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Incidence and characterization of acute kidney injury after acetaminophen overdose

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ABSTRACT

Purpose: Acute kidney injury (AKI) occurs in 2–10% of patients with acetaminophen (APAP) overdose. Elevation in creatinine (SCr) typically occurs 2 to 5 days after ingestion, with a mean peak on day 7, and normalization over a month. However, it remains unclear whether renal impairment occurs without hepatotoxicity. We hypothesized that APAP-associated acute renal failure occurs in patients with and without severe liver dysfunction after APAP overdose.

Materials and methods: We retrospectively evaluated all patients admitted to the Medical Intensive Care Unit at a tertiary hospital and received acetylcysteine between June 2009 and December 2014. Of the 303 patients meeting these criteria, 139 of these patients received acetylcysteine for APAP overdose. Of these patients, 138 had Model for End-Stage Liver Disease (MELD) Scores on Day 1 of admission. Using a modified MELD (m-MELD) score, only containing total bilirubin and international normalized ratio not the SCr, the median m-MELD score was calculated. Patients with m-MELD scores below the median were compared to those with scores above the median (low m-MELD score <2.9 or high m-MELD score >2.9).

Results: Baseline demographics were similar in the two groups with the exception of more hypertension in the low m-MELD group (24 vs 7%; $P = .02$). Time to admission was shorter in the low m-MELD group (7.9 ± 9.3 vs. 25.7 ± 29.2 hours; $P = .001$). The mean admission APAP level was 96.9 (±119) μg/mL in the low compared to 52.3 (±85.3) μg/mL in the high m-MELD group ($P = .012$). Day one SCr (1.2 ± 0.9 vs 2.7 ± 2.2 mg/dL; $P < .0001$) and change from baseline to highest SCr (0.2 ± 0.3 vs. 2.7 ± 3.3 mg/dL; $P < .0001$) were both lower in the low m-MELD group compared to the high m-MELD group. In addition, renal failure resolved upon discharge in all 2 patients (3%) with AKI in the low m-MELD group as compared to only 19 patients (44%) in the high m-MELD group.

Conclusions: Mean day one SCr, maximum change in SCr, and lack of renal failure resolution were higher in patients with higher m-MELD scores. However, patients with low m-MELD scores presented much earlier than patients with high m-MELD scores and 26% developed AKI.

1. Background

In 2005, more than 28 billion doses of acetaminophen (APAP) containing products were dispensed [1]. The American Association of Poison Control Center's National Poison Data System reported 400 deaths in 2013 secondary to APAP or an APAP combination product [2]. Nearly half of the cases of acute liver failure in the United States Acute Liver Failure Study Group were due to APAP toxicity making APAP the number one cause of liver failure in the United States [1].

APAP induced liver failure has been extensively studied [3]. However, extrahepatic effects of APAP overdoses such as acute kidney injury (AKI) are not widely discussed in the literature. AKI occurs in 2% to 10% of patients after APAP overdose [4]. However, one study reported that 79% of patients admitted to a tertiary referral liver intensive therapy unit developed AKI after APAP overdose [5]. Elevation in creatinine (SCr) typically occurs 2 to 5 days after ingestion, with a mean peak on day 7, and normalization over a month [4]. The proposed mechanism for APAP induced renal tubular damage is through the toxic metabolite *N*-acetyl-*p*-benzoquinoone-imine (NAPQI), produced via APAP metabolism by cytochrome P-450 isoenzymes present in the kidney. At therapeutic doses, less than 5% of APAP is metabolized to NAPQI. However, after

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overdose, glutathione depletion results in the generation of more NAPQI reactive intermediates [4]. Although 2 case reports have demonstrated renal impairment without evidence of hepatotoxicity [6,7], systematic evaluation of risk factors for AKI with APAP overdose are lacking. This retrospective review was performed to determine if AKI associated with APAP overdose is more frequently associated with severe liver dysfunction.

2. Methods

All patients admitted to the Medical Intensive Care Unit (MICU) of a large, tertiary care academic medical center who received acetylcysteine between June 2009 and December 2014 were identified through a retrospective medication review. Patients were included if they received acetylcysteine for APAP overdose and had a Measure of End Stage Liver Disease (MELD) Score recorded on day 1 of admission. Using a modified MELD (m-MELD) score, only containing total bilirubin and international normalized ratio (INR), not the SCr, the median m-MELD score was calculated. Patients were divided into 2 groups (low m-MELD Group [m-MELD <2.9] and high m-MELD Group [m-MELD ≥2.9]). Patients with baseline renal dysfunction were not excluded. The Vanderbilt University Institutional Review Board approved this study with waiver of informed consent.

2.1. Study objective

The primary objective was to determine if AKI was associated with higher severity of liver dysfunction.

2.2. Definitions

Nephrotoxins were defined as methotrexate, cyclosporine, tacrolimus, or nonsteroidal anti-inflammatory drugs. Inducers were defined as carbamazepine, phenytoin, phenobarbital, primidone, rifampin, and sulfonylureas. AKI was defined as SCr greater than 1.5 times baseline or an increase in SCr by 0.3 mg/dL in a 48-hour period. Baseline SCr was defined as the SCr before the admission for APAP overdose. Acute overdose was defined as an ingestion of an amount greater than the maximum recommended daily dose of APAP within a 24-hour period. Chronic overdose was defined as ingestion of an amount greater than the maximum recommended daily dose of APAP for a period of time greater than a 24-hour period. Hypoglycemia was defined as a glucose value of ≤60 mg/dL. Peak SCr was defined as the highest SCr value during the patient's hospitalization. Delta SCr was defined as the change from baseline to peak SCr. Resolution of renal failure was defined as no continuation of dialysis and a SCr clearance greater than 60 mL/min [8,9].

