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

A Case Against

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Abstract

The widespread practice of using a lower plasma paracetamol (acetaminophen) concentration threshold for the treatment of paracetamol poisoning in patients with chronic alcoholism has been introduced on the basis of anecdotal case reports.

In animals, acute alcohol loading inhibits toxic metabolic activation of paracetamol whilst chronic alcohol administration results in cytochrome P450 (CYP) 2E1 induction with increased toxic metabolic activation of paracetamol by CYP2E1 and increased hepatotoxicity. However, due to species differences in CYP expression, activity and induction, it is not possible extrapolate the results of these animal studies to clinical situations in humans. Isoenzymes are also responsible for the metabolic activation of paracetamol in humans and human studies to date have not convincingly demonstrated increased toxic metabolic activation of paracetamol in patients with chronic alcoholism. Acute alcohol ingestion at the time of a paracetamol overdose is probably protective and the timing and chronicity of alcohol intake is therefore crucial in the interpretation of the effects of alcohol on paracetamol overdose. One of the problems in the interpretation of the literature to date is that insufficient information is available on the timing of alcohol intake in relation to the ingestion of paracetamol.

Whilst it is possible that chronic exposure to excessive amounts of alcohol does predispose patients with paracetamol overdose to hepatotoxicity, a critical review of the literature reveals that the evidence to date *does not* support this. A prospective, controlled study is required. On the basis of the scientific evidence to date, use of the 100 line for patients with chronic alcoholism, in countries where the 200 line represents the standard treatment line, is unjustified.

Paracetamol (acetaminophen) is the commonest drug taken in overdose in the UK accounting for 40 to 50% of all hospital admissions with self-poisoning and an estimated 150 to 250 deaths per year.[1] Paracetamol poisoning is also a significant clinical problem in many other countries including Australia and the USA.[2-4]

The widespread practice of using a lower plasma paracetamol concentration threshold for the treatment of paracetamol poisoning in 'high risk groups', such as patients with chronic alcoholism,[5] has been introduced on the basis of anecdotal case reports and small case series.[6-24] There have been no studies specifically addressing the

issue of the treatment threshold for acute paracetamol overdose in patients with chronic alcoholism. This paper explores the evidence against the theory of increased risk and use of a different treatment line in patients with chronic alcoholism with paracetamol poisoning.

1. Why Not Treat Everyone with Acetylcysteine?

Acetylcysteine provides virtually complete protection against hepatotoxicity if given within 12 hours of a paracetamol overdose.[25] However, adverse reactions occur in 3 to 5% of patients treated with intravenous acetylcysteine.[26,27] Whilst the vast majority of these 'anaphylactoid' serum concentration-dependent reactions are mild (with effects such as vomiting, flushing and rashes),[26,27] there are a few case reports of serious adverse reactions including status epilepticus, bronchospasm, angio-oedema, hypotension and death.[27-30] The kinetics of acetylcysteine are altered and its clearance is reduced in patients with alcoholic liver disease thus resulting in higher plasma concentrations of the drug.[31] Acetylcysteine is also a potent vasodilator and this effect is seen to a greater extent in patients with alcoholic liver disease.[32,33] Adverse reactions to acetylcysteine are therefore predicted to be more likely to occur in patients with chronic alcoholism[31] and we would therefore particularly caution against indiscriminate use of acetylcysteine in this patient group.

2. Multiple Treatment Lines – a Lesson in Anxiety

Paracetamol poisoning has no specific clinical features in the early phase and so diagnosis is usually based on a history of ingestion and measurement of plasma paracetamol concentrations plotted on a nomogram related to the estimated time of ingestion. The nomograms or 'treatment lines' used to guide the management of paracetamol poisoning are all based on an analysis by Prescott et al.[25] of plasma paracetamol concentrations and outcome in a group of patients with paracetamol poisoning in Edinburgh, Scotland, between 1969 and 1973 before effective treatment was available. The data looked at 79 patients with paracetamol poisoning and would have certainly included patients with alcohol problems. 'Severe liver damage' was defined by Prescott et al.[25] as an ALT level of >1000 IU/L which has a substantial margin of safety. This nomogram (the '200 line' or Prescott nomogram) joined plots of 200 mg/L at 4 hours and 30 mg/L at 15 hours on a semilogarithmic graph.[25] Rumack et al.[34] using the same data extended the plot to 24 hours (the Rumack-Matthew nomogram).

