Liver Enzymes After Acetaminophen Error in Critically Ill Children: A Cohort Study

Nadia Roumeliotis (nadia.roumeliotis@gmail.com)
The Hospital for Sick Children https://orcid.org/0000-0001-7463-1233
Eleanor Pullenayegum
SickKids Research Institute
Anna Taddio
University of Toronto
Paula Rochon
Women's College Hospital
Chris Parshuram
University of Toronto

Research Article

Keywords: Acetaminophen, critical care, pediatrics, pharmacoepidemiology, transaminases, adverse drug event

Posted Date: December 16th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1157913/v1

Abstract

Objectives

Drug-associated harm is common but difficult to detect in the hospital setting. In critically ill children, we sought to evaluate drug-associated hepatic injury following enteral acetaminophen error; defined as acetaminophen dosing that exceeds daily maximum recommendations.

Design

Retrospective cohort study.

Setting

Two pediatric intensive care units within a pediatric hospital center.

Patients

Children (<18 years of age) admitted to the pediatric and cardiac intensive care unit between January 2008 and January 2018, and receiving enteral acetaminophen. We defined acetaminophen dosing error as exceeding daily acetaminophen dosing by > 10% the upper limit of maximum recommended dose for weight and age (>82.5mg/kg/day or > 4400mg/day).

Main Results

We included 14,146 admissions, who received 147,485 doses of acetaminophen. Acetaminophen dosing errors occurred 1 in every 9.5 patient-days on acetaminophen. ALT and AST decreased significantly over the course of ICU admission ($p<0.0001$). In patients with acetaminophen errors, ALT and AST measured in the 24 to 96 hours post error were not significantly different than when measured outside this window. A sensitivity analysis using >100 mg/kg/day as the upper daily acetaminophen error cut-off did not reveal any subsequent significant increase in ALT or ALT in the 24 to 96-hour post-error window, compared to measurements taken outside the window.

Conclusions

Although the administration of acetaminophen in critically ill children frequently exceeds the daily recommended limit and vigilance is needed, we did not find any associated increase in liver transaminases following acetaminophen errors.

What Is Known

- Acetaminophen dosing errors are common in pediatric outpatients
- Excessive acetaminophen dosing in can be associated with harm, including hepatic injury.

What Is New

- Exceeding daily acetaminophen dosing limit occurs 1 in every 9.5 patient-days in children admitted to the critical care unit.
- In patients with daily dose excess of acetaminophen, we did not find a significant increase in the measured liver enzymes in the 24 to 96 hours following the overdosing.

Introduction

Acetaminophen is the most commonly administered analgesic in children worldwide; used for both its analgesic and antipyretic properties. Although acetaminophen is considered safe at recommended doses and intervals (15 mg/kg every 4-6 hours to a maximum of 5 doses/day), acute acetaminophen overdose is associated with hepatotoxicity and possible liver failure [1–3]. In the intensive care unit, acetaminophen is one of the most frequently administered medications [4, 5], and errors are common in the pediatric intensive care unit (PICU) due to the number of medications administered [4]. Indeed, Bonafide et al. reported that the most common medication alert (7.9%) in a PICU was for acetaminophen [4]. While acetaminophen dosing errors occur frequently in outpatient, dosing error of acetaminophen has not been evaluated, and the harm associated with these hospital-administered overdoses is not established. Compared to other inpatients, critically ill children are at particular risk for drug induced harm given weight-based dosing, concurrent toxic medications, disease related organ dysfunction– and thus more often have altered drug metabolism and elimination. Therefore, critically ill children have a heightened risk for harmful adverse drug events [6].

Furthermore, drug-induced harm is difficult to detect and often relies on clinical judgement or subjective reviewer evaluation. This study uses pharmacoepidemiology, with a large dataset of drug administrations, to more objectively detect the organ specific harm associated with acetaminophen dosing errors, while controlling for confounders. The objective was to evaluate hepatic injury following acetaminophen dosing errors, in the high risk population of critically ill children.

