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Should a Lower Treatment Line Be Used When Treating Paracetamol Poisoning in Patients with Chronic Alcoholism?

A Case For

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Abstract

A lower threshold for treatment of paracetamol (acetaminophen) poisoning has been advocated in chronic heavy users of alcohol, based originally on animal studies indicating that chronic alcohol ingestion increased hepatotoxicity. This was attributed to increased production of the toxic metabolite, *N*-acetyl-p-benzoquinoneimine, by cytochrome P450 (CYP)2E1 induction. The clinical evidence for increased risk is limited to four retrospective studies with potential for referral and reporting bias and conflicting results. No study has specifically addressed the issue of the treatment threshold for acute paracetamol overdose in chronic alcohol users. However, animal studies in multiple species have consistently shown a lower dose of paracetamol is required to produce hepatotoxicity after chronic alcohol use. The knowledge of potential mechanisms has expanded to include effects of other alcohols, such as isopentanol, induction of CYP enzymes other than CYP2E1 and glutathione depletion. There are no convincing reasons or data to suggest these findings do not apply to humans. However, further human toxicokinetic and clinical research is required to quantify the extent of the interaction. Arguments about treating overdoses should not be confused with those about whether there is an alcohol-paracetamol interaction at therapeutic doses. Halving the threshold dose/concentration for treatment is a conservative educated guess that has been widely adopted. In overdose, the potential benefits of treatment at this lower threshold clearly outweigh the minimal risks of acetylcysteine.

The widespread practice of using a lower threshold for treatment of paracetamol (acetaminophen) poisoning in people deemed to be at high risk, such as chronic heavy users of alcohol, was introduced with no specific studies to support (or refute) this change to standard management.[1] It continues to be recommended in review articles and national guidelines despite the lack of conclusive clinical 'evidence'.[2,3] We argue that a lower threshold for treatment continues to be justified on the basis of animal studies indicating that chronic alcohol ingestion increases hepatotoxicity by a

number of mechanisms, and human studies indicating that alcohol alters the toxicokinetics of paracetamol.

Clinical evidence of an increased risk of hepatotoxicity after overdose is largely anecdotal, consisting of case reports or small case series from which no definite conclusion can be drawn.[4] The best data available consists of two studies, from the same unit but with opposite results, in patients with established paracetamol hepatotoxicity.[5,6] These studies could only examine whether hepatotoxicity was more severe, not whether it was more common. Bray et al.[5] found survival was lower in patients whose regular alcohol consumption was above recommended guidelines than in those who drank less than this (33 *vs* 66%, $p < 0.01$).[5] Conversely, Makin and Williams[6] in a later, larger study found no significant differences in survival in deliberate overdoses with moderate to heavy alcohol consumption compared with those with nil or light alcohol consumption patterns (57 to 60% *vs* 62 to 66%, respectively).[6] The authors did not attempt to explain, nor refer to, the different results in the previous study from their centre (which included Williams as an author). It is possible the first study influenced referral patterns or that the lower treatment threshold for those deemed at high risk due to alcohol consumption[1] affected the results of the second study.

More recently a study of consecutive cases admitted to a liver unit in Denmark showed a significantly increased risk of hepatic encephalopathy, acidosis, and higher international normalised ratio, creatinine, bilirubin and transaminase levels in those who were chronic alcohol abusers (>50 g/day for at least 3 months). These differences persisted after adjustment for other prognostic variables such as time to acetylcysteine treatment.[7] There was also a higher, but not statistically significant, risk of death (12.3 *vs* 8.6%) or liver transplant. The mortality in this series was much lower than the Kings unit studies with only 20 of 209 patients dying and thus this study did not have the power to detect differences in mortality.

A case control study from Taiwan found previous alcohol consumption was strongly associated with hepatotoxicity (adjusted odds ratio 8.14).[8] However, the high absolute rate of hepatotoxicity (19 of 71 patients) suggests that some of these patients must also have been referred, leaving substantial scope for bias in the assessment of alcohol exposure. The other observational study examining this association did not provide sufficient details in those who had taken acute overdoses to allow any conclusions to be drawn in this group.[9]

I*n conclusion*, the clinical data are contradictory and have study designs prone to referral and reporting bias. No study specifically addressing the issue of the treatment threshold for acute overdose in chronic alcohol abusers has been conducted. However, there is clear evidence that some individuals are at risk of significant hepatotoxicity below standard treatment lines. For example, in the largest series of paracetamol poisonings reported, 3 of 214 (1.4%) and 7 of 403 (1.7%) of individuals with concentrations below the US and UK treatment lines, developed significant hepatotoxicity despite receiving acetylcysteine within 8 hours.[10] No analysis was done of why these individuals were more susceptible.

