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CASE REPORT

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Impact of malnourishment on the pharmacokinetics of acetaminophen and susceptibility to acetaminophen hepatotoxicity

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Abstract

Background: Acetaminophen hepatotoxicity is thought to be primarily caused by formation of the specific reactive metabolite N-acetyl-para-benzo-quinone imine (NAPQI). Malnourished individuals are at increased risk of acetaminophen-related hepatotoxicity. We report a case of low acetaminophen clearance in a severely underweight young woman, and elaborate on the possible effects of malnutrition on the total clearance of acetaminophen as well as on the separate contributions of the different metabolic pathways.

Case report: An 18-year-old Caucasian woman weighing 43 kg with a history of eating disorder-related hospital admissions presented at the emergency department after having ingested 33 tablets of acetaminophen 500 mg two hours earlier. She then received intravenous N-acetylcysteine for 33 h. Nine hours after ingestion, the acetaminophen elimination half-life (t½) was estimated to be >100 h.

Discussion: While decreased total acetaminophen clearance (twofold) due to malnutrition has been reported in literature, the extremely low clearance in this specific patient cannot be explained. Malnourished individuals generally have reduced antioxidant reserves, coinciding with a shift in metabolic routes toward oxidative metabolism. This may result in increased formation of NAPQI and reduced neutralizing capacity, thereby increasing the risk of acetaminophen-induced hepatotoxicity. Evidence for this observation can be found in animal and to a lesser extent in human studies.

KEYWORDS

acetaminophen, eating disorders, fasting, glutathione, hepatotoxicity, metabolism, pharmacokinetics

1 | INTRODUCTION

Acetaminophen (paracetamol; APAP) intoxications and subsequent liver damage are commonly seen in clinical practice. Worldwide, acetaminophen toxicity is the leading cause for hepatotoxicity. Particularly in the United States, acetaminophen toxicity accounts for 50% of the drug-related hepatotoxicity and roughly 20% of the liver transplantations.[1] The

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ingested dose is suggested to be the key determining factor for acetaminophen-related hepatotoxicity, together with the interval elapsed from ingestion to antidote administration.[1] Other risk factors are chronic alcohol abuse, liver insufficiency, intake of drugs causing cytochrome-P (CYP) 2E1 induction, and malnourishment, either or not related to an eating disorder.

Acetaminophen-related hepatotoxicity is thought to be primarily caused by the formation of specific reactive metabolites. Acetaminophen is eliminated through various metabolic pathways,[2] illustrated in Figure 1. In healthy young adults, the majority of acetaminophen undergoes phase II metabolism, in which acetaminophen is conjugated with glucuronic acid (~55%) and sulfated (~30%) to form non-toxic metabolites, which are renally excreted. A small fraction (~2% to 5%) is renally excreted as unchanged acetaminophen. The remainder (~5% to 10%) undergoes CYP-mediated phase I metabolism, primarily via CYP2E1, resulting in the formation of the reactive and potentially toxic N-acetyl-parabenzo-quinone imine (NAPQI).[3] Under normal conditions, NAPQI is immediately conjugated with glutathione (GSH) to form non-toxic cysteine and mercapturate metabolites, which are renally excreted. However, once GSH stores are exhausted, such as in case of an acetaminophen overdose, or a malnourished state, NAPQI is thought to conjugate to cytosolic and mitochondrial proteins, resulting in hepatocellular necrosis.[1,4]

In this case report, we describe a severely underweight patient, admitted to the emergency department (ED) with an acetaminophen intoxication. Interestingly, this patient showed a highly decreased total acetaminophen clearance, measured in clinical practice as an increased acetaminophen elimination half-life (t½) of over 100 h (reference value 1–4 h[5]). In this case report, we subsequently discuss first the possible effects of eating disorders and malnutrition statuses on the total clearance of acetaminophen. Secondly, since one of the metabolic pathways of acetaminophen (*ie*, the CYP2E1-mediated pathway) is involved in hepatotoxicity, we assess the effect of malnutrition statuses on the separate contributions of the different metabolic pathways. Overall, the aim of this case report was to review literature on the relation between malnourishment and acetaminophen metabolism to further understand the clinical presentation (reduced clearance) of the discussed case. To this end, we collected and discuss both preclinical and clinical findings.

