REVIEW ARTICLE

Drug Safety 2001; 24 (7): 503-512
0114-5916/01/0007-0503/$22.00/0

Management of Paracetamol Overdose
Current Controversies

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Contents

Abstract

Paracetamol (acetaminophen) is one of the most frequently used analgesics, and is the most commonly used substance in self-poisoning in the US and UK. Paracetamol toxicity is manifested primarily in the liver. Treatment with *N*-acetylcysteine (NAC), if started within 10 hours from ingestion, can prevent hepatic damage in most cases.

Pharmacokinetic data relating plasma paracetamol concentration to time after ingestion have been used to generate a 'probable hepatoxicity line' to predict which cases of paracetamol overdose will result in hepatotoxicity and should be treated with NAC. However, later studies use a 25% lower line as their 'possible hepatotoxicity line'. Although adopting the original line may save considerable resources, further studies are needed to determine whether such an approach is safe.

On the basis of the metabolism of paracetamol, several risk factors for paracetamol toxicity have been proposed. These risk factors include long term alcohol (ethanol) ingestion, fasting and treatment with drugs that induce the cytochrome P450 2E1 enzyme system. Although some studies have suggested that these risk factors may be associated with worse prognosis, the data are inconclusive. However, until further evidence is available, we suggest that the lower line should be used when risk factors are present.

In Canada and the UK, the intravenous regimen for NAC is used almost exclusively; in the US, an oral regimen is used. Both regimens have been shown to be effective. There is no large scale study with direct comparison between these 2 therapeutic protocols and controversy still exists as to which regimen is superior.

During the last few years there has been an increase in the number of reports of liver failure associated with prolonged paracetamol administration for therapeutic reasons. The true incidence of this phenomenon is not known. We suggest testing liver enzyme levels if a child has received more than 75 mg/kg/day of paracetamol for more than 24 hours during febrile illness, and to treat with NAC when transaminase levels are elevated.

Paracetamol overdose during pregnancy should be treated with either oral or intravenous NAC according to the regular protocols in order to prevent maternal, and potentially fetal, toxicity. Unless severe maternal toxicity develops, paracetamol overdose does not appear to increase the risk for adverse pregnancy outcome.

Paracetamol (acetaminophen) is frequently used by adults and children as an antipyretic or analgesic and it is the most frequently used over-the-counter medication in children in the US.[1] Not surprisingly, paracetamol is also the most commonly used substance in self-poisoning in the US and UK.[2-5]

Despite being used for many years and studied extensively, the plasma concentrations of paracetamol at which treatment with an antidote should be commenced, the best regimen of treatment, the management of long term exposure, the risk factors for paracetamol toxicity and the management of paracetamol overdose during pregnancy are still controversial. In this review we will focus on these controversies and propose measures to address them.

1. Metabolism

The 2 major metabolic pathways of paracetamol, glucuronidation and sulphation, take place in the liver. Glucuronide is provided by UDP-glucuronic acid, whereas sulphation is dependent on phosphoadenylylsulphate.[6] At therapeutic concentrations, the mixed-function oxidase system cytochrome P450 (CYP) 2E1 participates in metabolising a small fraction of the ingested drug. The metabolism by this system leads to the formation of the highly reactive intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI).[7] When paracetamol is consumed in therapeutic dosages, this metabolite is detoxified in hepatocytes by glutathione. In contrast, when the concentrations of NAPQI exceed the amount of intracellular glutathione, it covalently binds to hepatocyte molecules, leading to cell death.[8]

2. Toxicity

2.1 Epidemiology

Paracetamol is the most frequent subject of inquiries to poison centres in the US,[5] it is also the most commonly used substance in self-poisoning in the UK.[2-4]

In 1999, 141 fatalities attributable to paracetamol overdose (as a single drug or in combination with other drugs) were reported to poison control centres in the US.[5] In the US, paracetamol overdose account for 20% of cases of acute liver failure among patients referred to liver transplant centres[9] and for 40% of cases of liver failure in patients admitted to general hospitals.[10] It is the leading cause of acute liver failure in the UK as well as in other western countries.[11]