The paracetamol nomogram indicates individuals are at risk of hepatic damage (and therefore warrant treatment) if they have a paracetamol concentration above a line drawn between 200 mg/L at 4 hours and 30 mg/L at 15 hours on a log-linear graph. This nomogram is a surrogate measurement to predict the amount of toxic metabolite formed in normal individuals. To apply this to patients with chronic alcoholism, makes a number of assumptions that are unlikely to be true. These include assumptions that the amount of toxic metabolite formed at a given concentration is not increased by alcohol, that detoxification of the metabolite is normal and that alcohol does not in any other way sensitise the liver to the effects of the toxic metabolite(s). Furthermore, validation of the nomogram in patients with chronic alcoholism (or any other 'high risk' groups) has not been performed.

1. The Conventional Explanation of Increased Risk of Hepatotoxicity in Patients with Chronic Alcoholism

With therapeutic paracetamol use, metabolism is largely (approximately 95%) via conjugation with sulphate and glucuronide derivatives, and subsequent renal excretion. The remainder is metabolised by the cytochrome P450 (CYP) system, where it undergoes oxidation to a toxic intermediate *N*-acetyl-p-benzoquinoneimine (NAPQI). With normal doses of paracetamol, NAPQI is then reduced with glutathione. At toxic paracetamol concentrations, both absolute and relative metabolism by the CYP system is increased.[11]

Once glutathione is depleted, the toxic metabolite binds to sulphydryl containing proteins in the liver cell, and also causes lipid peroxidation, which disrupts the cell membrane. Both of these events can lead to cell death. Therefore, toxicity is more likely if CYP enzymes are induced, such as with chronic alcohol ingestion, and anticonvulsant or barbiturate use. More recent animal studies raise the possibility that it is glutathione depletion and not the toxic metabolite per se that causes hepatic damage.[12]

In most patients who overdose on paracetamol, there is a threshold dose for hepatotoxicity (limited data suggest it is around 150 mg/kg). This, in normal individuals, generally corresponds with being above the treatment line in the paracetamol treatment nomogram.[2] The assumption that has been made is that in patients with a history of chronic alcohol ingestion who overdose on paracetamol, twice as much NAPQI may be formed per gram of paracetamol and the threshold dose for toxicity should be lowered approximately by half, (i.e. to 75 mg/kg).[2] Therefore, a correspondingly lower treatment line (halving the threshold concentration for trearment) should be used in this situation.

2. Animal Evidence

It is over 20 years since it was demonstrated that alcohol over the days preceding an overdose greatly reduced the threshold for hepatotoxicity and the median lethal dose (LD_{50}).[4] This has been confirmed repeatedly by numerous authors in mice, rats and baboons.[13-18]

These data have been criticised as not necessarily applicable to humans due to inter-species differences in paracetamol metabolism by CYP. The argument that has been put is that CYP2E1, which is inducible, is the predominant enzyme in rodents but CYP3A, which is not inducible, is predominant in humans.[19]

A close examination of recent studies suggest CYP3A is involved in paracetamol hepatotoxicity in rodents. Rodents lacking CYP2E1 (gene knockout) still experience paracetamol hepatotoxicity; and the toxicity is greatly increased by alcohol pretreatment.[20] Furthermore, specific inhibitors of CYP3A, reduce (but do not abolish) paracetamol hepatotoxicity in rodents. This occurs in rodents with and without CYP2E1 and after induction by pretreatment with alcohol.[14,15,18] Conversely, data in humans demonstrate that CYP2E1 is the main enzyme involved in NAPQI production in therapeutic concentrations.[21] Alcoholic beverages also contain other alcohols in addition to ethanol such as isopentanol. These have been shown to be synergistic with ethanol in increasing hepatotoxicity by induction of CYP3A.[16] To summarise, the important CYP enzymes in producing NAPQI in both humans and rodents include both CYP2E1 and CYP3A and (in any case) both enzymes are inducible by alcohols.

Increased hepatotoxicity by other mechanisms are unlikely to be subject to qualitative interspecies differences. In rats, chronic alcohol consumption has been shown to reduce hepatic glutathione; this is thought to be secondary to increased cell turnover, hepatic efflux of glutathione, and vitamin B deficiency impairing glutathione synthesis.[22]

3. Human Toxicokinetics

Numerous studies indicate altered pharmacokinetics in chronic alcohol abusers.[23-26] Many 'negative' studies showed differences that could be clinically significant (in an overdose context) but that were not statistically significant. These small

studies may have made type II errors in their conclusions.[27,28] Some studies have demonstrated increased clearance and decreased half life but did not explore the mechanism and will not be discussed further.[23,29]

