



Psychosocial and behavioral factors in acetaminophen-related acute liver failure and liver injury



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ABSTRACT

Objectives: Acetaminophen overdoses result in nearly 500 deaths annually and a much larger number of hospitalizations. Suicidal overdoses are exceeded in number in the United States by unintentional overdoses. We evaluated clinical, demographic and psychosocial factors among unintentional and intentional overdose patients whose acetaminophen (APAP) toxicity had resulted in acute liver failure. We hypothesized that APAP overdose patients would be more likely to suffer from behavioral health issues and display higher impulsivity scores than the general population.

Methods: Within 4 days of admission and initial recovery of alertness, we administered a detailed questionnaire that included questions on APAP intake (e.g., dose taken, intent, other substances ingested), the Mini International Neuropsychiatric Interview modules on depression, alcohol use, substance use, and pain disorders and The Barratt Impulsiveness Scale-11.

Results: The group included 44 intentional (single time point ingestions with the intent to self-harm) and 51 unintentional (multiple time point ingestions to manage pain or other condition) APAP patients enrolled in the Acute Liver Failure Study Group registry between 2007 and 2013. Both groups were characterized by similar frequencies of chronic pain, depressive symptoms at time of ingestion and alcohol and substance use disorders, all at higher rates than the general population. Overall, APAP patients scored higher than the general population for Non-planning aspects of impulsivity, with no apparent differences between other impulsivity scores or between intentional and unintentional APAP patients.

Conclusions: Depression, mismanagement of problematic chronic pain, frequent substance abuse, and increased impulsivity appear to provide the substrate for many APAP overdoses.

1. Introduction

Acetaminophen (APAP)-related overdose is the leading cause of acute liver failure (ALF) in the United States and other Western countries [1–3]. Approximately 46% of patients within the Acute Liver Failure Study Group (ALFSG) registry have ALF thought to be due to APAP overdose, while the next most common etiology (drug-induced liver injury due to prescription or herbal medications) only accounts for 11% of cases [4,5]. The frequent occurrence of APAP ALF is attributed in part to readily available APAP, both in prescription and over-the-counter preparations [6,7] and its reputation of safety and effectiveness when used as directed [6]. Since the first descriptions of cases in the

1980's, most APAP overdoses are categorized into two groups: intentional (e.g., those that are attempts at self-harm, suicidal, single time point ingestions) and unintentional (e.g., those that occur in the setting of inadequate pain relief, continuing to take excessive doses over several days to weeks) [2]. While the groups differ in some respects, both intentional and unintentional APAP overdose patients use more alcohol, other substances, and anti-depressants on average, compared to the general population. Unintentional APAP overdose patients also are observed to more frequently use APAP-opioid combination products for pain relief [3].

Several UK studies suggest that APAP overdoses typically occur “impulsively,” meaning that APAP is ingested within an hour of initially

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considering taking the medication [8,9]. There is a paucity of studies which quantify the role of “impulsivity” as a behavioral attribute in the ALF setting. In the US, most of the research to date regarding APAP ALF continues to focus on incidence and other estimates (e.g., developing prognosis models). Although impulsivity [10], depressive disorders [11], alcohol and substance use disorders [12], and pain disorders [13] have all been associated with drug overdosing, there are limited data regarding the psychosocial and behavioral characteristics of the APAP overdose population, since APAP itself is not a substance of abuse. In this study, we examine a cohort of patients admitted to sites participating in the ALFSG with ALF secondary to APAP overdose, using a detailed questionnaire to identify psychosocial and behavioral factors related to overdosing. We hypothesized that APAP overdose patients are more likely to suffer from behavioral health issues and to display higher impulsivity scores compared to the general population. We further examined these characteristics to determine how APAP overdose patients may or may not differ between each other based on intentionality of overdose.

