Retrospective Review of Acetaminophen/ Diphenhydramine Overdose: Features of Toxicity and Outcomes as Reported to California Poison Control

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Abstract

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Lucinda Lai, Hallam M. Gugelmann, Kent R. Olson, Raymond T. Chung.

Purpose: Acetaminophen (APAP) combination products are commonly involved in overdose. We hypothesize that patients who ingest APAP/diphenhydramine combination products experience prolonged gastrointestinal absorption of APAP, such that the standard diagnostic nomogram and 21-hour treatment protocol would underestimate the true risk of hepatotoxicity.

Methods: We retrospectively reviewed 213 cases of APAP/diphenhydramine and 149 cases of plain APAP overdose that had resulted in hepatotoxicity and were reported to the California Poison Control System from 1997 to 2013.

Results: No significant differences were observed between the APAP/diphenhydramine and plain APAP groups in terms of demographics or clinical presentation, except that the former group was more likely to have received activated charcoal ($p = 0.0015$). We identified cases of hepatotoxic APAP/diphenhydramine overdose that demonstrated prolonged APAP absorption that necessitated extended NAC therapy. This study did not find evidence, however, that this group of patients experienced worse clinical outcomes in terms of mortality or need for liver transplantation. Comparing cases of hepatotoxicity versus minor hepatic injury in the setting of APAP/diphenhydramine overdose, an APAP-aminotransferase multiplication product (APAP x AT) greater than the pre-specified cut-off point of 1500 mg · IU/L^2 had a sensitivity of 95% (95% confidence interval [CI]: 88% to 99%) for predicting hepatotoxicity, and an odds ratio of 5.7 (95% CI: 1.6. – 20.0). No cases of hepatotoxicity were observed among patients who had presented initially with undetectable APAP and normal transaminase levels.

Conclusions: These data provide evidence that APAP combination products pose unique risks to patients and modification of the NAC treatment protocol may be necessary to prevent significant hepatic injury and death.

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Glossary of Abbreviations

APAP: acetaminophen
APAP/diphenhydramine: the combination product of acetaminophen and diphenhydramine
APAP x AT: acetaminophen-aminotransferase multiplication product; the multiplication product of the first-measured aminotransferase concentration times the simultaneously measured serum acetaminophen concentration
ALT: alanine aminotransferase
AST: aspartate aminotransferase
AT: aminotransferase
CI: confidence interval
FDA: Food and Drug Administration
IQR: interquartile range
IU: International Unit
NAC: *N*-acetylcysteine
NAPQI: *N*-acetyl-p-benzoaquinone imine
OR: odds ratio
mg/L: milligram per liter

Section 1: Introduction

Acetaminophen (APAP) and APAP combination products are commonly used as pain relief and anti-pyretic medications, readily available over the counter, and liberally prescribed.[1] They are also commonly involved in cases of overdose.[2,3] APAP overdose represents a significant public health problem with at least 50,000 emergency department visits and 30,000 hospitalizations each year.[4,5] While APAP is a safe and effective drug at recommended doses, APAP overdose is the leading cause of acute liver failure in the United States and causes more than 450 deaths each year.[4,6,7] It is the most commonly ingested substance in suicide attempts in the United States.[8]

The biological mechanism of APAP-induced liver injury is well described: doses of APAP greater than four grams lead to excess production of *N*-acetyl-p-benzoaquinone imine (NAPQI), resulting in depletion of protective glutathione and subsequent hepatotoxicity.[4] *N*-acetylcysteine (NAC) can be administered to prevent hepatotoxicity following APAP overdose, as well as alleviate the severity of the illness once it has developed. It works by replenishing hepatic glutathione stores.[6,9-11] Increased APAP concentration and delayed NAC therapy are risk factors for hepatotoxicity due to a higher NAPQI load and more prolonged depletion of glutathione.[11] The APAP elimination half-life is normally 2 to 2.5 hours, but is greater than 4 hours in patients who develop hepatotoxicity.[12] In the largest study of APAP elimination kinetics in patients with hepatotoxicity, Sivilotti et al. found that the elimination half-life was greater than four hours in 16 of 17 untreated patients who developed hepatotoxicity and in 56 of 64 patients with an alanine aminotransferase (ALT) level >1,000 IU/L despite NAC treatment.[12]

Emergency physicians routinely have to manage patients who have overdosed on APAP-containing products and have to decide if antidotal therapy is necessary in order to prevent hepatotoxicity.[13] The only accepted parameter for the assessment of hepatotoxicity risk in acute APAP overdose is the Rumack-Matthew nomogram, which plots serum APAP concentration versus time since ingestion (see Appendix 1).[6,11] It requires a single serum APAP concentration measured between 4 and 24 hours after time of ingestion. The nomogram was developed based on the typical pharmacokinetics of APAP in the setting of a single, acute ingestion, in which serum APAP concentrations are expected to peak within 4 hours of ingestion, then drop quickly with a half-life of 2 to 4 hours.[14,15] In the United States, a line beginning at 150 mg/L at 4 hours post-ingestion and declining with a half-life of 4 hours (the "treatment line") is used to determine

whether to initiate antidotal treatment with NAC.[16] The upper line on the nomogram, starting at 200 mg/L at 4 hours post-ingestion, defines patients who are at "probable" risk of hepatotoxicity if not given NAC.[17] Risk stratification based on this tool remains relatively crude, resulting in both over- and undertreatment with the antidote NAC and may increase the risk of hepatotoxicity or prolong hospitalization, respectively.[12,18]

The nomogram cannot be used to predict risk in cases of delayed presentation, chronic or multiple ingestions, or an unknown time of ingestion.[12] In fact, one population-based study of all APAP-related visits to two hospitals in central Virginia over a ten-year period by Bond et al. found that almost half of all patients hospitalized for treatment of APAP ingestion, and an even higher proportion of the those with significant hepatic injury, presented with an ingestion for which the nomogram could not be used to predict toxicity.[19,20] Physicians have no evidence-based guidelines for the management of such patients.[20,21] In the United Kingdom, for example, the standard is to treat any patient with a serum APAP level equivalent to 100 mg/L at four hours post-ingestion (based on the modified Rumack-Matthew nomogram) or any patient with staggered overdose or unknown time of ingestion.[6] Research efforts are being directed at characterizing the historical, physical, and biochemical markers of risk and at determining in which circumstances hospitalization for NAC or other therapies is justified.[20]

A promising new instrument for early risk stratification is the multiplication product of the first measured aminotransferase (AT) concentration and simultaneously measured serum APAP concentration: APAP x AT. This approach does not require knowledge of the exact time of ingestion, information that may often be inaccurate or unknown, or that the overdose have been taken at a single point in time, two major limitations of the Rumack-Matthew nomogram.[12,18,22] The calculated value of APAP x AT takes advantage of the fact that as serum APAP decreases through drug elimination over time, patients who develop APAP-induced hepatitis will experience an increase in hepatic aminotransferases.[11] This increase occurs with a faster onset and achieves a higher magnitude in patients who develop hepatotoxicity. In the original APAP x AT study, Sivilotti et al. found that all patients with hepatotoxicity had multiplication products that were 1,500 mg · IU/L^2 or greater.[12] Moreover, larger multiplication products were associated with a faster onset of hepatotoxicity. In their retrospective review of acute APAP overdose cases who were treated with NAC at a hospital in Thailand, Chomchai and Chomchai found that APAP x AT had high sensitivity (90.6%) and low negative likelihood ratio

(0.2).[11] They concluded that APAP x AT would be a useful tool for predicting a low likelihood of hepatotoxicity after standard NAC therapy among late-presenting patients. In their study population, APAP x AT excluded over half of the patients from further follow up and treatment. Specificity for predicting hepatotoxicity was only 62.8%, however. The authors suggested that such a tool might ultimately be used to inform management decisions, such as when to discontinue or when to intensify treatment following APAP overdose.[12] APAP x AT has not been studied in cases of APAP/diphenhydramine overdose.

