Review Article

Writing Club

MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

# Fomepizole's Role in Acetaminophen Toxicity

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## Abstract

Acetaminophen (APAP) toxicity is the leading cause of acute liver failure and results from overproduction of N-acetyl-p-benzoquinone-imine (NAPQI), a toxic metabolite formed via cytochrome P450 2E1 (CYP2E1). While N-acetylcysteine (NAC) is the standard treatment, its efficacy is limited in delayed or massive overdoses, necessitating adjunctive therapies. NAC works by replenishing glutathione stores, enhancing non-toxic metabolism of NAPQI, and improving hepatic perfusion, but its protective effect diminishes once significant liver injury has occurred. Therefore, alternative or complementary interventions are being explored to address these limitations. Fomepizole (4MP), a CYP2E1 inhibitor, shows promise in mitigating APAP-induced hepatotoxicity and nephrotoxicity. Animal studies demonstrate that 4MP reduces hepatic injury by more than 80%, largely through CYP2E1 inhibition and suppression of c-Jun N-terminal kinase (JNK)-mediated mitochondrial dysfunction, preventing oxidative stress and apoptosis. Additionally, 4MP attenuates endoplasmic reticulum (ER) stress-induced apoptosis in proximal tubular cells, reducing renal injury. Studies suggest initiating 4MP when plasma APAP levels >300 mcg/mL, with efficacy observed even in delayed treatment scenarios. Human data corroborate these findings. A case report showed that adding 4MP to NAC prevented hepatotoxicity in a 33-year-old with severe APAP overdose. In another case, a 7-month-old with acute liver failure from repeated APAP dosing avoided transplantation with 4MP-NAC therapy. Larger case series, including Toxicology Investigators Consortium (ToxIC) data, report favorable outcomes, with reduced transaminase levels and avoidance of liver failure in critically ill patients treated with 4MP. Further randomized controlled trials are essential to establish its role in clinical practice.

Acetaminophen (APAP), also known as "paracetamol" in other areas of the world, was first identified in the United Kingdom in 1889 as a metabolite of phenacetin, an earlier analgesic discovered in 1887.[1] Phenacetin was one of the first widely used analgesics in the 19th century, but it was later found to cause kidney damage with prolonged use. As a result, the need for safer alternatives arose. It wasn't until 1949 that APAP began to be used and marketed in the UK as paracetamol. Unlike phenacetin, APAP was found to cause fewer kidney injuries over long-term use, making it a safer option.[1] Acetaminophen is a widely used over-the-counter medication recognized for its analgesic and antipyretic effects, although its exact mechanism of action remains not fully understood. While it may exhibit some cyclooxygenase (COX) inhibition, APAP has no anti-inflammatory effects in peripheral tissues; its effects are more central, primarily affecting the central nervous system (CNS). Interestingly, APAP directly does not bind to the active sites of COX-1 and COX-2 enzymes but reduces COX activity through a different mechanism. It is theorized to reduce a heme on the peroxidase portion of the prostaglandin H2 synthase. All in all, APAP reduces the production of prostaglandins in the CNS to contribute to its analgesic and antipyretic effects.[2] Acetaminophen is primarily excreted through glucuronidation

and sulfation, accounting for 90% of its elimination without producing toxic metabolites, while about 5% is excreted unchanged. In therapeutic dosing, the remaining 5% is metabolized by CYP2E1 into the toxic compound N-acetyl-p-benzoquinone-imine (NAPQI), which is detoxified by glutathione and excreted as NAPQI-glutathione. In overdose, excessive NAPQI production depletes glutathione, leading to hepatotoxicity and potential liver failure.

## Fomepizole

Hugo Theorell, a Swedish biochemist specializing in enzymatic activity, observed that medications containing pyrazole had inhibitory effects. Theorell and his team discovered that these effects influenced the alcohol dehydrogenase (ADH) complex, and animal studies showed increased survival rates when these animals were poisoned with methanol or ethanol. Although pyrazole inhibited ADH, it also affected other enzymes, like catalase, and caused adverse effects, including bone marrow, kidney, and liver toxicity. This spurred further research, leading to the discovery that fomepizole (4MP) had similar ADH inhibitory effects but was much safer to use, especially in cases of ethylene glycol or methanol poisoning.[3] Fomepizole is widely used in toxicology for its three primary mechanisms of action, particularly in patients presenting with acute ethylene glycol or methanol poisoning. First, it acts as a competitive inhibitor of ADH, an enzyme responsible for metabolizing ethanol, ethylene glycol, and methanol into their respective aldehyde and, ultimately, carboxylic acid metabolites. Second, 4MP inhibits hepatic CYP2E1, an enzyme involved in the metabolism of various substrates, including toxic alcohols. Lastly, 4MP may play a role in inhibiting c-Jun N-terminal kinase (JNK), an enzyme implicated in the mitochondrial intrinsic apoptosis pathway.[2,4]