2. Methods

2.1. Participants

Participants for this study were patients from APAP-related hospitalization that were enrolled at eight different study sites participating in the ALFSG registry (February 2007–June 2013). Patients met established criteria for either Acute Liver Failure (ALF) or Acute Liver Injury (ALI); clinical markers of International Normalized Ratio (INR) ≥ 2.0 and ALT $\geq 10 \times$ elevated (irrespective of bilirubin level) were used to identify ALI, while INR ≥ 1.5 and any degree of hepatic encephalopathy were used to identify ALF. A primary diagnosis of APAP hepatotoxicity was determined by site principal investigators, experienced hepatologists, using standard diagnostic criteria: a history of ingestion of APAP compounds, biochemical pattern commonly associated with APAP liver injury (very high aminotransferases and low bilirubin), with or without detectable acetaminophen serum levels at study admission [3]. Diagnoses were also confirmed through patient self-reporting of prior APAP use at the time of the interview. Overdoses were classified into two categories: intentional where the patient admits to self-harm by ingesting significant quantities of APAP at a single time point versus unintentional overdoses, where patients consume excessive quantities of APAP over several days for pain or other related symptom relief [2]. Patients were placed in one of these categories based on self-reporting and chart review at time of admission. In six cases, intentionality was initially marked in the chart as “unknown” by the principal investigator and subsequently clarified through patient self-reporting (1 intentional and 5 unintentional). Patient self-reporting and clinician assessment of intentionality of overdose matched 86% of the time. When cases did not match, we categorized patients based on fit within our working definitions of intentionality. As such, two patients who reported having suicidal thoughts but denied a suicidal gesture were categorized as “unintentional” because they had been using APAP regularly for pain management. Eighteen patients denied a suicidal gesture but since their overdose occurred from a single time point ingestion of APAP we classified them as “intentional.” While it is possible some of these may have indeed been unintentional overdoses, our categorization of these as “intentional” is based on a probable clinical assumption that many of these patients might have had reasons to deny suicidal intent. Other deviations from our working definition included two patients who admitted to a suicide attempt yet consumed APAP over multiple time points within a 24-h period. These were considered “intentional” due to the patient reporting self-harm. Reported use of APAP-containing compounds in the “unintentional” group denoted daily usage ranging from four days to over five years.

This study was approved by Institutional Review Boards at each site. To collect initial data for ALF patients enrolled in the ALFSG registry,

patients' next of kin were required to have signed permission, since the ALF patient by definition is encephalopathic and would have impaired judgment. ALI patients were allowed to give consent directly for the registry. After recovery from encephalopathy, enrolled ALF, as well as the ALI patients were approached for participation in the questionnaire study. Patients provided separate signed informed consent for the administration of the questionnaire prior to the start of any research activity. Due to the self-reporting component of the study, the site investigators referred participants to study coordinators once the patients were no longer considered medically or psychiatrically unstable; as a result, these were not consecutive patients but represented those deemed appropriate, having recovered and not requiring further medical support at the time of the questionnaire.

Research coordinators who had agreed to participate at eight of the ALFSG sites selected patients who had made a satisfactory recovery without transplantation to determine whether they were willing to participate in this additional questionnaire study. If they agreed and signed a separate consent, the coordinator then administered a multi-part, structured questionnaire to recovering patients nearing hospital discharge. After initial screening questions to determine whether the overdose was intentional or unintentional, the second part of the questionnaire sought to obtain detailed dosing information—the exact doses taken, circumstances leading up to the overdose, the level of understanding of possible harm from acetaminophen, and patient perspectives on several types of preventive interventions. The next part of the questionnaire consisted of administering the Barratt Impulsiveness Scale 11 (BIS-11) and four modules of the Mini International Neuropsychiatric Interview (M.I.N.I.) Plus. The questionnaire administration took place during their recovery process while still in the hospital but near to discharge (median four days after admission).

2.2. Measures

The BIS-11 is a 30-item questionnaire that assesses the personality trait of impulsivity using three subscales (attentional, non-planning and motor) and a total score [14]. Impulsivity is defined as “a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individuals or to others” [15], with the following sub-traits: attentional (“focusing on the task at hand” and cognitive instability), non-planning (self-control and cognitive complexity) and motor (acting without thinking and perseverance) impulsiveness [14]. Items are scored on a 4-point scale (rarely/never = 1, occasionally = 2, often = 3, almost always/always = 4) without relation to any specific time-period. Higher summed scores for all items indicate higher levels of impulsivity.

The M.I.N.I. Plus 5.0.0 was developed from the M.I.N.I. as an efficient diagnostic interview and is used in clinical as well as research settings [16]. The questionnaire follows DSM-IV and ICD-10 criteria, screening for a number of Axis I diagnoses. For this study, the following modules were used: major depressive disorders, alcohol use disorders, non-alcohol substance use disorders, and pain disorders. Other relevant modules, such as suicidality and anxiety disorders, were considered but to ensure the questionnaire did not pose excessive burden on the patient, we elected to ask more specifically about history of suicide attempts and to review charts for documented history of anxiety.

2.3. Data analysis

Descriptive statistics (percentage, median and interquartile range (IQR)) for demographic and clinical data within the ALFSG registry were calculated for the intentional and unintentional groups. The primary outcome measures were impulsivity (subscales and total score) and the M.I.N.I. Plus 5.0 scores. Exact 95% binomial confidence intervals were computed for MINI Plus scores for intentional and unintentional groups. Wald 95% confidence intervals were computed for

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