Another approach to risk prediction when time of ingestion is uncertain is to ask whether a patient who presents with both a normal transaminase level and undetectable APAP is at risk of developing hepatotoxicity if not given NAC, as is the current standard of care. Sivilotti et al. in their study population found that no patient who developed hepatotoxicity had a normal AT level and undetectable APAP level at initial presentation.[12] Furthermore, Froberg et al. found that an APAP concentration of <100 mg/L between one and four hours after ingestion had a high negative predictive value for hepatotoxicity. They did not, however, recommend reliance on concentrations obtained between one and four hours to exclude toxicity due to a potential false-negative rate of 6.5%.[23]

Exceptions to the typical APAP pharmacokinetics have been reported in cases of massive ingestion or coingestion of drugs that slow gastrointestinal motility. There are case reports of patients with acute overdoses of APAP combination products with an initially non-toxic APAP level at 4 hours, but subsequently found to have a subsequent APAP level that "crossed the line" into high risk of hepatotoxicity, especially if coingestants that slow gastrointestinal motility are involved.[16] The nomogram failed to predict toxicity based on a single serum APAP level in this subset of patients.[13] Tighe et al described a 20-year-old female with an APAP/propoxyphene (650 mg/100 mg) overdose whose APAP level at 4.5 hours was 83 mg/L (non-toxic), but increased to 124.6 mg/L at 6.75 hours (toxic).[24] Ho et al. reported a 19-year-old female who intentionally ingested 92 tablets of APAP/diphenhydramine (500 mg/25 mg).[25] Serum APAP at 4.25 hours post-ingestion was 77 mg/L (non-toxic), but was then found to be 258 mg/L (toxic) almost 4 hours later. It continued to rise to 312 mg/L at 10.5 hours after ingestion. In a retrospective study at a single U.S. poison center, Dougherty et al. found that the majority of line-crossing cases involved overdose of either APAP/diphenhydramine or APAP-opioid combination products.[13]

To estimate the true incidence of line crossing, Kirschner et al. conducted a prospective cohort study of hospitalized patients reported to a regional poison center after acute overdose of an APAP combination product containing an opioid or antihistamine.[16] They found that 6.6% of patients had toxic APAP levels after an initially non-toxic 4-hour level. The authors concluded that patients with acute overdose of APAP combination products and detectable but non-toxic 4-hour concentrations should have repeat concentrations obtained in a time frame that would allow providers to initiate NAC treatment, if needed, without undue delay. Because published reports of line crossings have been available for over twenty years, some poison centers already routinely recommend that a measurable 4-hour APAP concentration below the nomogram treatment line be repeated if opioids or anticholinergics are coingested.[16]

Although the mechanism for this is not entirely clear, the delayed rise in blood levels may be related to reduced gastrointestinal motility and delayed absorption when APAP is combined with an anticholinergic agent such as diphenhydramine, a coingestant that slows gastric emptying and gastrointestinal peristalsis.[24-26] Cases of an unusual double-peak pattern of serum APAP, in which the APAP peaked, then declined, only to be followed by a subsequent unexpected increase in APAP concentration to a second peak, may be associated with large ingestions (26 to 100 grams acetaminophen) or coingestions of anticholinergic or opioid drugs.[27] Double-peaks of serum APAP concentration, delayed peaks in APAP concentration, and development of liver injury have been observed in patients with large ingestions of APAP combined with diphenhydramine.[24-26] In one report by Hendrickson et al., a second peak was observed occurring as late as 37 hours post-ingestion.[27] Patients with double-peak APAP concentrations may be at greater risk for liver injury, with aspartate aminotransferase (AST) elevations occurring later than what are typically expected for acute APAP overdoses.[24-26] Burda and Sigg reported a late second peak after APAP and diphenhydramine (non-combination product) overdose.[2]

Schwartz et al. reported a case of massive APAP/diphenhydramine overdose with a 4-hour concentration that was below the treatment line, followed by an atypical, delayed, bimodal pattern with peaks at 48.75 and 75.5 hours.[9] Although this patient was given intravenous NAC early due to altered mental status and an unclear time of ingestion (later provided by the family), the patient developed liver failure and died.[9] This case suggested that individual-specific dosing of antidotal therapy may be needed for preparations of APAP that result in delayed absorption or

after massive overdose. This case and others raised the concern that the standard, FDA-approved 21-hour course of intravenous NAC may not be sufficient for all early-presenting APAP overdose patients, especially those with massive ingestions or involving drugs that slow gastrointestinal motility. Physicians should be aware of these differences in pharmacokinetics because the decision not to treat with NAC based on a single early level can result in later serious hepatotoxicity.[10]

To date, only one large-scale study has examined differences in clinical presentation and clinical outcomes of APAP combination products overdose compared to plain APAP overdose. Serper et al. used data from the Acute Liver Failure Study Group database from 1998 to 2012 to analyze a total of 666 cases of APAP-related liver failure.[4] They compared baseline patient characteristics, initial clinical presentation, and clinical outcomes among three groups of patients: APAP alone, APAP/diphenhydramine, and APAP/opioids. They found that patients taking APAP combined with opioids were older, had more comorbidities, and were more likely to have unintentionally overdosed. Patients with APAP/diphenhydramine overdose presented with the highest serum aminotransferase levels, but no differences in laboratory values were noted at three days post-enrollment. Remarkably, no significant differences were observed among the three groups in terms of delayed hepatotoxicity or clinical outcomes, but the authors noted that they had relatively few patients in the APAP/diphenhydramine group and that the study may have been underpowered to detect important differences in clinical outcomes.

Given the public health significance of the problem of APAP/diphenhydramine overdose, and the clinical questions raised by case reports of delayed hepatotoxicity, the objectives of this investigation were to (1) compare patient demographics, clinical variables, and outcomes related to plain APAP overdose versus APAP/diphenhydramine overdose; (2) identify delayed peaks and second peaks of serum APAP levels in patients with APAP/diphenhydramine overdose; (3) determine the sensitivity of the APAP x AT multiplication product to predict hepatotoxicity after acute overdose of APAP/diphenhydramine; and (4) to determine whether any patients developed hepatotoxicity despite initial presentation with undetectable APAP and normal transaminase levels.

