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Risk Factors, Clinical Presentation, and Outcomes in Overdose With Acetaminophen Alone or With Combination Products:

Results From the Acute Liver Failure Study Group

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Abstract

Background and Aims—Acetaminophen (APAP) is the most common cause of acute liver failure (ALF) in the west. It is unknown if APAP overdose in combination with diphenhydramine or opioids confers a different clinical presentation or prognosis. Study objectives were to compare (1) baseline patient characteristics; (2) initial clinical presentation; and (3) clinical outcomes among patients with ALF due to APAP alone or in combination with diphenhydramine or opioids.

Methods—We analyzed 666 cases of APAP-related liver failure using the Acute Liver Failure Study Group database from 1998 to 2012. The database contains detailed demographic, laboratory, and clinical outcome data, including hemodialysis, transplantation, and death and in-hospital complications such as arrhythmia and infection.

Results—The final sample included 666 patients with APAP liver injury. A total 30.3% of patients were overdosed with APAP alone, 14.1% with APAP/diphenhydramine, and 56.6% with APAP/opioids. Patients taking APAP with opioids were older, had more comorbidities, and were

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more likely to have unintentional overdose (all $P < 0.0001$). On presentation, 58% in the APAP/opioid group had advanced encephalopathy as compared with 43% with APAP alone ($P = 0.001$). The APAP/diphenhydramine group presented with the highest serum aminotransferase levels, no differences in laboratory values were noted at 3 days postenrollment. No significant differences were observed in clinical outcomes among the groups.

Conclusions—Most patients with APAP-induced ALF were taking APAP combination products. There were significant differences in patient characteristics and clinical presentation based on the type of product ingested, however, there were no differences noted in delayed hepatotoxicity or clinical outcomes.

Keywords

drug overdose; liver toxicity; combination analgesics

Acetaminophen (APAP) is the most widely used over the counter (OTC) product and is commonly included in many prescription medications. In any given week, about 1 in 5 US adults take APAP.¹ In 2011, hydrocodone-APAP was the most prescribed medication, with 136.7 million prescriptions written nationally.² APAP overdose has become a considerable public health problem resulting in at least 50,000 emergency department visits and 30,000 hospitalizations each year.^{3,4} APAP is the leading cause of acute liver failure (ALF) in the United States and was responsible for an estimated 401 deaths in 2009.^{5,6} APAP-associated ALF is on the rise, accounting for about one third of cases in 1998 and nearly half of all cases as of 2003.⁷ About half of toxic APAP ingestions are unintentional and a significant proportion is attributed to combination compounds, most commonly opioid analgesics.^{7,8}

Several recent studies have demonstrated that many patients are unaware of the maximum recommended daily dose of APAP or its potential for hepatotoxicity, cannot recognize it as an active ingredient in combination products, and have difficulty interpreting medication instructions.^{9–12} Patients with limited health literacy and lower socioeconomic status are at even higher risk of misinterpreting drug labels.⁹ According to administrative data of APAP-containing prescriptions, up to 25% of patients may be exceeding the daily recommended daily dose of 4 g and about 3% may ingest toxic doses of >10 g.¹³ To effectively address this significant public health problem, investigations are needed to determine whether there is a specific patient risk profile among those with APAP-related toxicity, and whether the risk of unintentional overdose may be greater for APAP-containing combination products.

In addition to the public health concern, clinically it remains unknown whether ingestion of APAP alone or in combination with other compounds (ie, anticholinergics and opioids) confers a different clinical presentation or prognosis. Once APAP is ingested, it undergoes rapid gastrointestinal absorption and subsequent extensive hepatic glucuronidation. Doses >4 g may lead to excess production of *N*-acetyl-*p*-benzoquinone imine, resulting in depletion of glutathione and subsequent hepatotoxicity.¹⁴ Although the biological mechanism of liver injury is well described, a few case reports have suggested that delayed hepatotoxicity and persistently elevated serum APAP levels may be associated with overdoses due to APAP combination compounds.^{15,16} Although the mechanism for this is not entirely clear, according to case reports and small case series, the delayed toxicity may be related to

delayed gastrointestinal motility and increased absorption when APAP is combined with either diphenhydramine or opioids.^{15,17–19} To date, no large-scale studies have examined differences in clinical presentation or clinical outcomes of APAP combination compounds.^{15,16,20}

Given the public health concerns and unanswered clinical questions, the objectives of this investigation from the Acute Liver Study Group were to examine differences in: (1) baseline patient characteristics; (2) initial clinical presentation; and (3) clinical outcomes in patients taking APAP alone compared with APAP in combination products, specifically, APAP with diphenhydramine and APAP with opioids.