2.2 Clinical Manifestations

Paracetamol toxicity exhibits itself primarily in the liver, where it can cause fulminant hepatic failure. Less common manifestations of paracetamol overdose include nephrotoxicity, either by direct damage to renal tissue or as a result of hepatorenal

syndrome,[12-14] hypokalaemia[15] and metabolic acidosis.[16,15] Rare effects such as hypophosphataemia resulting from renal loss of phosphate,[17] haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency,[18] pancreatitis[19] and agranulocytosis[20] have also been described.

2.3 Treatment

In volunteer studies, activated charcoal reduced the absorption of paracetamol when given within an hour of ingestion.[21,22] In a study of patients with paracetamol overdose, those treated with charcoal were less likely to have serum concentrations predicting a high risk of hepatotoxicity.[23] Other methods of gastric decontamination, including syrup of ipecac and gastric lavage, are less effective and are not usually recommended.[24,25]

Hepatic failure may be prevented by timely administration of *N*-acetylcysteine (NAC).[15,26-28] Among 62 patients with paracetamol overdose treated with NAC intravenously within 10 hours of ingestion, only 1 had severe liver damage.[15] In comparison, the rate of liver damage among historical controls treated only with supportive care was 58%. Oral treatment with NAC was also shown to be effective in preventing liver injury in cases of paracetamol overdose.[26,27] A large multicentre study evaluated 11 195 cases of paracetamol overdose, of which 2023 had concentrations above the study treatment line (see section 3 for discussion of 'treatment lines').[27] The rate of hepatotoxicity among patients treated with NAC within 10 hours of ingestion was 6.1%, compared with 26.4% among patients treated 10 to 24 hours after ingestion.

NAC prevents paracetamol toxicity by serving as a glutathione precursor and by increasing sulphate conjugation.[29,30] It also has an enhancing effect on intrahepatic microcirculation.[31]

Oral methionine, when given within 10 hours of ingestion, can also reduce the incidence of hepatotoxicity.[32] Cysteamine has been used in the past,[33] but it is less effective and exhibits more adverse effects when compared with NAC,[15] and is therefore not commonly used.

3. Where to Draw the Line – Which Patients Should Be Treated?

3.1 Nomograms and Treatment Lines

In 1971, Prescott and colleagues described the pharmacokinetics of paracetamol in 30 adult patients with overdose admitted to a regional poison treatment centre in Scotland during the late 1960s.[14] 22 of these patients were females and in 10 cases there was co-ingestion of other drugs. Since at that time there was no known antidote for paracetamol toxicity, the patients received only supportive care. The investigators found that plasma paracetamol concentrations greater than 300 mg/L 4 hours after ingestion were always associated with severe hepatic damage, whereas there was no hepatic damage in patients with paracetamol concentrations lower than 120 mg/L at that time. They could not predict the prognosis if the concentrations fell between these values, and concluded that the plasma paracetamol half-life is the most reliable early guide to prognosis.

In 1975, Rumack and Matthew[34] suggested a nomogram to determine which cases of paracetamol overdose would result in hepatotoxicity (fig. 1). This nomogram was based on the same data published by Prescott et al.,[14] plus 'additional cases from the same centre', although the number of additional cases was not specified.