Section 2: Methods

Study population:

We analyzed cases of plain APAP and APAP/diphenhydramine overdose using the California Poison Control System database from 1997 to 2013. The Poison Control System records contain demographic, laboratory, and clinical outcome data on patients who were managed in a health care facility and reported to the Poison Control System. A total of 362 cases were reviewed: 72 cases of APAP/diphenhydramine overdose that resulted in minor hepatic injury (peak transaminase greater than 100 but less than 1000 IU/L), 141 cases of APAP/diphenhydramine overdose that resulted in hepatotoxicity (peak transaminase greater than 1,000 IU/L), and 149 cases of plain APAP overdose that resulted in hepatotoxicity. This study was reviewed by the Committee on Human Research at the University of California at San Francisco, the host institution for the Poison Control System, and determined to be exempt. This study was a review of existing Poison Control Center electronic records and did not involve contact with patients or their families. Data were provided to the investigators with all patient identifiers removed.

Data collection:

An electronic search of the California Poison Control System database identified all patients who had been managed in a health care facility for a single-substance, acute APAP/diphenhydramine overdose and reported to the Poison Control System between 1997 and 2013. We used the National Poison Data System's standard definition of "minor hepatic injury" as AST or ALT >100 IU/L and ≤1,000 IU/L.[3,19,28] We defined "hepatotoxicity" as AST or ALT ≥1,000 IU/L. We chose transaminase elevation as the marker of APAP-induced hepatic injury, instead of other indicators of acute liver failure, because it is collected in a standard manner in this database and is a more sensitive marker of injury to prompt public health intervention to prevent acute liver failure.[19] There were two groups of patients with APAP/diphenhydramine overdose: 72 patients who developed minor hepatic injury and 141 patients who developed hepatotoxicity. From the same database, we identified 650 cases of acute, single-substance plain APAP overdoses that developed hepatotoxicity. We selected every fourth case to create a randomized subset of 149 cases to serve as a comparison group to the APAP/diphenhydramine hepatotoxic cases.

Cases of multidrug ingestions and chronic ingestions taken over a period of eight hours or more were excluded. "Acute overdose" was defined to mean ingestion at one single point or within the period of eight hours.[3] Standardized data collection forms were used to extract information which included demographic characteristics, history of prior alcohol use, time of ingestion, whether activated charcoal was administered, lag-time to initiation of NAC therapy, peak APAP and aminotransaminase levels, peak measured INR, and final outcome of the case (discharge, liver transplantation, or death). For each case of APAP/diphenhydramine overdose with hepatotoxicity, data was collected about every measured serum APAP level and the time it was collected relative to the time of ingestion. Vague descriptions such as "a handful", "a whole bottle", or "a pile" of pills were excluded from calculations of ingestion sizes. Serum APAP concentrations were measured at local institution laboratories. Some laboratories reported non-detectable concentrations as <10 mg/L while others reported concentrations down to 0 mg/L.

Analysis plan:

The study dataset from the California Poison Control System database from 1997 to 2013 was analyzed using descriptive statistics to characterize patient demographics and other clinical variables describing illness severity, treatment, and outcomes. Descriptive categorical variables were summarized as frequencies with percentages. These categorical variables were analyzed using the Fisher exact test. Because of non-normally distributed data, continuous variables were reported as medians with interquartile ranges (IQR) and compared using the Mann-Whitney-U test.[4,11] Statistical analyses were performed using the GraphPad Software and Social Science Statistics calculators (available online).[29,30] All tests were assessed at the 0.05 significance level. Sensitivity, odds ratios, and ninety-five percent confidence intervals (95% CIs) were measured using the MedCalc Software online calculator.[31]

For each case, APAP x AT was calculated from the initial laboratory values. Only the higher value of either AST or ALT was used in the calculation.[11] In a secondary analysis, for patients in whom the APAP level had been reported as undetectable, we imputed an arbitrary value of 5 mg/L to allow for calculation of the multiplication product. This was the method of Wong et al. and was chosen because it was 50% below the laboratory limit of detection of 10 mg/L, as per the original Sivilotti (2010) study.[12,18] In the primary analysis, 32 out of 72 cases of minor hepatic injury and 58 out of 141 cases of hepatotoxicity were excluded due to missing data about either the initial APAP or aminotransferase value. In the secondary analysis, 26 out of 72

cases of minor hepatic injury and 17 out of 141 cases of hepatotoxicity were excluded due to missing data.

A descriptive method was used to create a graphical representation of serum APAP levels versus time since ingestion for each case of APAP/diphenhydramine overdose with hepatotoxicity and identify cases of prolonged APAP absorption and/or delayed hepatotoxicity.

Section 3: Results

We identified 141 cases of APAP/diphenhydramine overdose that resulted in hepatotoxicity: 89 cases were female (63%) and 52 were male (37%), with a median age of 30.0 (IQR, 18.0 – 42.0). Fifteen (11%) had known prior alcohol use. Median size of ingestion was 25.0 grams (IQR, 15.0 – 50.0). Activated charcoal was given in 30 cases (21%). Median lag-time to initiation of NAC therapy was 24.0 hours (IQR, 12.0 – 43.5) after ingestion. Median peak measured serum APAP concentration was 72.0 mg/L (IQR, 2.0 – 180.5). Median peak measured aminotransferase level was 4524 IU/L (IQR, 2053 – 8360) and median time to peak measured aminotransferase was 63.8 hours (IQR, 52.6 – 81.4). Peak measured INR was 1.8 (IQR, 1.5 – 2.8). Liver transplantation occurred in zero cases. Deaths occurred in 6 cases (4%). The results are summarized in Table 2.

Patients with APAP/diphenhydramine overdose were more likely than patients with plain APAP overdose to have been given activated charcoal. Otherwise, there were no significant differences in terms of age, sex, size of ingestion, proportion of cases above the 1500 mg • IU/L^2 cut-off for the APAP x AT multiplication product, time to NAC treatment, peak measured serum APAP, peak measured AT, time to peak measured AT, peak measured INR, or adverse outcomes such as liver transplantation or death.

The graph of serum APAP levels versus time since ingestion (Figure 1) was used to identify cases APAP/diphenhydramine overdose that demonstrated delayed peaks in serum APAP. There were three such cases identified. The first delayed peak case was a 77-year-old female without any known history of alcohol abuse who presented to the emergency department with altered mental status after ingesting an unknown amount of Tylenol® PM. The time of ingestion was reported as sometime between the "evening" of the previous day and 7:00 a.m. of the day of admission. The first measured APAP at 11:00 a.m. on the day of admission was found to be 215 mg/L, and rose to 249 mg/L 2 hours and 40 minutes later. Given the vague history, the study protocol was applied to indicate that the initial ingestion was at midnight, time of arrival was at 11 hours postingestion, time to peak APAP was 14 hours, and time of NAC initiation was at 12 hours. Transaminases began to rise within the first 24 hours and continued to rise on the third day post-ingestion, then decreased the next day. NAC was continued beyond the 21-hour standard course due to continued rise in transaminase levels. By the fifth day post-ingestion,

transaminase levels had fallen. The patient's hospital course was uneventful and she was cleared for psychiatric evaluation approximately four days postingestion.

