates, who have a rapidly changing metabolism impacting population pharmacokinetics (PK) [1]
- Different maturation processes have a competing impact on important PK metrics such as half-life, clearances and volumes
- The main challenge was to incorporate the extensive external knowledge [1,2,4] from the literature in the model to allow for an adequate description of relevant maturation processes, despite the very sparse data from IV infusions of APAP which was collected.
- Furthermore, no urine excretion data nor IV administered metabolites experiments were available leading to non-identifiability of formation rates or metabolite volumes.

Methods

A one-cmt model for APAP with the two main metabolites APAPgluc & APAPsulf were fit in a Bayesian approach using Stan [3]. The Stan program developed was designed to process NONMEM formatted datasets to facilitate rapid analysis.

Background Information & Parametrization

- **Allometric '1/4' power scaling** to relate to adult estimates
- Use **reference time-point of post menstrual age (pma)=34 weeks**, i.e. use maturation function [4]

$$\pi_{34} = \mathrm{mat}_{\mathrm{GFR}}(pma = 34) = 0.24$$

- **Organ maturation**: locally describe pma-changes via exponentials in pma with intercept at reference time-point pma=34weeks
  - Glomerular filtration rate (GFR) increase
  - Glucuronidation increase (implicit total clearance increase)
  - Central volume decrease
  - Increase in elimination rate of APAPgluc & APAPsulf
- **Simultaneous fit of GFR** as function of pma with PK model provides GFR maturation rate as prior for all required growth rates

$$\mathrm{GFR}_j(pma_j) = \mathrm{GFR}_{\mathrm{ref}}\,\pi_{34}\exp(\lambda_{\mathrm{GFR}}\,(pma_j - 34))$$

- **Parametrization** chosen to **mirror current literature knowledge**
  - Total fraction of metabolites known to be ~90% in adults

$$Cl_{\mathrm{tot,j}} = \frac{Cl_{\mathrm{APAP,G,j}} + Cl_{\mathrm{APAP,S,j}}}{\pi_{\mathrm{G+S}}}$$

$$\mathrm{logit}(\pi_{\mathrm{G+S}}) \sim (\mathrm{logit}(0.85), \mathrm{logit}(0.95))_{95}$$

  - Elimination of metabolites via the kidney which matures, adult ~7.2 l/h/70kg

$$Cl_{\mathrm{G,j}} = Cl_{\mathrm{G,ref}}\,\pi_{34}\left(\frac{w_j}{70}\right)^{3/4}\exp\left(\lambda_{\mathrm{GFR}}\left(pma_j - 34\right)\right)$$

$$\log Cl_{\mathrm{G,ref}} \sim (\log(5), \log(10))_{95}$$

  - Growth rates in relation to GFR maturation, i.e. for formation of G

$$Cl_{\mathrm{APAP,G,j}} = Cl_{\mathrm{APAP,G,ref}}\,\pi_{34}\left(\frac{w_j}{70}\right)^{3/4}\exp\left(\lambda_{\mathrm{G}}\left(pma_j - 34\right)\right)$$

$$\lambda_{\mathrm{G}} = \frac{\log(2)}{T_{2,\mathrm{G}}}$$

$$T_{2,\mathrm{G}} = T_{2,\mathrm{GFR}}\,\delta_{\mathrm{G}}$$

$$\delta_{\mathrm{G}} \sim \mathrm{LogNormal}(0, \log(5)/1.96)$$

- Use of informative priors on random effects, i.e.

