# A Massive Acetaminophen Overdose with Unusual Pharmacokinetics

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**Abstract**

A clinical case report demonstrates the importance of managing a massive overdose of immediate-release acetaminophen using the same approach reserved for an overdose involving an extended-release formulation because of altered pharmacokinetics.

**Résumé**

Cet article présente un rapport de cas cliniques démontrant l'importance de traiter une surdose massive d'acétaminophène à libération immédiate en utilisant la même approche que celle utilisée pour traiter une surdose mettant en cause une préparation à libération prolongée en raison de la modification de la pharmacocinétique.

*Keywords: acetaminophen; immediate-release; overdose; pharmacobezoar*

## Introduction

Acetaminophen (*N*-acetyl-*p*-aminophenol, APAP) is an over-the-counter drug for treating mild to moderate pain and fever. APAP normally reaches peak concentration 30–60 min after ingestion, but the duration of therapeutic effect depends on the dosage formulation. Immediate-release (IR) is the most common oral form, where the drug completely dissolves and is released after ingestion. Extended-release (ER) forms are designed to slowly release the drug over a set time, allowing for a longer therapeutic effect.[1] APAP is considered safe but is hepatotoxic in overdose situations that may occur unintentionally (*e.g.,* misinterpreting directions) or intentionally (*e.g.,* suicidal intent). Clinically, it is important to rapidly identify and treat the overdose to prevent liver necrosis and possible death.

We report a case of a massive overdose with IR APAP that exhibited atypical pharmacokinetics.

## Case

An adult presented to the emergency department (ED) following an intentional APAP overdose. They reported that

they ingested approximately 130 × 500 mg tablets (65 grams) of APAP 4 hours (h) prior. The patient vomited before arrival and then again in the ED. They had no prior medical conditions and had not consumed any alcohol or recreational substances. They were not taking any other medications.

Based on their presentation, *N*-acetyl-cysteine (NAC) therapy was promptly initiated to treat the overdose. Four and a half hours after the initial ingestion (t = 4.5 h) vital signs and lab values were all within normal limits and the patient was appropriately responsive (GCS = 15). Their serum APAP level was 743 µmol/L (Table 1). This was plotted on a Rumack-Matthew Nomogram, which suggested they were unlikely to develop hepatotoxicity and did not require NAC therapy. A poison control centre was consulted and advised discontinuing the NAC treatment, and that no further APAP draws were warranted. The rationale may have been that prior vomiting had reduced the absorption of the ingested dose, resulting in the low serum level at 4.5 hours. The patient was still admitted to the hospital that night by the general internal medicine service, and a psychiatry consult was requested.

A day later, the attending physician requested an additional serum APAP level be drawn. At t = 33 h, the serum APAP was 555 µmol/L. Knowing that APAP conforms to first order elimination kinetics, the elimination constant (k) was calculated to be 0.01 $h^{-1}$ (expected value greater than 0.10 $h^{-1}$). This would indicate a severe reduction in the APAP metabolism, yet it would have been too soon for overt liver failure. The physician hypothesized that the value recorded at t = 4.5 h (743 µmol/L) had been obtained before the APAP level had peaked (*i.e.,* the peak concentration ($C_{max}$) had not yet been attained) and that a higher level must have subsequently occurred. Under normal circumstances with IR APAP, a serum level obtained more than 4 hours after the ingestion reflects a level obtained after the $C_{max}$ has been attained. The NAC was immediately restarted with the identification of these peculiar results, and repeat liver enzyme tests were ordered. The resulting AST and ALT were now significantly elevated, indicating liver damage.

**Table 1. Pertinent Patient Laboratory Values**

| Time post-ingestion (h) | 4.5 | 33 | 46 | 51 | 62 |
|---|---|---|---|---|---|
| [APAP] (µmol/L) | 743[a] | 555 | 157 | 99 | <66 |
| K ($h^{-1}$) | – | 0.01 | 0.10 | 0.09 | – |
| AST (IU/L) | 21 | 1900 | >7500 | >7500 | >7500 |
| ALT (IU/L) | 14 | 1871 | 3949 | 7137 | >7500 |

[a]Drawn before the $C_{max}$ level was achieved.

APAP levels were subsequently drawn at t = 46 h, t = 51 h and t = 62 h. They showed a downward trend with a relatively normal calculated elimination rate (k) (Table 1). However, the liver transaminase enzymes continued to increase, exceeding the labs ability to provide precise quantification. After 3 days, the patient was transferred to a facility with a liver transplantation program. Over the next 30 days, the patient's transaminase values returned to within normal limits and fully recovered without needing a liver transplant.