In the US, the non–high-risk 'treatment line' has been modified further and a '150-line' introduced, joining 150 mg/L at 4 hours and 30 mg/L at 12 hours.[35] More recently some Accident and Emergency departments in the UK have adopted the 100 or 150 lines for all patients with paracetamol poisoning;[24,36,37] the UK poisons service provided a note of resistance to such change.[38] Some authors advocate treating every patient regardless of their paracetamol concentrations.[39]

In addition to the use of these multiple treatment lines discussed above, the use of a lower treatment line (the '100 line' or 50% line) joining 100 mg/L at 4 hours and 15 mg/L at 15 hours has been widely adopted for patients in a high-risk group for paracetamol poisoning in the UK.[5] The evidence for the 50% line is scanty.[40] In particular, in patients with chronic alcoholism there have been only four reported cases with apparent hepatotoxicity below the standard 200 Prescott treatment line, though clearly it is possible others remain unpublished.[18,20,24,41] One problem with case reports is that the alleged dose ingested is not accurate and therapeutic intent is often confused with therapeutic dose.

There are thus many different nomograms or treatment lines in use for the management of paracetamol poisoning (figure 1). The use of these many different nomograms, we believe, introduces an element of confusion to the management of paracetamol poisoning and this paper will explore the argument against the use of a lower treatment

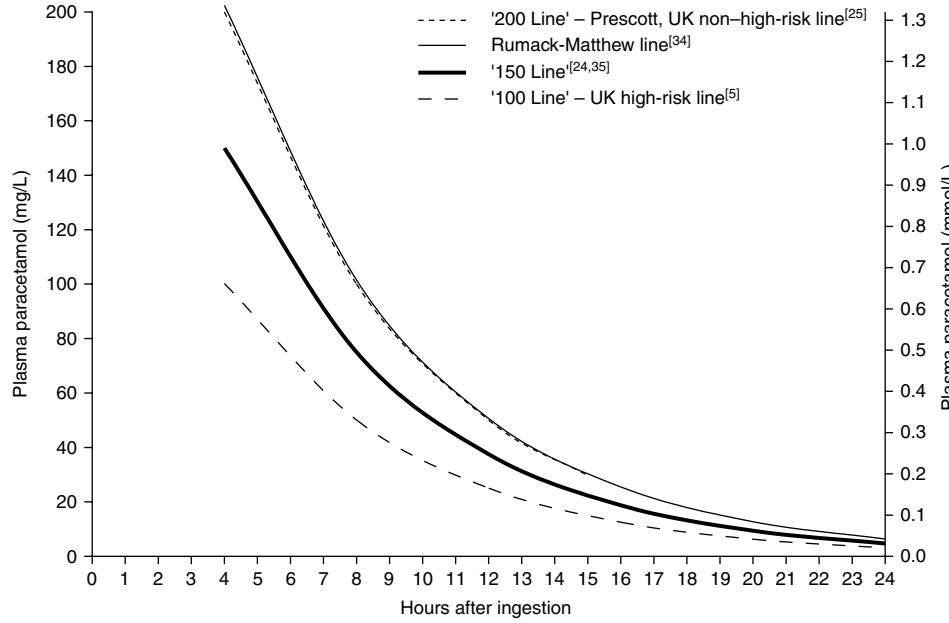

Fig. 1. The multiple treatment lines that have been advocated by different authors for the management of paracetamol (acetaminophen) poisoning.

line in patients with chronic alcoholism with paracetamol poisoning.