$$\omega_{\mathrm{V,APAP}} \sim \mathrm{LogNormal}(\log(0.2), \log(1.5)/1.96)$$

Estimates

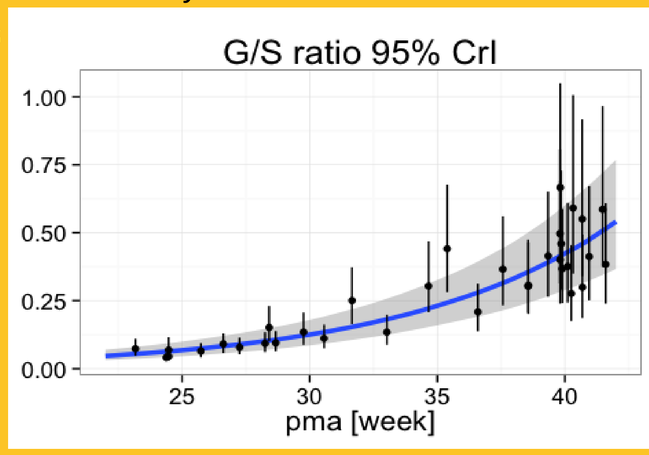
	mean	se_mean	sd	2.5%	97.5%	n_eff	Rhat
CL[1]	17.08	0.04	0.75	15.68	18.68	333.22	1.00
CL[2]	8.15	0.05	1.13	5.99	10.57	586.28	1.00
CL[3]	7.02	0.04	0.61	5.92	8.24	255.76	1.01
CL_M[2]	2.62	0.02	0.39	1.91	3.40	481.00	1.00
CL_M[3]	12.86	0.04	0.91	11.10	14.65	444.07	1.00
V[1]	78.19	0.19	4.29	70.18	86.68	518.08	1.00
V[2]	49.51	0.36	7.86	35.78	65.80	479.01	1.00
V[3]	28.46	0.06	1.94	24.75	32.26	1000.00	1.00

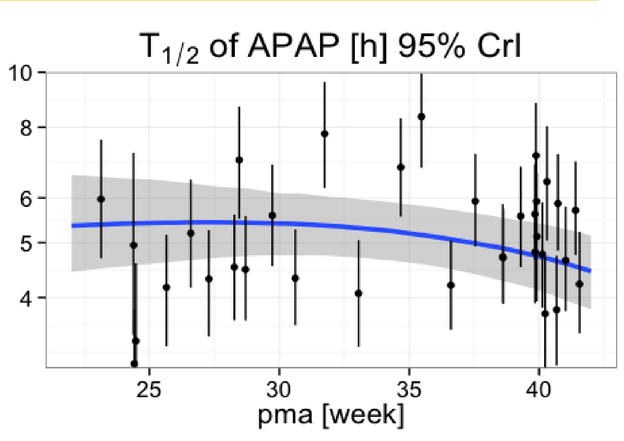
Clearance [l/h/70kg], formation clearance [l/h/70kg] and volume [l/70kg] of a typical neonate (pma=34 weeks), CL&V: 1=APAP, 2=APAPgluc, 3=APAPsulf; CL_M: 2=APAP,G, 3=APAP,S

Conclusions

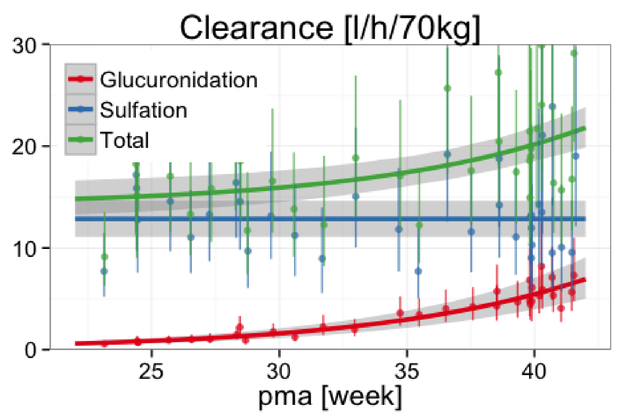
Using a Bayesian approach we were able to interpret the sparse data set using relevant background knowledge