Materials And Methods

Study Design and Population

This is a retrospective cohort study of patients admitted to two intensive care unit (ICU) of the Hospital for Sick Children, using the local hospital dataset (Oracle) of drug administrations. The dataset contains patient demographics and all medication names, doses, units and routes administered. We included all consecutive pediatric admissions to the PICU and cardiac ICU (CICU) between January 1st 2008 and January 1st 2018, having received at least one dose of enteral acetaminophen. We excluded admissions over 18 years of age, and those that did not have a documented weight during their admission. The study reporting followed the STROBE guidelines[7] (checklist included in Supplement).

Exposure and outcomes

The primary exposure of interest is an enteral acetaminophen dosing error; defined here as administered acetaminophen exceeding the daily maximum dose recommendations while admitted to the ICU. Enteral acetaminophen includes any oral, nasogastric, nasojejunal or rectal dose of acetaminophen given. Intravenous acetaminophen was not available in Canada during the study period. We defined exceeding daily maximum dose as receiving a cumulative daily dose > 10% above daily maximum dosing[8] according to our local hospital formulary (SickKids formulary) [9] and reference guidelines [10, 11]. Exceeding daily maximum acetaminophen dosing was therefore defined as > 82.5 mg/kg/24h (10% above 75mg/kg) or > 4400 mg/24h (10% above 4000mg/day) for patients > 50kg. Daily dose excess categories were incrementally divided from >82.5- 85mg/kg/day to >105 mg/kg/day. The primary outcome of interest was a change in mean measured alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or gamma-glutamyl transferase (GGT), after the exposure to acetaminophen dosing error.

Data management

We examined all variables in the dataset for sparseness and distribution characteristics (count, mean and standard deviation, median and interquartile range). Length of ICU stay was calculated as number of whole or part calendar days in the unit. All drug names entered into the dataset were cleaned and categorized according to generic name, then reviewed by frequency to include all permutations and spellings of acetaminophen. Units were standardized to milligrams if entered in other units. Drug doses with a nul value or inappropriate/missing units were deleted (n=404 doses). Weight based dosing was calculated based on the most recent weight measured in the chart. If the last measured weight was incompatible with the age, this was considered a documentation error and the admission weight was used (n=5). Daily acetaminophen dosing was calculated with a rolling sum of administered acetaminophen doses in the last 24-hour period.

Statistical Analysis

Descriptive statistics were used to describe the population. Normally distributed variables are expressed as mean and standard deviation (SD) and non-normally distributed variables as median and interquartile range (IQR). Mixed regression models were constructed with acetaminophen error as the independent variable and each of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl-transferase (GGT) as the dependant variables. The effect of acetaminophen error on each liver enzyme (ALT, AST, GGT) was measured in the 24 to 96 hour window after the first daily acetaminophen error in that patient (whether first daily acetaminophen overdosing sustained for 1 day or more), as this time frame is typically associated with the rise in liver enzymes [12]. Baseline liver enzymes were the first measured values after PICU admission and admissions were assumed to be independent. Potential confounding variables were established *a priori* and included age, sex, admission to cardiac ICU, severity of illness using Pediatric risk of mortality 3 score (PRISM III score), and length of ICU stay (ICU day). The change in frequency of the outcome measurement (number of labs taken in the 24 to 96-hour post cumulative overdose window) was also included in the model to reduce differential surveillance bias. A

sensitivity analysis was conducted in all patients using a higher acetaminophen error definition (>100 mg/kg/24-hour), to evaluate outcomes within the same time windows. Exploratory sensitivity and subgroup analysis were conducted for ICU admission subgroups, severity of illness (PRISM III quartiles) and age categories. A p-value of 0.05 was considered significant. The Research Ethics Board of the Hospital for Sick Children (#1000059340) and the University of Toronto (# 00037936) approved this study.

