Beware of paracetamol use in alcohol abusers: a potential cause of acute liver injury
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Abstract
There may be under-recognition of acute liver injury following reported therapeutic use of paracetamol in alcoholics. We present the case of an alcoholic patient who developed acute liver injury suspicious for chronic paracetamol toxicity on two occasions. The likely contribution of chronic paracetamol was not recognised at her second presentation, reflecting a need for increased awareness of this potential cause of acute liver injury.

The biochemical hallmark of the syndrome is the ‘towering’ aspartate-aminotransferase (AST), often in the thousands; transaminases above 500 U/L should never be dismissed as secondary to alcoholic liver disease alone. Whether alcoholics are at increased risk of toxicity from therapeutic doses of paracetamol remains controversial, although many cases have been described for over 30 years.

Randomised controlled trials to date have failed to show significant hepatic derangement in newly abstinent alcoholics exposed to short courses of paracetamol. We argue that these studies do not reflect the realities of paracetamol use in this population. In addition, alcoholics are at risk of accidental ‘staggered overdoses’, or repeated supra-therapeutic ingestions. In cases of suspected paracetamol toxicity, administration of the antidote n-acetyl cysteine (NAC) should be considered, even when the patient’s serum paracetamol level is normal.

It is 20 years since the NZMJ published a case report of paracetamol hepatotoxicity in a heavy drinker taking no more than 6 grams of paracetamol daily.1 Sporadic cases of life-threatening liver necrosis in heavy drinkers continue to be encountered in those taking alleged therapeutic doses of paracetamol, prompting us to report on a recent case.

Case report
A 52-year-old woman with a 12-year history of alcohol dependence was admitted electively for detoxification in December 2011. Her past medical history included possible seizure disorder (not treated with anticonvulsants), gastric bypass (admission weight 61 kg, body mass index 23 kg/m²), previous DVT, asthma and depression.

She was regularly drinking two bottles of wine per day up to the day of admission; breath alcohol on admission was 680 mcg/L. Examination showed mild tachycardia, tremor and right upper quadrant tenderness; there was no delirium, seizures or signs of liver failure.

Liver function tests (LFTs) 1 month earlier were consistent with alcoholic liver disease, with an ALT (alanine amino-transferase) of 146 U/L(<28), GGT (gamma-glutamyl transpeptidase) 212 U/L(<36), INR (international normalised ratio) 1.3,
albumin 40 g/L (34-46), mean cell volume 103 fL, platelets 177×10^9/L; an AST (aspartate-aminotransferase) level was not taken.

On admission, her AST was markedly elevated at 1453 (<27 U/L), ALT 332, GGT 732, INR 2.5, albumin 27. Transaminases peaked the next day (AST 8015, ALT 1260). Serology for hepatitis B and C, Epstein-Barr virus and cytomegalovirus, and ANA were unremarkable. No contributing medications were noted; on admission she was taking omeprazole, citalopram (20mg daily), Symbicort® (budesonide with eformoterol) inhaler, zopiclone and multivitamins, and was treated for alcohol withdrawal with diazepam.

On enquiry, the patient reported using paracetamol for neck pain, as prescribed by her general practitioner (GP) at 4 grams a day for the preceding month. This was consistent with her pharmacy’s dispensing records. Paracetamol was ceased on admission and she was administered the antidote NAC. Her LFTs improved markedly; by day 6 AST had fallen to 333, INR 1.4. She was discharged with strong advice to avoid paracetamol.

Unfortunately, she relapsed into alcohol abuse the next day. Two months later, a follow-up blood test by her GP revealed further hepatic insult with an AST of 3322, ALT 595 and INR 1.7. Remarkably, she admitted to resuming paracetamol at 4 grams a day for 2 weeks while concurrently drinking alcohol. She was referred to the acute medical service and assessed by a different team. A liver ultrasound was normal. She was not treated with NAC on the basis of an undetectable paracetamol level on admission.

Paracetamol was ceased and her LFTs improved after 2 days (AST 291, ALT 176). She continues to struggle with abstinence but her transaminases have never exceeded the low hundreds since.

**Discussion**

We have reported a case of acute liver injury in an alcoholic woman taking paracetamol with therapeutic intent. Other causes of acute liver injury were considered but felt less likely, including viral hepatitis, ischaemia, autoimmune liver disease, and other drug-induced hepatotoxicity.

At her second presentation, the potential role of paracetamol was discounted based on a falsely reassuring paracetamol level. In chronic hepatotoxicity, paracetamol levels are frequently ‘therapeutic’. They are dependent on the time from last dose to medical presentation, and therefore cannot be used to exclude toxicity in the setting of chronic use.