2 | CASE REPORT

An 18-year-old Caucasian woman (patient X) weighing 43 kg presented at the ED around 01:00 a.m. at the 28th of December 2019. She said to have ingested 33 tablets of 500 mg acetaminophen between 22:00 and 23:00 on the 27th of December to punish herself for eating. She also had self-inflicted wounds in her left arm and right leg. Her physical condition was stable, with no suspicion of abuse of substances other than acetaminophen. She did not experience heart palpitations, chest pain, stomach ache, and dyspnea, which she had experienced in the past after eating insufficiently. Activated charcoal and sodium sulfate were administered directly, and the hospital pharmacist was consulted. It appeared that she had been admitted to the hospital previously for health issues related to an eating disorder. Two weeks ago, she had been treated for dehydration, hypoglycemia, renal impairment, and a metabolic acidosis after not having eaten and drunk for two days and having ingested 2000 mg of ibuprofen. She lives in an assisted living facility and uses 100 mg quetiapine daily.

2.1 | Management and outcome

The treatment of acetaminophen intoxication is based on the theoretically ingested acetaminophen dose, the blood

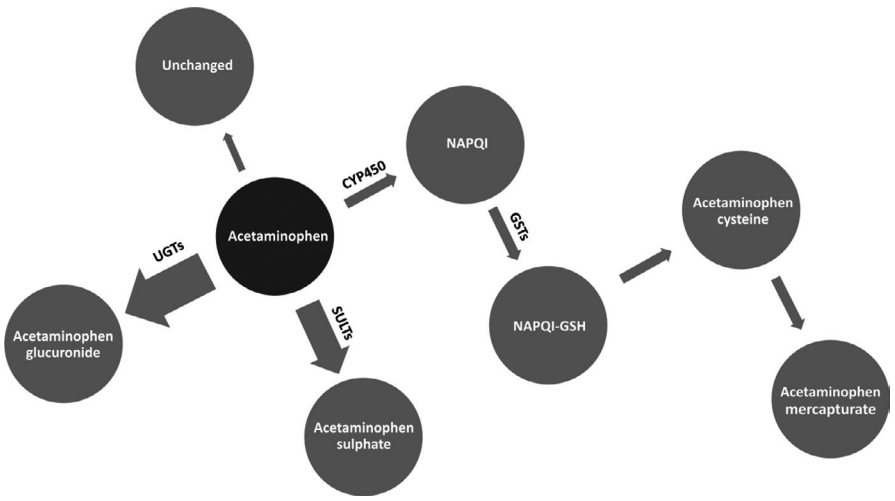

FIGURE 1 Metabolic pathways of acetaminophen2. CYP450, cytochrome-P-450; SULTs, sulfotransferases; GSH, glutathione; NAPQI, N-acetyl-p-benzoquinone imine; UGTs, Uridine 5'-diphospho-glucuronosyltransferases

concentration, and the clearance. Activated charcoal and laxatives should be administered within 4–6 h of ingestion. Subsequently, N-acetylcysteine (NAC) administration may be started dependent on the acetaminophen blood concentration. This will replenish and maintain the GSH stores. Immediate NAC administration is warranted in case of several circumstances, including suspected ingestion of >100 mg/kg.[6] If NAC administration is started, subsequent treatment depends on several factors. If the acetaminophen blood concentration at 4 h is >150 mg/L, NAC treatment is continued for at least 24 h, until the blood concentration is <10 mg/L. This is illustrated by the Rumack-Matthew nomogram (Figure 2, continuous line). The treatment time to reach <10 mg/L may be estimated from the measurement concentrations at 4 h and subsequent measurements 4–8 h later. Furthermore, the acetaminophen t½ calculated is predictive for liver toxicity, as t½ of >4 h is associated with an increased risk of hepatotoxicity.[6] For patients at increased risk of hepatotoxicity (*eg*, those suffering from eating disorders), blood concentration indicating the need for NAC treatment is reduced by 50% (Figure 2, the dotted line). Liver enzyme blood concentrations may be indicative for hepatotoxicity and should be monitored during treatment.[7]

Because the patient's theoretically ingested dose was 383 mg/kg (>100 mg/kg), intravenous NAC treatment (150 mg/kg) was initiated immediately at 01:26 a.m., for at least 24 h. The acetaminophen blood levels determined 4 and 9 h after ingestion were, respectively, 138.5 and 134.0 mg/L, indicating risk for hepatotoxicity according to Figure 2. These values indicate low clearance and yield an estimated t½ (used in clinical practice) of 103 h, hence extremely higher than the reference value of 4 h. Therefore, the pharmacist advised to treat for at least 24 more h. The acetaminophen blood level obtained at 12 h after ingestion (11:00 a.m.) was 118 mg/L, still suggesting low clearance. As a precaution, interpatient sample exchange was ruled out. The NAC treatment was continued until the acetaminophen concentration had decreased to <1 mg/L at 08:00 a.m., 33 h after ingestion. During hospitalization, the patient's liver enzyme values were within the reference range.