METHODS

Study Population

We analyzed cases of APAP-related liver failure using the Acute Liver Failure Study Group (ALFSG) database from January 1, 1998 to February 2012. This national registry of 23 academic medical centers in North America is funded by the National Institute of Diabetes and Digestive Kidney Diseases of the National Institutes of Health to examine clinical data and outcomes in adult patients with ALF or acute liver injury (ALI). The study procedures and protocols have been previously described in detail.⁶ The ALFSG registry contains demographic, laboratory, and clinical outcome data on eligible patients with the diagnosis of ALF defined as: the presence of hepatic encephalopathy, international normalized ratio of 1.5, disease duration of <26 weeks, and the absence of prior chronic liver disease.²¹ ALI was defined as coagulopathy [international normalized ratio (INR) ≥ 2.0] with no encephalopathy and 2 additional thresholds of severity: aspartate aminotransferase (AST) > ×10 the upper limit of normal and total serum bilirubin >3.0 in the setting of an acute hepatic illness. Patients classified as having APAP overdose were included in the study. A complete list of ingested medications was reviewed by 2 of the manuscript's authors. As the study objective sought to compare patients taking APAP alone versus APAP in combination with diphenhydramine or opioids; patients taking APAP with products other than diphenhydramine or opioids were excluded. Patients with ALF secondary to viral hepatitis, ischemia, Wilson disease, and other causes were excluded. Informed consent for the study was obtained from the patients' health care proxies. The Institutional Review Board approved the study at all sites.

A total of 680 individuals were confirmed to have APAP ingestion, accounting for 46% of all cases of ALF. A total of 14 patients were excluded on the basis of taking APAP combination products that did not contain diphenhydramine or opioids, leaving 666 patients in the final sample.

Data Collection

The following baseline variables were obtained from the database: age, education, gender, race/ethnicity, and information reported by the patients' health care proxy such as the total number of medications taken, total number of chronic conditions, intentionality of overdose (suicidal intent or not), presence of psychiatric disease, and substance abuse. Alcohol data

were available on 148 subjects before 2010 and 99 subjects since 2010. Alcohol abuse was defined as 40 g or more of alcohol per day or >14 drinks/wk for men, and 20 g of alcohol or more per day or >7 drinks/wk for women. Subjects reporting no alcohol abuse or those with missing data were considered to not have a history of alcohol abuse. Hepatic encephalopathy was graded 1 to 4 by the West Haven criteria; with grade 1 defined as mild changes in sensorium to grade 4 considered to be coma.²² The King's College criteria for APAP-induced liver failure were defined as having an arterial pH <7.30 or all 3 of the following: (1) grade 3 or 4 encephalopathy; (2) prothrombin time >100 seconds (international normalized ratio >6.5); and (3) serum creatinine (Cr) >3.4 mg/dL.²³ The maximum dose of APAP taken in the past 6 months was collected via self or third party report and was available for 360 subjects. Medication chronicity was reported for 423 subjects. Patients taking APAP for >7 days were considered to have chronic ingestion, those with ≤7 days were considered to have acute ingestion.⁷ Some patients taking >1 APAP-containing medication reported acute and chronic ingestion; this is reported separately.

Clinical outcome variables included APAP level on admission and daily laboratory values such as INR, AST, alanine aminotransferase (ALT), total serum bilirubin, serum Cr, phosphate, and serum lactate. The model for end-stage liver disease (MELD) score was calculated by the established formula.²⁴ The primary clinical outcomes of interest included: hemodialysis, transplantation, and death within 7 days of enrollment. Death data were confirmed using National Vital Statistics. Additional clinical outcomes included in-hospital complications such as seizure, arrhythmia, gastrointestinal bleeding, acute respiratory distress syndrome, and infection.