According to the Rumack and Matthew[34] nomogram, hepatotoxicity will probably occur if paracetamol concentrations fall above the 'probable hepatotoxicity line', a semilogarithmic plot joining 200 mg/L at 4 hours and 30 mg/L at 15 hours. The nomogram was extended to 24 hours postingestion by extrapolating the line without any additional data. The investigators suggested caution when using the nomogram, since it is generally difficult to obtain the precise time of ingestion. Whether or not the extrapolation to 24 hours is valid is not clear. For example, 31% of patients with initial concentrations above the treatment line may have 'nontoxic' concentrations in subsequent measurements, whereas 10% of patients with initial nontoxic concentrations may have concentra-

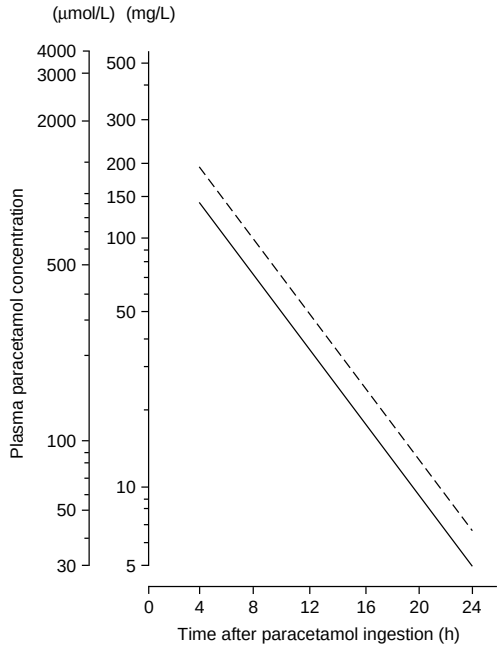

Fig. 1. Treatment lines for paracetamol (acetaminophen) hepatotoxicity. The upper (broken) line is the line suggested by Rumack and Matthew,[34] also known as the 'probable hepatotoxicity line'. The lower (solid) line is the 'possible hepatotoxicity line', arbitrarily drawn 25% lower in order to allow for possible laboratory errors and inaccuracy in history taking (reproduced from Smilkstein et al.,[27] with permission).

tions above the treatment line in subsequent measurements.[35]

Six studies[15,26-28,35,36] have assessed the efficacy of NAC in preventing liver damage in patients with paracetamol overdose. In 2 of these studies,[15,35] patients were treated if paracetamol concentrations were above the line suggested by Rumack and Matthew.[34] Patients with lower paracetamol serum concentrations were not treated with NAC and the outcome of these patients is not reported in 1 of these studies.[15] In the second study, although it was stated that treatment with NAC was started if concentrations were above the line suggested by Rumack and Matthew,[34] most of the patients with concentrations higher than the 'possible hepatotoxicity line' (see below) were also treated with NAC.[35]

The other 4 studies[26-28,36] used a lower treatment line (fig. 1). This line joins 150 mg/L at 4 hours and 30 mg/L at 12 hours and is extended to 24 hours. This line, as stated by Rumack et al.,[26] was arbitrarily drawn 25% lower than the original one, and is called the 'possible hepatotoxicity line'. It was introduced in order to accommodate potential errors in obtaining the exact time of ingestion as well as potential laboratory errors. In the study by Smilkstein and colleagues,[27] all deaths related to paracetamol toxicity occurred in patients with concentrations above the the (lower) study protocol line. The incidence of hepatotoxicity in 189 patients with paracetamol concentrations higher than the study protocol line and below the original line suggested by Rumack and Matthew[34] was not different from that in patients with paracetamol concentrations above the Rumack and Matthew[34] line.

A recent study used a computerised model for the pharmacokinetics of paracetamol after ingestion of paracetamol syrup.[37] The authors suggested that peak concentrations are achieved prior to 4 hours after ingestion and that treatment strategies can be based on concentrations taken after 2 hours. However this model has not been validated prospectively and at this point there are not enough data to support its use.

Among patients with initial concentrations above the 'possible hepatotoxicity line', 32 to 37% had concentrations that were lower than the 'probable hepatotoxicity line' (the original line suggested by Rumack and Matthew[34]).[26,27] A decision not to treat these patients can save considerable resources. Yet, since the largest studies showing the efficacy of NAC used the 'possible hepatotoxicity line' as their treatment line, before such an approach is adopted one has to ensure that it will not result in increased morbidity and mortality.

