

Bactrian (“Double Hump”) Acetaminophen Pharmacokinetics: A Case Series and Review of the Literature

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Abstract After acute ingestion, acetaminophen (APAP) is generally absorbed within 4 h and the APAP concentration ([APAP]) slowly decreases with a predictable half-life. Alterations in these pharmacokinetic principles have been rarely reported. We report here three cases of an unusual double hump, or Bactrian, pattern of [APAP]. We review the literature to describe the case characteristics of these rare cases. A 38-year-old woman ingested 2 g hydrocodone/65 g acetaminophen. Her [APAP] peaked at 289 mcg/mL (8 h), decreased to 167 mcg/mL (31 h), then increased to 240 mcg/mL (39 h). She developed liver injury (peak AST 1603 IU/L; INR1.6). A 25-year-old man ingested 2 g diphenhydramine/26 g APAP. His [APAP] peaked at 211 mcg/mL (15 h), decreased to 185 mcg/mL

(20 h), and increased again to 313 mcg/mL (37 h). He developed liver injury (peak AST 1153; INR 2.1). A 16-year-old boy ingested 5 g diphenhydramine and 100 g APAP. His [APAP] peaked at 470 mcg/mL (25 h), decreased to 313 mcg/mL (36 h), then increased to 354 mcg/mL (42 h). He developed liver injury (peak AST 8,686 IU/L; peak INR 5.9). We report three cases of Bactrian (“double hump”) pharmacokinetics after massive APAP overdoses. Cases with double hump pharmacokinetics may be associated with large ingestions (26–100 g APAP) and are often coingested with antimuscarinics or opioids. Several factors may contribute to these altered kinetics including the insolubility of acetaminophen, APAP-induced delays in gastric emptying, opioid or antimuscarinic effects, or enterohepatic circulation. Patients with double hump APAP concentrations may be at risk for liver injury, with AST elevations and peaks occurring later than what is typical for acute APAP overdoses.

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Introduction

The pharmacokinetics of acetaminophen after acute overdose has been well described [1, 2]. Typically, acetaminophen is completely absorbed and peak serum concentrations occur within 4 h of ingestion. Acetaminophen concentrations quickly drop from this initial peak with a half-life of 2–4 h [1, 2]. The modified Rumack–Matthew nomogram is used to determine treatment for patients with acute acetaminophen ingestions and was based on these pharmacokinetic principles [3, 4].

Exceptions to these typical pharmacokinetics have rarely been reported including delayed absorption associated with

coingestants that slow gastric emptying or gastrointestinal peristalsis [5–9]. We report here three cases where the acetaminophen concentration peaked, then declined, only to be followed by a subsequent unexpected increase in acetaminophen concentration to a second peak. The etiology of these altered pharmacokinetics and the implications for therapy of these double peaks is unknown.

Case Reports

Case 1

A 38-year-old female presented to an Emergency Department (ED) approximately 2 h after ingesting 200 tablets of hydrocodone/acetaminophen (Vicodin® 10/325; 2 g hydrocodone, 65 g acetaminophen). She denied any other coingestion.

On presentation to the ED, she was awake, alert, and oriented. Her presenting vital signs were: blood pressure 170/48 mmHg, temperature 36.7°C, heart rate 67 bpm, respiratory rate 16/min, and oxygen saturation 100% on room air. Her physical examination revealed pupils that were 2 mm and reactive bilaterally, moist mucous membranes, a regular cardiac rate and rhythm without murmurs, and a benign abdominal examination with normal bowel sounds. Opiates and benzodiazepines were detected by urine immunoassay, while ethanol, amphetamines, barbiturates, cannabinoids, and cocaine were undetectable.

Gastrointestinal decontamination was not performed. Laboratory studies are noted in Table 1. Initial (approximately 2 h postingestion) acetaminophen concentration was 282 mcg/mL, salicylate <3 mg/dL, and ethanol <10 mg/dL. The patient was started on intravenous (IV) N-acetylcysteine (NAC) 4 h after ingestion and admitted to the hospital with one-to-one observation by a sitter. Repeat (approximately 8 h postingestion) acetaminophen concentration was 289 mcg/mL. Serial acetaminophen concentrations, transaminases, and INRs are shown over the course of her hospital stay (Table 1).