Analysis Plan

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). A population of 666 subjects enrolled in the ALFSG Registry from January 1998 through February 2012 was analyzed using descriptive statistics to characterize demographics and other clinical variables describing illness severity, treatment, and outcomes. Differences between groups based on categorical variables were tested using the χ^2 test or Fisher exact test for measures with expected cell sizes of <5. Because of non-normally distributed data, continuous variables were reported as medians with interquartile (IQR) ranges and compared using the Kruskal-Wallis test. All tests were assessed at the 0.05 significance level.

RESULTS

Among the ALSFG sample, a total of 202 (30.3%) patients ingested APAP alone, 87 (13.6%) were taking APAP/diphenhydramine, and 377 (56.7%) APAP/opioid. Table 1 displays the baseline demographics and characteristics for the total study sample and stratified by APAP group. The median age of the sample was 37.0 years (IQR, 28.0 to 46.0 y); patients with APAP/opioid ingestion were significantly older ($P < 0.001$). Patients had 12 years of education on average, were predominantly female and of non-Hispanic white race. A higher proportion of African Americans had liver injury with APAP alone; by contrast, more whites ingested APAP combination products. The median number of coexisting

chronic conditions was 2.0 (IQR, 1.0 to 3.0) and the median number of medications was 4.0 (IQR, 2.0 to 6.0). Patients in the APAP/opioid group were taking a higher total number of medications and had a higher number of chronic conditions than patients in the other 2 groups (all $P < 0.001$).

The majority of cases in the registry (61.8%) had an unintentional overdose; one third had a suicide attempt; the rest were due to unknown causes (7.7%). Patients were more likely to attempt suicide with APAP alone or APAP/diphenhydramine than with the APAP/opioid combination (pairwise comparisons: APAP vs. APAP/diphenhydramine, $P = 0.02$; APAP vs. APAP/opioid, $P = 0.001$; APAP/diphenhydramine vs. APAP/opioid, $P < 0.001$). About one half of patients had a history of psychiatric disease and >40% had a reported history of substance abuse, nearly 20% had a significant history of alcohol abuse. Patients in the APAP alone group were less likely to report alcohol abuse. Upon study enrollment, the majority of patients (88.3%) were classified as having ALF and 10.8% as ALI; 0.9% progressed from ALI to ALF during the hospitalization. Patients who ingested APAP/diphenhydramine were more likely to initially present with ALI (19.5%), compared with those with APAP alone (12.9%) or APAP/opioids (7.7%) ($P = 0.004$). By contrast, the APAP/opioid group was more likely to present with ALF (91.8%—APAP/opioid, 86.1%—APAP alone, 78.2%—APAP/diphenhydramine, $P = 0.004$).

Baseline clinical characteristics for the entire sample and stratified by APAP group are shown in Table 2. More than half of cases were classified as having grade 3 or 4 hepatic encephalopathy on presentation (grade 3 hepatic encephalopathy 20.7%, grade 4 hepatic encephalopathy 31.7%). Patients in the APAP/opioid group were more likely to present with grade 3 or 4 encephalopathy than patients in the APAP alone group (pairwise comparison, $P = 0.001$). The serum APAP level was highest on presentation in the APAP/diphenhydramine group, but the difference did not reach statistical significance. Patients with APAP/diphenhydramine overdose reported a higher maximum APAP dose than the other 2 groups, whereas patients in the APAP/opioid group were more likely to report chronic ingestion. About one quarter of patients fulfilled King's college criteria with no significant differences among the 3 groups. The median MELD score for the entire sample was 29.7 (IQR, 19.9 to 36.8); patients who ingested APAP alone had higher median MELD score and total serum bilirubin than in the other 2 groups ($P = 0.021$), no differences were noted in INR or serum Cr values. Patients in the APAP/diphenhydramine group had higher initial median AST and ALT values than other 2 groups. No significant differences were noted in the serum phosphate or lactate levels.