Results

During the study period, 17,998 included admissions were admitted to the PICU and CICU. Of these, 14,146 admissions (10 203 patients) received 147,485 doses of acetaminophen over 65,564 patient-days (Flow diagram in supplement). The characteristics of the patient cohort are included in Table 1. Patients received a median of 2 doses of acetaminophen per day (IQR 1-5), with the median dose being 12.37 mg/kg (IQR 11.0-13.7). Acetaminophen error (defined as > 4400 mg/24-hour or > 82.5 mg/kg/24-hour) occurred on 6813 patient days in 3348 admissions –a rate of 103 acetaminophen error days per 1000 patient-days, or 1 for every 9.5 patient-days on acetaminophen. On 119 patient days, acetaminophen error was both above 4400 mg and above 82.5 mg/kg. In patients with acetaminophen errors, the median time from admission to first daily overdose error was 23.7 hours (IQR 99.1 to 29.1, N=3348), suggesting the majority of dosing errors occurred on the first ICU day. There were 3446 patient-days where an acetaminophen error was > 100mg/kg/day, occurring in 1118 admissions. The stratification of acetaminophen errors of daily dose severity by year, is displayed in Figure 1.

Outcomes – Liver enzymes

The baseline and 14-day trend of liver enzymes (ALT, AST and GGT) for admissions with and without acetaminophen errors are displayed in Figure 2 (median, IQR). There was as significant difference in the baseline liver enzymes values between the admissions without an acetaminophen error (blue bars) and those with an acetaminophen error (red bars); baseline AST values were higher in patients with errors (Figure 2B) whereas baseline ALT and GGT values were higher in patients without errors (Figure 2A and C). Mean values (Figure 2, circles connected with line) were heavily weighted by significant outliers for each of the liver enzymes. On ICU day 1 for example, there were 8194 ALT values, 7565 AST values and 7696 GGT values that exceeded 500 U/L in admissions without acetaminophen errors, and 2496, 2281 and 2316 in admissions with errors, respectively (outlier data not shown in Figure). Trends in ALT and AST were decreasing significantly over the first 14 days of ICU stay (Figure 2A and B), whereas GGT trend was increasing during the ICU stay (Figure 2C). With every advancing ICU day, ALT and AST significantly decreased (0.27 per day for ALT, 0.6 for AST, $p<0.0001$) but GGT significantly increased by 1.34 per day ($p<00001$). Increasing patient severity of illness was significantly associated with worse liver enzymes; with every increase in PRISM III score associated with an average increase in ALT by 4.95, AST by 10 and GGT by 2 ($p<0.0001$). Cardiac ICU patients had significantly lower liver enzymes on average than pediatric ICU patients (26.6 units lower for ALT, 6.5 units lower for AST and 22 units lower for GGT). Both

age and sex had no effect on liver enzymes. Multivariable regression for changes in liver enzymes are presented in Table 2. Univariate mixed models of dependant variables are included in Supplement.

In the liver enzymes drawn in the 24 to 96-hour window after an acetaminophen error (>82.5 mg/kg/day), ALT and AST were not significantly different than when measured outside this window. The GGT measured in the 24 to 96-hour window post acetaminophen error was significantly lower (<0.0001) compared to other measurements outside the post-error window. The sensitivity analysis using >100 mg/kg/day as the acetaminophen error cut-off was performed for all patients, and did not reveal any subsequent significant increase in ALT or ALT in the 24 to 96-hour post-error window, compared to measurements taken outside the window (Table 3). There was a significant decrease in GGT in the post-error window.

In a subgroup analysis by admission to PICU or CICU, there was a no significant increase in ALT and AST in the window post -acetaminophen error (Table 4). The subgroup analysis using PRISM III quartiles and age groups did not reveal any significant increase in liver enzymes in the 24 to 96-hour post acetaminophen error window (Supplement).

Discussion

In critically ill children having received acetaminophen dosing error (one or more day exceeding maximum recommended doses), we did not find any significant difference in the mean measured liver enzyme levels (ALT, AST, and GGT) taken in the 24 to 96 hours post error, compared to those without error. Mean liver enzyme levels were also similar with a sensitivity analysis using a larger daily acetaminophen dosing error (>100mg/kg/day), and when evaluating sub-populations such as cardiac patients and less severely ill patients (as per PRISM III score). The findings may suggest that acetaminophen has a larger safety profile than previously reported.