After 21 h of treatment with IV NAC (150 mg/kg/h×41 h, 12.5 mg/kg/h×4 h, then 6.25 mg/kg/h×416 h), and contrary to poison center advice, NAC was discontinued for 3.5 h, and then an infusion was restarted at 6.25 mg/kg/h without a bolus. The repeat acetaminophen concentration was 167 mcg/mL

(31 h after ingestion). The acetaminophen concentration subsequently increased to 240 mcg/mL (39 h after ingestion), then decreased to 142 mcg/mL (43 h after ingestion), and continued to decline to <5 mcg/mL (73 h). The patient remained on one-to-one observation with a sitter during her entire hospital stay.

Approximately 44 h after ingestion, an abdominal/pelvic CT scan without contrast was obtained, which did not detect the presence of pills in her gastrointestinal tract. The patient remained on IV NAC and her transaminases and INR peaked 97 h after ingestion. IV NAC was discontinued 111 h after ingestion, and she was discharged on day 8.

Evaluation of other causes of hepatic failure included negative tests for hepatitis A IgM Ab, hepatitis B surface Ag, hepatitis B core IgM, hepatitis C Ab, ceruloplasmin, immunology screen (anti-dsDNA, anti-ssDNA, anti-ENA, anti-SSA [ro], anti-SSB [la], IgA, IgG, IgM), and mitochondrial M2 Ab IgG.

Case 2

A 25-year-old woman arrived to an ED approximately 2 h after ingesting 80 tablets of a combination acetaminophen/diphenhydramine product (Tylenol PM®; 26 g acetaminophen and 2 g diphenhydramine). On arrival, she appeared intoxicated and was tachycardic at 143 bpm with a blood pressure of 124/82 mmHg, temperature of 37.6°C, respirations 22/min, and oxygen saturation of 100% on 2 L by nasal cannula. Her physical examination on arrival was significant for reactive pupils and cool dry skin. She had normal cardiac rate and rhythm, clear lung sounds, and an abdomen that was nontender with normal bowel sounds.

Laboratory values are listed in Table 2. Her initial acetaminophen concentration was 164 mcg/mL (2 h after ingestion), serum ethanol was 148 mg/dL, and she was started on IV NAC (150 mg/kg/h×1 h, 12.5 mg/kg/h×4 h, then 6.25 mg/kg/h×16 h) approximately 4 h after her ingestion. Her tachycardia resolved over several hours. Her acetaminophen concentration initially peaked at 211 mcg/mL (15 h after ingestion). She developed mild antimuscarinic symptoms (i.e., mydriasis and mild agitation). Her acetaminophen concentration then dropped to 185 mcg/mL (20 h after ingestion), only to rebound to 313 mcg/mL (37 h after ingestion). NAC therapy never lapsed during her care. Her

Table 1 Case 1 laboratory values

Postingestion (h)	2	8	15	31	39	43	59	73	87	97	111	135	158
APAP (mcg/mL)	282	289	261	167	240	142	15	<5	<5	<5	<5	<5	
AST (IU/L)	12			34	67		119	491	1409	1,603	608	144	82
ALT (IU/L)	10			35	83		185	576	1765	2,351	1,672	988	683
INR	1.1				1.5		1.5			1.6	1.4	1.2	1.0

Table 2 Case 2 laboratory values

Postingestion (h)	2	5	9	15	20	26	37	45	61	85	109	133	157	181	229	
APAP (mcg/mL)	164	172	191	211	185	192	313	281	76	13		<5	<5	<5		
AST (IU/L)	45	31		37		124	444	571	798		1,153	415	166	81	42	
ALT (IU/L)	22	17		18		82		311			2,236	1,528	981	692	402	
INR							1.4	2.1	1.3	2.1	1.3	1.1				

AST peaked at 1,153 IU/L and ALT peaked at 2,236 IU/L 109 h after her admission.