Figures 1A to F demonstrate the trends in median daily values for AST, ALT, total serum bilirubin, INR, serum Cr, and phosphate for the first 3 days of study enrollment. Patients in the APAP/diphenhydramine group had significantly higher levels of AST and ALT on presentation than the other 2 groups, whereas the patients in the APAP alone group had a higher total bilirubin. In general, the median AST, ALT, and INR values showed consistent downward trends in all 3 groups, whereas the total serum bilirubin levels continued to rise from initial presentation. The serum Cr appeared to plateau in the APAP/diphenhydramine group only, however, this was not statistically significant ($P = 0.57$, Appendix Table, Supplemental Digital Content 1, <http://links.lww.com/JCG/A185>). The median serum

phosphate was generally stable for all the 3 groups. No notable differences were observed in the absolute changes of the mean laboratory values from day 1 to day 3 of enrollment (Appendix Table, Supplemental Digital Content 1, <http://links.lww.com/JCG/A185> for details).

Table 3 demonstrates the primary clinical outcomes stratified by the type of APAP overdose. Nearly one third of the patients required hemodialysis within 7 days of study enrollment. A minority of patients (7.1%) required transplantation within 7 days of admission and the median time to transplantation was 2.0 days. Nearly 17% of patients died within 7 days of admission, the median number of days to death was 4.0. There were no significant differences in the above-reported outcomes by the APAP group. Additional in-hospital complication rates are shown in Table 4. Nearly one quarter of patients had an in-hospital arrhythmia or infection and an additional 10% had gastrointestinal bleeding. Seizures and acute respiratory distress syndrome were less common, occurring in about 5% of cases. No significant differences by APAP group were noted in complication rates.

DISCUSSION

The ALFSG is one of the largest multicenter registries of ALF and ALI in the United States. We aimed to examine whether there were differences in baseline patient characteristics, clinical presentation, and clinical outcomes in patients with ALF/ALI due to either APAP alone or APAP in combination with diphenhydramine or opioids. In this racially and ethnically diverse sample, we found that APAP was responsible for nearly half of the cases of ALF, as previously reported.⁷ More than half of the cases were secondary to prescription APAP/opioid combination products, whereas the rest were attributed to commonly available OTC medications, such as APAP, APAP/diphenhydramine, and preparations for the common cold in a minority of cases. The majority of APAP overdoses (62%) were unintentional and among unintentional overdoses, 72% were due to combination products. Patients who overdosed with the APAP/opioid combination were older, predominantly female, and had more medical comorbidities than patients in the other 2 groups. Patients who took APAP alone were more likely to be African American, whereas patients in the APAP/diphenhydramine group were more likely to present with suicide attempts.

In addition to important differences in patient characteristics, notable differences were found in clinical presentation between the APAP groups. Patients with APAP ingestion alone were more likely to present with ALF, whereas patients taking APAP/diphenhydramine were more likely to present with ALI. Individuals in the APAP/opioid group were initially classified as having more severe encephalopathy, which is a significant prognostic indicator; however, there were no significant differences in MELD scores or the proportion of patients that met King's College criteria, suggesting that the altered sensorium on presentation could have been due to opioid effects rather than hepatic encephalopathy. The difficulty in distinguishing hepatic encephalopathy from drug-induced delirium presents a significant prognostic challenge for managing clinicians.

Patients who took APAP with diphenhydramine had significantly higher values of serum aminotransferases on presentation than patients taking APAP alone or in combination with

opioids. However, these differences did not affect overall prognosis and thus the clinical significance of elevated serum aminotransferases is not clear. It is possible that patients who overdose with a combination product present for medical care later in their clinical course due to a prolonged period of altered mental status, however, this hypothesis would need to be prospectively verified. Furthermore, we are unable to ascertain from our data whether diphenhydramine in combination with APAP may predispose to a higher degree of hypoperfusion or muscle injury causing aminotransferase elevations.

Our findings again confirm the significant morbidity and mortality associated with severe APAP-induced liver injury. Nearly 20% of the patients died without transplantation, one third required hemodialysis, and 7% required liver transplantation. Of those who received a transplant, 10 patients died (5 of them within 7 d of enrollment). Patients with APAP overdose alone had a higher serum bilirubin and MELD scores on presentation, however, these differences did not translate into a significant increase in adverse clinical outcomes such as need for the transplantation, hemodialysis, or mortality.