3 | DISCUSSION

We presented the case of a severely underweight young woman, who suffered from an acute acetaminophen intoxication, which resulted in an extremely prolonged acetaminophen t½, used to guide treatment in clinical practice. Malnutrition is one of the potential risk factors for acetaminophen-related hepatotoxicity, as decreased clearance may lead to an increased acetaminophen blood concentration. Below we first discuss the possible effects of malnutrition on the total clearance of acetaminophen. Secondly, since one of the metabolic pathways of acetaminophen (*ie*, the CYP2E1-mediated pathway) is involved in hepatotoxicity, we also assess the effect of several malnutrition statuses on the separate contributions of the different metabolic pathways.

Generally, severe weight loss is known to induce change in mucosal architecture and function, which may alter the pharmacokinetics of numerous drugs. Irrespective of the underlying disease, comorbid weight loss was found to be associated with changes in the gut wall, *for example*, increased bowel wall thickness, increased intestinal permeability, changes in intestinal motility, decreased splanchnic perfusion, and impaired transport protein functionality. Consequently, these changes may impact absorption, bioavailability, and drug clearance, like the reduced clearance we observed in the described case.[8,9] A literature search with search terms acetaminophen, anorexia nervosa, eating disorders, acetaminophen metabolism, and hepatotoxicity yielded limited results. Therefore, we also included several malnutrition statuses preliminary to eating disorders, such as starvation and protein-calorie deficiency, as well as more controlled statuses such as dietary fasting, addressed in both animal and human studies.

In rats subjected to a protein-calorie deficient diet for 4 weeks, toxically dosed acetaminophen clearance significantly decreased, resulting in an increase in t½ of approximately 156%.[10] In horses, low dosed acetaminophen clearance was reduced by 19% after the horses had been fasted for 72 h.[11] Mehta et al[12] showed a significant decrease in therapeutically dosed acetaminophen clearance in children suffering from protein-calorie malnutrition, resulting in a doubled t½ of 8.14 (±1.30) h compared to 4.33 (±0.52) hours in healthy age-matched controls. A recent study showed a ~10% decrease in therapeutically dosed acetaminophen clearance in healthy men who had fasted for 36 h.[13] Similarly, a reduction in clearance of roughly 15% was found in men who had fasted for 36 h.[14] Overall, both in animals and humans an apparent effect of malnutrition is increased exposure to total acetaminophen due to a decreased clearance, clinically presented as an increased t½.

As mentioned, acetaminophen hepatotoxicity may primarily be explained by the formation of the reactive NAPQI, through CYP2E1-mediated phase I metabolism. However, the effect of malnutrition on phase II metabolic pathways should also be assessed, since the metabolic capacity of each pathway may influence the formed metabolites fractions. Firstly, we address the effect of several malnutrition statuses on the metabolism of NAPQI. Secondly, we address the impact of these statuses on glucuronidation and sulfation.

Kato et al[15] found an increase in CYP2E1 after rats had been starved for 48 h. In another study, both 16-h fasting and a week of food restriction (70% of *ad libitum*) resulted in CYP2E1 induction in rats.[16] Furthermore, rat renal CYP2E1 content in microsomes was shown to increase twofold by starvation for 72 h, suggesting induction of CYP2E1 due