Case 3

A 16-year-old boy stated that he ingested 200 tablets of acetaminophen/diphenhydramine (Tylenol PM®; 100 g acetaminophen and 5 g diphenhydramine), approximately 1.5 h prior to arrival. This timing was confirmed by his parent. On arrival, his vital signs were significant for tachycardia, 125 bpm, with normal temperature, 36.8°C, and blood pressure, 130/70 mmHg. He was awake and alert but confused. His pupils were 3 mm and reactive bilaterally, and he had normal bowel sounds. The remainder of his physical exam was unremarkable.

His initial acetaminophen concentration was 225 mcg/mL 2 h after his ingestion. He was treated with an initial 50 g dose of activated charcoal and started on IV NAC (150 mg/kg/h × 1 h, 12.5 mg/kg/h × 4 h, then 6.25 mg/kg/h × 16 h) 4 h after his ingestion. He was transferred to an academic pediatric hospital where he became increasingly somnolent and was intubated. His 5.5-h acetaminophen concentration was 418 mcg/mL and salicylate concentration <4 mg/dL. The urine immunoassay did not detect amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, or opiates. Whole bowel irrigation with polyethylene glycol was initiated, but was discontinued due to loss of bowel sounds. He received several 1 mg doses of physostigmine with improvement in mental status.

Laboratory values are displayed in Table 3. His acetaminophen concentration peaked at 25 h after ingestion at 470 mcg/mL, decreased to 313 mcg/mL at 36 h, then increased again at 42 h to 354 mcg/mL, and then slowly declined until it became undetectable (<10 ug/mL) 109 h after ingestion. INR peaked at 5.9 at 79 h and AST peaked at 8,686 IU/L 91 h after ingestion.

Discussion

In most acute acetaminophen overdoses, the drug is predictably absorbed from the gastrointestinal tract, reaches peak concentrations within 2–4 h, followed by a rapid decrease in serum concentration with distribution and hepatic metabolism [1, 2]. In rare circumstances, significant

alterations of these pharmacokinetics characteristics have been reported [5–9].

We report three cases of delayed acetaminophen peak and double hump pharmacokinetics (initial peaks 8, 15, and 25 h after ingestion and second peak 39, 37, and 42 h after ingestion). Nine additional cases of double hump pharmacokinetics have been reported previously [10–17]. The characteristics of all 12 cases of double peak acetaminophen concentrations are summarized in Table 4.

Analysis of these double peak acetaminophen cases reveal that there are several commonalities among the cases that are unusual in acute acetaminophen overdoses. First, all of the overdoses were large oral ingestions (26–100 g). Second, most of the overdoses had coingestions of an antimuscarinic or opioid medication, both of which may decrease gastric emptying [18]. Third, it seems that liver injury is common in patients with a second peak who are reported in the literature. Whether this is due to publication bias or due to the amount ingested or altered pharmacokinetics is not known.

Possible Etiologies of Altered Kinetics

The etiology of the altered kinetics of acetaminophen in these cases is unclear. Several theoretical causes exist and may, individually or in some combination, explain this double hump phenomenon. These mechanisms reflect some manner of delay in absorption of acetaminophen from the gastrointestinal tract and include decreased gastric emptying, decreased solubility of tablets, and/or pharmacobezoar formation.

In all three of our cases, as well as five other reported cases [10, 12–15], a coingestion of an antimuscarinic or opioids was reported or suspected. In one case, a coingestant was not reported [14].

Interestingly, there are four described cases of patients who developed double peaks after acute acetaminophen overdose where there are no reported or recognized coingestions (Table 4). Smith et al. recently presented a case of a double peak acetaminophen concentration in which no coingestants were reported [11]. In this case, the patient ingested 48 g of acetaminophen and developed an acetaminophen concentration peak at 6 h, nadir at 27 h, and second peak at 48 h. Urine immunoassay did not detect opioids, including

Table 3 Case 3 laboratory values

Postingestion (h)	2	5.5	25	30	36	42	50	54.5	60	66	73	79	85	91	97	103	109
APAP (mcg/mL)	225	418	470	385	313	354	272	216	170	138	96	76	50	37	22	15	<10
AST (IU/L)		17	41	44	85	125	505	667	1,025	1,864	1,968	1,929	5,371	8,686	5,892	3,457	2,045
ALT (IU/L)		16	63	73	131	205	836	1,059	1,673	2,986	3,634	3,902	7,795	10,832	9,046	7,341	6,566
INR				1.8	2.1	2.7	3.3	2.9	2.6	4.9	4.8	5.9	4.4	4.3	2.9	2.8	3.2

methadone or propoxyphene, but no further comprehensive testing for coingestions was performed.

