

Alcohol exposure and paracetamol-induced hepatotoxicity.

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Most instances of hepatotoxicity due to paracetamol in the United Kingdom and Australia are the result of large overdoses of the drug taken with suicidal or parasuicidal intent. In contrast, serious hepatotoxicity at recommended or near-recommended doses for therapeutic purposes has been reported, mainly from the United States and in association with chronic alcohol use, leading to the widely held belief that chronic alcoholics are predisposed to paracetamol-related toxicity at relatively low doses. Yet the effects of alcohol on paracetamol metabolism are complex. Studies performed in both experimental animals and humans indicate that chronic alcohol use leads to a short-term, two- to threefold increase in hepatic content of cytochrome P4502E1, the major isoform responsible for the generation of the toxic metabolite from paracetamol, although increased oxidative metabolism of paracetamol at recommended doses has not been demonstrated clinically. A reduced hepatic content of glutathione, required to detoxify the reactive metabolite, has been documented in chronic alcoholics, due probably to associated fasting and malnutrition, providing a metabolic basis for any possible predisposition of this group to hepatotoxicity at relatively low paracetamol doses. Simultaneous alcohol and paracetamol ingestion reduces oxidative metabolism of paracetamol in both rodents and humans, predominantly as a consequence of depletion in cytosol of free NADPH. The possibilities that chronic alcohol use may predispose to paracetamol-related hepatotoxicity and that alcohol taken with paracetamol may protect against it, based on these metabolic observations, are examined in this review.

