Modeling and Simulation of Acetaminophen Pharmacokinetics and Hepatic Biomarkers After Overdoses of Extended-Release and Immediate-Release Formulations with DILIsym, a Quantitative Systems Toxicology (QST) Software Platform

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BACKGROUND & PURPOSE

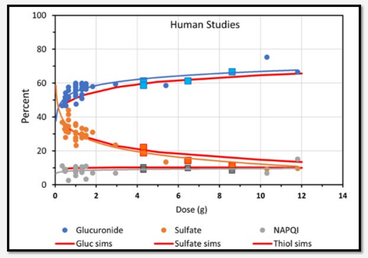
- The analgesic/antipyretic acetaminophen (APAP) has multiple formulations including immediate-, modified-, and extended-release preparations
- In 2017, the European Medicines Agency recommended suspending medicines containing a modified-release (MR) preparation from the market as there was concern that in large overdose, it could form a bezoar resulting in unexpected pharmacokinetics (PK), with markedly prolonged absorption and delayed plasma peak concentrations, compared to an immediate-release (IR) formulation
- There was also a concern that current treatment guidelines developed for APAP overdose were inappropriate for MR formulations
- In the US, the extended-release (ER) formulation of APAP (TYLENOL® 8 HR Arthritis Pain, Johnson & Johnson Consumer Inc., NJ) is designed with an IR layer and an erodible ER layer
- This project utilized a modeling and simulation approach to compare predicted PK and hepatotoxicity biomarkers following various acute overdose and repeated supratherapeutic ingestion (RSTI) scenarios to determine if there is a difference between the US APAP-IR and APAP-ER preparations

METHODS

- The existing APAP-IR representation within DILIsym® v8A, a QST model of drug-induced liver injury (DILI), was updated [*e.g.*, formation of the reactive metabolite N-acetyl-*p*-benzoquinone imine (NAPQI) and other APAP metabolites] using newly acquired *in vitro* and clinical datasets (**Fig. 1**)
- Exposure-dependent cytochrome P450 (CYP) 2E1- and CYP3A4-mediated contributions to NAPQI formation (>85% and <15%, respectively) were implemented
- An APAP-ER model was developed by modifying the representation of APAP absorption in the APAP-IR model to recapitulate the fast- and slow-release from IR and ER layers of the APAP-ER caplet and was verified with clinical data (**Fig. 2**)
- *In vitro* dissolution of APAP from the IR and ER formulations was experimentally evaluated using different systems (*e.g.*, Tiny-TNO Gastro-Intestinal Model smartificialgut, Tiny-TIM*sg*)
- These experimental data were used as input for the Z-factor (Takano) dissolution model within GastroPlus® to inform the *in vivo* dose-vs-fraction absorbed (Fa) relationship for APAP-IR and APAP-ER that was subsequently leveraged within the DILIsym model (**Fig. 3**)
- Simulated populations (SimPops®) representing healthy adults, moderate chronic alcohol users (MCAU), excessive chronic alcohol users (ECAU), and individuals with low glutathione (GSH) were developed and verified using clinical PK and hepatic biomarker data (**Fig. 4**)
- The DILIsym model was then used to simulate PK and three clinically useful hepatic biomarkers [plasma alanine aminotransferase (ALT), total bilirubin (TB), and international normalized ratio (INR)] after single acute overdoses (3.9, 9.75, 19.5, 32.5, 65, 78 and 100.1 g; **Fig. 5**; **Table 1**) and RSTI (3.9, 5.2 and 7.8 g/day; **Table 2**) of APAP-ER and APAP-IR
- Simulations were carried out in the absence of clinical interventions (*e.g.*, decontamination, N-acetylcysteine treatment), such that they represent worst-case scenarios

RESULTS

Fig. 1: Updated APAP metabolism simulations reasonably recapitulated clinically observed percent urinary recovery of metabolites over wide dose ranges[1-32]. Simulations averaged within 9.55% of the dose-response lines generated from clinical data.



