

Overview of Antidote Therapy for Acute Paracetamol Poisoning

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Abstract: The major target organ in paracetamol poisoning is the liver and the primary lesion is acute centrilobular hepatic necrosis. Without specific antidotal therapy, less than 10% would suffer severe liver damage but 1 to 2% will develop fulminant hepatic failure and this is often fatal. One to 2% of patients develop acute renal failure requiring dialysis. GSH precursors such as *N*-acetylcysteine have been found to be effective both in experimental animals and in humans *N*-acetylcysteine may reduce the severity of liver necrosis by directly conjugating with and/or reducing the reactive metabolite NAPQI. *N*-acetylcysteine has been shown to decrease the amount of paracetamol bound covalently to proteins, possibly by dissociation of the covalently bound paracetamol from proteins and or enhancing degradation of the arylated proteins. It appears to be safe to use intravenous *N*-acetylcysteine in these patients, and since they may benefit from this treatment, the use of *N*-acetylcysteine.

Keywords- Paracetamol, Antidotal activity, *N*-acetylcysteine, GSH precursors, Hepatic necrosis

1. INTRODUCTION AND HISTORICAL REVIEW [1, 2]

Paracetamol (acetaminophen, *N*-acetyl- *p*-aminophenol, APAP, NAPA, 4-hydroxy-acetanilide) was first introduced into clinical medicine towards the end of the last century but it attracted little attention and was soon forgotten (Smith, 1958). There was a resurgence of interest in paracetamol when it was found to be the major metabolite of acetanilide and phenacetin and it was commonly assumed to be responsible for the therapeutic effects of both of these drugs. Paracetamol has since been used increasingly as a substitute for other analgesics such as aspirin and phenacetin, and in the United Kingdom its sales have exceeded those of aspirin for more than a decade. As a consequence of the "back door" introduction of paracetamol, there were no formal preclinical animal toxicity studies such as would be required today, and its potential hepatotoxicity was not suspected until the first clinical reports of severe and fatal liver damage following overdose. Severe hepatic necrosis was first observed in cats treated with paracetamol (25 mg/kg and then 50 mg/kg) for 22 weeks (Eder, 1964), and it was also described in rats given doses in the range of the acute LD₅₀ and the 100-day LD₅₀. The ability of paracetamol to produce acute centrilobular hepatic necrosis in experimental animals has since been confirmed repeatedly and there are major species differences in susceptibility. Mice and hamsters are very sensitive while rats are resistant, and these differences have been related to species differences in the extent of the metabolic activation of paracetamol.

Apart from single case reports from South Africa and the USA, the initial clinical descriptions of liver damage following paracetamol overdose came from the United Kingdom, and substantial numbers of patients were involved. With its increasing use, poisoning with paracetamol has since emerged as a significant problem in many other countries. In the United Kingdom, paracetamol is taken in overdose most frequently by young adults who are not being prescribed psychotropic drugs by their general practitioners. In one study of 737 patients in Newcastle-upon-Tyne it was taken by 11% of patients aged more than 65 years, 25% of those aged 35-64 years and 41% of patients less than 35 years of age. Overall, paracetamol is involved in some 15 to 30% of deliberate self-poisonings in the United Kingdom, and there is considerable regional variation.

Much publicity has been given to paracetamol poisoning and there is no doubt that the problems have often been exaggerated. Only a small minority of patients is at risk of severe liver damage and the liver has remarkable powers of regeneration. Recovery from even severe damage is usually rapid and complete, and the overall mortality rate is low. In England and Wales in 1984, a total of 176 deaths were attributed to poisoning with paracetamol alone and a further 305 to paracetamol taken with other drugs, notably d-propoxyphene. However, a survey of such deaths showed that half of those officially recorded as being due to paracetamol and a quarter of those attributed to paracetamol taken with d-propoxyphene could not be substantiated. Furthermore, more than 90% of patients dying outside hospital had no evidence of hepatic necrosis at necropsy. In a series of 394 fatal poisonings in New Zealand from 1975 to 1982, only 2 deaths were related to paracetamol overdose, and over a period of 20 years only one death was attributed to paracetamol among children in the United Kingdom.