This patient’s LFT derangement is similar to that described in previous case reports, with a markedly raised AST, said to ‘tower’ over the relatively less elevated ALT. In one case series, ASTs ranged from 3000 to 48,000 U/L in 90% of subjects. In contrast, transaminases are only moderately raised in alcoholic liver disease (usually AST <500, ALT <200), with an AST:ALT ratio in the order of 2:1 or greater. Similar cases have been described for over 30 years. One case series in 1995 identified 67 cases of hepatotoxicity in alcoholics taking paracetamol with therapeutic
intent, alarmingly associated with a 20% mortality rate.\textsuperscript{3} This effect has been dubbed the ‘alcohol-paracetamol syndrome’.\textsuperscript{4}

Therapeutic doses of paracetamol are predominantly metabolised into non-toxic metabolites by glucoronidation or sulfation; a small proportion is metabolised by the cytochrome-P 2E1 (CYP2E1) enzyme into the hepatotoxic metabolite n-acetyl-p-benzoquinone imine (NAPQI). With excessive doses of paracetamol, the glucoronidation and sulfation pathways become saturated, resulting in the accumulation of toxic NAPQI.

Chronic alcohol ingestion induces CYP2E1 up to threefold; the effect of which persists in the early days of alcohol abstinence.\textsuperscript{5} Acute ingestion of alcohol in fact has a protective effect as it competes with paracetamol for CYP2E1; therefore, newly abstinent alcoholics who continue to take paracetamol may be most at risk.\textsuperscript{6}

Alcoholics are also less able to clear NAPQI, as its breakdown is mediated by glutathione, stores of which are decreased with chronic alcohol ingestion and malnutrition.\textsuperscript{7}

In the United States, the Food and Drug Administration has mandated that all paracetamol packets sold over-the-counter carry an alcohol warning: ‘If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen (paracetamol)’.

Critics argue such warnings are unfounded. Some call into question the validity of case reports of the ‘alcohol-paracetamol syndrome’, in particular, pointing to incomplete dosing histories and instances when measured paracetamol levels imply higher dosages ingested than reported.\textsuperscript{8}

A recently published meta-analysis cites five randomised controlled trials where paracetamol was given at up to 4 grams a day to newly abstinent alcoholics for up to 10 days; no statistically significant increase in ALT was seen at day 4.\textsuperscript{9}

All trials in the meta-analysis excluded alcoholics with baseline transaminases greater than 200, and only two allowed patients with ALTs greater than 120; thus severe alcoholic liver disease was excluded. Paracetamol was given in short courses only (for up to 10 days). However alcoholics are more likely to use paracetamol for extended periods; one study suggests alcoholics are twice as likely than non-regular drinkers to use paracetamol on a daily basis.\textsuperscript{7} It may be that a longer period of paracetamol use increases the risk of developing toxicity.

We argue that these clinical trials do not reflect the realities of paracetamol use in the most vulnerable or malnourished alcoholics. It is also likely that alcoholics are at increased risk of taking medication unreliably, and therefore clinical trials do not simulate risk in practice.

While the ‘alcohol-paracetamol syndrome’ is controversial on a purely pharmacological level, there is evidence that alcoholics are at increased risk of non-intentional ‘staggered overdoses’, i.e. repeated supra-therapeutic ingestions.\textsuperscript{10} In a prospective study of at-risk drinkers, 31.9\% of 128 alcoholic subjects were found to use paracetamol at supra-therapeutic doses.\textsuperscript{7}
Alcoholic patients are over-represented in the most severe cases of chronic paracetamol toxicity; in 2012, authors at the Scottish Liver Transplant Unit reported that of 663 patients admitted there with liver failure from paracetamol, one-quarter were due to staggered overdoses; of these cases, half involved alcohol abuse. The contribution of the antidote NAC to our patient’s initial recovery is uncertain; her improvement may have been due to paracetamol cessation alone. Nevertheless, the New Zealand National Poisons Centre advises that patients with repeated supra-therapeutic ingestions of paracetamol with a raised ALT be treated with the antidote NAC even when the serum paracetamol level is undetectable.

In summary, we recommend caution in the prescribing of paracetamol to alcoholic abusers, especially in longer courses and to those with known alcoholic liver disease or malnutrition. Diagnosing paracetamol toxicity in the alcoholic requires a high index of suspicion. The diagnosis may be missed by physicians, due to insufficient history taking, incorrect interpretation of liver function tests, and false reassurance by blood paracetamol levels.

When staggered paracetamol overdoses, or therapeutic dose paracetamol toxicity are suspected, treatment with the antidote NAC is recommended, even when the serum paracetamol level is undetectable.

Unintentional acute liver injury from paracetamol in heavy drinkers is not new, having been reported in the medical literature for over 30 years. Nevertheless, we believe the awareness of the potential life-threatening interaction remains low within health professionals and the community, and believe it is important to raise the issue.

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