The choice of liver enzymes (ALT, AST and GGT) as a marker of patient harm after daily acetaminophen overdose, stems from the acute hepatotoxicity associated with large single overdoses of acetaminophen and longer chronic overdosing of acetaminophen[4, 13, 14]. In critically ill patients, liver enzymes might not have been the most accurate marker of harm given the significant increase in these markers at baseline and the significant change in these outcomes over the course of the PICU stay; ALT and AST decreased with advancing ICU stay. This is likely explained by improving organ dysfunction post recovery (whether infectious, surgical, or traumatic). GGT increased with advancing ICU stay which may be explained by prolonged fasting in PICU or cholestasis associated with medications and/parenteral nutrition. Notwithstanding, a change in liver enzymes associated with an excessive acetaminophen dosing may not have been large enough to change the PICU trends in the liver enzymes. Furthermore, liver enzymes may be a poor marker of liver injury, while altered hepatic function is seen with severe drug overdose and likely not sensitive for more mild hepatic events. Another possible explanation for not finding a significant increase in liver enzymes post dosing error, is confounding by indication. Patients with abnormal liver enzymes may not have been selected to receive higher doses of acetaminophen

(such as loading doses of 30 mg/kg) [9], and therefore the excessive daily acetaminophen dosing may have only occurred in patients with low or normal liver enzymes. Despite that, a previous study by Temple et al, found that doses maintained between 60-90 mg/kg/day (with 10-15mg/kg/dose or 20-30mg/kg/dose) did not significantly increase ALT from baseline in children [15].

Strengths of the study include the large sample size and long period of study. The mixed model allowed us to use all the available repeated measures data for outcomes over the desired period post error. Furthermore, the model can control for confounders, and performs well with missing data. We controlled for ascertainment bias by including the change in enzyme measurements in the outcome window; i.e. controlling for liver enzymes measured in patients with likely abnormalities or suspicion for abnormalities because of an error. Several sensitivity analyses were conducted to evaluate effect in different subgroups, but no increase in liver enzymes related to acetaminophen dosing error was detected.

Limitations of the study include the retrospective nature of the analysis, with liver enzymes not systematically measured in all patients at the desired time frame or intervals. The single center cohort also may limit the generalizability of the patients, practices and findings. Informative observation is also a limitation – as the likelihood of the enzymes being measured increases if the enzyme levels are higher. The outliers in the outcome measurements for certain patients may also have been a limitation that prevented detecting a significant effect. Lastly, missing data for outcome measures of liver enzymes (50% in exposed group, 60% in unexposed group) is unlikely to be missing at random, which introduces the potential for measurement bias.

The findings used pharmacoepidemiology to underline the safety profile of acetaminophen, which does not appear to be associated with organ dysfunction when large doses are administered for a short time in an acute care monitored setting of critically ill children, or when exceeding daily dosing is not prolonged. The study highlights the use of pharmacoepidemiology to measure associations between dosing error and harm in large datasets of patients and administered medications. These studies are increasingly important given the difficulty and cost of performing large prospective pharmacologic studies in children, and the increasing use of data technology and registries in healthcare.

Conclusion

Although the administration of acetaminophen in critically ill children frequently exceeds the daily recommended limit (defined here as errors), we did not find any associated increase in measured liver transaminases in the days following acetaminophen dosing errors. Although vigilance for the administration of medications in hospitals is needed, acetaminophen likely remains safe beyond its currently recommended doses.

Abbreviations

ADE: Adverse Drug Events,

ALT: Alanine Aminotransferase,

AST: Aspartate Aminotransferase,

CICU: Cardiac Intensive Care Unit

GGT: Gamma-Glutamyl Transferase

ICU: Intensive Care Unit

IQR: Interquartile range

PICU: Pediatric Intensive Care Unit,

PRISM: Pediatric Risk of Mortality

SD: Standard deviation

Declarations

Acknowledgements

Special thanks to local pharmacists Winnie Seto and Angela Trope for their help with dosing practice in the unit over time. Thanks to Melanie Gaetani for coding support with medication identification.