Kobrinsky et al. reported a prospective trial of 78 therapeutic massive (up to 1 g/kg) acetaminophen ingestions followed by NAC rescue at 8 h for the treatment of a variety of cancers [16]. In this trial, 3 of 78 (4%) patients developed a double peak in acetaminophen concentration. Unfortunately, no specific details were provided for any of these cases and all case data has since been destroyed. No liver injury was reported in any of the study patients. The authors state that some patients in the study may have been therapeutically taking chronic opioids that might alter gut motility, but as these were patients in a prospective chemotherapeutic trial, it is evident that these patients did not coingest other medications in overdose quantities.

There remains some controversy as to whether opioids or antimuscarinics significantly affect absorption. In scintigraphy studies, gastric emptying half-time is more than doubled by opioids and antimuscarinic agents [18]. In volunteer studies of subtoxic but suprathreshold acute acetaminophen ingestions, peak acetaminophen concentrations are delayed with oxycodone ingestion, but not with diphenhydramine [19]. In overdose patients, calculated 4-h acetaminophen concentrations for patients with opioid/acetaminophen overdoses were not significantly different from those who reported similar amounts of ingested acetaminophen alone [20]. Together, these studies suggest a delay in gastric emptying with coingestion of an opioid or antimuscarinic, but without a clearly defined impact on early serum acetaminophen concentrations. Unfortunately, no comprehensive prospective study on overdose patients has been performed to determine the rate of absorption, peak time of acetaminophen concentration, or clinical effects of any delayed absorption.

Several other factors may play a role in prolonging gastric emptying in patients who ingest acetaminophen. Stress, fear, and pain may decrease gastric emptying and are often present after overdose [18]. In addition, the simple presence of a large number of acetaminophen tablets in the stomach doubles the gastric emptying half-life in overdose patients [18]. This effect may explain the altered kinetics in the Kobrinsky and Smith cases where there may be no pharmacologic reason for delayed absorption [11, 16]. However, a threshold amount of acetaminophen tablets for this effect is not currently known.

Another possible etiology for the altered kinetics is that acetaminophen formed a pharmacobezoar resulting in the delayed acetaminophen peak. Though described in several other medication overdoses, pharmacobezoars have not been previously described with acetaminophen products [21–23]. In our first case, radiological imaging did not detect a pharmacobezoar.

Yet another potential etiology was detailed by Smith and suggests that double peaks or delayed absorption may be

Table 4 Reported cases with double peak [APAP]

Authors	APAP ingested [g (mg/kg)]	Coingestion	First peak [APAP], time to first peak (mcg/dL, h)	Nadir [APAP], time at nadir (mcg/dL, h)	Second peak [APAP], time to second peak (mcg/dL, h)	Time when AST>100 (h)	Peak AST, time to peak AST (IU/L, h)
Hendrickson	65	Hydrocodone (2 g)	282 (6 h)	167 (28 h)	240 (36 h)	96	1,603 (120 h)
	26	Diphenhydramine (2 g)	211 (16 h)	185 (19 h)	313 (36 h)	23	1,153 (61 h)
	100	Diphenhydramine (5 g)	470 (25 h)	313 (36 h)	354 (42 h)	42	8,686 (91 h)
Bizovi	48 (APAP ER)	Doxylamine, dextromethorphan	170 (2 h)	50 (10 h)	160 (14 h)	n/a	n/a
Ferguson ^e	?	Diphenhydramine	311 (5 h)	33 (13h)	133 (20 h) ^a	55	4,442 (120 h)
Chan ^f	100	Diazepam (200 mg), alprazolam (10 mg)	443 (6 h)	386 (14 h)	492 (29 h)	41	5,367 (>41 h)
Schwartz	75	Diphenhydramine (3.75 g)	264 (41)	209 (65 h)	508 (75 h)	^b	6,000 (96 h)
Stolbach ^e	? (APAP ER)	^g	584 (on arrival)	281 (14 h) ^c	562 (36 h) ^c	?	2,954 (85 h) ^c
Smith	48	None. Chronic meds: Sertraline, metoprolol, and lorazepam	281 (6 h)	100 (16 h)	228 (48 h)	90	4,350 (120 h)
Kobrinisky	150 mg/kg-1 g/kg	None, ?chronic opioids	unknown	unknown	unknown	unknown	unknown
	150 mg/kg-1 g/kg	None, ?chronic opioids	unknown	unknown	unknown	unknown	unknown
	150mg/kg-1g/kg	None, ?chronic opioids	unknown	unknown	unknown	unknown	unknown