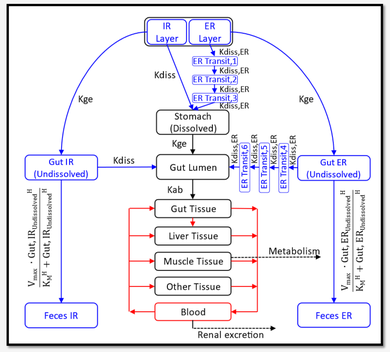


Fig. 2: The APAP model within DILIsym was revised to accommodate administration of APAP-IR and APAP-ER formulations. For APAP-IR simulations, 100% of APAP follows the IR layer pathway, while for APAP-ER simulations, 50% of APAP uses the IR layer pathway, and another 50% uses the ER layer pathway. Once absorbed in the gut, APAP derived from the APAP-IR or APAP-ER layers are handled in a similar fashion.

Fig. 3: Mechanistic modeling of *in vitro* dissolution data predicted that the dose-dependent human *in vivo* Fa (%) of APAP-ER was generally lower than for APAP-IR and declined from ~100% to ~50% when increasing the APAP-IR and APAP-ER dose from therapeutic doses to 100 g overdoses. APAP Fa for both formulations as predicted in GastroPlus (solid lines) was reasonably recapitulated by the DILIsym model (dashed lines) of APAP-IR and APAP-ER. USP, United States Pharmacopeia.

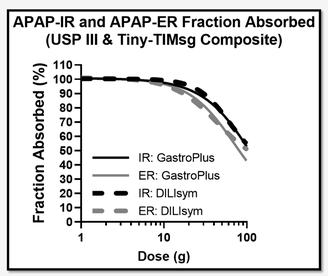


Fig. 4: Calibration and validation of APAP-IR and APAP-ER models[32-34]. A large variety of clinical PK datasets (examples shown) and hepatic biomarker datasets (not shown) at therapeutic and overdose levels for both APAP-IR and APAP-ER were reasonably recapitulated by the baseline (top panels) and SimPops (bottom panels) models. Healthy SimPops for both APAP-IR and APAP-ER covered >80% of individual clinical PK data (C_{max} and AUC values).

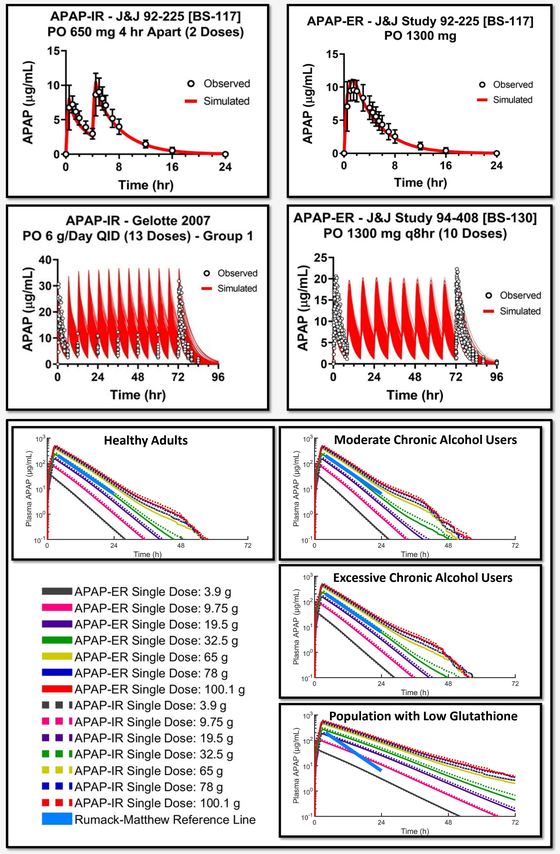


Fig. 5: Simulated mean APAP PK profiles after acute overdoses of APAP-ER (solid lines) and APAP-IR (dotted lines) in healthy adults, moderate chronic alcohol users, excessive chronic alcohol users, and a population with low glutathione. Simulated APAP PK profiles showed no apparent Rumack-Matthew reference line crossing differences between APAP-ER and APAP-IR within each population.