In the second case, a 23 year old female was found obtunded by her husband after ingesting an unknown amount of APAP/diphenhydramine. Her initial serum APAP was 811 mg/L, which was presumed to have been drawn 6 hours postingestion with reference to the time she was last seen normal. Initial AST was 680 IU/L and ALT 122 IU/L. She was started on intravenous NAC immediately. At 9 hours postingestion, APAP was still elevated at 462 mg/L, with AST risen to 2100 IU/L and ALT to 602 IU/L. By 35 hours post-ingestion, APAP was found to be 146 mg/L with AST risen to 2807 IU/L and ALT 937 IU/L. At this point, Poison Control Center staff recommended that intravenous NAC be continued until serum APAP dropped to undetectable levels and transaminases improved. Thus, NAC was continued until these parameters were achieved at 83 hours postingestion.

In the third case, a 60 year old male was found unresponsive after reported ingestion of up to 300 tablets of Tylenol® PM. His initial APAP level was 528 mg/L at 13 hours postingestion and he was started on intravenous NAC. Gastric lavage was attempted in the emergency department. The patient then aspirated and required sedation and intubation for airway protection. At 24 hours postingestion, serum APAP was still found to be elevated at 311 mg/L, with AST of 71 IU/L and ALT of 55 IU/L. At 43 hours postingestion, his APAP level was 25 mg/L with AST risen to 1461 IU/L and ALT to 1273 IU/L, so intravenous NAC was continued until 118 hours postingestion, once both the APAP level fell to undetectable levels and transaminases decreased to below 1000 IU/L. The patient was transferred to psychiatric services in stable condition.

One case of APAP/diphenhydramine overdose that demonstrated a second peak in serum APAP levels was identified: a 33 year old male with no history of alcohol abuse reportedly ingested 379 tablets of Tylenol® PM (189.5 grams of APAP). He called a family member to tell them what happened and was brought to the emergency department 2 hours after the time of ingestion. His 4-hour APAP level was 336 mg/L, which dropped to 197 mg/L at 13.5 hours post-ingestion, but rose again at 43 hours post-ingestion to 376 mg/L, and finally peaked at 80 hours post-ingestion at 418 mg/L. From that peak, serum APAP levels dropped continuously until reaching undetectable levels at 180 hours post-ingestion. Activated charcoal was given and intravenous NAC was started at 5 hours post-ingestion. NAC was continued beyond the 21-hour

standard course due to rising APAP levels. Transaminases began to rise on the third day post-ingestion. During the course of his hospitalization, he required intubation and was started on dialysis (discontinued after one day). The patient was discharged home in stable condition on the 11th day of hospitalization without having required a liver transplantation.

There were five cases of APAP/diphenhydramine overdose that presented initially with APAP below the Rumack-Matthew treatment line, but subsequently developed hepatotoxicity. In all five cases, however, it was ultimately determined that the reported times of ingestion were likely inaccurate.

In the first case, a 23 year old female presented to the emergency department lethargic and drowsy 3 hours (by self-report) after an unknown size of ingestion of APAP/diphenhydramine. Her initial serum APAP was 28 mg/L with AST already elevated to 1600 IU/L and ALT 1240 IU/L and an INR of 1.5. Intravenous NAC was started, but AST increased to 7678 IU/L, ALT increased to 7768 IU/L, and INR increased to 2.35. After 24 hours of NAC treatment, her AST decreased to 3300 IU/L, ALT to 598 IU/L, and INR to 2.13. She was discharged to a psychiatric facility in stable condition. Due to the initial presentation with transaminases already in the hepatotoxic range, the managing doctor concluded that the time of ingestion was likely much earlier than reported by the patient.

In the second case, a 45 year old female presented to the emergency department with a vague history of having ingested Tylenol® PM (acetaminophen 500 mg/diphenhydramine 25mg) 8-10 hours prior to presentation. Her initial APAP was 36 mg/L; two hours later it was 21 mg/L. The patient had already been medically cleared to the psychiatry service, but was sent back to the emergency department for "incidental reasons" and was found to have AST elevated to 8000 IU/L and ALT to 2000 IU/L. Oral NAC was started and 20 hours later, the patient's AST decreased to 2048 IU/L and ALT to 680 IU/L. The patient's AST continued to decrease to 400 IU/L and ALT to 905 IU/L. She was discharged home without other complications. Although this may appear to be a case of delayed peak in serum APAP, the history from the patient was vague and likely inaccurate.

In the third case, a 22 year old male with past medical history of alcohol use disorder presented "sometime this morning" after an unwitnessed overdose of Tylenol® PM at 1 a.m. At 6:44 a.m. (5 hours and 44 minutes after the reported time of ingestion), APAP level was 106 mg/L. Subsequent APAP levels were 80 mg/L (at 8:45 a.m.) and 57 mg/L (at 9:40 a.m.). Oral

NAC was started and 24 hours later Poison Control Center records indicated that the patient's AST was 223 IU/L and ALT was 283 IU/L; no repeat APAP was noted at that time. AST increased to 494 IU/L and ALT to 1099; additional NAC and repeat labs were recommended, but the patient had been sent to psychiatry and lost follow-up. The history from this patient regarding the time of ingestion was likely inaccurate.

In the fourth case, a 37 year old male with past medical history of cocaine and ethanol abuse ingested an unknown amount of Tylenol® PM with estimated time of ingestion between 10 a.m. and 11:30 a.m. An APAP level at 12:45 p.m. (between 1 hour 15 minutes and 1 hour 45 minutes post-ingestion) was 129 mg/L. NAC was not started because this value was considered to be "below" the treatment line, but the level had been drawn too early to actually make that estimation. A repeat APAP level drawn at 5 p.m. (between 5 hours 30 minutes and 7 hours postingestion) was found to be 95.6 mg/L (above the nomogram line); oral then intravenous NAC was started. AST was initially 116 IU/L and ALT 139 IU/L, which subsequently increased to AST of 2479 IU/L and ALT of 2520 IU/L, then decreased to AST 573 IU/L and ALT 1510 IU/L with continued NAC administration. This is not a case of delayed hepatotoxicity because the initial level had been drawn too early and the 7-hour level was indeed above the treatment line.

In the fifth case, a 24 year old male with past medical history of alcohol use disorder ingested an unknown amount of Tylenol® PM at an uncertain time ("sometime before 18:00"). The first APAP level was 136 mg/L, with AST 306 IU/L and ALT 472 IU/L. The patient received intravenous NAC. The patient subsequently developed hepatotoxicity with AST increased 2322 mg/L and ALT to 2409 IU/L. Although this may appear to be a case of delayed hepatotoxicity, the history of time of ingestion was uncertain. There was no repeat APAP level drawn until the next day, when it was found to be <10 mg/L.