2.3. Data collection

Baseline data collected from the medical record included demographics, past medical history, and Acute Physiology and Chronic Health Evaluation (APACHE) II score. The following data were collected with regard to APAP: time to hospital admission, type of overdose, APAP levels and acetylcysteine administration. Measures of SCr, requirement of new dialysis, development and resolution of AKI, liver function tests, mental status assessments, determinants of coagulopathy, and outcome were collected.

2.4. Statistical analysis

Categorical data are reported as numbers and percentages and analyzed using χ^2 test. Continuous data are reported as means ± SD and analyzed using Student *t* tests. A logistic regression was performed to assess whether variables were associated with the development of AKI. A linear regression was performed to assess whether variables were associated with the change in SCr. Variables were chosen to be placed in the regressions based off statistical significance and primary features seen with acute liver failure while ensuring not to include co-linear variables such as SCr or the individual components of the m-MELD. Statistical analyses were performed with SPSS Version 23 (IBM, Inc, Armonk, NY).

3. Results

Acetylcysteine was administered to 303 patients admitted to the MICU between June 2009 and December 2014. Of these, 139 received acetylcysteine for APAP overdose and 138 had MELD scores calculated on day 1.

3.1. Baseline demographics and admission diagnosis

The median baseline m-MELD score was 2.9 (IQR, 1.7-7.5). There was no difference in baseline demographics between the low and high m-MELD groups except in hypertension (Table 1). Admission to the outside hospital (7.9 ± 9.3 vs 25.7 ± 29.2 hours, $P = .001$) and to Vanderbilt University Medical Center (VUMC) (11.4 ± 14.6 vs 40.4 ± 30.6 hours, $P < .0001$) both occurred earlier in the low m-MELD as compared to the high m-MELD group. The low m-MELD group had more acute overdoses as compared to the high m-MELD group (63 [93%] vs 52 [76%], $P = .01$), although the amount of APAP ingested and the initial APAP level did not differ significantly between groups. Time until the first APAP level (8.4 ± 8.2 vs 35.1 ± 30.6 hours, $P \leq .0001$) and time between ingestion and acetylcysteine administration (12.6 ± 11.1 vs 35.4 ± 23.9 hours, $P < .0001$) were lower in the low m-MELD group (Table 1). AKI occurred in 8 patients (26%) with an initial m-MELD score below 2.9 as compared to 46 (69%) in the high m-MELD group, $P < .0001$ (Table 3). Baseline SCr was 0.8 ± 0.2 mg/dL in the low as compared to 1.0 ± 0.9 mg/dL in the high m-MELD group, $P = .26$ (Table 1). Day 1 SCr (1.2 ± 0.9 vs. 2.7 ± 2.2 mg/dL; $P < .0001$) and peak SCr (1.4 ± 1.3 vs. 3.3 ± 2.8 mg/dL; $P < .0001$) were both lower in the low m-MELD

Table 1
Baseline demographics

Characteristics	Low m-MELD (<2.9) (N = 68)	High m-MELD (≥2.9) (N = 70)	*P*
Age	41.9 ± 14.4	39.1 ± 13.9	.39
Sex (female)	37 (54%)	48 (70%)	.06
Race (white)	61 (89%)	64 (91%)	.35
APACHE II Score	12.6 ± 8	11.3 ± 8.4	.36
Past medical history			
Diabetes mellitus	7 (10%)	2 (3%)	.08
Chronic kidney disease	0 (0%)	1 (1%)	.32
Hypertension	16 (24%)	5 (7%)	.02
Chronic Alcohol Ingestion	9 (13.2%)	16 (23%)	.14
Acute APAP ingestion	63 (93%)	52 (76%)	.01
Nephrotoxins*	6 (9%)	2 (3%)	.13
Inducers**	2 (3%)	0 (0%)	.15
Amount of APAP ingested (gm)	21.3 ± 18.2	22.9 ± 32.5	.85
Time before admission to OSH	7.9 ± 9.3	25.7 ± 29.2	.001
Time before admission to VUMC	11.4 ± 14.6	40.4 ± 30.6	<.0001
1st APAP Level (μg/mL)	96.9 ± 119	52.3 ± 85.3	.012
Time Until 1st APAP Level (h)	8.4 ± 8.2	35.1 ± 30.6	<.0001
Time between ingestion and acetylcysteine administration (h)	12.6 ± 11.1	35.4 ± 23.9	<.0001
Baseline SCr (mg/dL)	0.79 ± 0.1	1 ± 0.9	.27
Admission sodium	138.9 ± 3.6	136.9 ± 7.2	.04
Admission ammonia	36.8 ± 22.7	128.9 ± 96.5	.005

* Nephrotoxins: methotrexate, cyclosporine, tacrolimus, and nonsteroidal anti-inflammatory drugs; **Inducers: carbamazepine, phenytoin, phenobarbital, primidone, rifampin, sulfonylureas; APACHE, Acute Physiology and Chronic Health Evaluation, OSH, outside hospital.