## Discussion

APAP is normally metabolized into mostly safe excretion products, with a small amount of the drug oxidized to *N*-acetyl-*p*-benzoquinone imine (NAPQI), a short-lived toxic intermediate that is rapidly conjugated with glutathione to a non-toxic form. In an acute overdose, glutathione may deplete, resulting in the accumulation of NAPQI, which can cause hepatic necrosis. NAC is an antidote and works as an alternative for the depleted glutathione levels and can prevent hepatic necrosis if given promptly after ingestion (*i.e.,* within 8 h of ingestion).[1–3] In an APAP overdose without NAC, liver toxicity typically occurs when there has been a single consumption greater than 150–250 mg/kg or greater than 12 g in a 24 h.[1,4] A "massive" overdose has been defined as an ingestion >32 g, and studies have reported that even when patients were given NAC within the 8 h window, there was up to a 33% chance of liver injury.[5]

The Rumack-Matthew nomogram (Figure 1) supplements clinical decision-making for administering NAC therapy. The nomogram is a plot of serum APAP against time since ingestion, with the recommendation that the first draw be 4 h after initial ingestion. Data points falling above the solid (treatment) line warrant therapy with NAC, while values below the line do not. In terms of toxicity, values between the solid and dashed lines suggest patients have a possible chance of developing hepatotoxicity, and those above the dashed line suggest a probable to high likelihood of hepatotoxicity.[6]

At t = 4.5 h this patient had a serum APAP of 743 µmol/L, which placed the patient just below the treatment line on the Rumack-Matthew Nomogram (Figure 1, Red square). The regional poison control centre (for anonymity) recommended that the NAC treatment be discontinued and that no further APAP levels were needed. Treatment guidelines vary based on the form of APAP that is orally ingested. In

this case, the patient ingested a large amount of IR APAP. Therefore, the assumption was that the $C_{max}$ of the drug had already passed and that the APAP concentrations would be declining.

Although not deemed initially necessary, a second APAP level was drawn (t = 33 h) and revealed a peculiarly high value of 555 µmol/L. The attending physician calculated the elimination constant as 0.01 $h^{-1}$ (Equation 1), a value that would be abnormaly low.

$$k = \frac{\ln\left(\frac{C_0}{C_t}\right)}{\Delta t} = \frac{\ln\left(\frac{743\frac{\mu mol}{L}}{555\frac{\mu mol}{L}}\right)}{28.5h} = 0.01\,h^{-1} \quad (1)$$

If APAP was conforming to standard first-order elimination kinetics in a healthy liver, an elimination rate greater than 0.10 $h^{-1}$ would have been expected. A low k value suggested that the metabolism was proceeding dramatically slower than normal. The alternative hypothesis would be that the levels were still rising when the first level was drawn and that the first-order kinetics elimination formula did not apply to the two levels of 743 ($C_o$) and 555 ($C_t$). The data suggested that the serum APAP at t = 4.5 h was not attained after the $C_{max}$ had occurred and that the APAP level would have exceeded the nomogram treatment threshold at some time after 4.5 hours.

Subsequent levels that were obtained produced more accurate k values between 0.09 and 0.1 $h^{-1}$, suggesting that the drug was being metabolized properly but at a slightly lower than normal rate, perhaps due to some mild impairment of liver function. The subsequent APAP levels (see Table 1) allowed for back-extrapolation (Equation 2) to estimate earlier APAP concentrations. Using the elimination rate of k = 0.1 $h^{-1}$ and the serum level collected at t = 33 h, 555 µmol/L, we can estimate that the serum APAP level 24 earlier (t = 9 h) was 6117 µmol/L. This value would have placed the patient significantly above the treatment threshold line on the Rumack-Matthew Nomogram (Figure 1, Green square), indicating that the patient had a high probability of hepatotoxicity if untreated and they needed NAC treatment.

$$C_0 = C_t(e^{\Delta t \times k}) = \left(555\frac{\mu mol}{L}\right)(e^{24\,h \times 0.1\,h^{-1}}) = 6117\frac{\mu mol}{L} \quad (2)$$

In prior case reports of unusual APAP IR overdoses, there have been accounts of "double-hump" pharmacokinetics. The serum APAP levels peaked between 8–25 h post-ingestion, followed by a decrease in concentration, and then a second peak 39–42 h post-ingestion. The patients in these case reports all had large oral ingestions (26–100 g), but many had co-ingestants that may have altered the pharmacokinetics.[7]