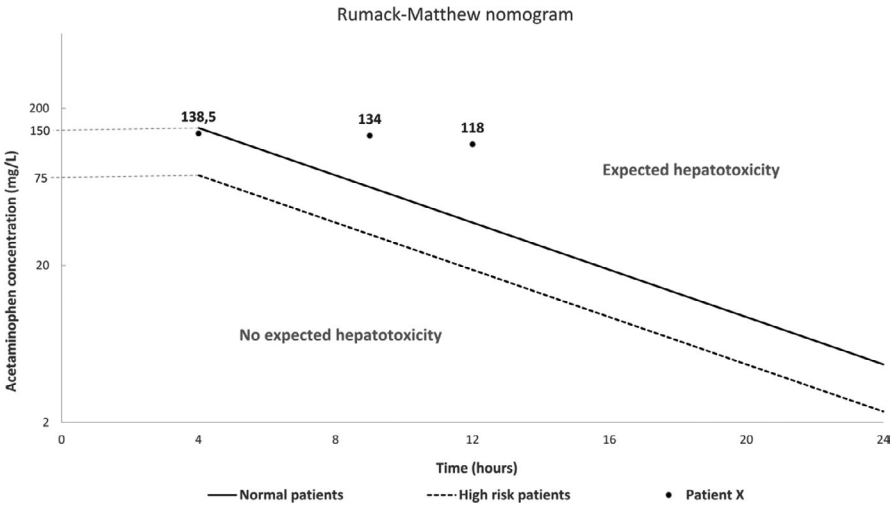

FIGURE 2 Rumack-Matthew nomogram showing the determined acetaminophen blood values 4, 9, and 12 h after ingestion for patient X

to malnutrition.[17] However, subjecting rats to a 4-week low protein-calorie diet led to a suppression of most hepatic CYP enzymes, including CYP2E1.[18] By contrast, prolonged fasting of humans seems to reduce CYP2E1 activity. After fasting for 38 h, healthy men showed a marked reduction in therapeutically dosed chlorzoxazone and 6-hydroxychlorzoxazone clearances. Chlorzoxazone is primarily metabolized by CYP2E1 and is often used as a probe drug for this specific enzyme. Chlorzoxazone t½ increased by 50% due to the reduced clearance, possibly due to reduced CYP2E1 activity.[19] Nevertheless, in healthy men who had fasted for 36 h, apparent clearance of acetaminophen-cysteine (the metabolite of NAPQI-GSH) was decreased by 12% after they had received a therapeutic dose of acetaminophen, suggesting increased exposure. The authors suggested that this was likely due to increased formation of CYP-specific metabolites due to fasting-induced CYP activity.[13] Unexpectedly, the apparent clearance of acetaminophen-cysteine-NAC (the metabolite of acetaminophen-cysteine) was increased by 15%. Generally, evidence regarding the impact of extreme forms of malnutrition on human CYP2E1 metabolism is scarce. Moreover, the impact of short-term starvation or fasting on CYP2E1 metabolism seems contradictory and subject to interspecies variation.

During acetaminophen metabolism, the reactive NAPQI may be neutralized by conjugation with glutathione. However, in individuals with eating disorders, glutathione synthesis and capacity may be decreased, as both animals and humans studied showed reduced glutathione levels due to malnutrition. In rats, both fasting for 16 h and 7 days of food restriction led to significant but similar reductions of total GSH. Following acetaminophen administration (800 mg/kg), rats suffering from centrilobular hepatic necrosis showed a 1.5- and threefold increase in AST/ALT levels, respectively.[16] In another study, fasting rats for 66 h and administering acetaminophen (1000 mg/kg) led to a 32-fold increase of AST/ALT levels, compared to rats fed sucrose *ad libitum*. These increases were accompanied by positively correlated hepatic necrosis.[20] Similarly, mice that had been starved for 2 weeks showed a marked reduction of total glutathione of ~40%. Following injection of acetaminophen (500 mg/kg), their glutathione levels were 5 times lower than levels in normally fed mice receiving a similar injection (30 vs 6 nmol/mg).[21] Rats subjected to a sulfur-containing amino (methionine) deficient diet for 3 weeks showed a decrease in basal levels of hepatic GSH of >50% within 72 h. Furthermore, the extent of hepatic necrosis in rats on a low methionine diet was significantly more severe with increasingly high doses of acetaminophen, compared to what was seen in rats on a normal diet.[22] Zenger et al found that children with anorexia nervosa had significantly lower concentrations of free cysteine (~25%) and free and total glutathione (resp. 30% and 31%) compared to healthy children. However, the authors did not investigate the impact of decreased glutathione on susceptibility to hepatotoxicity.[23] In conclusion, fasting in rats resulted in decreased glutathione, possibly resulting in increased susceptibility to acetaminophen hepatotoxicity. In humans suffering from eating disorders, decreased glutathione due to fasting was also observed, possibly resulting in similar increased susceptibility to acetaminophen hepatotoxicity. Nonetheless, additional research in adults is required to confirm whether malnourishment-induced glutathione reduction may be extrapolated from animal studies to humans.