2. TOXICITY IN MAN [3]

The major target organ in paracetamol poisoning is the liver and the primary lesion is acute centrilobular hepatic necrosis. In adults the single acute threshold dose for severe liver damage (which has been arbitrarily defined as elevation of the plasma alanine or aspartate aminotransferase activity above 1000 U/l) is 150 to 250 mg/kg but there is marked individual variation in susceptibility. Children under the age of about 10 years appear to be much more resistant than adults, but in any event they rarely ingest enough paracetamol to cause liver damage. Only a small proportion of unselected adult patients who take an overdose of paracetamol are at risk of severe liver damage. Without specific antidotal therapy, less than 10% would suffer severe liver damage but 1 to 2% will develop fulminant hepatic failure and this is often fatal. One to 2% of patients develop acute renal failure requiring dialysis.

When the patient is first seen, the severity of intoxication with paracetamol cannot usually be determined on clinical grounds alone, as there are no specific symptoms or signs. Consciousness is not depressed unless other drugs have also been taken or there is a very high plasma paracetamol concentration of the order of 6.62 mmol/l (1000 mg/l) with a metabolic acidosis. Nausea and vomiting usually develop within a few hours of ingestion of a hepatotoxic dose of paracetamol and at this stage liver function tests may be normal or only slightly deranged. From about 18 to 72 h after ingestion there may be hepatic tenderness and abdominal pain due to swelling of the liver capsule. Unless hepatic failure develops, there is usually rapid improvement after the third day with eventual complete recovery.

The maximum abnormality of liver function tests is usually delayed until the third day. The characteristic changes include dramatic elevation of the plasma alanine and aspartate transaminase activity from normal values of less than 40 to as much as 10,000 or even 20,000 U/l with mild to moderate increases in the plasma bilirubin concentration and prothrombin time ratio. The sudden dramatic increase in the activity of plasma transaminases is presumably caused by their release from a large mass of necrotic hepatocytes, and the prolongation of the prothrombin time reflects acute impairment of synthesis of the vitamin K-dependent clotting factors. There is little or no increase in the plasma alkaline phosphatase activity unless liver damage is severe or the patient is a chronic alcoholic. Liver biopsies show extensive centrilobular hepatic necrosis with little inflammatory reaction. In patients who recover, liver function tests become normal within 1 to 3 weeks and follow-up histological examination reveals regeneration, repair and eventually a return to normal appearances. Other reported complications of paracetamol poisoning include disturbances of coagulation with disseminated intravascular coagulation, acute pancreatitis, impaired carbohydrate tolerance, myocarditis and hypophosphataemia. In the context of massive hepatic necrosis and fulminant hepatic failure (severe impairment of hepatic functions in the absence of pre-existing liver disease), it is doubtful whether these abnormalities can be specifically related to paracetamol toxicity *per se*. Serial measurements of the prothrombin time probably give the best guide to prognosis.

Oliguric renal failure may become apparent within 24 to 48 hrs after the overdose of paracetamol, and in this setting it is almost always associated with back pain, microscopic haematuria and proteinuria. This early impairment of renal function can occur in the absence of significant hepatic injury. Renal failure may be mild and transient or severe and prolonged requiring dialysis. It may also occur later, after the onset of hepatic encephalopathy.

Fulminant hepatic failure may develop in severely poisoned patients from the third to the sixth day. It is characterized by deepening jaundice, encephalopathy, increased intracranial pressure, grossly disordered haemostasis with disseminated intravascular coagulation and haemorrhage, hyperventilation, acidosis, hypoglycaemia and renal failure. The prognosis is very poor.

