

Acetaminophen toxicity with concomitant use of carbamazepine

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ABSTRACT – Acetaminophen is a widely used analgesic that can cause acute liver failure when consumed above a maximum daily dose. Certain patients may be at increased risk of hepatocellular damage even at conventional therapeutic doses. We report a case of a 34-year-old man on carbamazepine for complex partial seizures who developed acute liver and renal failure on less than 2.5 grams a day of acetaminophen. This raises caution that patients on carbamazepine should avoid chronic use of acetaminophen, and if required use at lower doses with vigilant monitoring for signs of liver damage.

Key words: acetaminophen toxicity, carbamazepine, liver failure, renal failure, epilepsy

Acetaminophen is a commonly used medication that is generally well tolerated. Problems relating to toxicity usually arise only in acute overdose of greater than seven grams or in chronic use of more than four grams per day. We report a case of hepatic and renal failure from a therapeutic dose of acetaminophen in a patient on carbamazepine. This patient raises concern that carbamazepine may predispose to acetaminophen induced toxicity and hepatic failure in some patients.

Case study

A 34-year-old man with complex partial seizures controlled for eleven years on carbamazepine 1,600 mg per day and clobazam 10 mg per day. He also had Crohn's disease treated with mesalazine 4 g per day. Two weeks prior to presentation, he developed musculoskeletal lower back pain. He started an analgesia containing acet-

aminophen and methocarbamol. For twelve days he received 2,000 mg of acetaminophen and 800 mg of methocarbamol. He developed abdominal pain that radiated into both flanks and was associated with a sense of unsteadiness. He increased his doses of analgesia to 2,500 mg of acetaminophen and 800 mg of methocarbamol.

On presentation he complained of diplopia, gait instability and anuria. On examination his bowel sounds were reduced and he had diffuse abdominal tenderness, with no rebound tenderness. No costovertebral angle tenderness was present. On neurological examination his extraocular movements were full with bilateral gaze evoked nystagmus. The remainder of his cranial nerve, motor, reflex and sensory examination was unremarkable. He had a postural tremor and mild dysmetria in both upper and lower extremities. His gait was slightly broad based. Routine labs identified an alanine aminotransferase (ALT) of 9,101 U/L and

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aspartate aminotransferase (AST) of 10,274 U/L. His PT INR was 2.2 and his albumin was 34 g/L. His creatinine was elevated at 592 $\mu\text{mol/L}$ with a urea level of 17.3 mmol/L . A serum acetaminophen level was 77 $\mu\text{mol/L}$ and carbamazepine level was 87 $\mu\text{mol/L}$. Viral hepatitis serology for B and C was negative, as was a work up for autoimmune diseases including normal anti-DS-DNA, ANA, complement levels, anti-GBM and ANCA. An abdominal ultrasound showed a diffusely echogenic liver, with no evidence of biliary ductal dilation or stones. Liver biopsy was not performed. A renal biopsy showed interstitial nephritis.

The patient was treated with IV fluids, N-acetylcysteine protocol and a course of prednisone. He was restarted on carbamazepine two days after admission and tolerated the medication well. His AST and ALT gradually normalized (*figure 1*). The patient was discharged home three weeks after admission and has remained medically stable for over two years.

Discussion

Acute hepatic failure is most commonly caused by acetaminophen toxicity. Other etiologies include idiosyncratic drug reactions (such as with carbamazepine, phenytoin and valproate), viral hepatitis, autoimmune hepatitis, liver hypoperfusion, Wilson's disease, pregnancy and malignancy. In our patient, acetaminophen was suspected to be responsible for the development of liver failure. Other etiologies were considered less likely given his history, negative viral hepatitis serology,

negative autoimmune workup and normal ceruloplasmin and 24-hour urine copper. Our patient was also on a number of medications that were considered a less likely cause. Carbamazepine can cause acute liver failure, however our patient had been on a stable dose for eleven years without complication. Clobazam and methocarbamol were also being taken by our patient, however neither medication induces or inhibits hepatic enzymes, and neither have reported cases of liver failure on medline (Ahmed and Siddiqi, 2006). Mesalazine can rarely cause hepatitis (3 per million) which could be an alternative explanation for the development of our patients liver failure. However since he had tolerated the medication well for over 2 years without a change in dose, we believe it a less likely etiology (Ransford and Langman, 2002).

The mechanism by which carbamazepine may predispose to acetaminophen toxicity can be understood by assessment of the metabolism of these medications. Acetaminophen is metabolised in the liver via conjugation. When this conjugation pathway becomes saturated, acetaminophen is metabolized by the cytochrome p450 enzymes CYP2E1 and CYP1A2. This pathway produces a toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI), which normally is conjugated with glutathione and renally excreted. When the glucuronidation capacity is exceeded, NAPQI accumulates and covalently binds to hepatic proteins leading to hepatocellular necrosis and apoptosis. This most commonly occurs in acute acetaminophen overdose of greater than seven grams or when the maximum daily dose of four grams per day is exceeded