The updated ALFSG registry data demonstrate that APAP misuse continues to be a considerable national public health problem. According to the American Association of Poison Control Centers, from 2000 to 2007, the cases of liver injury have increased by 44% with APAP and 70% with APAP/opioid combination prescriptions.²⁵ The high proportion of unintentional overdose found in this study highlights the continued need for interventions to improve label readability and enhance patients' understanding of the maximum safe dose and potential side effects. A recent study by King and colleagues showed significant variability in labeling practices among APAP-containing prescriptions with regards to abbreviations, maximum dose, and concomitant use warnings. This practice variation among pharmacies may have significant public health consequences.²⁶ In 2011 the Food and Drug Administration (FDA) required drug manufacturers to limit APAP to 325mg per unit dose and include an additional boxed warning about potential for liver failure. In 2013, the FDA's Acetaminophen Best Practices Task group released industry guidance for improved product labeling of APAP-containing prescriptions by introducing complete spelling of active ingredients, including concomitant use warning, prioritizing warning labels, including specific icons to improve patient understanding, and simplifying the readability of labels for the average consumer.²⁷ As of October 2014, the FDA has mandated changing the scheduling of combination analgesics containing hydrocodone from schedule III to schedule II, it will be important to evaluate the public health consequences of this action in the future. Although the above-mentioned proposals pertain to prescription medications, no significant progress has been made to improve the safety of OTC APAP. Recent studies have suggested parallel labeling initiatives to ensure that similar messages for concomitant use warnings, active ingredient icons, and front-of-packaging identification of active ingredient should be utilized on both prescription and OTC products. More aggressive packaging interventions have been implemented in Great Britain, including blister packing and limiting the number of pills available to the consumer. These initiatives have resulted in a marked decrease in intentional overdose, however, similar strategies have not been employed in the United States.²⁸

There are several limitations that should be mentioned. This was a study of patients with ALF who were transferred to large, tertiary care centers. Thus, the results may not be generalizable to patients who did not present with overdose as severe or those who did not receive care at specialized centers. There was a significant proportion of missing data with regards to alcohol use; it is possible that the prevalence of alcohol abuse may be underestimated. We do, however, report on the available alcohol history in detail to the extent possible (Supplementary Table 2, Supplemental Digital Content 1, <http://links.lww.com/JCG/A185>). We did not have reliable information on lactate levels on presentation, both known to be important factors in APAP-related liver injury.²⁹ In addition, we were unable to determine the precise period of time between APAP ingestion and study enrollment (as these data started to be collected after the time period for this study), which would affect APAP levels and could affect clinical outcomes. Given the study design, it was difficult to differentiate between a one-time overdose versus chronic ingestion. The grade of encephalopathy was subjectively determined by clinicians. The information regarding intentionality of suicide and medical history was limited because of reliance on third party report. We had relatively few patients with APAP and diphenhydramine overdose and may have been underpowered to detect important differences in clinical outcomes. Because of the limitations of the data, we were not able to examine additional important outcomes such as length of hospitalization and cost, which may be different for the various types of ingestion. We suggest that future studies prospectively examine these outcomes.

In summary, APAP overdose and subsequent liver injury remain significant public health concerns. APAP remains the number 1 cause of ALF in the United States and unintentional ingestions continues to be very common. Broad health measures in APAP product labeling and patient, and provider education are strongly needed to address this ongoing health concern.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Trends in median daily laboratory values from Day 1 to Day 3 of admission for acute liver failure due to acetaminophen alone, acetaminophen/opioid, and acetaminophen/diphenhydramine combination products are shown in Panels A through F. Cr indicates creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

TABLE 1
Baseline Demographics and Characteristics of the Total Study Sample and by Acetaminophen Group