3. MECHANISMS OF TOXICITY AND ANTIDOTAL ACTIVITY [4]

Until Mitchell and his colleagues elucidated the mechanisms of paracetamol hepatotoxicity, there was no effective treatment for paracetamol poisoning. In a series of classical studies they showed that a minor route of paracetamol metabolism involved its conversion by cytochrome P-450-dependent mixed-function oxidase to a reactive arylating metabolite, now known to be *N*-acetyl- *p*-benzoquinone imine (NAPQI), which may cause acute hepatic necrosis with toxic doses of paracetamol. Initially, the reactive metabolite of paracetamol was believed to result from oxidation of the drug to *N*-hydroxy-paracetamol followed by dehydration to NAPQI. More recent studies indicate a direct two-electron oxidation of paracetamol to NAPQI by cytochrome P-450, or alternatively, a one-electron oxidation to *N*-acetyl- *p*-benzosemiquinone imine by peroxidase, prostaglandin H synthetase or cytochrome P-450. NAPQI causes a depletion of both the mitochondrial and cytosolic pools of reduced glutathione (GSH). Once GSH is depleted, cellular proteins are directly arylated and oxidized by the reactive metabolite, resulting in inhibition of enzyme activities. Two of the enzymes that have been shown to be inhibited in paracetamol-treated animals are glutathione peroxidase and thiol transferase. Inhibition of these enzymes renders the cell vulnerable to endogenous activated oxygen species with further oxidation of protein thiols. Decreased plasma membrane Ca^{2+} -ATPase activity and impaired mitochondrial sequestration of Ca^{2+} lead to influx of extracellular Ca^{2+} , with large-scale calcium cycling by mitochondria resulting in oxidative stress and cell death. Disturbed Ca^{2+} homeostasis is likely to activate Ca^{2+} -dependent catabolic processes such as phospholipid degradation, protein degradation, disruption of the cytoskeleton and DNA fragmentation. Although several lines of evidence suggest that Ca^{2+} influx is an early event in the development of toxicity, results from a recent paper indicate that this is not always the case. Furthermore, secondary microcirculatory changes may exacerbate the original injury and extend the necrosis through ischaemic infarction of the periapical region. Macrophages and neutrophils are attracted to the damaged areas and lead to additional protein thiol modification by releasing oxidants.

The maintenance of hepatic glutathione (GSH) concentrations by administration of *N*-acetylcysteine was first suggested as a treatment for paracetamol poisoning by Prescott & Matthew (1974). GSH itself, due to its inability to cross the plasma membrane, cannot be used as an antidote. However, GSH precursors such as *N*-acetylcysteine have been found to be effective both in experimental animals and in humans *N*-acetylcysteine may reduce the severity of liver necrosis by directly conjugating with and/or reducing the reactive metabolite NAPQI. In addition, *N*-acetylcysteine forms other nucleophiles, such as cysteine and GSH that are also capable of detoxifying NAPQI.

N-acetylcysteine is effective as an antidote when given some time after paracetamol exposure. It appears that *N*-acetylcysteine, either directly or through synthesis to cysteine and GSH, decreases the toxic effect of activated oxygen and reduces oxidized thiol groups on enzymes. In addition, *N*-acetylcysteine has been shown to decrease the amount of paracetamol bound covalently to proteins, possibly by dissociation of the covalently bound paracetamol from proteins and/or enhancing degradation of the arylated proteins.