One of the first studies observed a 'non-significant' 20 to 30% increase in NAPQI conjugated metabolites. However, the effect may have been in just a proportion of the 16 heavy alcohol users; 'Four heavy drinkers did excrete an abnormally high proportion of the dose as mercapturic acid (8 to 14%) and cysteine conjugates (5 to 12%)'.[27] A possible explanation for the marked changes in just some individuals is provided by preliminary evidence that common genetic polymorphisms in CYP2E1 may have different propensity to induction.[30] Another possibility is that there was some residual alcohol in the remainder. The presence of alcohol blocks the production of the toxic metabolite by inhibition of CYP and also facilitates the reduction of NAPQI to paracetamol.[31] Non-experimental studies (i.e. those in patients with chronic alcoholism) are difficult to interpret. The length of abstinence is critical yet in most published studies was not precisely determined. Unfortunately, in the largest study addressing this interaction, changes in paracetamol pharmacokinetics or metabolism were not reported.[32]

The proposed mechanism of the alcohol-paracetamol interaction is that alcohols induce production of NAPQI. As alcoholic beverages contain inducers of both CYP3A and 2E1, arguments based on the relative contribution in different species are unlikely to be convincing.[18] However, the major criticism of the relevance of the animal data is that CYP3A4 (and not CYP2E1) is the main source of NAPQI in humans so we will elaborate.

CYP2E1 is clearly induced by ethanol in humans.[33,34] The proposition that CYP2E1 is of little relevance to paracetamol metabolism in humans[35] does not stand up to scrutiny. In healthy volunteers given a nontoxic dose of paracetamol, mean NAPQI was increased by 22% (range 2 to 38%) 8 hours after the end of a 6-hour ethanol infusion.[25] The administration of disulfiram, a potent (but not specific) CYP2E1 inhibitor, reduced the production of NAPQI conjugates by about 70% after a therapeutic dose.[21] As CYP2E1 has a higher Michaelis-Menten constant (Km) and maximum rate of metabolism (V_{max}) than CYP3A,[36,37] the proportion of metabolism by CYP2E1 would increase in overdose. This has been shown in *ex vivo* human microsome studies where the correlation between NAPQI production and CYP2E1 activity was linear at high but not low concentrations with an R^2 of 0.13 and 0.94 at 50 and 250 μmol/L, respectively.[38] In the same study inhibitors of CYP2E1 and 2A6 reduced NAPQI production but inhibitors of CYP3A4 and 1A2 did not.[38]

CYP3A may also be important in NAPQI production (10 to 50% of total) based on *in vitro* human microsome studies.[36,37] However, induction of 3A4 with rifampicin (rifampin) had no effect on NAPQI metabolite formation after a single dose of 500mg of paracetamol.[21] Prior use of potent inducers of CYP3A did not have any effect on the proportion of paracetamol excreted as NAPQI metabolites.[24] Conversely, carbamazepine (another potent CYP3A4 inducer) did induce paracetamol metabolism (generally) and appear to lower the threshold for hepatotoxicity in a single case report.[39] Thus, *in vivo* evidence that CYP3A is a major source of NAPQI in humans is very limited. These studies may be confounded by a protective effect of parallel induction of conjugation pathways.

Fasting has also been implicated in paracetamol hepatotoxicity in humans with a possible mechanism of low levels of hepatic glutathione.[9] Preceding chronic and acute alcohol use has been shown to be associated with low plasma glutathione concentrations.[28,40] As both poor diet and fasting are also common in chronic alcohol abusers this provides a further justification for regarding this group as being at higher risk than the general population.

4. Conclusions

There is a sound argument and overwhelming animal data that paracetamol hepatotoxicity is increased during the period after a regular high intake of alcoholic beverages. This may be due to ethanol or isopentanol and mediated through induction of CYP2E1 or 3A or other mechanisms. There are no convincing reasons or data to suggest these findings do not apply to humans. Further human toxicokinetic and clinical research is required before a more precise measure of the clinical significance of the interaction can be made. In the meantime, treatment of 75 mg/kg ingestions of paracetamol or concentrations above the line that is 50% of the UK treatment line in patients with chronic alcohol abuse is a conservative educated guess that has been widely adopted.[2] Other situations where this lower line should be considered include chronic use of other CYP2E1 and CYP3A inducers (e.g. isoniazid, rifampicin, carbamazepine) and prolonged fasting for any reason.

Arguments about treating overdoses should not be confused with those about the veracity of the alcohol-paracetamol interaction at therapeutic doses. For this 'interaction', there is a lack of supporting animal data, clear evidence that most reports of hepatotoxicity involved therapeutic overdose,[19] and experimental data do not show measurable adverse hepatic effects at therapeutic doses of paracetamol.[32]

In overdose, however, the decision for the clinician is simple: do the potential benefits of treatment at a lower threshold outweigh the minimal risks[41] of that treatment? The answer is an emphatic 'Yes'.

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