3. Evidence Against Chronic Alcohol Ingestion as an 'At Risk' Group for Paracetamol (Acetaminophen) Poisoning in Humans

3.1 Isoenzyme Specificity, Animal Evidence and the Applicability of This to Human Paracetamol Poisoning

The problem with interpretation of the data is that the paracetamol overdose-alcohol interaction is very complex. Paracetamol causes liver damage in overdose by being converted into the toxic intermediate *N*-acetyl-p-benzoquinoneimine (NAPQI) by hepatic cytochrome P450 (CYP) enzymes.[42] The susceptibility to liver damage has been shown to be increased in animals when enzyme inducing agents were given such as phenobarbital (phenobarbitone).[43] In animal studies, chronic alcohol exposure causes induction of hepatic CYP2E1 and increases paracetamol toxicity.[44-49]

In humans, chronic excessive alcohol exposure causes a very minor (2-fold and short lived) induction of CYP2E1[50,51] and there is no commensurate toxicologically significant increase in production of toxic metabolites like that seen in animals.[52-54] Indeed, one patient with chronic alcoholism was reported to take 15 to 25g paracetamol daily without liver damage and there was no increase in toxic metabolite formation.[53] In another study, the plasma paracetamol half-life was not different in patients with chronic alcoholism and was not related to CYP2E1 genotypes, though it would require a substantial change in CYP activity to alter half-life dramatically.[55] Isoenzymes other than CYP2E1 (particularly CYP3A4, but also others e.g. 1A2, 2A6, 2C11) are responsible for the oxidative metabolism of paracetamol in humans.[56-58] One semiquantitative immunohistological study in humans suggests activa-

tion of CYP2E1, 3A4 and 2A6 but the degree and overall time course is uncertain.[56] Thus, due to species differences in CYP expression, activity and induction, it is not justifiable to directly extrapolate the results of animal studies to clinical conditions and paracetamol overdose in humans.

3.2 Clinical Evidence

Clinical evidence in support of the view that patients with chronic alcoholism have liver damage after taking paracetamol poisoning is anecdotal[6-24] and the same degree of liver damage, with the same time course, is observed by clinicians on a daily basis in the UK in patients without chronic alcoholism.[59] The doses of paracetamol claimed to have been taken in these anecdotal reports range from 10g to 30g and these doses would be associated with toxicity in non 'high-risk' individuals.[5,60] The collection of these reports has been taken as evidence of increased hepatotoxicity in patients with chronic alcoholism.

If patients with chronic alcoholism were at risk of paracetamol poisoning, their most vulnerable time should be during alcohol withdrawal (because at this time any enzyme induction would be unopposed by the presence of acute alcohol (see section 4). However, studies rechallenging patients with chronic alcoholism who are withdrawing from alcohol with maximum supratherapeutic doses of paracetamol showed no effect on liver function tests.[61-63]

A number of studies have looked at the formation of glutathione-derived metabolites of paracetamol and urinary excretion of cysteine and mercapturic acid conjugates as a marker of whether or not chronic alcohol consumption results in increased formation of the toxic metabolites of paracetamol. Two studies have shown small increases formation of these metabolites.[54,64] However, other investigators have failed to demonstrate any increase in the toxic metabolic activation of paracetamol in heavy drinkers,[53,65] or abstaining drinkers.[65,66] In another study, the plasma paracetamol half-life was not abnormal in patients with chronic alcoholism and was not related to the different genotypes of CYP2E1.[55] Taken together the results of these studies have failed to show a toxicologically significant increase in the formation of the toxic metabolites of paracetamol in patients with chronic alcoholism.

There have been no prospective case-matched studies (matched on the basis of extrapolated log plasma paracetamol concentrations at 4 hours) in which outcome of paracetamol poisoning has been compared in patients with and without chronic alcoholism and the plasma concentration of alcohol measured. A number of retrospective, uncontrolled series have attempted to assess whether hepatotoxicity was more severe (but not whether it occurs at a lower paracetamol dose or whether it is more common). One study that is commonly quoted looked at selected patients with paracetamol hepatotoxicity who were referred to a liver unit.[67] Survival was lower in patients whose regular alcohol consumption was above recommended guidelines than in the 'non-alcoholics'.[67] However, patients in the alcoholic group had taken larger doses of paracetamol and data on alcohol intake was not available for an unspecified number of patients.[67] Conversely other reports from the same unit and elsewhere have shown no difference in severity of liver damage or outcome in paracetamol poisoning in patients with chronic alcoholism.[35,68-72]

If patients with chronic alcoholism were at increased risk of paracetamol poisoning many would develop significant hepatotoxicity at non-toxic plasma paracetamol concentrations below the treatment line. However, there have only been four case reports of cases falling in to this category.[18,20,24,41]