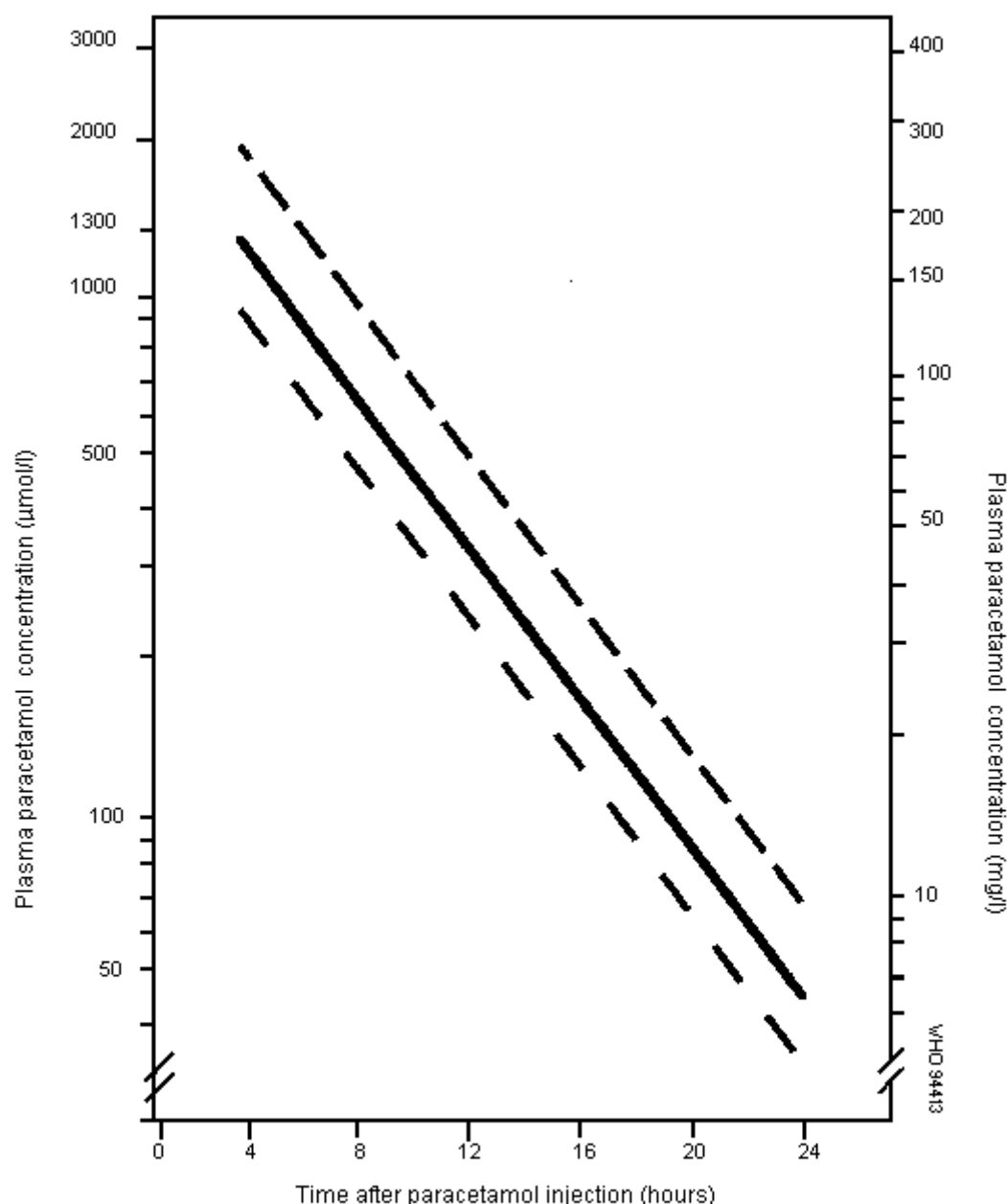


Fig. 1. Treatment nomogram for paracetamol poisoning. The solid line represents the "treatment line". The upper broken line defines the patients at more than 90% risk of developing liver damage. The lower broken line represents the treatment nomogram line used in many American studies (see text).

The ability of *N*-acetylcysteine to restore the function of enzymes after paracetamol exposure and its capacity to detoxify, either directly or indirectly, reactive metabolites through facilitation of GSH synthesis, are probably both responsible for its protective effect against paracetamol toxicity in humans.