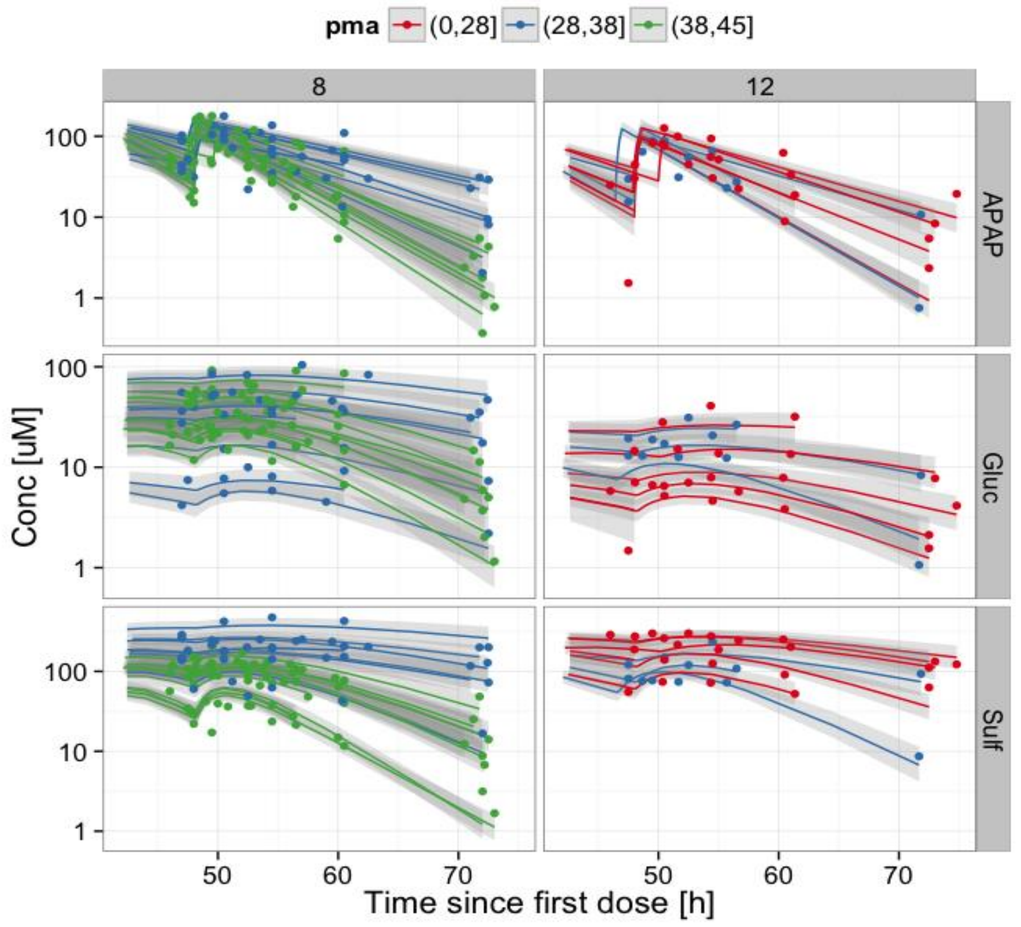
- Allometric '1/4' power scaling & organ maturation was used to relate adult knowledge to pma=34 weeks reference time-points
- Organ maturation was described using pma. Results:
  - A rapidly changing metabolism, i.e. a fast increase in G/S ratio
  - Overall increase in half-lives from pma=40 to pma=35
  - Given the total evidence, half-lives for pma<35 are yet uncertain but appear to remain constant
- Using the known renal elimination clearance of the metabolites enabled estimation of metabolite cmt volumes
- The analysis was conducted using Stan [3] with NONMEM input data sets which facilitates rapid analysis. Computation times were ~30min using an analytic solution.





Upper left: Organ maturation quickly changes the G/S ratio which is 2:1 in adults.
Upper right: Population mean of half-lives of APAP with pma weight correction. Uncertainty for pma<35 considerable, model suggests a constant half-life for early pma. Half-live decreases slowly for pma>35.
Right: Total clearance, formation clearance of sulfation & glucuronidation





Study design

30min IV infusions of APAP
GA<28 (10): 5x 15mg/kg/12h
GA≥28 (25): 7x 15mg/kg/8h
Left: Washout phase for the parent, G & S metabolites. Color codes correspond to pma at baseline and group the patients in very early, early preterm & term neonates. Shown are the individual mean estimates with their 95% credible interval in grey. Key results:

- G concentration much lower for preterms due to immature APAP G formation
- Early preterm show increased APAP half-life (separation of green & blue), but very early preterm show large variability

References:

[1] Allegaert K, et al. (2008) *Pediatr Anesth,*18, 388–392
[2] Pacifici G.M., Allegaert K (2014) *Cur. Thera. Res*. 77 24–30
[3] Stan Dev Team (2015), Version 2.6. http://mc-stan.org
[4] van der Marel CD, et al. (2003), *Eur J Clin Pharmacol*. 59(3):243-51