4. Risk Factors

We suggest that the 'possible hepatoxicity line' should be used for cases where the exact time of ingestion cannot be determined or when risk factors are present. These risk factors include long

term alcohol (ethanol) ingestion, fasting and treatment with drugs that induce the CYP2E1 enzyme system. (e.g. isoniazid).

4.1 Alcohol

Long term alcohol consumption induces the CYP2E1 enzyme system, and therefore more paracetamol is transformed into the toxic metabolite NAPQI. In contrast, short term alcohol ingestion may block the CYP system and reduce the amount of NAPQI formed. In an animal model[38] and in humans,[26] short term alcohol consumption reduced the severity of paracetamol-induced hepatotoxicity, whereas long term alcohol exposure increases the severity of hepatotoxicity in a rat model.[39] Whether the prognosis of long term alcohol users is worse after paracetamol overdose, as compared with other patients with similar paracetamol plasma concentrations, is controversial. Schiodt et al.[10] found that long term alcohol abuse was more common among patients with accidental paracetamol overdose when compared with patients who had taken paracetamol as part of a suicide attempt. These patients had more severe disease when compared with the suicidal patients despite taking smaller amounts of paracetamol. In a retrospective review of 79 cases of paracetamol overdose, alcohol consumption was associated with worse prognosis.[40] Zimmerman and Maddrey[41] describe a case series of 67 patients who developed hepatic injury after ingestion of paracetamol with therapeutic intent. All were regular users of alcohol. Doses of paracetamol were in the nontoxic range (<4 g/day) in 40% of the group.

In contrast with these findings, Makin and Williams[42] published the outcome of 553 patients with paracetamol overdose. There were 168 patients who consumed moderate to large amounts of alcohol. There were no differences in survival rates or in illness severity between the patients who had consumed alcohol and those who had not. This report is in agreement with the report by Whitcomb and Block,[43] who found that paracetamol toxicity is more likely to be associated with recent fasting than with alcohol use.

The differences among the results of the various studies may be related to differences in patient selection, ethnic distribution or differences in length of exposure to paracetamol in the accidental overdose groups.

In a recent review article, Prescott[44] suggested that 'although the possibility that acute alcoholics are at increased risk of paracetamol hepatotoxicity can by no means be excluded, the available evidence does not support claims for a major toxic interaction between alcohol and paracetamol in man'. This statement, as well as previous studies indicating alcohol as a risk factor in cases of paracetamol overdose, should be tested in further clinical studies.

Until additional data are available, we suggest adopting a conservative approach in the assessment and treatment of alcohol users, using the 'possible hepatotoxicity line' for cases of acute ingestion and in cases of long term exposure checking liver enzyme levels if more than 4 g/day of paracetamol has been consumed.

4.2 Fasting

During catabolic metabolism, such as in fasting, hepatic metabolic pathways are directed toward gluconeogenesis, thus reducing the amount of glucose precursors available for glucuronidation.[45] Hepatic sulphur stores may also be depleted after starvation.[46] As a result, a larger portion of paracetamol is metabolised through the mixed-function oxidase system, producing larger amounts of the toxic metabolite NAPQI. Under normal circumstances NAPQI is detoxified through reaction with glutathione; however, fasting also depletes intrahepatic glutathione,[47,48] thus increasing the risk of hepatic toxicity.

Limited information is available on the clinical significance of fasting as a risk factor for paracetamol toxicity. Fasting has been associated with increased risk for hepatotoxicity after prolonged treatment with supratherapeutic dosages of paracetamol.[43] Eating disorders may cause severe malnutrition, thus increasing the risk for hepatotoxicity. The reported cases of paracetamol over-

dose in patients with anorexia have described both favourable and fulminant courses.[49,50] Although clinical data are limited, they are in agreement with theoretical reasoning, leading us to suggest to consider patients with prolonged fasting or malnutrition as being at a higher risk for paracetamol hepatotoxicity.