Theoretically, *N*-acetylcysteine could be preferred to methionine for the treatment of paracetamol poisoning. Unlike *N*-acetylcysteine and glutathione, methionine is not a thiol and therefore cannot form an adduct directly with the reactive metabolite of paracetamol. Furthermore, enzymes such as cystathione synthetase and cystathionase, which are necessary for the essential conversion of methionine to cysteine *in vivo*, themselves have functional SH groups which might be expected to be vulnerable to inactivation by paracetamol. In such circumstances, it might also be expected that methionine would be less effective than *N*-acetylcysteine in the late treatment of severe paracetamol poisoning. Despite these theoretical arguments, clear differences in clinical efficacy have not been established.

4. FACTORS INFLUENCING THE TOXICITY OF PARACETAMOL [5, 6]

Paracetamol hepatotoxicity depends on the metabolic balance between the rate of formation of the toxic arylating metabolite and the rate of glutathione conjugation. In animals, experimental stimulation of metabolic activation of paracetamol and glutathione depletion increases toxicity, while, conversely, toxicity is decreased by inhibition of paracetamol oxidation and stimulation of glutathione synthesis. In addition, inhibition of direct detoxification such as sulfate conjugation and glucuronidation may increase

the proportion of the dose which is activated. One might assume that the same factors apply in humans but this has never been proved. Both the rate of formation and the total amount of NAPQI formed depend on the rate of absorption and environmental and genetic determinants of oxidative drug-metabolizing enzyme activity, as well as on the capacity of parallel pathways for elimination of paracetamol (glucuronide and sulfate conjugation).

4.1 Factors That May Increase Paracetamol Toxicity

A number of purified rabbit hepatic isoenzymes of cytochrome P-450, P-4502E1 and P-4501A2 exhibit appreciable activity in the bioactivation of paracetamol. Using monoclonal antibodies, isoenzymes P-4502E1 and P-4501A2 have been found to be approximately equally responsible for paracetamol bioactivation in human hepatic microsomes. There are large human interindividual differences in the oxidative metabolism of paracetamol. In animals cytochrome P-4502E1 is induced by pretreatment with ethanol, and diabetes, acetone or fasting. Song and others. (1990) have been able to quantify cytochrome P-4502E1 in the peripheral blood lymphocytes of some individuals and have shown the level to be considerably enhanced in diabetic patients who do not respond to insulin. The level of hepatic cytochrome P-4502E1 has been found to be elevated in alcoholics.

Chronic administration of ethanol to mice, rats or hamsters can enhance the hepatotoxic effects of paracetamol, and there have been a number of anecdotal case reports of paracetamol-induced hepatic injury among alcoholics resulting from apparent therapeutic misadventure. There is, however, some disagreement as to whether therapeutic doses of paracetamol produce liver injury in patients with chronic alcoholism. Of interest is the fact that acute intake of ethanol at the time of paracetamol overdose is protective in animals and humans. Taking into consideration animal and human studies, a reduction of the threshold for use of *N*-acetylcysteine after paracetamol overdose in patients with chronic alcoholism has been suggested by McClements and others. (1990). There are, however, no firm data in support of this recommendation.

Depletion of hepatic glutathione stores by feeding a low protein diet or by pretreatment with diethylmaleate will markedly augment paracetamol toxicity (Price & Jollow, 1983). Decreased concentrations of glutathione may also explain any increased susceptibility to paracetamol in alcoholics.

A possible protective effect of antioxidants and a possible increased toxicity of paracetamol in vitamin E-deficient mice (Fiarhurst and others., 1982) have no documented clinical significance.

4.2 Factors That May Reduce Paracetamol Toxicity

Many compounds, such as *N*-acetylcysteine and methionine, have been shown to reduce paracetamol toxicity either by reacting directly with NAPQI or by facilitating glutathione synthesis. Since the first step in paracetamol metabolism is its bioactivation to NAPQI, inhibition of this process is, theoretically, of clinical relevance. Several experimental studies have shown a more or less protective effect on paracetamol toxicity, as discussed below.