? denote that that data is not known

^a Went on to have an additional second nadir at 72 mcg/dL at 30 h, followed by a third peak at 140 mcg/dL at 38 h

^b Patient died

^c Time after admission. Time of ingestion was unknown

^d Unclear if there was a coingestion. Urine opioid screen negative. Patient was “obtunded” on arrival and required intubation on day 2 for suspected aspiration

^e Abstract. No published manuscript found in MEDLINE

due to the poor water solubility of acetaminophen (1.1 g acetaminophen/100 mL of water at 25°C, with slightly higher solubility at higher temperatures, e.g., 37°C) [11]. Given this solubility, the amount of gastric fluid needed to dissolve 100 g of acetaminophen (as was ingested in our third case) is approximately 9 L which is likely beyond the capacity of the stomach. It is possible that this explains the correlation between the double peak phenomena and massive ingestions (>26 g).

Enterohepatic circulation has also been suggested as a reason for the double peak phenomena in addition to prolonging the apparent half-life [24]. While no studies have been performed in humans, animal studies have shown a dose-dependent increase in biliary excretion of acetaminophen as well as the biliary secretion of the glucuronide conjugate which was converted back to parent drug by hydrolysis by intestinal gut flora [25, 26]. In addition, oral doses of both activated charcoal and cholestyramine decrease acetaminophen concentration and half-life and increase urinary excretion after IV administration of acetaminophen [25, 27].

Liver Injury in Patients with Double Hump Kinetics

Liver injury does appear to be a prominent feature of the double peak phenomenon. Perhaps this should not be surprising given that these are massive overdoses. However, all three of our cases were treated with IV NAC within 6 h of reported ingestion, and our third case was treated within 4 h of a witnessed ingestion. The onset of AST concentration increase appeared to be somewhat delayed. In our cases, the AST increased above 100 IU/L at 26, 42, and 59 h after ingestion and crossed 1,000 IU/L at 60, 87, and 109 h. For comparison, in one prospective study, 75% of patients developed AST elevations within 24 h and all developed AST elevation by 36 h [28]. Other double hump cases in the literature also note delayed initial AST elevation (>100 IU/L) at 41, 55, and 90 h (Table 4) [11–13].

One concerning factor in our first case was the inappropriate cessation of NAC after the standard 21 h protocol. In this case, and two others in the literature [11, 12] with double hump kinetics who were treated with a 21-h protocol, subsequent liver injury was observed. In all three cases, NAC was stopped after the standard 21-h protocol while the acetaminophen concentration remained highly elevated (>100 mcg/mL; Table 5); NAC was restarted after a delay and the patient developed delayed onset of liver injury (i.e., AST>1,000 IU/L; 55, 87, and 96 h). These cases highlight the need to carefully reassess patients prior to cessation of NAC. As our other two cases demonstrate, however, even with prolonged continuous infusion of NAC, delayed hepatotoxicity may be seen.