## Animal Literature for 4MP for APAP

Animal studies investigating 4MP in APAP toxicity have provided critical insights into its mechanism of action and efficacy in mitigating both hepatic and renal injury. These studies consistently highlight 4MP's ability to inhibit CYP2E1, thereby reducing the formation of NAPQI, the toxic metabolite responsible for APAP-induced hepatotoxicity. By intervening early in the metabolic pathway, 4MP prevents glutathione depletion, oxidative stress, and mitochondrial injury, which are the three main hallmarks of severe APAP toxicity.

One pivotal study using rodent models examined the effects of 4MP administered after a high-dose APAP challenge, simulating delayed clinical presentations. Mice receiving 600 mg/kg of APAP developed significant hepatotoxicity, as evidenced by substantial elevations in plasma transaminases, with alanine aminotransferase (ALT) levels exceeding 10,000 IU/L in untreated controls.[6] Plasma APAP concentrations were markedly elevated in this model, and 4MP was introduced when toxicity was already evident. The administration of 4MP significantly reduced hepatic necrosis and ALT levels by more than 80%, indicating its ability to halt ongoing injury even when introduced post-exposure.[6]

In addition to liver injury, 4MP demonstrated protective effects against APAP-induced nephrotoxicity. A study focusing on renal outcomes found that APAP overdose caused significant endoplasmic reticulum stress in proximal tubular cells, leading to apoptosis mediated by caspase-12 activation.[7] Fomepizole effectively reduced these markers of renal injury by inhibiting CYP2E1-dependent NAPQI formation in kidney cells, which was confirmed through reduced apoptotic signaling and histological evidence of preserved renal structure.[7] Plasma biomarkers of kidney injury, such as blood urea nitrogen, were also significantly lower in mice treated with 4MP compared to untreated controls.[7]

Intriguingly, 4MP was shown to impact the activation of the JNK pathway, a critical driver of mitochondrial dysfunction in APAP toxicity.[6,7,8] In one study, 4MP-treated animals demonstrated reduced JNK translocation to the mitochondria, which correlated with improved mitochondrial membrane stability and lower rates of cell death.[6,7,8] This protective effect extended the window of therapeutic efficacy, as 4MP administered several hours post-APAP exposure still conferred significant reductions in both hepatic and renal injury compared to untreated controls.[6,7,8] These animal models also provided guidance on the threshold for 4MP intervention. In studies where plasma APAP levels exceeded 300 mcg/mL, the introduction of 4MP was associated with marked reductions in downstream injury markers, suggesting that plasma APAP concentration, alongside clinical markers of toxicity, could guide the timing of 4MP administration.[6,7,8]

## Human Literature for 4MP and APAP

Following compelling findings in animal studies highlighting 4MP's ability to inhibit CYP2E1 and mitigate toxic metabolite formation in APAP toxicity, human research has focused on evaluating its clinical potential, particularly in complex or delayed treatment scenarios. These investigations have reinforced its value, with dosing protocols for APAP toxicity mirroring those established for toxic alcohol poisonings. Typically, 4MP is administered as an initial IV loading dose of 15 mg/kg, followed by maintenance doses of 10 mg/kg q12h for up to 48 hours. This standardized approach has been adopted in multiple human studies and case reports, consistently demonstrating benefits in reducing liver injury and improving patient outcomes.

One example of 4MP's potential in severe APAP toxicity comes from a 2020 case report by Shah and Buehler. They described a 33-year-old male who ingested 25 g of APAP over two days. Laboratory results revealed an APAP concentration of 337 mg/L, aspartate aminotransferase (AST) of 137 IU/L, ALT of 194 IU/L, international normalized ratio (INR) of 2.2, and metabolic acidosis with a pH of 7.24. The calculated APAP half-life was 10.2 hours. Despite delayed initiation of n-acetylcysteine (NAC) therapy, the addition of a single 15 mg/kg dose of 4MP, administered 11 hours post-arrival, significantly improved clinical outcomes.[9] AST and ALT levels peaked well below thresholds for hepatotoxicity, coagulation parameters normalized within three days, and the patient recovered without complications.[11] This case underscores 4MP's ability to mitigate hepatocellular injury, even in delayed treatment scenarios.