However, the clinical relevance of these experimental results has yet to be established.

Pretreatment with piperonyl butoxide or cobaltous chloride, which inhibit hepatic microsomal function, protects against paracetamol-induced hepatotoxicity in animals. Cimetidine protects against hepatotoxicity of paracetamol in animals by inhibiting its metabolic activation. However, the effect of cimetidine in the prevention of liver damage in humans is uncertain. Concomitant exposure to ethanol appears to reduce activation of paracetamol to reactive metabolites in rats. *In vitro* studies with liver slices, however, indicate that ethanol also protects after paracetamol exposure has ceased, which could be due to an increase in the NADH/NAD ratio. Ethanol given acutely appears to reduce the metabolic activation of paracetamol in humans.

Calcium channel blocking agents such as nifedipine and diltiazem have been shown to reduce marginally the development of paracetamol-induced liver necrosis in rats. Similar effects have been reported with inhibitors of phospholipase A₂, cyclooxygenase and thromboxane synthetase.

The hepatotoxic effect of paracetamol in female mice is reduced by feeding the animals a diet containing 0.75% butylated hydroxyanisole, possibly by increasing the concentration of reduced glutathione in the liver. Other antioxidants and inhibitors of lipid peroxidation such as diethyldithiocarbamate and anisoyldithiolthione, may also protect against paracetamol-induced liver damage.

5. DIAGNOSIS OF PARACETAMOL INTOXICATION [7, 8, 9]

Many methods have been described for the estimation of paracetamol in plasma. These include procedures based on ultraviolet (UV) spectrophotometry, colorimetry, gas liquid chromatography and high performance liquid chromatography with UV or electrochemical detection. More advanced techniques for the identification and estimation of paracetamol and its metabolites include fast atom bombardment mass spectrometry, thermospray liquid chromatography/mass spectrometry and proton nuclear magnetic resonance. At the same time, a number of operationally simple methods have been introduced for clinical use. These depend on electrochemical or colour reactions after enzymatic hydrolysis of paracetamol to *p*-aminophenol and immunoassay including techniques based on fluorescence polarisation.

The ideal method for the emergency estimation of plasma paracetamol in poisoned patients should be inexpensive, simple, rapid and accurate at least over the range of 0.1-3.31 mmol/l (15 to 500 mg/l). It should not be subject to interference by metabolites or other drugs not require the use of complex apparatus and are capable of being used by staff without special skills or training. No one method meets all of these criteria, and the subject has been reviewed critically. Whatever method is used, it is particularly important to check the units used by the laboratory for reporting plasma paracetamol concentrations. Most clinical toxicologists still use mass units such as mg/l, while some laboratories report results in SI units. This can cause confusion which may be dangerous (1 mmol/l is equivalent to 151 mg/l). Serious problems have also arisen through the inappropriate use of non-specific methods which can give gross overestimates of plasma paracetamol concentrations because they also measure metabolites.

6. ROLE OF *N*-ACETYL-CYSTEINE IN PARACETAMOL-INDUCED LIVER FAILURE [10, 13]

The original studies of *N*-acetylcysteine treatment for paracetamol poisoning gave no evidence of benefit when this treatment was delayed for more than 15 h. Later the prospective studies suggested that treatment with oral *N*-acetylcysteine may be effective up to 24 h after ingestion of the paracetamol. None of these studies were, however, designed for studying the effect of *N*-acetylcysteine on established paracetamol-induced liver failure. In patients with fulminant hepatic failure after paracetamol overdose (without previous *N*-acetylcysteine treatment), *N*-acetylcysteine significantly increased the survival rate (48%, 12/25 patients) as compared to controls (20%, 5/25). The intravenous dose regimen in this prospective randomised controlled study was the same as recommended for paracetamol overdose, and *N*-acetylcysteine was given 53 h (range 36-80 h) after the overdose.