Table 5 Acetaminophen concentrations and AST values when N-acetylcysteine infusions were stopped in cases of liver injury

Authors	[APAP] at time that NAC was discontinued	AST at time that NAC was discontinued	AST at time that NAC was reinstated
Ferguson. et al.	133 mcg/mL	?	395
Hendrickson. et al.	167 mcg/mL	34	~67
Smith. et al.	116 mcg/mL	<50	395

? denote that that data is not known

Treatment Considerations and Controversies

These cases are clearly rare and seem to occur in select cases with coingestion of opioids and/or antimuscarinics or in cases of massive acetaminophen ingestion. Given that they have a high risk for liver injury, it may be reasonable to assess previous assumptions about acetaminophen and whether there are prediction factors that might change management.

First, given that there is evidence for delays in gastric emptying with acetaminophen overdoses, is it reasonable to treat patients with oral activated charcoal (AC) after the first 1–2 h after an acute massive ingestion of acetaminophen? There are several reasons to consider that acetaminophen may remain in the stomach in these unusual cases and contribute to the late absorption; low solubility of acetaminophen [11] and decrease in gastric emptying after massive doses of acetaminophen [18]. Indeed, there is some evidence that late treatment of acetaminophen ingestions (up to 12 h postingestion) with charcoal may be beneficial [29]. Whether this benefit is due to delayed gastric emptying or interruption of enterohepatic circulation is not clear. A prospective evaluation of patients with either massive ingestions or significant coingestants may clarify whether late (>2 h after ingestion) charcoal may be effective.

Dose is another consideration in AC therapy. Activated charcoal binds optimally to medications when provided in a 10:1 activated charcoal (AC) to drug ratio or greater [30]. In cases of massive ingestion, the amount of AC given is not capable of binding all of the acetaminophen in the stomach. It may be a reasonable approach in massive ingestions or ingestions with significant coingestants that the AC dose be repeated as with multidose activated charcoal regimens (50 g AC PO q 2–4 h). Again, a prospective evaluation would help to clarify this question.

As stated above, one of our cases and two previously reported cases [11, 12] of double hump pharmacokinetics have been associated with premature NAC discontinuation. We are unable to correlate discontinuation of NAC with acetaminophen pharmacokinetics; however, these cases of altered pharmacokinetics likely represent massive ingestions

with a high likelihood of persistent acetaminophen concentration at the completion of a standard 21-h intravenous infusion of NAC (Table 4). For this reason, it must be stated again, once NAC is initiated, it should be given for the duration of the protocol chosen. When nearing the end of the NAC protocol, NAC should be continued if the patient has (1) evidence of liver failure (e.g., encephalopathy, coagulopathy), (2) remaining acetaminophen in the serum, or (3) elevations of the transaminases [17].

Finally, our third case developed liver injury and coagulopathy despite early and continuous IV NAC therapy. The patient had IV NAC bolused within 4 h after ingestion and had continuous IV NAC, yet developed a peak INR of 5.9. It is difficult to determine if an increased or altered NAC dose would change outcomes or if the oral dosing protocol, which provides larger amounts of NAC, would be more effective in these patients. Prospective studies on alternative NAC dosing may be able to determine if additional NAC is necessary in cases of massive ingestion or altered kinetics.

Conclusions

We describe three patients with large ingestions of acetaminophen combined with hydrocodone or diphenhydramine who had significantly altered pharmacokinetics including a double peak of their serum acetaminophen concentration, delayed peaks in acetaminophen concentration, and with development of liver injury 60, 87, and 109 h after ingestion.

It is important for clinicians to be aware that acetaminophen pharmacokinetics may not be predictable in massive overdose and that altered pharmacokinetics may occur, not only when coingested with an antimuscarinic or opioid, but also in cases of isolated APAP overdose. Clinicians should be aware that these overdose patients are at risk for this double peak phenomenon, and at significant risk for liver injury from these overdoses if not treated appropriately and thoroughly. Further, it is important to understand that treatment with NAC involves two decisions, when to initiate NAC and when to discontinue NAC [31]. Under all circumstances, patients with massive ingestions of acetaminophen should be evaluated with an acetaminophen concentration and an AST concentration prior to discontinuation of NAC, regardless of the protocol instituted [17, 31]. If either the AST or acetaminophen concentrations are abnormal, the NAC should be continued at a steady state.

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