IPCS/CEC EVALUATION OF ANTIDOTES SERIES

VOLUME 3

ANTIDOTES FOR POISONING BY PARACETAMOL

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IPCS/CEC Evaluation of Antidotes Series

IPCS International Programme on Chemical Safety
CEC Commission of the European Communities

Volume 1 Naloxone, flumazenil and dantrolene as antidotes
Volume 2 Antidotes for poisoning by cyanide
Volume 3 Antidotes for poisoning by paracetamol

This important new series will provide definitive and authoritative guidance on the use of antidotes to treat poisoning. The International Programme on Chemical Safety (IPCS) and the Commission of the European Communities (CEC) (ILO/UNEP/WHO) have jointly undertaken a major programme to evaluate antidotes used clinically in the treatment of poisoning. The aim of this programme has been to identify and evaluate for the first time in a scientific and rigorous way the efficacy and use of a wide range of antidotes. This series will therefore summarise and assess, on an antidote by antidote basis, their clinical use, mode of action and efficacy. The aim has been to provide an authoritative consensus statement which will greatly assist in the selection and administration of an appropriate antidote. This scientific assessment is complemented by detailed clinical information on routes of administration, contraindications, precautions and so on. The series will therefore collate a wealth of useful information which will be of immense
practical use to clinical toxicologists and all those involved in the
treatment and management of poisoning.

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The need for an international evaluation of the clinical efficacy of antidotes and other substances used in the treatment of poisoning was first recognized at a joint meeting of the World Federation of Associations of Clinical Toxicology Centres and Poisons Control Centres, the International Programme on Chemical Safety (IPCS) and the Commission of the European Communities (CEC), held at WHO headquarters, Geneva, 6-9 October 1985. At the same time, the need to encourage the more widespread availability of those antidotes that are effective was recognised. As a result, a joint IPCS/CEC project was subsequently initiated to address these problems.

In the preparatory phase of the project, an antidote was defined for working purposes as a therapeutic substance used to counteract the toxic action(s) of a specified xenobiotic. A preliminary list of antidotes for review, as well as of other agents used to prevent the absorption of poisons, to enhance their elimination and to treat their effects on body functions, was established. For the purpose of the review process, antidotes and other substances were classified
according to the urgency with which treatment with the antidote was thought on current evidence to be required and the (currently judged) clinical efficacy of the antidote in practice. Those corresponding to the WHO concept of an essential drug were designated as such. Some have already been incorporated into the WHO list of essential drugs\(^a\). Antidotes and similar substances for veterinary use were also listed. A methodology on the principles for evaluation of antidotes and other agents used in the treatment of poisonings was developed and this has subsequently been used as a framework for drafting monographs on specific antidotes (see also the introduction to this series in volume I for more information on the programme).

Among the priorities established for evaluation in this project were antidotes for paracetamol poisoning. The reason for this was the many patients poisoned with this over-the-counter analgesic, many of whom suffered serious liver damage and subsequently died, and the fact that there were two antidotes available, namely \(N\)-acetylcysteine and methionine, with apparently similar efficacy but with different availability and therapy costs. Furthermore, there were significant disagreements between research centres concerning the route by which the antidotes should be administered.

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\(^a\) Now World Federation of Associations of Poisons Control Centres and Clinical Toxicology.


Another important factor for avoiding complications in paracetamol poisoning is early administration of the antidotes; there is marked loss of efficacy when they are administered more than 10 h after ingestion of paracetamol. It is of interest that, during the course of preparation of this volume, there was increasing published evidence of the beneficial effect of therapy with \(N\)-acetylcysteine even when administered at a very late stage of poisoning. This observation further underlined the need for a scientific evaluation of this area by leading experts in the field.

Of the two antidotes in this volume, \(N\)-acetylcysteine has been most widely studied clinically. There are far fewer published clinical data on methionine and therefore a special attempt has been made to evaluate both the preclinical and the few clinical data available for this antidote.

The review and evaluation of these antidotes was initiated at a joint meeting of the IPCS and the CEC, organized by the Northern Poisons Unit and held at the Medical School of the University of Newcastle-upon-Tyne, United Kingdom, 13-17 March 1989. In preparation for this meeting, monographs were drafted, using the proforma, on \(N\)-acetylcysteine by Dr B.H. Rumack and Dr D.G. Spoerke, and on methionine by Dr T.J. Meredith and Ms J. Tempowski. After presentation in plenary, the draft documents on \(N\)-acetylcysteine and methionine were reviewed by a Working Group consisting of Dr D.N. Bateman (Chairman), Dr T.J. Meredith (Rapporteur), Dr L. Prescott, Dr B.H. Rumack and Dr J.A. Vale. Following the meeting, preliminary revisions of the \(N\)-acetylcysteine monograph were undertaken by Dr T.J. Meredith in consultation with Dr D.N. Bateman, Dr L. Prescott and
Dr B.H. Rumack. Both monographs were again reviewed at a Working Group consisting of Dr D.N. Bateman, Dr J.-C. Berger, Dr J.A. Haines, Dr T.J. Meredith and Dr L. Prescott, held at the Royal Infirmary, Edinburgh, United Kingdom, 25-26 September 1989, after which Dr L. Prescott prepared an overview chapter of antidotal therapy for acute paracetamol poisoning.