The mechanism(s) for this protective effect of *N*-acetylcysteine on established liver failure is not clear but may be related to increased tissue oxygen consumption and decreased oxidant stress, thus reducing the oxidation of important protein thiol groups.

Earlier fears that the late administration of intravenous *N*-acetylcysteine might be hazardous have proved to be unfounded. The antidote is therefore indicated both in the acute phase of paracetamol intoxication, provided that serum paracetamol concentrations fall above the so-called treatment line and in established paracetamol liver failure.

7. SPECIFIC ANTIDOTAL THERAPY [11]

7.1 Intravenous *N*-acetylcysteine

Treatment with intravenous *N*-acetylcysteine is indicated in patients who present within 15 h of taking paracetamol in overdose and who have plasma paracetamol concentrations above the treatment defined in section 1.3. The regimen consists of intravenous administration of 150 mg/kg made up in 200 ml of 5% dextrose over 15 min, followed by 50 mg/kg in 500 ml of 5% dextrose over 4 h and 100 mg/kg in 1 litre of 5% dextrose over 16 h. The total dose is 300 mg/kg given over 20 h. This regimen effectively prevents liver damage, renal failure and death if started within 8 h of paracetamol ingestion but efficacy falls off rapidly after this time.

Later studies have suggested that treatment with oral or intravenous *N*-acetylcysteine may be effective up to 24 h after ingestion of the paracetamol. It therefore appears reasonable to propose treatment with *N*-acetylcysteine as an antidote up to 24 h after ingestion. In the most recent study by Smilkstein and others. (1991), the intravenous dose regimen of *N*-acetylcysteine was increased to 980 mg/kg over 48 h. Although this study was not scientifically comparable with that of Prescott and others. (1979), there are indications that less hepato-toxicity may occur using the 48-h treatment protocol among patients at "high risk" (Fig. 1) and admitted more than 10 h post-ingestion.

Because of the critical ingestion-treatment interval of 8 h, patients who are thought to be at risk and who present at or after this time should be treated with intravenous *N*-acetylcysteine immediately. A blood sample should be taken for the emergency estimation of the plasma paracetamol concentration, and if this subsequently turns out to be below the treatment line, *N*-acetylcysteine can easily be discontinued. The plasma paracetamol concentration should also be determined in patients who present earlier, but treatment with *N*-acetylcysteine must always be started by 8 h if the laboratory result is not available. Although it might appear simpler to give all patients *N*-acetylcysteine on admission, this is not appropriate because a majority of patients would be treated unnecessarily. Moreover, the use of *N*-acetylcysteine is sometimes accompanied by adverse effects.

"Anaphylactoid" reactions to intravenous *N*-acetylcysteine have been reported but the overall incidence is low. In some cases the doses were excessive, while in others the drug was not indicated in the first place and should never have been given. The reactions have usually consisted of urticaria, hypotension or bronchospasm and most have been mild and transient. They usually occur during the first 15 to 60 min of therapy at a time when plasma concentrations of *N*-acetylcysteine are highest, and they probably represent a concentration-dependent pharmacological effect.

7.2 Oral *N*-acetylcysteine [12, 14]

N-acetylcysteine is given orally in the USA and there have been several reports of the results of a National Multicentre Study. The dose was 140 mg/kg followed by 17 doses of 70 mg/kg every 5 h, and the total dose was 1330 mg/kg over 72 h (i.e. about 100 g in a 70 kg adult). This dose is much larger than that used in any other study.