Alcoholic patients may appear to be more susceptible to the hepatotoxicity of paracetamol because of other confounding variables. In particular they present late and this is an independent predictor of outcome in poisoning with paracetamol, regardless of alcohol intake.[2,67-69,73] Also patients with chronic alcoholism are more likely to take overdoses[69] and it is our clinical experience that they often take larger doses of paracetamol. Thus, there is a systematic reporting bias that exaggerates the belief that patients with chronic alcoholism

experience more liver damage after a paracetamol overdose than patients without chronic alcoholism. It has been suggested that patients with chronic alcoholism may be at greater risk of paracetamol hepatotoxicity due to poor dietary intake.[21] Studies in fasting rats have shown that decreased liver glutathione reserves but this has not been demonstrated in humans.[74,75]

4. Acute Versus Chronic Alcohol Intake and Paracetamol Overdose

Animal studies have shown that acute alcohol loading inhibits the oxidation of paracetamol and protects against liver damage in animals, even those with previous chronic alcohol administration.[46,48,76-81] This effect is associated with inhibition of toxic metabolite formation,[81-84] at concentrations as low as 2 mmol/L.[84] Alcohol may produce this hepatoprotective effect by competitive inhibition of CYP2E1 or by cytosolic NADPH depletion.[76,83,85]

In human studies, acute alcohol intake has been shown to decrease toxic metabolic activation of paracetamol in liver microsomes.[76] As mentioned in section 3.2, urinary excretion of cysteine and mercapturic acid conjugates can be used as a marker of formation of the toxic metabolites of paracetamol. In studies in both healthy volunteers[52,86-88] and patients with chronic alcoholism,[65] acute alcohol loading has been shown to decrease urinary excretion of these conjugates.

Thus, there is good evidence from both animal and human studies that acute alcohol intake decreases toxic metabolic activation of paracetamol. Alcohol is a common co-ingestant in self-poisoning[4] and is commonly taken acutely with paracetamol overdoses;[22,89] it is our clinical experience that approximately 50% of patients with self-poisoning co-ingest alcohol. There are two case series in which the effect of acute alcohol in paracetamol overdose has been assessed, one report of 662 cases and another of 417 cases of paracetamol overdose. In both of these reports, hepatotoxicity (as judged by liver function tests) was less severe in the patients with acute alcohol co-ingestion.[70,90]

The timing and chronicity of alcohol intake is therefore crucial in the interpretation of the effects of alcohol on paracetamol overdose. We feel that insufficient attention has been paid to this confounding factor in the interpretation of the anecdotal case reports claiming to show increased hepatotoxicity in patients with chronic alcoholism with paracetamol overdose.[6-24]

5. Conclusions

The widespread practice of using a lower plasma paracetamol concentration threshold for the treatment of paracetamol poisoning in patients with chronic alcoholism has been introduced on the basis of anecdotal case reports and similar toxicity to that reported in these cases is seen in patients without chronic alcoholism. Furthermore, these anecdotal cases are difficult to interpret because insufficient information is available on the timing of alcohol intake in relation to the ingestion of paracetamol. There have been no prospective case-matched studies in which outcome of paracetamol poisoning has been compared in patients with and without chronic alcoholism.

In animals, acute alcohol loading inhibits toxic metabolic activation of paracetamol whilst chronic alcohol administration results in CYP2E1 induction with increased toxic metabolic activation of paracetamol by CYP2E1 and increased hepatotoxicity. However, it is not possible to extrapolate these animal studies to clinical situations in man. Isoenzymes other than CYP2E1 are primarily responsible for the metabolic activation of paracetamol in man and human studies to date have not demonstrated increased toxic metabolic activation of paracetamol in patients with chronic alcoholism. Acute alcohol ingestion at the time of a paracetamol overdose is probably protective and the timing and chronicity of alcohol intake is therefore crucial in the interpretation of the effects of alcohol on paracetamol overdose.

Whilst it is possible that chronic alcohol excess does predispose patients with paracetamol overdose to hepatotoxicity, a critical review of the literature reveals that the evidence to date *does not*

support this. On the basis of the scientific evidence to date use of the 100 line for chronic alcohol users, in countries where the 200 line represents the standard treatment line, is unjustified.

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