It is known that longer periods of fasting lead to reduced glucuronidation, as hepatic metabolism shifts to gluconeogenesis, therefore decreasing available precursors for glucuronidation.[24,25] Fasting rats for 24 h led to a 60% decrease of hepatic uridine diphosphate (UDP)-glucose, the precursor for hepatic UDP glucuronic acid used in acetaminophen glucuronidation, which was not ameliorated by feeding glucose after fasting.[26,27] Furthermore, hepatic sulfur stores may be depleted by fasting,[13] as dietary sulfur intake may become insufficient. Subjecting rats to a range of diets deficient of either sulfur-containing amino acids or

inorganic sulfate resulted in significant decreases in acetaminophen sulfation.[28,29] Similarly, Price et al found that after fasting rats for 24 h, the formation of acetaminophen-glucuronide and -sulfate decreased by 40% and 30%, respectively. Particularly in the high dose range, phase II reactions were found to be decreased, with a marked increase in hepatotoxicity as seen by increased transaminase levels and more severe hepatic necrosis, compared to the fed rats.[25,30] Adding to this, healthy men showed an increase in bilirubin after fasting for 36 h. This may indicate reduced glucuronidation, as bilirubin is a substrate for conjugation with glucuronic acid. In contrast, in the same population, apparent acetaminophen-glucuronide clearance following a therapeutic dose remained unchanged.[14] Thus, reduced capacity for phase II metabolism due to fasting may lead to a higher fraction of acetaminophen shunted toward phase I (CYP2E1) metabolism, leading to increased formation of NAPQI, irrespective of CYP2E1 activity.[13,25,31]

In conclusion, notably studies in animals but also in humans showed decreased total acetaminophen clearance due to a range of malnutrition statuses, resulting in increased acetaminophen exposure. Nevertheless, we found no clear explanation for the extremely low clearance in the described case. A possible reason is that the acetaminophen plasma concentration was measured only thrice. More measurements might have yielded a better understanding of the course of acetaminophen clearance in this patient, marking specific turning points such as the ending of a lag phase in absorption or metabolism. Overall, decreasing the interval and increasing the frequency of acetaminophen concentration measurements may help in predicting the risk of liver damage and establishing proper treatment duration, when treating malnourished patients for an acetaminophen intoxication.

There are some limitations to the implications of the discussed studies. Generally, caution is advised in extrapolating findings in animal models to humans, due to interspecies variation. Moreover, while acetaminophen toxicity in humans and mice is similar, rats were found to be highly resistant to acetaminophen toxicity comparatively. When exposing both rats and mice to acetaminophen to study toxicity, rats showed significantly lower mitochondrial dysfunction and its related toxicity.[32] Nevertheless, both human and animal studies were included in this discussion. We still consider rat studies valuable as we highlight not only hepatotoxicity, but also the impact of malnutrition on acetaminophen metabolism, irrespective of consequent injury. Furthermore, extrapolation of the impact of short-term fasting or dietary deficiency to chronic malnourishment introduces additional uncertainty. Nonetheless, as short-term fasting is a well-defined status, we included this in our literature review. Lastly, acetaminophen bezoar formation could result in increased acetaminophen plasma concentrations over time, of which the cause is misinterpreted as reduced clearance. However, the formation of acetaminophen bezoars is unlikely for a dose such as the patient ingested.[33]

4 | CONCLUSION: WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

When looking specifically at the metabolic routes, literature on the effect of eating disorders on CYP2E1 is inconsistent. Nonetheless, malnourishment appears to reduce capacity of phase II metabolism, especially sulfation conjugation, leading to a shift in metabolism with a higher acetaminophen fraction metabolized by CYP, as well as decreased GSH levels. We speculate that, consequently, more NAPQI may be formed with a concurrent decrease in neutralizing capacity. Even though acetaminophen metabolites are accountable for hepatotoxicity, in clinical practice we use the total acetaminophen concentration and liver enzymes as markers for hepatotoxicity and subsequent treatment. Especially in the case of malnutrition, concentrations of metabolite fractions may have more predictive value of potential acetaminophen hepatotoxicity. In the future research, the impact of severe statuses of malnutrition on total acetaminophen clearance and formation of metabolite fractions, in relation to liver enzymes, should be further investigated.

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CONFLICT OF INTEREST
Daan Zillen, Kris Movig, Gert Kant, Joost Masselink, and Paola Mian have no conflicts of interest directly related to this case presentation.

AUTHOR CONTRIBUTIONS
Daan Zillen wrote this manuscript. Kris Movig, Gert Kant, Joost Masselink, and Paola Mian assisted in proofreading and critical revision of this manuscript.

ETHICAL APPROVAL
Written consent was obtained from the patient described in this case report.

PATIENT CONSENT
The described patient gave consent to publish her case, a signed consent form is available.

DATA AVAILABILITY STATEMENT
Data sharing not applicable—no new data generated.

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