



Alcohol and paracetamol

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Summary

There are concerns that therapeutic doses of paracetamol may be hepatotoxic in patients who regularly drink moderate to large amounts of alcohol. Critical examination of case histories reveals that overdoses of paracetamol were responsible for the hepatotoxicity in many cases. Experimental studies in which paracetamol was taken for short periods also show no interaction. Paracetamol is therefore a suitable analgesic for patients who regularly drink moderate to large amounts of alcohol but, as with all patients, care should be taken to minimise the chances of overdose.

Key words: acetaminophen, analgesia, hepatotoxicity, liver.

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Introduction

It is well known that overdoses of paracetamol are hepatotoxic. There have been claims that alcohol potentiates this hepatotoxicity to such an extent that therapeutic doses of paracetamol become hepatotoxic in some patients. The so-called 'alcohol-paracetamol syndrome' describes the hepatotoxicity which is said to occur from the ingestion of therapeutic doses of paracetamol in moderate to heavy drinkers of alcohol.¹

The belief about the hepatotoxicity of paracetamol in people who drink alcohol regularly is shared by the USA Food and Drug Administration (FDA) which now requires that paracetamol sold in the USA be labelled with the warning stating that, 'If you consume 3 or more alcoholic drinks every day, you should ask your doctor whether you should take acetaminophen (paracetamol) or other pain relievers/fever reducers. Acetaminophen may cause liver failure.' Canada has also issued a warning about the possibility of liver damage in heavy users of alcohol who take more than the recommended dose of paracetamol.

Are these warnings justifiable? Should the Australian authorities mandate a similar warning on the label of paracetamol products? What can doctors say to patients who consume alcohol regularly?

Examining the evidence

Several reasons for the warnings about the hepatotoxicity of paracetamol may be put forward and examined:

- case reports of hepatotoxicity produced by therapeutic doses of paracetamol in alcoholics
- a metabolic interaction between alcohol and paracetamol
- depletion of glutathione
- erring on the side of patient safety.

Case reports

There are many case reports which claim that therapeutic doses of paracetamol have been associated with hepatotoxicity in alcoholics. However, recent critical examination shows that many of these cases of hepatotoxicity were caused by overdoses of paracetamol, not therapeutic doses.^{2,3} The patients may have claimed that they only consumed therapeutic doses, but the plasma concentrations indicate that many had taken overdoses of paracetamol. There is no evidence that therapeutic doses of paracetamol can accumulate to the levels found in many of these patients. 'Although the possibility remains that chronic consumption of alcohol does increase the risk of paracetamol hepatotoxicity in man, there is insufficient evidence to support the alleged major toxic interaction'.³

A metabolic interaction between alcohol and paracetamol

The hepatotoxic metabolites of paracetamol are produced in the liver largely through the activity of cytochrome P450 2E1. Alcohol has variable, although generally modest, effects on this enzyme system. Although alcohol induces cytochrome P450 2E1, it inhibits the enzyme while it is present in the body. Theoretically, alcohol may therefore protect the liver by inhibiting the oxidative metabolism of paracetamol. Alcohol could, however, make the liver more sensitive to paracetamol, during the period of continuing induction of cytochrome P450 2E1, after alcohol has been eliminated from the body. However, alcohol appears to produce only a small increase in the oxidative metabolism of paracetamol.⁴ There was no biochemical evidence of liver damage, when paracetamol 4 g daily was given to alcoholics for two days.⁵

Depletion of glutathione

The hepatotoxic quinoneimine metabolite of paracetamol reacts with glutathione. When concentrations of glutathione are very much reduced, there is a reaction with proteins which leads to centrilobular necrosis. The depletion of glutathione in chronic alcoholics may lead to hepatotoxicity, however, this is probably unlikely.⁶

Patient safety

In 2000, the American College of Rheumatology recommended that paracetamol should be avoided in patients with chronic alcohol abuse and used with caution in patients with existing liver disease. At the time, there was considerable criticism about this warning and, in reply, the College stated, 'We believe it better to err on the side of patient safety given that alternative treatments are available ...'.⁷

Following the critical analyses which have been published since 2000^{2,3}, the case for a label which may 'err on the side of patient safety' is now very weak. Poorly justified statements are not helpful and distract attention from well-based warnings. Alternative treatments may also present considerable problems.

Alternative analgesics

The non-selective non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, are relatively contraindicated in heavy drinkers because of the gastrointestinal damage produced by these drugs and alcohol. Furthermore, NSAIDs may also cause bleeding from varices. The selective COX-2 inhibitors, such as celecoxib and rofecoxib, may decrease the likelihood of gastrointestinal bleeding although evidence for the safety of these drugs in alcoholics with liver disease is currently lacking. Narcotic analgesics may be used in severe pain, but care should be taken with their dosage because of possible decreased metabolic clearances and respiratory depression in alcoholics.

Conclusions

Hepatotoxicity from therapeutic doses of paracetamol is unlikely in patients who consume moderate to large amounts of alcohol daily. However, patients with severe alcoholism should be instructed or supervised about the correct dosage of paracetamol. The depression often associated with alcoholism may make them more likely to take an overdose of paracetamol. Furthermore, the memory loss often seen in severe alcoholism may make patients unaware of having taken more than the recommended dose.

In the UK limiting the single sale of paracetamol tablets or capsules to 16 in general stores and 32 in pharmacies has been correlated with a reduction in the number of overdoses with paracetamol. Restricting the availability of paracetamol to patients with severe alcoholism and/or depression associated

with alcohol abuse may similarly be associated with a decreased number of overdoses of paracetamol.

Overdoses of paracetamol are a major problem. The occurrence of hepatotoxicity in patients who consume alcohol regularly and who take therapeutic doses of paracetamol is a very contentious topic. At this stage, paracetamol appears to be a reasonable analgesic or antipyretic drug to use in compliant patients who consume alcohol regularly. However, longer-term controlled studies are still required to clarify further the safety of paracetamol when taken regularly in combination with moderate to large amounts of alcohol.

After a recent review, the Therapeutic Goods Administration's decision that no warning regarding alcohol should be added to labels on paracetamol products seems reasonable.⁸

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References

1. Draganov P, Durrance H, Cox C, Reuben A. Alcohol-acetaminophen syndrome. Even moderate drinkers are at risk. *Postgrad Med* 2000;107:189-95.
2. Dart RC, Kuffner EK, Rumack BH. Treatment of pain or fever with paracetamol (acetaminophen) in the alcoholic patient: a systematic review. *Am J Ther* 2000;7:123-34.
3. Prescott LF. Paracetamol, alcohol and the liver. *Br J Clin Pharmacol* 2000;49:291-301.
4. Thummel KE, Slattery JT, Ro H, Chien JY, Nelson SD, Lown KE, et al. Ethanol and production of the hepatotoxic metabolite of acetaminophen in healthy adults. *Clin Pharmacol Ther* 2000;67:591-9.
5. Kuffner EK, Dart RC, Bogdan GM, Hill RE, Casper E, Darton L. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 2001;161:2247-52.
6. Lauterburg BH. Analgesics and glutathione. *Am J Ther* 2002;9:225-33.
7. Hochberg MC. Reply [letter]. *Arthritis Rheum* 2001;44:2455-6.
8. Medicines Evaluation Committee. Review of non-prescription analgesics: an update. Canberra: Commonwealth Department of Health and Ageing; 2003. <http://www.health.gov.au/tga/docs/html/analgupd.htm>

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Self-test questions

The following questions are either true or false (answers on page 23)

5. Alcohol forms a toxic complex with paracetamol.
6. People who need paracetamol regularly should be advised not to drink alcohol.