No cases of APAP overdose were identified that demonstrated a second peak in the serum APAP level. In one case plain APAP overdose with a delayed rise in serum APAP, an 18 year old female without known history of alcohol abuse ingested 50 tablets of acetaminophen (25 grams) and presented to the emergency department 2 hours after the time of ingestion. She was given activated charcoal. The initial APAP level of 177 mg/L rose to peak of 189 mg/L at 4 hours post-ingestion. NAC was not initially recommended because the first level was below 200 mg/L, but the APAP level the next morning at 13 hours post-ingestion was found to be 122

mg/L, now well above the probable toxicity line. NAC was advised and started at 15 hours post-ingestion. NAC was continued beyond the 21-hour standard course due to rising transaminase levels on the third day post-ingestion. The patient was discharged home on the sixth day of hospitalization in stable condition.

Sufficient data was available to calculate the APAP x AT multiplication product in 123 APAP/diphenhydramine cases (83 who developed hepatotoxicity and 40 who developed minor transaminitis) and 80 plain APAP cases. The APAP x AT was above the cut-off point of 1500 mg • IU/L^2 in 79/83 cases (95%) of APAP/diphenhydramine overdose with hepatotoxicity, and in 31/40 cases (78%) that developed minor hepatic injury (odds ratio 5.7, 95% CI: 1.6. – 20.0). 79/80 cases (99%) of plain APAP overdose with hepatotoxicity had initial APAP x AT multiplication products >1500 IU/L^2. Comparing cases of APAP/diphenhydramine overdose with hepatotoxicity to cases of plain APAP overdose with hepatotoxicity, an odds ratio of 0.25 (95% CI: 0.027 – 2.29) was found (Table 2).

In the secondary analysis, in which a value of 5 mg/L was imputed for serum APAP levels that had been reported as below the laboratory's level of detection, 119/124 cases (96%) of APAP/diphenhydramine overdose with hepatotoxicity had a APAP x AT above the pre-specified cut-off point, compared with 33/46 cases (72%) that developed minor hepatic injury (odds ratio 9.4, 95% CI: 3.1 – 28.2). We were not able to calculate specificity or negative likelihood ratio because we were not able to determine the APAP x AT for cases with no transaminase elevation due to insufficient laboratory data collected on these patients.

None of the 213 patients with APAP/diphenhydramine overdose with either minor hepatic injury or hepatotoxicity, and none of the 149 patients with plain APAP overdose with hepatotoxicity, had initially presented with both undetectable APAP levels and normal transaminase levels ("negative-negative" numbers).

Section 4: Discussion

Discussion:

Cases of overdose with APAP/diphenhydramine combination products carry the theoretical risk of delayed hepatotoxicity. The anticholinergic effect of diphenhydramine might cause slowing of gastrointestinal motility resulting in prolonged absorption. In such cases, use of the Rumack-Matthew nomogram to guide decision-making based upon a single APAP level could cause physicians to miss a subsequent rise in serum APAP and transaminase levels. The most serious consequence of discontinuation of NAC at the completion of the standard 21-hour protocol, but prior to the complete absorption, metabolism, and elimination of APAP, would put these patients at higher risk for significant hepatic injury and death.[32]

This study found no significant differences in baseline patient characteristics, illness severity, or clinical outcomes of patients with hepatotoxicity due to plain APAP overdose compared to APAP/diphenhydramine overdose, except that patients who presented with APAP/diphenhydramine overdose were significantly more likely to have received activated charcoal for gastrointestinal decontamination. This difference did not affect laboratory markers of hepatotoxicity or overall clinical outcomes. It is possible that the greater use of gastrointestinal decontamination in patients with APAP/diphenhydramine overdose served to counteract the effect of prolonged absorption of APAP, but this hypothesis would need to be prospectively verified. The more plausible explanation, and the one demonstrated in our descriptions of outlier cases, is that patients with delayed toxicity were administered extended NAC therapy (beyond the standard 21-hour treatment protocol) because of observed ongoing rises in APAP and/or transaminase levels. Prolongation of the NAC treatment protocol was likely sufficient to prevent serious adverse outcomes such as liver transplantation and death.

These findings corroborate those of Serper, et al., who also found no significant differences between patients with APAP/diphenhydramine versus plain APAP overdose with regards to adverse clinical outcomes, such as mortality or the need for liver transplantation.[4] This was true even though their study included patients with both intentional and unintentional ingestions. Serper et al. note that one important limitation of their study, however, was that they had relatively few patients with APAP/diphenhydramine overdose, so their study may have been underpowered to detect important differences in clinical outcomes.

Graphical representation of serum APAP levels versus estimated time since ingestion for every case of APAP/diphenhydramine overdose with hepatotoxicity (Figure 1) served to identify outlier cases of delayed toxicity. Two outlier cases in which serum APAP levels continued to rise beyond what would be expected according to typical APAP pharmacokinetics are described. In the first case, serum APAP did not peak until 14 hours post-ingestion. The second case was a massive ingestion of APAP/diphenhydramine that demonstrated double-peak absorption, with peaks of serum APAP at 4 and 80 hours post-ingestion. In both cases, the decision was made to continue NAC treatment beyond the standard 21-hour protocol due to ongoing rises in transaminase levels. In both cases, hepatotoxicity resolved without the need for liver transplantation and the patients were discharged in stable clinical condition.

Our findings contrast with the well-described pharmacokinetic model of APAP overdose, in which serum APAP concentration peaks by 4 hours post-ingestion, has an elimination half-life of 2 to 4 hours (in the non-hepatotoxic patient), and reaches low-to-negligible levels at 24 hours post-ingestion. The divergence of our findings from the classical model is best explained by the continued absorption of APAP well beyond 4 hours in some patients and is supported by the literature.[17]

The FDA-approved 21-hour intravenous NAC regimen is indicated for acute APAP overdoses presenting within eight to ten hours of ingestion, regardless of the type of APAP preparation ingested or the presence of coingestants.[17] The manufacturer recommends treatment for only 21 hours, regardless of clinical parameters.[17] Our data suggest that the 21-hour regimen is suboptimal in certain patients. In patients with APAP toxicity who co-ingest other medications that may potentially delay gastric emptying and thus delay absorption of APAP, we recommend close monitoring of transaminase levels, as well as trending APAP concentrations until undetectable before discontinuing NAC therapy.[32] Doyon et al. propose that NAC should not be discontinued at 21 hours unless the following laboratory parameters are met: undetectable serum APAP and normal transaminases ("negative-negative" numbers).[17] Their observational case series found that 70/70 patients who had the combination of undetectable serum APAP and normal transaminases after 21 hours of intravenous NAC had good outcomes. Further study is needed to determine the optimal intravenous NAC protocol, including dose and duration of infusion, in patients who fail to meet those laboratory parameters at 21 hours. It would also be

useful to determine the safety of stopping NAC earlier than 21 hours if the "negative-negative" rule is met.

Patients who present after APAP/diphenhydramine overdose with detectable but non-toxic 4-hour APAP concentrations may need to have repeat concentrations obtained in a time frame that would allow providers to initiate NAC treatment as necessary, without undue delay.[16] Furthermore, although repeat testing of post-peak APAP concentrations has historically been discouraged in part for cost considerations, serial testing may be necessary to detect a second peak.[18] Serial testing is inexpensive and would avoid the pitfall of premature discontinuation of NAC at 21 hours, given the evidence for persistently elevated APAP concentrations in patients with APAP/diphenhydramine overdose.