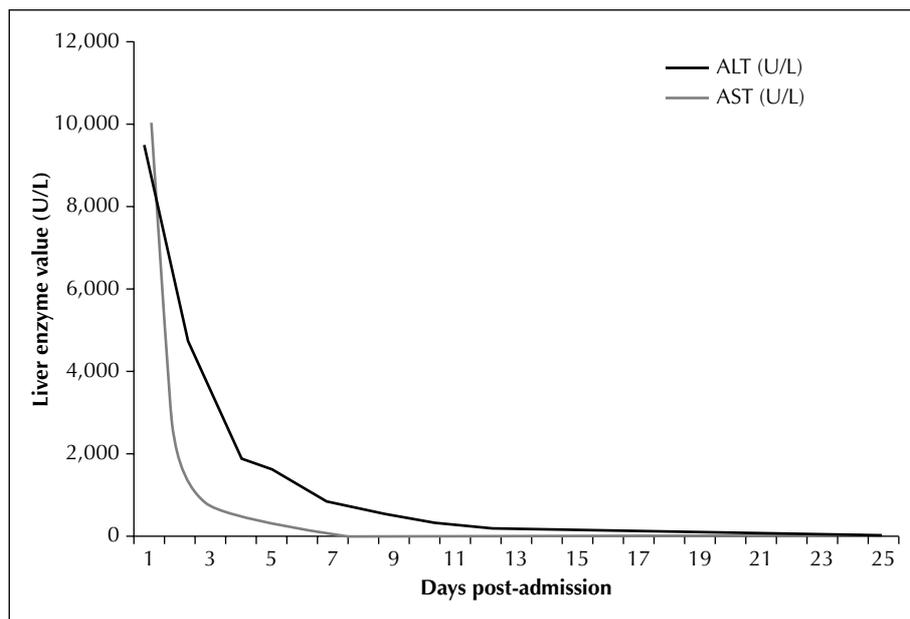


Figure 1. Liver function tests shown to decrease after cessation of acetaminophen on admission. This occurred despite the patient remaining on carbamazepine for the majority of this time period. Prior to this elevation in liver enzymes, the ALT and AST levels had been within the normal range for several years.

for an extend period of time. Though our patient was taking 2.5 g of acetaminophen per day, he had an elevated serum acetaminophen level at 77 $\mu\text{mol/L}$ and was also taking carbamazepine. Carbamazepine is an antiepileptic medication that induces the p450 enzyme CYP3A4, which also is involved in the metabolism of acetaminophen to NAPQI, though a lesser extent than CYP2E1 and CYP1A2 (Kostrubsky *et al.*, 1997). The induction of CYP3A4 by carbamazepine thus can lead to an increase in NAPQI and subsequent liver damage.

Two case reports also suggest that carbamazepine reduces the dose of acetaminophen required to induce hepatocellular damage. An 80 year old female on carbamazepine developed liver dysfunction after receiving four grams of daily acetaminophen for 18 days (Parikh *et al.*, 2004). She subsequently improved with N-acetylcysteine (NAC) and cessation of acetaminophen use. A 17 year old female with anorexia and a mood disorder treated with carbamazepine, developed acute hepatic failure with a 7.5 grams overdose of acetaminophen (Young and Mazure, 1998). Despite this low dose of acetaminophen and the use of NAC, the patient required a liver transplant. Though these two case reports are confounded by age and anorexia respectively, there is a suggestion carbamazepine may lower the required acetaminophen dose to induce liver failure. It is also possible that these few case reports represent patients with a genetic mutation in the metabolic pathways of acetaminophen when combined with carbamazepine. A retrospective study showed that carbamazepine is associated with worse outcomes in patients who develop liver failure from acetaminophen overdose, suggesting that carbamazepine may potentiate the hepatotoxic effects of acetaminophen (Bray *et al.*, 1992).

Other medications and conditions have been also been associated with an increased risk of hepatotoxicity from acetaminophen (table 1). Phenytoin induces the p450 enzymes CYP3A4 and CYP2C but not CYP2E1 or CYP1A2. Like carbamazepine, the induction of CYP3A4 by phenytoin may lead to increased production of NAPQI

Table 1. Medications and conditions associated with an increased risk of acetaminophen induced hepatotoxicity.

Medication/condition	Mechanism of action
Smoking Isoniazide, chronic ethanol use	p450 CYP1A2 enzyme induction p450 CYP2E1 enzyme induction
Carbamazepine, phenytoin	p450 CYP3A4 enzyme induction
Infants Chronic ethanol use AIDS Malnutrition	Low Glutathione
Verapamil	P-glycoprotein efflux pump inhibitor

from acetaminophen. Several case reports have also been described of liver failure related to low dose acetaminophen in patients on phenytoin (Suchin *et al.*, 2005). Our patient also developed acute renal failure with the biopsy showing interstitial nephritis. Medications are a cause of interstitial nephritis, and both acetaminophen and carbamazepine are among the medications associated with this immune reaction to the kidneys (Eijgenraam *et al.*, 1997). The management of acute interstitial nephritis warrants cessation of offending medication, and initiation of brief course of corticosteroids (John and Herzenberg, 2009). In the presented case, the patient had been on carbamazepine for eleven years without complication, and therefore the treating physicians suspected acetaminophen as the primary culprit responsible for the interstitial nephritis. Carbamazepine was restarted during admission with no recurrent hepatic or renal problem. If an anti-epileptic medication is considered as a cause of interstitial nephritis alternative agents that could be initiated include benzodiazepines, gabapentin and levetiracetam. Phenytoin, lamotrigine and valproate should be avoided, as each has been associated with the development of interstitial nephritis (John and Herzenberg, 2009; Monckeberg *et al.*, 2004).

This case raises caution regarding the daily use of acetaminophen in patients on carbamazepine, though it should be emphasised that further study is required before any recommendations can be made. Consideration however could be given to a dose reduction of acetaminophen, and patient education alerting them to early signs of liver dysfunction, such as nausea, vomiting, icterus and anorexia. The role of frequent liver function monitoring is uncertain, however we suggest at a minimum obtaining liver function testing when patients report such symptoms consistent with possible liver dysfunction. □

Disclosure.

None of the authors has any conflict of interest to disclose.

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