4.3 Drug Interactions

Prolonged treatment with drugs that induce the CYP system may increase the risk for hepatotoxicity after paracetamol overdose. Although in some animal models treatment with phenobarbital potentates paracetamol hepatotoxicity,[51,52] it did not do so in other animal models.[53-55]

Case reports have described patients treated with carbamazepine[50,56] and phenytoin[57] who experienced liver injury after paracetamol overdose despite having paracetamol serum concentrations below the treatment line. Bray et al.[58] described higher mortality after paracetamol overdose in 18 patients who had been taking anticonvulsants when compared with patients who had not been treated with anticonvulsants.

Isoniazid also causes liver CYP2E1 induction. Cases of liver injury in patients treated with isoniazid who took normal doses of paracetamol have been reported.[59,60]

There are no controlled trials that have evaluated the true risk associated with the use of drugs capable of liver enzyme induction in patients with paracetamol overdose. We recommend erring on the side of caution in such cases, adopting the 'possible hepatotoxicity line' as a treatment line.

5. Intravenous or Oral N-Acetylcysteine?

In Canada and the UK, the intravenous regimen for NAC is used almost exclusively and delivers a total dose of 300 mg/kg over 20 hours. This is based on the high rate of nausea and vomiting among these patients and the use of charcoal, which may decrease the absorption of NAC.[61] Intravenous administration of NAC may be associated with anaphylactoid reactions in 5 to 14% of the patients.[35,62,63] Although in most cases the adverse reactions to intravenous NAC are mild, case reports of severe adverse reactions, including respiratory arrest and seizures, have also been described.[64,65] Most adverse effects related to NAC treatment were described while patients were receiving the loading dose of 100 mg/kg which originally was given over 15 minutes.[15] Giving the loading dose over 1 hour may result in fewer adverse reactions,[35] although it is not clear whether it prevents the rare but more severe adverse reactions.

In the US, the oral regimen is used, and delivers a total dose of 1330 mg/kg administered over 72 hours. Although there have been concerns about the efficacy of such treatment, mainly because of vomiting associated with paracetamol poisoning,[15] this regimen has been shown to be an effective treatment strategy.[27]

Other protocols have been suggested[28,36] but not widely accepted. A recent meta-analysis[35] combined the results of 4 different studies of intravenous NAC for paracetamol overdose and compared it with the results of oral NAC treatment obtained by Smilkstein and colleagues.[27] The author found similar rates of hepatotoxicity among patients treated with intravenous and oral NAC. The validity of this meta-analysis is questionable because of the different study protocols and patient populations among those studies.

The rate of liver injury is higher if treatment is delayed, and an early report suggested that NAC has no effect if treatment is started more than 15 hours postingestion.[15] However, later studies[27,35,36] indicated that even when given 16 to 24 hours after the ingestion, NAC can reduce the rate of liver injury. The differences in the results of late treatment are unlikely to be due to the route of NAC administration or the protocol used, but are probably attributable to differences in patient selection among different series. This is suggested by the fact that the rate of liver injury was decreased both with intravenous NAC at 20 or 48 hours[35,36] and with oral NAC.[27] Moreover, retrospective[66] and prospective[67] studies suggested that NAC

may improve the outcome even in cases of established liver failure attributable to paracetamol overdose.

Controversy still exists as to which regimen is superior. A large-scale study with direct comparison between these 2 therapeutic protocols will be the only way to resolve this controversy.

6. Long Term Exposure in Children

During the last few years there has been an increase in the number of reports of liver failure associated with prolonged paracetamol administration given for therapeutic reasons.[68-74] Heubi et al.[73] described 47 children with paracetamol treatment overdoses, of whom 53% died, with an additional 3 surviving after liver transplantation. Five of the children in this series received only 50 to 75 mg/kg/day of paracetamol. Accidental paracetamol overdose was the most common cause for fulminant hepatic failure among 18 Australian children referred to a liver transplant service.[74]

It has been suggested that fasting may facilitate paracetamol toxicity[43] and since many children do not eat well when they are sick, they might become more sensitive to paracetamol toxicity.