Ingested	AUC_∞ (µg·h/mL)		C_{max} (µg/mL)		Fa		ALT_{max} (U/L)		TB_{max} (mg/dL)		INR_{max}	
Dose (g)	APAP-ER	APAP-IR	APAP-ER	APAP-IR	APAP-ER	APAP-IR	APAP-ER	APAP-IR	APAP-ER	APAP-IR	APAP-ER	APAP-IR
3.9	195.7 (24.10%)	200.0 (23.97%)	32.8 (19.73%)	46.1 (18.67%)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	30.0 (30.00-30.00)	30.0 (30.00-30.00)	0.55 (0.55-0.55)	0.55 (0.55-0.55)	1.0 (1.00-1.00)	1.0 (1.00-1.00)
9.75	542.7 (25.35%)	553.9 (25.44%)	84.5 (19.78%)	103.4 (19.08%)	0.97 (0.95-0.99)	1.00 (0.99-1.00)	36.8 (30.00-201.65)	38.3 (30.00-225.90)	0.55 (0.55-0.59)	0.55 (0.55-0.59)	1.0 (1.00-1.00)	1.0 (1.00-1.00)
19.5	1046.6 (26.79%)	1174.2 (27.02%)	155.7 (20.27%)	201.2 (19.07%)	0.87 (0.81-0.94)	0.97 (0.89-0.99)	272.5 (30.00-4491.62)	421.0 (30.00-6998.37)	0.62 (0.55-2.29)	0.68 (0.55-6.60)	1.0 (1.00-1.86)	1.0 (1.00-4.93)
32.5	1634.6 (27.99%)	1903.2 (28.28%)	234.2 (20.53%)	311.4 (20.27%)	0.77 (0.69-0.87)	0.89 (0.74-0.97)	1268.8 (30.01-8640.56)	1984.7 (32.37-8885.89)	1.12 (0.55-13.86)	1.64 (0.56-12.05)	1.2 (1.00-7.91)	1.5 (1.00-7.92)
65	2841.9 (29.96%)	3255.1 (31.66%)	392.5 (20.83%)	495.6 (22.89%)	0.61 (0.51-0.74)	0.70 (0.50-0.88)	4104.9 (116.74-8894.11)	4756.5 (197.77-8816.65)	3.44 (0.58-15.08)	4.10 (0.59-14.43)	2.5 (1.00-7.90)	2.7 (1.00-7.87)
78	3237.5 (30.59%)	3646.7 (32.59%)	443.7 (21.04%)	545.9 (23.75%)	0.57 (0.46-0.70)	0.64 (0.44-0.84)	4688.0 (176.50-8688.58)	5119.3 (263.87-8741.29)	3.95 (0.59-14.22)	4.53 (0.60-14.88)	2.6 (1.00-7.79)	2.9 (1.00-7.91)
100.1	3822.7 (31.53%)	4190.9 (33.88%)	518.6 (21.54%)	612.9 (24.97%)	0.51 (0.39-0.65)	0.56 (0.36-0.79)	5249.2 (273.63-8800.01)	5398.2 (366.74-8690.06)	4.66 (0.62-14.86)	4.97 (0.61-15.23)	2.9 (1.00-7.92)	3.0 (1.00-7.94)

Table 1 (left) and **Table 2** (right): Comparison of simulated plasma APAP PK parameters and hepatic biomarkers after acute overdoses (Table 1) or RSTI (Table 2) of APAP-ER and APAP-IR in healthy adults. On average, APAP exposure after acute overdose or RSTI in healthy adults was predicted to be lower for APAP-ER compared to APAP-IR. Similar ALT, TB and INR levels were predicted for APAP-ER and APAP-IR after overdoses in healthy adults. These findings were similar when making comparisons between APAP-ER and APAP-IR in the compromised adult SimPops (*i.e.*, MCAU, ECAU, low GSH).