The potential benefits of 4MP not only have implications in adult populations but also have been utilized in pediatric care. In

a 2023 case report, a 7-month-old female developed acute liver failure after receiving repeated supratherapeutic doses of liquid APAP (99 mg/kg/day for five days).[10] Initial labs revealed profound hepatotoxicity, with AST exceeding 25,000 IU/L, ALT over 16,000 IU/L, an INR of 4.95, and an APAP concentration of 239.6 mcg/mL. Although NAC therapy was initiated using a three-dose protocol, the prolonged APAP half-life (26.4 hours) indicated insufficient detoxification.[12] Fomepizole was introduced at the standard loading dose, followed by maintenance doses of 10 mg/kg every 12 hours. Over the next 48 hours, the patient demonstrated improvement in liver function and coagulation and, most importantly, avoided the need for liver transplantation.[10] These cases illustrate 4MP not only demonstrates its ability to prevent severe hepatotoxicity but even shows promise in delayed or high-risk scenarios.

Larger patient series further validate the efficacy and safety of 4MP in severe APAP toxicity. A prospective case series by Link et al. included 14 high-risk patients treated with 4MP in conjunction with NAC. All patients presented with persistently elevated APAP levels and were deemed at high risk for hepatotoxicity based on laboratory findings and clinical judgment.[11] Initial APAP concentrations ranged from 10.8 mcg/mL to over 791 mcg/mL, with many exceeding thresholds associated with severe toxicity.[11] The APAP-aminotransferase (APAP×AT) multiplication product, a predictive metric for hepatotoxicity, often surpassed 10,000 in this cohort, far exceeding the threshold of 1,500 that indicates low hepatotoxic risk.[11] Despite these concerning indicators, none of the patients developed clinically significant hepatotoxicity.[11]

Established 4MP dosing protocols were utilized across the cohort, with an initial loading dose of 15 mg/kg IV over 30 minutes, followed by maintenance doses of 10 mg/kg every 12 hours. The majority of patients required one or two doses of 4MP; however, additional doses were administered in cases with altered pharmacokinetics, such as renal replacement therapy (RRT). For example, a patient undergoing continuous RRT required a third dose of 10 mg/kg due to the clearance of 4MP during the procedure. Clinical outcomes were favorable across all cases, even among patients with severe presentations and significant comorbidities, such as chronic alcohol use and end-stage renal disease.[13] One patient with an initial APAP concentration of 791 mcg/mL and an APAP×AT product of 27,640 demonstrated minimal liver enzyme elevation, with ALT peaking at 23 IU/L and AST at 73 IU/L.[11] Another patient, whose APAP×AT product exceeded 50,620, recovered without liver failure after timely administration of 4MP and NAC.[11] Importantly, no adverse events related to 4MP administration were observed, reaffirming its safety profile even in critically ill patients.[13] These findings highlight the need for early recognition and aggressive management of patients with high APAP levels and elevated APAP×AT products.[11] Although the study demonstrated better-than-expected outcomes, the authors advocate for randomized controlled trials to establish the efficacy of 4MP more conclusively.[11]

The findings of Filip et al. provide additional insights from a broader cohort of critically ill patients.[12] The Toxicology Investigators Consortium (ToxIC) database revealed outcomes from 25 patients treated with 4MP for APAP toxicity. Despite severe clinical presentations, including hepatotoxicity (72%), coagulopathy (40%), and metabolic acidosis (72%), mortality was significantly lower than anticipated at 24%.[14] Mechanistically, 4MP's dual action as a CYP2E1 inhibitor and its attenuation of oxidative stress via the JNK pathway effectively targets key contributors to APAP-induced hepatotoxicity.[12,13] By preventing NAPQI formation and mitigating mitochondrial damage, 4MP complements NAC's glutathione-replenishing effects.[12,13] Its established safety profile further supports its use in severe APAP toxicity, with the standard dosing regimen proving effective across diverse patient populations.[12]

Taken together, these studies highlight 4MP's emerging role as an adjunctive therapy in severe APAP toxicity. By reducing hepatocellular injury and improving clinical outcomes, 4MP addresses some limitations of NAC monotherapy, particularly in delayed or massive overdoses.[12,13] While these findings provide promising data on 4MP's utilization in APAP-induced hepatotoxicity, further randomized controlled trials are needed to refine its clinical role and establish evidence-based guidelines for its use.[12,13] Currently, a randomized controlled trial is underway evaluating the adjunctive use of 4MP in APAP toxicity scheduled to complete enrollment in 2025.[14]