In this study population, the initial multiplication product of APAP x AT was >1500 in 95% of patients who developed hepatotoxicity, suggesting that it may be a sensitive marker for patients needing NAC treatment. We did not have sufficient data, however, to determine the specificity or negative likelihood ratio, so it is not known whether it will be a useful tool to exclude patients from further follow-up or treatment. This is consistent with the findings of Chomchai and Chomchai, who reported 90.6% sensitivity of APAP x AT in their retrospective review of acute APAP overdose cases at a hospital in Thailand.[11] Our study population included a larger proportion of hepatotoxic cases compared to theirs and excluded all patients whose peak transaminase level was <100 IU/L. Their study population comprised a total of 255 patients, only 32 of whom had hepatotoxicity, whereas our study population comprised 213 patients with APAP/diphenhydramine overdose, 141 of whom developed hepatotoxicity.

Ideally, the APAP x AT multiplication product would be able to reliably identify patients at very low risk of hepatotoxicity. This could have important clinical and financial implications. Nonetheless, a risk prediction instrument with a sensitivity near 100% will be needed to reduce unnecessary treatment, given the relatively low cost of an individual course of treatment and the high stakes of preventing avoidable fulminant hepatic failure. While these findings show promise, it is important to note that the APAP x AT multiplication product was determined in the setting of patients being treated with NAC. Thus, unlike the Rumack-Matthew nomogram, it cannot be used to determine whether or not to initiate NAC therapy upon first presentation of the patient. The multiplication product assesses the risk of hepatotoxicity in treated patients. It is important to note that a transaminase level greater than 1,000 IU/L has limited clinical meaning.

Many patients with transaminases elevated above 1,000 IU/L have few if any significant signs or symptoms of hepatic dysfunction, require minimal specialized care, and recover completely without sequelae.[21]

Another risk prediction tool that performed consistently well in this study population was the "negative-negative" criterion. Of the 213 patients with any degree of hepatotoxicity (peak transaminase greater than 100 IU/L) following APAP/diphenhydramine overdose and the 149 patients with hepatotoxicity (peak transaminase greater than 1,000 IU/L) after plain APAP overdose, there was not a single case that had initially presented with both an undetectable serum APAP and normal transaminase levels. The predictive value of the "negative-negative" criterion in this study population is consistent with the findings of Froberg, et al.[23] It is reassuring that the standard practice of not treating those patients with normal initial laboratory values, whether or not the time of ingestion is known, does not result in adverse outcomes such as delayed hepatic injury.

This study looked specifically at intentional overdoses. The study by Gymlani et al., however, has suggested that unintentional overdose is associated with worse mortality and morbidity outcomes than intentional overdose.[33] APAP combination products present a greater risk to the public both because of the altered physiological mechanism as well as how difficult it is for a layperson to predict the cumulative effects of multiple active ingredients in a single medication. These data support action to improve the safety of APAP products, including proposals to separate acetaminophen from products with diphenhydramine. Initiatives to improve the safety of APAP combination products such as active ingredient icons and front-of-packaging identification of active ingredients should be applied to both prescription and over-the-counter products. More aggressive packaging interventions have been implemented in the United Kingdom, including blister packing and limiting the number of pills available to the consumer. These initiatives have resulted in a marked decrease in intentional overdose, but similar strategies have not been employed in the United States.[4] The public should be made aware of the unique risks posed by APAP combination products.

Limitations:

This study is limited by its retrospective design. The retrospective nature of the study presented a challenge in terms of estimation of times of ingestion and blood collection for laboratory data. It was assumed that morning blood draws were done at 6:00 a.m. and that the

time of arrival to the emergency department was also the time of the first blood draw. Ingestions that were reported as having taken place "sometime last night" were coded as having occurred at midnight and "yesterday" as noon the day prior. If a time range is given for the time of ingestion, the midpoint of that range was used as the time of ingestion. Given the hurried nature of care in the emergency department, the measurements of serum APAP and transaminase levels were likely to be at varying time points, thus limiting the comparability of the data across cases. We had limited clinical and laboratory data for many of the cases, especially those considered low-risk by Poison Control Center staff due to initial APAP levels. This made it impossible to accurately assess the multiplication product and the "negative-negative" criterion for cases without any degree of reported hepatic injury.

One limitation of poison center data in general is that reporting of poisonings is not mandatory across all healthcare facilities in California, so there is the possibility of reporting or selection bias.[17] Not all cases may be reported and not all features of every case may be documented.[19] For example, emergency physicians might be more likely to consult the Poison Control System about a new drug they are unfamiliar with, but not an older one that they feel comfortable managing without the help of Poison Control. No method was used to determine how many patients treated for APAP ingestions in California were not reported to the Poison Control System. Because the purpose of this study was not to compare incidence data, this was less of a problem for this study. A matched case-control study of APAP/diphenhydramine cases compared to plain APAP would have allowed for stronger conclusions to be drawn about the relative toxicity of the combined drug, but finding the case matches was beyond the scope of this study. Because of reliance on third party report for information, patients' medical history was limited, even though medical co-morbidities could potentially affect APAP pharmacokinetics. It was possible that the prevalence of alcohol abuse was underestimated given the missing data regarding alcohol use history. Because the study population was comprised of patients with minor to significant hepatotoxic outcomes, the conclusions of this study may not be generalizable to all patients who present with APAP or APAP/diphenhydramine overdose.[22]

Conclusions:

Overdoses of APAP and APAP combination products and subsequent liver injury are growing public health concerns. More than ever, physicians are in need of evidence-based risk predictors to accurately risk-stratify patients and make decisions about when to initiate, intensify,

or discontinue treatment following an overdose of APAP-containing products. This study found no significant differences in baseline patient characteristics, clinical variables, or outcomes related to APAP/diphenhydramine overdose versus plain APAP overdose in patients who develop hepatotoxicity. Despite evidence that APAP/diphenhydramine overdoses may not follow typical pharmacokinetics of acetaminophen, leading to prolonged absorption and second peaks of serum APAP levels, this study did not find evidence that these patients experienced worse clinical outcomes in terms of mortality or need for liver transplantation. This may be because, in practice, providers have been able to anticipate and/or recognize those late rises in APAP and transaminase levels and intervene to provide prolonged NAC treatment beyond the standard 21-hour protocol. In this study population, APAP x AT was found to have high sensitivity to assess hepatotoxicity in the setting of acute APAP/diphenhydramine overdose, but its specificity and negative likelihood ratio remain unknown. Patients presenting with both undetectable serum APAP and normal transaminase levels following acute APAP/diphenhydramine overdose were not found among our cases with any degree of hepatotoxicity, suggesting that a "negative-negative" criterion may be a promising clinical tool to guide management decisions. These data support action to address this epidemic, including proposals to remove acetaminophen from products with diphenhydramine and educate the public on the risk of acetaminophen combination products.