Parameter	Scenario A (3.9 g/day)		Scenario B (5.2 g/day)		Scenario C (7.8 g/day)	
	APAP-ER	APAP-IR	APAP-ER	APAP-IR	APAP-ER	APAP-IR
AUC_t (µg·h/mL)	55.2 (25.69%)	54.9[b] (25.73%)	56.6 (26.60%)	57.5 (26.30%)	59.5 (27.97%)	60.2 (27.70%)
$C_{max,ss}$ (µg/mL)	11.9 (21.52%)	10.9 (21.45%)	13.7 (22.94%)	18.6 (20.49%)	18.0 (25.42%)	23.2 (22.63%)
AccR	0.97 (0.85-1.18)	1.01 (0.85-1.29)	0.99 (0.85-1.26)	0.97 (0.84-1.21)	1.04 (0.85-1.43)	1.01 (0.84-1.36)
Fu APAP (%)	3.2 (23.22%)	3.2 (23.34%)	3.3 (24.20%)	3.4 (23.90%)	3.5 (25.72%)	3.5 (25.45%)
Fu APAP-G (%)	60.3 (13.36%)	60.1 (13.41%)	61.7 (12.58%)	62.5 (12.43%)	64.2 (11.26%)	64.8 (11.19%)
Fu APAP-S (%)	21.7 (28.49%)	22.1 (28.26%)	20.1 (28.73%)	19.2 (29.14%)	17.2 (29.22%)	16.6 (29.49%)
Fu Thiols (%)	9.8 (22.81%)	9.7 (22.88%)	9.8 (22.39%)	9.7 (22.50%)	9.4 (21.61%)	9.3 (21.73%)
Fu Catechols (%)	4.9 (35.64%)	4.9 (35.71%)	5.0 (35.99%)	5.0 (35.93%)	5.2 (36.43%)	5.2 (36.39%)
ALT_{max} (U/L)	31.5 (30.00-137.79)	31.5 (30.00-136.25)	36.0 (30.00-263.33)	35.9 (30.00-262.47)	56.7 (30.00-386.29)	56.1 (30.00-385.04)
TB_{max} (mg/dL)	0.55 (0.55-0.57)	0.55 (0.55-0.57)	0.55 (0.55-0.59)	0.55 (0.55-0.59)	0.56 (0.55-0.62)	0.56 (0.55-0.62)
INR_{max}	1.0 (1.00-1.00)	1.0 (1.00-1.00)	1.0 (1.00-1.00)	1.0 (1.00-1.00)	1.0 (1.00-1.00)	1.0 (1.00-1.00)

Simulated exposure parameters (AUC_∞, C_{max}, AUC_t and $C_{max,ss}$) as well as fraction excreted in urine (Fu) for 300 virtual adults in the APAP-ER and APAP-IR SimPops are reported as mean (% coefficient of variation), whereas Fa, and simulated maximum concentrations of hepatic biomarkers (ALT_{max}, TB_{max}, and INR_{max}) are reported as median and range. Baseline biomarker values in the DILIsym model are 30, 0.55 and 1 for ALT (U/L), TB (mg/dL) and INR, respectively.

CONCLUSION

- Modeling and simulation consistently demonstrate that the difference in PK between the two APAP formulations in the US:
  - has a relatively small, if any, effect on APAP metabolism and biomarkers of hepatotoxicity following overdose
  - does not result in marked differences in the expected time course of APAP plasma concentrations
- Based on these results, the updated APAP overdose treatment guidelines, published in 2023, are not further impacted by this report

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CONFLICTS OF INTEREST

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