Funding: This study was not funded, but N. Roumeliotis received doctoral salary support from the Fonds de Recherche Santé- Québec, and the Canadian Critical Care Trials Group (CCCTG).

Competing interests

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Availability of Data: Data may be available upon request.

Code availability: Coding availability in SAS may be available upon request.

Contributor's Statement Page

Dr Roumeliotis conceptualized and designed the study, conducted the statistics, summarized results, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Pullenayegum contributed to study design, analysis plan, interpretation of results, critical appraisal of intellectual content and approved final version.
Drs Taddio and Rochon contributed to study design, critically appraised it for intellectual content, and

reviewed and revised the final version of manuscript.
Dr Parshuram conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethics: Ethics approval was obtained from The Hospital for Sick Children (#1000059340) and the University of Toronto (# 00037936) approved this study.

Consent to participate: Not applicable

Consent for publication: Not applicable.

References

1. Mort JR, Shiyanbola OO, Ndehi LN, Xu Y, Stacy JN: Opioid-paracetamol prescription patterns and liver dysfunction: a retrospective cohort study in a population served by a US health benefits organization. *Drug Saf* 2011, 34(11):1079-1088.

2. Brune K, Renner B, Tiegs G: Acetaminophen/paracetamol: A history of errors, failures and false decisions. *Eur J Pain* 2015, 19(7):953-965.

3. Locci C, Cuzzolin L, Capobianco G, Antonucci R: Paracetamol overdose in the newborn and infant: a life-threatening event. *Eur J Clin Pharmacol* 2021, 77(6):809-815.

4. Bonafide CP, Miller JM, Localio AR, Khan A, Dziorny AC, Mai M, Stemler S, Chen W, Holmes JH, Nadkarni VM *et al*: Association Between Mobile Telephone Interruptions and Medication Administration Errors in a Pediatric Intensive Care Unit. *JAMA Pediatr* 2020, 174(2):162-169.

5. Gaetani M, Frndova H, Seto W, Parshuram C: Concurrent intravenous drug administration to critically ill children: Evaluation of frequency and compatibility. *Journal of critical care* 2017, 41:198-203.

6. Sharek PJ, Classen D: The incidence of adverse events and medical error in pediatrics. *Pediatric clinics of North America* 2006, 53(6):1067-1077.

7. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet (London, England)* 2007, 370(9596):1453-1457.

8. Roumeliotis N, Pullenayegum E, Rochon P, Taddio A, Parshuram C: A modified Delphi to define drug dosing errors in pediatric critical care. *BMC Pediatr* 2020, 20(1):488.

9. Lau E: The Hospital for Sick Children's Drug Formulary and Handbook: Wolters Kluwer Clinical Drug Information (2017); 2017.

10. Dlugosz CK, Chater RW, Engle JP: Appropriate use of nonprescription analgesics in pediatric patients. *J Pediatr Health Care* 2006, 20(5):316-325; quiz 326-318.

11. Temple AR, Temple BR, Kuffner EK: Dosing and antipyretic efficacy of oral acetaminophen in children. *Clin Ther* 2013, 35(9):1361-1375.e1361-1345.

12. Acetaminophen. In.: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]; 2012.

13. Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, Chyka PA, Caravati EM, Wax PM, Keyes DC, Woolf AD *et al*: Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clinical toxicology (Philadelphia, Pa)* 2006, 44(1):1-18.

14. Dart RC, Green JL, Kuffner EK, Heard K, Sproule B, Brands B: The effects of paracetamol (acetaminophen) on hepatic tests in patients who chronically abuse alcohol – a randomized study. *Alimentary Pharmacology & Therapeutics* 2010, 32(3):478-486.

15. Temple AR, Zimmerman B, Gelotte C, Kuffner EK: Comparison of the Efficacy and Safety of 2 Acetaminophen Dosing Regimens in Febrile Infants and Children: A Report on 3 Legacy Studies. *The Journal of Pediatric Pharmacology and Therapeutics* 2017, 22(1):22-32.