The true incidence of paracetamol intoxication attributable to repeated supratherapeutic doses is not known.[75] Since many parents are worried when their child has fever[76,77] and only an estimated 30% of caregivers are able to give their child over-the-counter medication correctly,[78] the true incidence of long term paracetamol overdose may be higher than reported. It is important to note that all the above mentioned studies are case reports or case series and there are no published population-based cohort or case-control studies. It is possible that in some of these cases the aetiology of the liver injury is the infectious disease itself and not the exposure to paracetamol.

It is also not clear what is the safe maximal daily dosage of paracetamol in young children. Until further data become available, one should not prescribe paracetamol at a dosage exceeding 75 mg/kg/day to young febrile children.

The Rumack and Matthew[34] nomogram is based on the pharmacokinetics of short term ingestion and does not help in predicting which patient will develop liver injury in cases of long term exposure. Smilkstein[79] suggests testing liver enzyme levels if a child received more than 75 mg/kg/day of paracetamol for more than 24 hours during febrile illness, and to treat with NAC when transaminase levels are elevated, even if paracetamol concentrations are below the treatment line of the Rumack and Matthew[34] nomogram. This approach has not been evaluated in clinical trials. Yet, based on the above-mentioned reports of toxicity with repeated supratherapeutic doses, we would recommend adopting this approach.

7. Paracetamol Overdose in Pregnancy

Paracetamol is one of the most common overdosed drugs in pregnancy.[80] The drug crosses the human placenta[81] and hence the fetus is theoretically at risk when maternal overdose occurs. Paracetamol can be transformed in the fetus to its toxic metabolite, since oxidative capacity of fetal microsomes is present by 14 weeks of gestation.[82]

Placental transfer of NAC in a sheep model was low.[83] Placental transfer of NAC in humans was demonstrated in 4 women treated with NAC for paracetamol overdose during labour. NAC blood concentrations in the fetuses were within the range resulting from therapeutic doses of NAC administered to adults.[84]

Fetal toxicity and neonatal death after large (35g) paracetamol overdose has been reported,[85] but others have reported favourable fetal outcome.[86,87]

A large case series investigated the outcome of pregnancy in 300 women who had paracetamol overdose.[88] 118 cases occurred during the first trimester, 103 in the second trimester and 79 in the third trimester. 49 of these mothers were treated with specific antidote (33 with NAC and 16 with methionine). The rate of congenital malformations was not higher than in the general population. Nine women were treated with NAC during the first trimester, and there were 2 elective terminations, 2

spontaneous abortions and 5 healthy babies in this group.

Paracetamol overdose during pregnancy should be treated with either oral or intravenous NAC according to the regular protocols in order to prevent maternal, and potentially fetal, toxicity. Unless severe maternal toxicity develops, paracetamol overdose dose not appear to increase the risk for birth defects or adverse pregnancy outcome.

8. Conclusions

Treatment with NAC given within 10 hours after paracetamol overdose has been shown to prevent severe liver damage in most cases. However, there is no consensus as to the serum paracetamol concentration at which treatment should be started. An integrated approach, in which all risk factors are considered, as well as the accuracy of the history regarding the dose taken and the time of ingestion, may allow one to choose the 'probable hepatotoxicity line' in cases where no risk factors are present. Such approach should be evaluated in clinical studies. The 'possible hepatoxicity line' should be used for cases when the exact time of ingestion cannot be determined or when risk factors are present. Both oral and intravenous NAC are effective in preventing liver injury, although controversy still exists as to which regimen is superior. Young children treated with supratherapeutic doses during febrile disease may develop liver injury. Clinicians should be aware of this phenomenon and should avoid exceeding the maximal daily dosage when prescribing paracetamol.

Acknowledgements

Dr Eran Kozer is a recipient of a fellowship grant from the Research Training Center, The Hospital for Sick Children, Toronto, Canada.

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