## Questions That Need to be Addressed

### *Question #1 - How does fomepizole interact with the metabolic pathways involved with APAP toxicity?*

APAP is excreted in four different routes. The first two are grouped together and account for 90% of APAPs' excretion. These two routes consist of glucuronidation and sulfation where APAP does not produce toxic metabolites. The third route, which accounts for around 5% of APAP excretion, is excreted unchanged in the urine or feces. The remaining 5% of APAP is metabolized by CYP2E1 to a toxic metabolite known as NAPQI. NAPQI as a molecule has a free radical which causes damage in our liver, but our liver has a protein named glutathione which binds to NAPQI and forms a new structure called NAPQI-glutathione which is excreted in urine. At high doses of APAP, NAPQI can deplete liver glutathione causing hepatotoxicity and possibly death. How 4MP works in this metabolic pathway is that it inhibits CYP2E1 reducing the production of NAPQI.

### *Question #2: What dose do we use for 4MP to treat acute intoxication of APAP?*

Always consult a toxicologist, as per dosing there is limited data, but the most frequently used dose is a loading dose of 15mg/kg, then a maintenance dose of 10mg/kg every 12 hours for 48 hours. Other regimens consist of just giving loading dose.

### *Question #3: Should we worry about long term effects of 4MP use?*

Fomepizole is typically a tolerable medication; most patients may experience a mild headache, possible vomiting, and nausea, but otherwise it is quite tolerable and does not cause long term effects.

### *Question #4: Which patients would benefit from 4MP use?*

Always consult a toxicologist. Patients with massive APAP ingestions with serum levels >300 mcg/mL and contemplation on hemodialysis for the patient.

## Student Opinions

### *Tyler Thao*

In my professional opinion as a student pharmacist, the use of fomepizole could be considered as an adjunctive therapy in cases of acute acetaminophen (APAP) intoxication, particularly in extremely severe cases where APAP levels exceed 700-800 mcg/mL. In such scenarios, the care team might be evaluating the need for dialysis or even a liver transplant. Although there is no conclusive data supporting fomepizole's efficacy in treating acute APAP intoxication, its theoretical benefits based on its mechanism of action suggest it might be helpful. However, it's important to note that the standard treatment for acute APAP intoxication remains N-acetylcysteine (NAC), used in conjunction with the Rumack-Matthew nomogram, which together provide an effective treatment protocol.

### *Devonta Parker*

After taking a deep dive into the available literature, in my professional opinion as a student pharmacist, 4MP shows significant promise as an adjunctive therapy in APAP toxicity, particularly in severe or delayed presentations. Its ability to inhibit CYP2E1 and prevent the formation of NAPQI provides a distinct advantage from a mechanistic standpoint that complements NAC. In cases of extremely high APAP concentrations (>300 mcg/mL), prolonged APAP half-life, or ongoing signs of mitochondrial injury, 4MP may help reduce further hepatic and renal damage. While the current human literature is encouraging, there is still a lack of randomized controlled trials (RCT's) that prevents its routine utilization and placement in guidelines. However, in high-risk scenarios, and based off patient specific factors, such as those with significantly elevated APAP×AT products or impending liver failure, 4MP could be a valuable addition to treatment. With further research and stronger evidence, I believe 4MP has the potential to become a significant part of standard care for APAP toxicity.

## Conclusion

Fomepizole (4MP) represents an emerging adjunctive therapy in the management of severe acetaminophen (APAP) toxicity, offering mechanistic benefits through inhibition of CYP2E1 and attenuation of oxidative stress and mitochondrial injury. While NAC remains the cornerstone of APAP overdose treatment, 4MP provides an additional layer of protection in cases involving massive ingestions, delayed presentations, or prolonged APAP half-life. Both animal and human studies highlight its potential to improve outcomes and prevent progression to acute liver failure, even in high-risk scenarios. Although existing clinical data are promising, randomized controlled trials are needed to definitively establish the role of fomepizole in APAP toxicity management. Until such data are available, its use should be guided by toxicology consultation and careful assessment of individual patient risk factors.

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PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

*Disclosure: The authors declare no relevant relationships, real or potential, with ineligible companies or product(s) or service(s) mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.*

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