Tables

Table 1. Baseline characteristics of admissions receiving Acetaminophen (N=14 146)

Characteristic	All Admissions (N=14 146)	Admissions with acetaminophen error (N=3 348)	Admissions without acetaminophen error (N=10 798)	p-value
Sex[a], male n (%)	7839 (55.4)	1885 (56.3)	5954 (55.1)	0.23
Age category, n (%)				<0.0001
0-1 month	1485 (10.5)	258 (7.7)	1227 (11.4)	
<1-12 months	4163 (29.5)	1508 (45)	2655 (24.6)	
<1-6 years	3970 (28.0)	933 (27.9)	3037 (28)	
<6-12 years	2090 (14.8)	319 (9.5)	1771 (16.4)	
<12-18 years	2438 (17.2)	330 (9.9)	2108 (19.5)	
Weight, kg median (IQR)	11.6 (5-26)	7.9 (5.2-15.8)	13 (6-30)	<0.0001
Visits per patient, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	0.83
PRISM III score, median (IQR)	4 (1-8)	5 (3-8)	4 (0-7)	<0.0001
Admission to Cardiac ICU, n (%)	6050 (43)	2672 (79.8)	3378 (31.3)	<0.0001
Diagnostic Category[b], n (%)				<0.001
Cardiac	4426 (42.5)	2097 (79.3)	2326 (30)	
Respiratory	1626 (15.6)	104 (3.9)	1522 (19.6)	
Neurologic	944 (9.1)	66 (2.5)	878 (11.32)	
Gastrointestinal/ Genitourinary	264 (2.5)	27 (1)	237 (3)	
Orthopedic	231 (2.2)	43 (1.6)	188 (2.4)	
Trauma/Burn	386 (3.7)	50 (1.9)	336 (4.3)	
Hematology/Oncology	533 (5.1)	45 (1.7)	488 (6.3)	
Renal/Metabolic	186 (1.8)	8 (0.3)	178 (2.3)	
Infectious Disease	175 (1.7)	13 (0.5)	162 (2.1)	
ENT/Craniofacial	227 (2.2)	45 (1.7)	212 (2.7)	

Other	1399 (9.9)	144 (5.4)		
Mechanical ventilation[c], n (%)	7057 (49.9)	4837 (68.5)	2220 (31.5)	<0.0001
Length of stay(days), median (IQR)	3 (2-7)	4 (2-7)	3 (2-7)	<0.0001
Meds administered /patient day, median (IQR)[d]	7 (4-11)	8 (5-11)	7 (4-11)	<0.0001
Baseline ALT value (U/L)[e]		26 (20-33)	27 (19-37)	<0.0001
Time of baseline ALT (h)		23 (4-77)	14.5 (1.8-60)	
Baseline AST value (U/L)[f]		45 (27-74)	33 (23-52)	0.01
Time of baseline AST (h)		37.8 (12.3-89)	16.1 (2.1-75)	
Baseline GGT value (U/L)[g]		15 (11-75)	19 (12-37)	<0.0001
Time of baseline GGT (h)		16.7 (4.1-39)	13.7 (1.9-39)	
Death in ICU, n (%)	306 (2.2)	34 (1)	272 (2.5)	<0.0001

IQR= Interquartile Range, PRISM III=Pediatrics Risk of Mortality III, ICU= Intensive Care Unit, ENT= Ear, Nose and Throat. h=hour

1. 1 missing
2. 3749 missing, missing N= 706 in dose excess (21%) N=3043 in non-dose excess (28%).
3. 2037 missing; missing 405 in dose excess, and N=1632 in non-dose excess.
4. missing 118 in dose excess, N=802 in non-overdose
5. N=3247 in dose excess and N=9674 in non-dose excess
6. N=3125 in dose excess patients and N= 9341 in non-dose excess
7. N=3181 in dose excess and N=9467 in non-dose excess

Table 2. Mixed random intercepts model of the effect of acetaminophen error (> 82.5 mg/kg/day, shaded grey) on baseline ALT, AST and GGT.