Suggestions for future work:

A large, prospectively-designed study may address some of the limitations of this retrospective study. We were not able to calculate specificity or the negative likelihood ratio of APAP x AT because there was insufficient clinical and laboratory data recorded for cases of APAP/diphenhydramine overdose whose transaminases did not exceed 100 IU/L. Such cases could be enrolled prospectively to ensure that a baseline AST or ALT is recorded with the initial serum APAP level. In order to ensure that the onset of delayed hepatotoxicity is not missed, these cases would need to have a follow-up AST and ALT drawn on day two or three, even in the absence of clinical symptoms and perhaps after having been discharged home from the emergency department.

Future studies may be able to enroll patients who cannot be stratified by the Rumack-Matthew nomogram and randomize those with an initial low-risk APAP x AT multiplication

product to either NAC or placebo. Those with higher-value multiplication products could be treated and systematically compared to accepted markers of hepatic dysfunction, as an aminotransferase greater than 1,000 IU/L, though sensitive, has little clinical meaning. The King's College Criteria, lactate or phosphate are markers of clinically significant hepatic dysfunction and may identify patient who actually require specialized care.[21] We suggest that APAP x AT's prediction of hepatotoxicity be prospectively investigated in scenarios of time-unknown ingestions. Moreover, correlation of APAP half-life and APAP x AT could be assessed to better conceptualize the APAP x AT.

Section 5: Acknowledgements

This project would not have been possible without the support of several outstanding individuals. First, I would like to thank Drs. Kent Olson and Hallam Gugelmann for lending their wisdom, patience, and brainpower toward this investigation. Thank you for entrusting me with such an important research question and inspiring in me a lifelong interest in toxicology. Thank you, as well, to the California Poison Control System for providing the dataset for this project and welcoming me to learn about the daily work of a poison control center. I never truly understood how essential of a role that these centers play in our nation's public health system until the first morning that I spent observing poison specialists field calls about everything from accidental laundry detergent ingestions to snake bites and hepatotoxic mushroom soups.

I would also like to express gratitude to Dr. Raymond Chung for lending his perspective as one of the world's leading hepatologists and providing feedback all along the way of this project. Furthermore, this project was supported by funding from the Scholars in Medicine Office at Harvard Medical School.

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Most importantly, I am grateful to all of the patients and their families who are represented by this dataset. From their stories, I hope that we have created some knowledge to the benefit of future patients.

Section 6: Student role

This work of independent scholarship was conceived with the help of Drs. Kent Olson and Hallam Gugelmann. Lucinda Lai was responsible for writing the literature review, extracting and organizing the data, performing the analyses, and writing the manuscript. Drs. Olson and Gugelmann provided guidance and feedback at every step of the process.

Tables and Figures

Table 1. Summary of plain APAP and APAP/diphenhydramine cases reported to the California Poison Control System 1997-2013.[1]

	Plain APAP N (%)	APAP/diphenhydramine N (%)	Statistical significance
Cases with peak AT >100<1,000 IU/L	568 (5.2%)	93 (3.4%)	***p* < 0.001**
Cases with peak AT >1,000 IU/L	695 (6.4%)	123 (4.4%)	***p* < 0.001**
Deaths	52 (0.5%)	8 (0.3%)	NS (*p*=0.18)
Total number of patients	10,915	2,773	

APAP indicates acetaminophen and AT indicates transaminase. NS, not significant.
[1]Acute self-harm ingestion, single drug ingestion, ages 18 years or older.

Table 2. Comparison of demographic and clinical variables: plain APAP with hepatotoxicity versus APAP/diphenhydramine with hepatotoxicity.

	Plain APAP *with hepatotoxicity*[1]	APAP/diphenhydramine *with hepatotoxicity*[1]	*p* value
	Median (IQR) or N (%)	Median (IQR) or N (%)	or OR (95% CI)
Age (years)	28.0 (21.0 – 44.0)	30.0 (18.0 – 42.0)	0.37
Female	97 (65%)	89 (63%)	0.81
Male	52 (35%)	52 (37%)	
Known prior alcohol use	12 (8%)	15 (11%)	0.55
Size of ingestion (grams)	25.0 (15.0 – 45.9)	25.0 (15.0 – 50.0)	0.82
Activated charcoal given	12 (8%)	30 (21%)	**0.0015**
Time to NAC treatment (hours)	24.0 (14.3 – 48.0)	24.0 (12.0 – 43.5)	0.30
Peak serum APAP level (mg/L)	40.7 (0.1 – 125.0)	72.0 (2.0 – 180.5)	0.13
Time to peak APAP level (hours)	16.0 (11.0 - 24.0)	15.0 (8.0 - 24.0)	0.54
Peak measured AT	4571 (2600 – 8012)	4524 (2053 – 8360)	0.90
Time to peak measured AT (hours)	62.0 (50.0 – 78.5)	63.8 (52.6 – 81.4)	0.64
Peak measured INR	1.9 (1.5 – 3.1)	1.8 (1.5 – 2.8)	0.31
Liver transplantation	0 (0%)	0 (0%)	1.00
Death	14 (9%)	6 (4%)	0.11
APAP x AT > 1500 mg · IU/L[2]	79/80 (99%)	79/83 (95%)	OR 0.25 (0.027-2.29)
Total number of patients	149	141	

APAP indicates acetaminophen; AT, transaminase; CI, confident interval; INR, international normalized ratio; IQR, interquartile range; OR, odds ratio.
[1]Hepatotoxicity is defined as peak transaminases greater than 1000 IU/L.

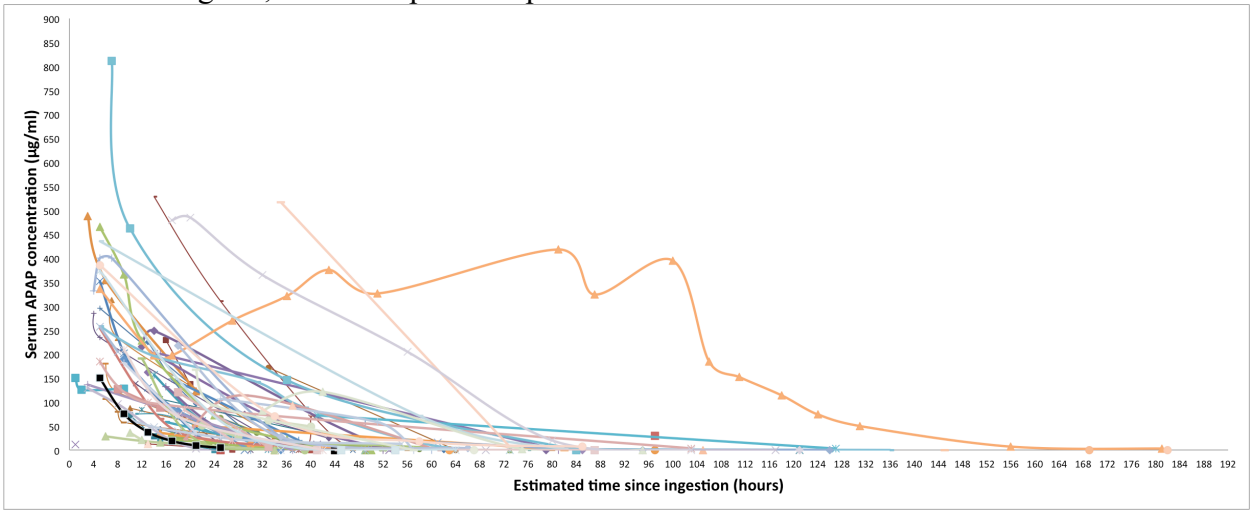
Table 3. Comparison of demographic and clinical variables.