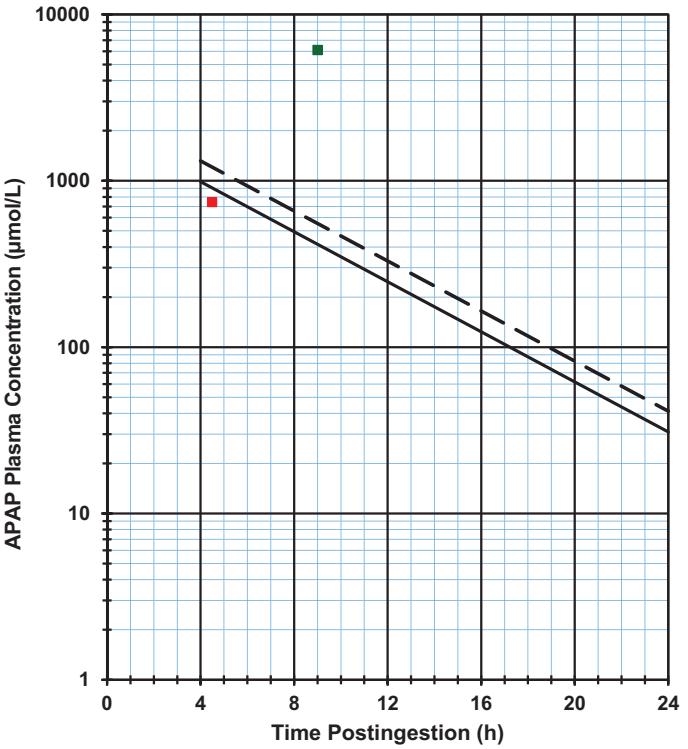


**Figure 1.** Rumack-Matthew Nomogram. Solid line is treatment line. Dashed line is hepatotoxic line. Red square represents apparent serum APAP concentration at t = 4.5 h. Green square represents estimated serum APAP concentration at t = 9 h.

In this present case, the APAP seems to have been absorbed similarly to an APAP ER formulation, despite being an IR formulation. Like an ER formulation, drug absorption occurred slowly over an extended period, and the peak serum APAP concentration was unlikely to occur before 4 h. Yet there is an assumption when using the Rumack-Matthew Nomogram with the levels obtained 4 hours after the ingestion that the $C_{max}$ would have occurred before 4 hours had passed.

We hypothesize that in this case of a massive overdose, the large amount of pills ingested accumulated together into a cluster at some point in the upper GI tract, potentially forming a pharmacobezoar. Pharmacobezoars can slowly release medication from the cluster and cause prolonged toxicity, persistent elevations in drug levels, and altered pharmacokinetics.[8] Only the exterior of this cluster would contribute

to drug absorption, thereby delaying the $C_{max}$. The contents of the inner core would remain in the GI tract to be absorbed later. This hypothetical process explains why the APAP level had not yet peaked by t = 4.5 h and was initially low and why the metabolism calculation implied that the drug was not adhering to classic first-order elimination kinetics. The premature cessation NAC therapy likely contributed to this clinical presentation.[9] It subverted the NAC's prophylactic benefit against hepatotoxicity, but the fact that they received some NAC is probably what saved this patient from fulminant hepatic failure.

This altered absorption pattern was initially missed partly due to the guidelines for managing an acute overdose of IR APAP. For an acute overdose, poison control online guidelines have suggested bloodwork at t = 4 h, and every 12 h afterward if the initial level is high and requires NAC.[10] Only with the ER formulation, where the drug is slowly released over an extended time frame, are clinicians advised to have APAP levels drawn every 4 h until a $C_{max}$ is identified. However, massive overdoses can also have altered pharmacokinetics. Had a second level been drawn at t = 9 h (*i.e.,* about 4 h later), the abnormality would have been detected sooner, and NAC treatment could have been resumed at a time that would have been helpful. This case supports that in the event of a massive overdose, the observed pharmacokinetics may have properties similar to the ER formulation and, therefore should be treated as such. In the case of a massive overdose, initiating NAC therapy and repeating the serum APAP at 4 h intervals would be warranted, even if the initial level is below the Rumack-Matthew nomogram threshold.

## Conclusion

This case demonstrates that a massive overdose of IR APAP can present with unusual or abnormal pharmacokinetics. The experience, in this case, shows the need for a minimum of two APAP levels four hours apart, even if the first level has a low probability of hepatotoxicity. In addition, it is beneficial to use the two measured concentrations of APAP and calculate the elimination rate to see if it conforms with expected values for first-order elimination kinetics. A deviation from expected values would indicate that the situation is more complicated than initially perceived. It is also necessary to revise the current toxicology protocols for managing massive APAP overdoses involving an IR formulation.

## Informed Consent/Research Ethics Board Approval

The authors declare that this case report does not contain any personal information (including age and sex) that may lead to the identification of the patient discussed. Instead, this case report was generated for quality assurance purposes to help prevent similar circumstances from repeating in the future.

## Contributions

- Conception & Design – BK & ML
- Procurement of Data – ML
- Analysis of Data – BK & ML
- Drafting of original manuscript – BK & ML
- Critical review of original manuscript – BK & ML

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## Conflict of Interest

Both authors declare that they do not have any competing interest in relation to this case report.

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