In the most recent update, the cumulative results were described for 2540 patients, and efficacy was assessed according to the initial plasma paracetamol concentration and the delay between ingestion and treatment. Hepatotoxicity developed in 6.1% of patients at "probable" risk when treatment was started within 10 h and in 26.4% when therapy was commenced 10 to 24 h after ingestion. Hepatotoxicity also occurred in 41% of the patients at "high risk" treated between 14 and 16 h after ingestion. There were 11 deaths (0.43% of 2540 patients), but none could clearly be attributed to paracetamol, when *N*-acetylcysteine was started within 16 h. On the basis of the results obtained, the authors suggest that treatment might still be effective when delayed for as long as 24 h, and that this oral regimen might be more effective than intravenous *N*-acetylcysteine, particularly when treatment was delayed.

This suggestion was, however, based on comparisons between patients given oral *N*-acetylcysteine and patients treated with intravenous *N*-acetylcysteine and control patients seen up to 15 years previously in the United Kingdom. The patients were not comparable from a demographic point of view and more importantly, the American patients were less severely poisoned than the patients with whom they were compared. Smilkstein and others (1988). presented results for a total of 2540 patients, but only 2023 had plasma paracetamol concentrations above a treatment line starting at 1 mmol/l (150 mg/l) at 4 h and only 1462 (58%) had concentrations above the treatment line accepted in the United Kingdom (which starts at 1.32 mmol/l (200 mg/l) at 4 h). Thus almost half of the American patients were at very low risk and would not have been treated in the United Kingdom or included in the study. It is therefore not surprising that oral *N*-acetylcysteine appeared to be more effective when given orally than intravenously. However, when the patients at "high risk" admitted late (16-24 h) were studied separately, there was an indication in favour of prolonged *N*-acetylcysteine treatment in this group.

Even so, oral *N*-acetylcysteine may be employed in the majority of patients with paracetamol poisoning who are thought to be at significant risk of liver damage. Treatment in this manner has been recommended up to 24 h after ingestion of the paracetamol. No serious adverse effects have been reported, although nausea and vomiting are common. Intravenous therapy should be considered in patients who are vomiting and in those who have been given emetics or oral activated charcoal.

8. CONCLUSION

N-acetylcysteine is indicated in the management of moderate to severe paracetamol poisoning. If at all possible, plasma paracetamol concentrations should be used to predict the likelihood of paracetamol toxicity (see Fig. 1), and therefore the need for treatment. The treatment line (Fig. 1) differs, in that American studies have generally used a line 25% below the one proposed originally (joining 200 mg/l at 4 h and 50 mg/l at 12 h). The treatment line used should therefore be identified before comparing results between studies.

In patients presenting up to 8 h after overdose, it is reasonable to measure paracetamol levels to assess the need for treatment according to the treatment line most commonly employed (Fig. 1) before starting treatment. After this time, if the history suggests an intake greater than 7 g (or 100 mg/kg) paracetamol in adults, therapy should be started immediately, even before the plasma paracetamol concentration has been measured. If the concentration suggests that paracetamol toxicity is unlikely (i.e. it falls below a line joining 200 mg/l at 4 h and 30 mg/l at 15 h, Fig. 1), *N*-acetylcysteine can be discontinued. In the case of a potentially toxic paracetamol concentration, *N*-acetylcysteine should be continued and the full treatment regimen completed even if paracetamol concentrations subsequently fall below the treatment line.

Treatment with *N*-acetylcysteine may be instituted up to 24 h after a paracetamol overdose. The efficacy of the oral and intravenous regimens falls when treatment is started more than 8 h after the ingestion of paracetamol. The antidotal efficacy, when treatment is started later than 24 h, has not been established.

Intravenous *N*-acetylcysteine has been shown to increase significantly the survival rate in patients with paracetamol-induced fulminant liver failure through unknown mechanisms, and should therefore be given in such cases. There are currently no data on the use of *N*-acetylcysteine in patients admitted 24-50 h post-ingestion and who are at particular risk of developing liver failure. However, it appears to be safe to use intravenous *N*-acetylcysteine in these patients, and since they may benefit from this treatment, the use of *N*-acetylcysteine.

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