	APAP/diphenhydramine *with minor hepatic injury*[1]	APAP/diphenhydramine *with hepatotoxicity*[1]	*p* value
	Median (IQR) or N (%)	Median (IQR) or N (%)	or OR (95% CI)
Age (years)	32.5 (23.0 – 44.0)	30.0 (18.0 – 42.0)	0.76
Female	44 (61%)	89 (63%)	0.88
Male	28 (39%)	52 (37%)	
Known prior alcohol use	3 (4%)	15 (11%)	0.13
Size of ingestion (grams)	20.0 (12.0 – 40.0)	25.0 (15.0 – 50.0)	0.11
Activated charcoal given	20 (28%)	30 (21%)	0.31
Time to NAC treatment (hours)	12.5 (4.0 – 24.0)	24.0 (12.0 – 43.5)	**<0.001**
Peak serum APAP level (mg/L)	108.0 (18.6 – 215.7)	72.0 (2.0 – 180.5)	0.20
Time to peak APAP level (hours)	10.0 (3.0 – 17.0)	15.0 (8.0 - 24.0)	**<0.001**
Peak measured AT	269 (152 – 459)	4524 (2053 – 8360)	**<0.001**
Time to peak measured AT (hours)	55.5 (30.4 – 67.9)	63.8 (52.6 – 81.4)	**0.002**
Peak measured INR	1.2 (1.0 – 1.3)	1.8 (1.5 – 2.8)	**<0.001**
Liver transplantation	0 (0%)	0 (0%)	1.00
Death	0 (0%)	6 (4%)	0.10
APAP x AT > 1500 mg · IU/L[2]	31/40 (78%)	79/83 (95%)	**OR 5.7 (1.6-20.0)**
Total number of patients	72	141	

APAP indicates acetaminophen; AT, transaminase; CI, confident interval; INR, international normalized ratio; IQR, interquartile range; OR, odds ratio.

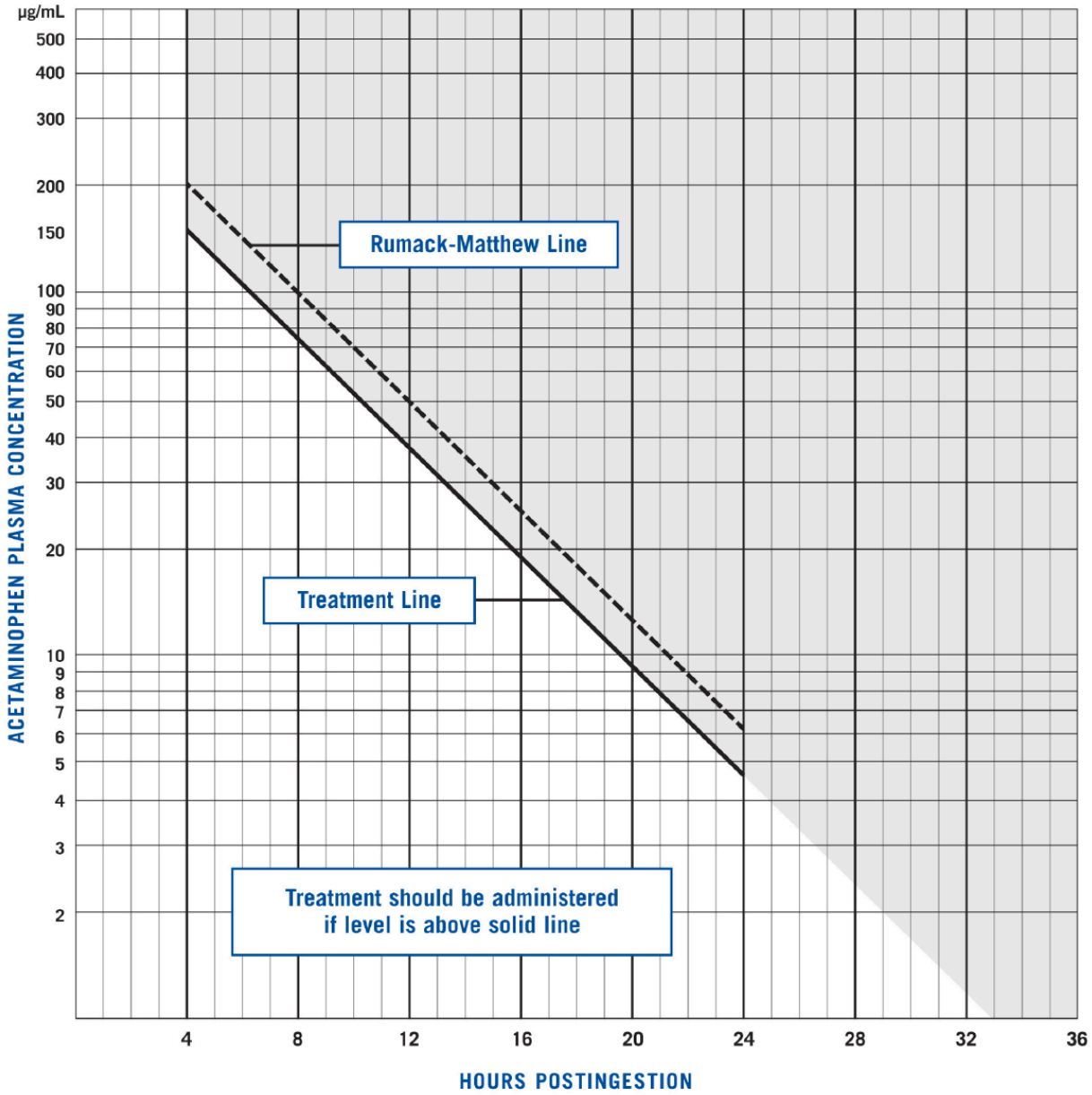
[1]Minor hepatic injury is defined as peak transaminases between 100 and 1000 IU/L; hepatotoxicity defined as peak transaminases greater than 1000 IU/L.

Figure 1. Serial serum APAP concentrations versus time in hours after ingestion, following acute overdose of APAP/diphenhydramine in patients who developed hepatotoxicity despite treatment. The line with black squares denotes the 150 mg/L-at-4 hours treatment line of the Rumack-Matthew nomogram, and its slope corresponds to a 4-hour elimination half-life.[12]



Appendix 1.

Rumack-Matthew Nomogram. A plot of serum APAP concentration versus time in hours after APAP ingestion. The nomogram was developed to estimate the probability of whether a serum APAP concentration in relation to the interval postingestion will result in hepatotoxicity and, therefore, whether NAC therapy should be administered.[34] The treatment line is plotted 25% below the Rumack-Matthew Line to allow for potential errors in serum APAP assays and estimated time from ingestion of an overdose.[35]



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