	Total Sample (N = 666)		APAP Alone (N = 202)		APAP/Diphenhydramine (N = 87)		APAP/Opioioid (N = 377)	
	N	Median (IQR) or N (%)	Median (IQR) or N (%)	Median (IQR) or N (%)	Median (IQR) or N (%)	Median (IQR) or N (%)	P	
Age	666	37.0 (28.0–46.0)	33.0 (25.0–45.0)	32.0 (24.0–43.0)	39.0 (32.0–47.0)	<0.001		
Education level (y)	424	12.0 (12.0–14.0)	12.0 (12.0–14.0)	12.0 (12.0–14.0)	12.0 (12.0–14.0)	0.11		
Female	666	520 (78.1)	139 (68.8)	68 (78.2)	313 (83.0)	<0.001		
Race	666					0.017		
White		575 (86.3)	162 (80.2)	79 (90.8)	334 (88.6)			
African American		57 (8.6)	28 (13.9)	3 (3.5)	26 (6.9)			
Other		34 (5.1)	12 (5.9)	5 (5.7)	17 (4.5)			
Ethnicity	665					0.94		
Hispanic or Latino		37 (5.6)	12 (6.0)	4 (4.6)	21 (5.6)			
Total # of medications taken [median (IQR)]	666	4.0 (2.0–6.0)	3.0 (1.0–5.0)	3.0 (1.0–5.0)	5.0 (3.0–7.0)	<0.001		
No. chronic conditions [median (IQR)]	666	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	3.0 (2.0–4.0)	<0.001		
Intentionality	652					<0.001		
Suicide attempt		199 (30.5)	72 (36.2)	46 (52.9)	81 (22.1)			
Unintentional		403 (61.8)	113 (56.8)	38 (43.7)	252 (68.9)			
Unknown		50 (7.7)	14 (7.0)	3 (3.5)	33 (9.0)			
Psychiatric disease	666	338 (50.8)	86 (42.6)	53 (60.9)	199 (52.8)	<0.01		
Substance abuse	666	279 (41.9)	89 (44.1)	32 (36.8)	158 (41.9)	0.52		
Alcohol abuse	666	125 (18.8)	51 (25.3)	23 (26.4)	51 (13.5)	0.004		
Injury Type	666					<0.01		
ALF		588 (88.3)	174 (86.1)	68 (78.2)	346 (91.8)			
ALI		72 (10.8)	26 (12.9)	17 (19.5)	29 (7.7)			
ALI to ALF		6 (0.9)	2 (1.0)	2 (2.3)	2 (0.5)			

ALF indicates acute liver failure; ALI, acute liver injury; APAP, acetaminophen; IQR, interquartile range.

