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Case Report

Acute Ingestions of Acetaminophen Combination Products Resulting in Marked Bactrian Pharmacokinetics

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Introduction

Acetaminophen (APAP) is a widely available analgesic and antipyretic that is presented in numerous over the counter and prescription preparations, frequently as part of a combination product with an antihistamine or an opioid. The ubiquity of acetaminophen-containing products explains why it is among the most commonly encountered substances involved in overdoses reported to the AAPCC's National Poison Data System [1]. The pharmacokinetics of acetaminophen in overdose has been well described and it is generally believed that acetaminophen is rapidly absorbed with resulting peak plasma concentrations seen between 1-4 hours [2]. However, there are case reports of double peak ("Bactrian") plasma concentrations occurring after overdose [3-9]. These have been described primarily with large ingestions of combination acetaminophen products. Bactrian pharmacokinetics of acetaminophen is a concerning phenomenon as the clinical decision to treat acute APAP overdoses with N-acetylcysteine is made primarily using the Rumack-Matthew nomogram which is based on the assumption that peak APAP serum concentrations occur around 4 hour after consumption and decrease with an elimination half-life of approximately 2-4 hours [8]. Potentially, a second peak could result in "treatment line" crossing with the potential for hepatotoxicity in a patient with an otherwise nontoxic appearing initial 4-hour APAP plasma concentration. Equally concerning is that in several of the reported cases involving Bactrian pharmacokinetics, hepatotoxicity developed despite early NAC therapy [6,7,9] We report two cases of acute ingestions of acetaminophen combination products resulting in marked Bactrian pharmacokinetics who manifested hepatotoxicity despite N-acetylcysteine therapy.

Case Reports

Case 1

A 48-year-old male with history of HIV and recent prior suicide attempts was found unconscious at home with empty pill bottles next to him. The empty bottles contained acetaminophen/oxycodone, acetaminophen/codeine, lorazepem, and alprazolem and were filled in 2009 and 2010. He was brought to the emergency department (ED) by EMS. He received 2 mg of intravenous (IV) naloxone en route and an additional 2 mg of IV naloxone in the ED, but continued to be unresponsive and was intubated. His temperature was 35.4°C, blood pressure 114/62 mmHg, heart rate 83 beats per minute (bpm), respiratory rate 18 breaths per minute (bpm), and oxygen saturation 100% on the ventilator. His pupils were 4 mm and reactive. The rest of his physical examination was unremarkable.

Initial laboratory studies are noted in Table 1. Initial acetaminophen concentration was 283.6 mcg/mL, AST 90 Units/L, ALT 42 Units/L, total bilirubin 2.2 mg/dL, creatinine 2.1 mg/dL, and INR was 1.1. Given the unknown time of ingestion, intravenous N-acetylcysteine (NAC) was initiated in the ED at the standard bolus and infusion rates with a

planned 21 hour course until acetaminophen concentrations were nondetectable. However, a prolonged elimination rate of acetaminophen was found, with a concentration of 64.7 mcg/mL on day 3 after ingestion, necessitating extending the NAC infusion. Surprisingly, on day 4 after ingestion, his acetaminophen concentration abruptly increased to 341.3 mcg/mL, declining to 245.5 mcg/mL on day 5. He was extubated on day 5.

Table 1. Case1 Laboratory Values.

hospital day	day 1	day1 +5hrs	day 2	day 3	day 4	day 5	day 6
apap level (mcg/ml)	283.6	144.7	50	26.3	341.3	245.5	21.7
AST (units/L)	90		44	84	1,512	>2,250	>2,250
ALT (units/L)	42		37	75	1,059	>2,250	2,488
INR	1.1		1.4	1.7	3.3	2.8	1.4
T bili (mg/dL)	2.2		2.1	2.1	2.5	4.3	5.8
Cr (mg/dL)	2.1		1.5	1.7	1.1	1.4	1.4

On hospital day 3, an abdominal/pelvic CT scan without contrast was obtained due to the unexpected rise in drug concentrations to evaluate for the presence of a drug bezoar presence. The scan did not reveal the presence of pills in his gastrointestinal tract. Nasogastric tube aspiration on day 2 revealed approximately 100 ml of pill fragments and sediments, approximately 100 ml on hospital day 3, and 25 ml on hospital day 4. Transaminases and INR peaked on day 5 prior to declining. The patient then made an uneventful recovery. NAC was infused for a total of 7 days. Evaluation of the patient's nursing and medical records revealed that no acetaminophen was administered in the hospital.

Case 2

A 42-year-old female with history of bipolar disorder was found confused at a supermarket parking lot with an empty bottle next to her that contained 150 tablets of Tylenol PM, acetaminophen 500 mg with diphenhydramine 25 mg. She was brought to the emergency department by EMS. Her initial vital signs in the ED were temperature 36.4 °C, blood pressure 106/71 mmHg, heart rate 88 bpm, respiratory rate 16 bpm, and oxygen saturation 100% on room air. Her pupils were 5 mm and reactive bilaterally. The rest of her physical examination was unremarkable except for her neurological examination that showed depressed mental status. She began to have nausea and vomiting after arriving in the ED.