Independent variable	ALT		AST		GGT	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Age in months	-0.013	0.62	-0.05	0.38	-0.009	0.53
PRISM III score	4.95	<0.0001	10.06	<0.0001	2.0	<0.0001
Sex (Ref male)	5.00	0.12	8.60	0.22	-3.3	0.06
ICU day	-0.26	<0.0001	-0.60	<0.0001	1.34	<0.0001
Cardiac patient	-26.6	<0.0001	-6.5	0.40	-22.05	<0.0001
Frequency of labs drawn in 24h to 96h post error (for >82.5 mg/kg/day)	0.18	0.24	0.26	0.43	0.29	0.04
Acetaminophen error (>82.5 mg/kg/day)	-5.8	0.32	-24.0	0.15	-19.4	<0.0001

Model run for 14 145 subjects. Negative estimate values suggest that for every 1 increase in the independent variable (predictor), the dependent variable (outcome) is lower by that value.

Table 3. Mixed random intercepts model of the effect of acetaminophen dosing error (> 100 mg/kg/day) on baseline ALT, AST and GGT.

Independent variable	ALT		AST		GGT	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Age in months	-0.013	0.62	-0.05	0.38	-0.009	0.53
PRISM III score	4.98	<0.0001	10.02	<0.0001	2.0	<0.0001
Sex (Ref male)	5.01	0.12	8.66	0.22	-3.3	0.06
ICU day	-0.26	<0.0001	-0.60	<0.0001	1.34	<0.0001
Cardiac patient	-26.6	<0.0001	-7.12	0.40	-22.6	<0.0001
Frequency of labs drawn in 24h to 96h post error (for >100 mg/kg/day)	0.02	0.30	-0.56	0.53	0.20	0.34
Acetaminophen error >100 mg/kg/day	-0.21	0.98	-8.02	0.82	-18.9	0.02

Model run for 14 145 subjects. Negative estimate values suggest that for every 1 increase in the independent variable (predictor), the dependent variable (outcome) is lower by that value

Table 4. Subgroup analysis for patients admitted to the cardiac ICU and pediatric ICU of the mixed random intercepts model of the effect of acetaminophen error (>82.5mg/kg/day, shaded grey) on baseline ALT, AST, GGT.

Independent variable	ALT		AST		GGT	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Cardiac ICU admissions (N=6050)						
Age in months	0.13	<0.0001	0.23	0.005	-0.11	<0.0001
PRISM III score	3.4	<0.0001	5.95	<0.0001	0.21	0.24
Sex (Ref male)	1.7	0.62	6.2	0.37	-2.91	0.10
ICU day	-0.19	<0.0001	-0.41	<0.0001	0.68	<0.0001
Frequency of labs drawn in 24h to 96h post error window (for >82.5 mg/kg/day)	-0.04	0.75	-0.58	0.06	0.28	0.0005
Acetaminophen error >82.5 mg/kg/day	-0.89	0.86	-5.5	0.65	-24.6	<0.0001
Pediatric ICU admissions (N=8095)						
Age in months	-0.08	0.03	-0.20	0.02	0.03	0.09
PRISM III score	6.2	<0.0001	13.2	<0.0001	3.2	<0.0001
Sex (Ref male)	8.5	0.11	11.6	0.33	-4.1	0.17
ICU day	-0.42	<0.0001	-1.04	<0.0001	2.80	<0.0001
Frequency of labs drawn in 24h to 96h post error window (for >82.5 mg/kg/day)	1.1	0.008	4.17	0.0014	0.45	0.11
Acetaminophen error >82.5 mg/kg/day	-25.16	0.13	-100.8	0.04	-7.60	0.48

Model run for 14 145 subjects, Mixed random intercepts model with cumulative overdose >82.5mg/kg/day in shaded grey.

Figures

Figure 1

Frequency of acetaminophen error by year, stratified by severity of excessive daily dose

Figure 2

Baseline and 14-day trend in AST (A), ALT (B) and GGT (C) in admissions with acetaminophen error (RED) and no acetaminophen error (BLUE). Figure demonstrates box plots with median and first and third quartile (whiskers), as well as means (circles) connected with a trend line. ALT, AST and GGT are measured in U/L

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalMaterial.pdf