TABLE 2

Baseline Clinical Characteristics Total Study Sample and by Acetaminophen Group

	Total Sample (N = 666)*		APAP Alone (N = 202)		APAP/Diphenhydramine (N = 87)		APAP/Opioid (N = 377)		P****
	N	Median (IQR) or N (%)	Median (IQR) or N (%)	Median (IQR) or N (%)	Median (IQR) or N (%)	Median (IQR) or N (%)	Median (IQR) or N (%)	Median (IQR) or N (%)	
Hepatic encephalopathy †	590								0.01
Grade 1		170 (28.8)	66 (37.9)		23 (32.9)		81 (23.4)		
Grade 2		111 (18.8)	33 (19.0)		15 (21.4)		63 (18.2)		
Grade 3		122 (20.7)	28 (16.1)		15 (21.4)		79 (22.8)		
Grade 4		187 (31.7)	47 (27.0)		17 (24.3)		123 (35.6)		
APAP level (mg/dL)	592	27.0 (10.0–73.5)	24.0 (10.0–62.0)		39.0 (12.0–105.0)		27.0 (10.0–71.0)		0.06
Maximum APAP dose taken in past 6 mo (mg)	360	5000.0 (1365.0–12500.0)	5478.0 (2000.0–15000.0)		17250.0 (4000.0–39500.0)		3000.0 (500.0–7500.0)		< 0.001
Type of ingestion									< 0.001
Acute	200	200 (47.3)	97 (68.8)		51 (77.3)		52 (24.1)		
Chronic	195	195 (46.1)	41 (29.1)		13 (19.7)		141 (65.3)		
Acute and chronic	28	28 (6.6)	3 (2.1)		2 (3.0)		23 (10.7)		
King's College (y/n)	666	168 (25.2)	59 (29.5)		21 (24.1)		88 (23.2)		0.25
MELD score	639	29.7 (19.9–36.8)	31.7 (23.0–39.7)		29.8 (19.1–35.6)		28.7 (19.3–35.9)		0.02
INR	646	2.6 (2.0–4.3)	2.6 (2.0–4.8)		2.9 (2.2–4.8)		2.5 (1.9–4.1)		0.11
Total bilirubin(mg/dL)	659	4.1 (2.4–5.9)	4.8 (3.0–6.8)		4.1 (2.6–6.0)		3.7 (2.3–5.4)		< 0.001
Creatinine (mg/dL)	664	1.7 (0.8–3.2)	1.9 (0.8–3.7)		1.5 (0.9–2.9)		1.7 (0.8–3.2)		0.28
AST (IU/L)	659	3488.0 (1315.0–7638.0)	3857.0 (1349.0–7815.5)		5654.0 (1955.0–11264.0)		2942.5 (1094.5–6816.5)		< 0.001
ALT (IU/L)	657	3468.0 (1847.0–5936.0)	4023.0 (2138.0–6455.0)		4862.0 (2552.0–8280.0)		3174.0 (1662.0–5225.0)		< 0.001
Phosphate (mg/dL)	593	2.4 (1.6–3.6)	2.3 (1.6–3.5)		2.4 (1.9–3.5)		2.5 (1.6–3.7)		0.82
Lactate (mmol/L)	388	4.5 (2.4–9.3)	4.4 (2.4–8.0)		4.3 (2.3–9.9)		4.5 (2.4–9.5)		0.92

* Six subjects converted from ALI to ALF. Values from the ALF admission day are included in the table.

† ALI patients will not have hepatic encephalopathy on admission.

**** Kruskal-Wallis Test.

ALF indicates acute liver failure; ALI, acute liver injury; ALT, alanine aminotransferase; APAP, acetaminophen; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range; MELD, model for end-stage liver disease.

TABLE 3

Clinical Outcomes by Type of Acetaminophen Overdose

	N (%)				P
	Total Sample (N = 666)	APAP Alone (N = 202)	APAP/Diphenhydramine (N = 87)	APAP/Opioid (N = 377)	
Hemodialysis during 7 days inpatient phase*	195 (29.3)	54 (27.0)	28 (32.2)	113 (29.8)	0.63
Transplantation within 7 days of admission	47 (7.1)	14 (6.9)	9 (10.3)	24 (6.4)	0.42
Median (IQR) days to transplantation (N = 50)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	0.86
Death within 7 days of admission	111 (16.7)	27 (13.4)	14 (16.1)	70 (18.6)	0.27
Median (IQR) days to death (N = 171)	4.0 (2.0–17.0)	4.0 (2.0–12.0)	4.0 (1.0–8.0)	4.0 (2.0–24.0)	0.71

ALF indicates acute liver failure; ALI, acute liver injury; APAP, acetaminophen; IQR, interquartile range.

TABLE 4
In-Hospital Complications for the Total Study Sample and by Acetaminophen Group

	Total Sample (N = 666)		APAP Alone (N = 202)		APAP/Diphenhydramine (N = 87)		APAP/Opioid (N = 377)	
	N	N (%)	N (%)	N (%)	N (%)	N (%)	P	
Arrhythmia	658	152 (23.1)	48 (24.0)	21 (24.7)	83 (22.3)	0.83		
Infection	121	27 (22.3)	10 (26.3)	2 (13.3)	15 (22.1)	0.64		
GI bleeding	595	64 (10.8)	24 (13.6)	6 (7.5)	34 (10.0)	0.29		
Seizures	663	39 (5.9)	10 (5.0)	2 (2.3)	27 (7.2)	0.20		
ARDS	121	6 (5.0)	1 (2.6)	1 (6.7)	4 (5.9)	0.71		

APAP indicates acetaminophen; ARDS, acute respiratory distress syndrome; GI, gastrointestinal.