Table 2. Case2 Laboratory Values.

hospital day	day 1	day1 +5hrs	day 2	day 3	day 4	day 5	day 6
apap level (mcg/ml)	307.6	246.8	103.9	185	346	207	32.7
AST (units/L)	40		308	19,685	7,320	1,706	381
ALT (units/L)	37		435	19,689	13,780	8,112	4,616
INR	1.1		1.8	3.6	3	2.8	1.9
T bili (mg/dL)	1.1		2.3	3.4	3.7	7.6	11
Cr (mg/dL)	0.6		0.5	0.8	2.1	2.5	2.5

Laboratory studies are noted in Table 2. Her initial acetaminophen concentration was 307.6 mcg/mL, AST 94 Units/L, ALT 37 Units/L, total bilirubin 1.1 mg/dL, creatinine 0.6 mg/dL, and INR was 1.1. Given the unknown time of ingestion at the time of presentation and vomiting, intravenous N-acetylcysteine was initiated in the ED at the standard bolus and infusion rates and she was admitted to a telemetry unit. NAC was continued past the 21 hour period due to a slowly declining acetaminophen concentration that was 103 mcg/mL on day 3 after ingestion. Unexpectedly, her acetaminophen concentration then rebounded to 346 mcg/mL on day 4 (See Table 2).

On hospital day 3, an abdominal/pelvic CT scan without contrast was obtained due to the slowly declining acetaminophen concentrations. The scan did not reveal the presence of pills in her gastrointestinal tract. The patient was offered a nasogastric tube and whole bowel irrigation during her hospitalization, but declined. Her liver transaminases and INR peaked on day 3 before declining, and she eventually made a full recovery. Evaluation of the patient's nursing and medical records revealed that no acetaminophen was administered in the hospital.

Discussion

The pharmacokinetics of acetaminophen in overdose are well described. Typically the peak serum concentrations occur within four hours of ingestion, and the half life generally ranges between 2-4 hours [10] The Rumack-Matthew nomogram has been employed based on the half life in the setting of acute poisoning [10]. In patients with large overdoses, the half-life of acetaminophen may be prolonged [11,12,13] Combination preparations have also been associated with unusually pharmacokinetics that may not follow the nomogram pattern [14] .

Dougherty et al retrospectively reviewed a poison center database for acetaminophen poisoning and found twenty patients to be "line crossers" who fell off the expected nomogram line predicted by the usual half-life range [15]. These patients had initially nontoxic acetaminophen concentrations, but eventually developed toxic acetaminophen concentrations. Thirteen of the twenty patients ingested combination products; eleven ingested acetaminophen combined with diphenhydramine, one ingested acetaminophen combined with hydrocodone, and one ingested acetaminophen combined with propoxyphene. Of the twenty line-crossers, four ingesting acetaminophen with diphenhydramine had a late elevation in acetaminophen concentrations. The initial acetaminophen concentrations in these four patients were measured between 4 and 5 h postingestion. One patient in particular had an initial acetaminophen concentration of 104 ug/mL at 4 h post ingestion, and 181 ug/mL at 24 h post ingestion. Her highest reported acetaminophen concentration occurred at 75 h post ingestion.

Twelve cases of double peak pharmacokinetics with acetaminophen have been reported previously [3-7,9,16,17]. Hendrickson et al reported the Bactrian "double hump" acetaminophen pharmacokinetics in a case series involving three patients who ingested acetaminophen combination formulations [9]. Two patients ingested acetaminophen with diphenhydramine, and one ingested acetaminophen with hydrocodone. The three patients had a second peak between 37 to 42 hours after ingestion. Unlike the case series where

the second peak occurs on day 2, our patients reached the second peak concentrations between the third and fourth day after ingestion. Our cases revealed that acetaminophen level may reach the second peak at a much later time than previously demonstrated. The delay in reaching second peak has clinically implication. If the acetaminophen levels are not trending downward according to the expected 4-hour half life, then clinicians caring for acetaminophen-overdose patients should recheck acetaminophen level daily since the level may peak 4 days after acute acetaminophen ingestion.

Halcomb et al evaluated the pharmacokinetics of acetaminophen with diphenhydramine preparations (5 gm/250 mg) and acetaminophen with oxycodone preparations (5 gm/0.5 mg/kg) in healthy volunteers [14]. They noted that the acetaminophen with oxycodone preparation caused delayed absorption of acetaminophen while acetaminophen with diphenhydramine did not. The delayed acetaminophen peak concentration may be due to a pharmacobezoar, which has been described with other medication overdose, but has not been described with acetaminophen [18-20]. Hendrickson did not reveal pharmacobezoar on radiological imaging in his Bactrian case series [9]. Abdominal computerized tomography in our patients failed to demonstrate pills or other abnormalities. However, its sensitivity for this purpose is unclear.

NAC minimizes the risk of hepatotoxicity when administered within 8 hours of acetaminophen ingestion [21]. However, in patients with Bactrian pharmacokinetics, hepatotoxicity appears to be possible if NAC is initiated within 8 h. The case report by Dougherty et al of poisoning with an acetaminophen with diphenhydramine combination had IV NAC initiated at 5 h post-ingestion and continued uninterrupted. However, they developed elevated transaminases with AST 5,943 Units/L and ALT 7,608 Units/L peaking on day four post-ingestion [15]. This pattern is similar to that we observed in our cases. This finding underscores the need to continue uninterrupted NAC therapy until acetaminophen is undetectable, as no effective alternative treatment is currently available in managing acetaminophen related hepatotoxicity.

Our report has some limitations. The time of ingestion and the quantity of ingestion reported may not be reliable in our cases. Furthermore, it was unclear if these patients had single large dose ingestion, or chronic ingestions.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the writing of the paper.

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