Following this meeting, further drafting work was undertaken by authors and the overview chapter was reviewed by Dr D.N. Bateman and Dr J.A. Holme. Draft texts were further revised by the series editors (Dr T.J. Meredith, Dr D. Jacobsen, Dr J.A. Haines, and Dr J.-C. Berger). The efforts of all who helped in the preparation and finalization of this volume are gratefully acknowledged.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ALAT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ASAT</td>
<td>aspartate aminotransferase</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<tr>
<td>GSH</td>
<td>glutathione</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>NAD</td>
<td>nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NAPQI</td>
<td>N-acetyl-p-benzoquinone imine</td>
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<td>U</td>
<td>units (international)</td>
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IPCS/EC Evaluation of Antidotes Series

Volume 3

Antidotes for Poisoning by Paracetamol

First drafts of the chapters, subsequently reviewed and revised by the Working Group, were prepared by:

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1. OVERVIEW OF ANTIDOTAL THERAPY FOR ACUTE PARACETAMOL POISONING

1.1 Introduction and historical review

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 (Brodie & Axelrod, 1948a,b) 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 overdosage (Davidson & Eastham, 1966; Thomson & Prescott, 1966). 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 LD$_{50}$ and the 100-day LD$_{50}$ (Boyd & Bereczky, 1966; Boyd & Hogan, 1968). 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 (Tee et al., 1987).

Apart from single case reports from South Africa (Pimstone & Uys, 1968) and the USA (Boyer & Rouff, 1971), the initial clinical descriptions of liver damage following paracetamol overdosage came from the United Kingdom, and substantial numbers of patients were involved (MacLean et al., 1968; Proudfoot & Wright, 1970; Prescott et al., 1971; Farid et al., 1972; Clark et al., 1973b). 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 (Prescott & Highley, 1985). 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 (Wynne et al., 1987). Overall, paracetamol is involved in some 15 to 30% of deliberate self-poisonings in the United Kingdom, and there is considerable regional variation (Platt et al., 1988).

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 was 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 (Meredith et al., 1986). In a series of 394 fatal poisonings in New Zealand from 1975 to 1982, only 2 deaths were related to paracetamol overdosage (Cairns et al., 1983), and over a period of 20 years only one death was attributed to paracetamol among children in the United Kingdom (Fraser, 1980).

1.2 Toxicity in man

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 (Mitchell, 1977; Prescott, 1983). 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 (Rumack, 1984). 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 (Hamlyn et al., 1978; Prescott, 1983).

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 (Gray et al., 1987). 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 (Portmann et al., 1975; Lesna et al., 1976). Other reported complications of paracetamol poisoning include disturbances of coagulation with disseminated intravascular coagulation (Clark et al., 1973a), acute pancreatitis (Gilmore & Tourvas, 1977), impaired carbohydrate tolerance (Record et al., 1975), myocarditis (Wakeel et al., 1987) and hypophosphataemia (Jones et al., 1989). In the context of massive hepatic necrosis and fulminant hepatic failure, 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 (Harrison et al., 1990).

Oliguric renal failure may become apparent within 24 to 48 h 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 (Cobden et al., 1982; Prescott,
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 (Clark et al., 1973b; Canalese et al., 1981).

1.3 Assessment of the severity of intoxication

Because of the absence of early specific symptoms and signs, the only reliable method of assessment of the severity of poisoning (and hence the need for antidotal therapy) is emergency measurement of the plasma paracetamol concentration in relation to the time since ingestion. Patients with concentrations above a line joining plots on a semi-logarithmic graph of 1.32 mmol/l (200 mg/l) at 4 h and 0.20 mmol/l (30 mg/l) at 15 h after ingestion (called the "treatment line") have about a 60% chance of developing severe liver damage as defined by elevation of the plasma transaminase activity above 1000 U/l. In patients with concentrations above a parallel line joining 2 mmol/l (300 mg/l) at 4 h and 0.33 mmol/l (50 mg/l) at 15 h the probability rises to 90% (Fig. 1).

Plasma paracetamol concentrations determined less than 4 h after the overdose cannot be interpreted because of the possibility of continuing absorption. The "treatment line" defined above was derived from studies in patients admitted to the Regional Poisoning Treatment Centre in Edinburgh from 1969-1973 before effective treatment became available (Prescott et al., 1971, 1974, 1977). Its validity for patients in the United Kingdom was subsequently confirmed in studies carried out in London (Gazzard et al., 1977) and Newcastle-upon-Tyne (Hamlyn et al., 1978). The data from the original studies carried out in Edinburgh were later used by Rumack & Matthew (1975) to develop the "nomogram" which is used in the USA. Although generally accepted as a good guide to management and the need for specific treatment, the "treatment line" is not infallible. Patients with values above the line often do not develop liver damage while severe liver damage may rarely occur in patients with paracetamol concentrations as low as 0.83 mmol/l (125 mg/l) at 4 h. In the USA, patients are given N-acetylcysteine when concentrations are above a lower treatment line corresponding to 1 mmol/l (150 mg/l) at 4 h (Smilkstein et al., 1988, 1991) (Fig. 1).

1.4 Mechanisms of toxicity and antidotal activity

Until Mitchell and his colleagues elucidated the mechanisms of paracetamol hepatotoxicity, there was no effective treatment for paracetamol poisoning (Mitchell et al., 1973a,b; Potter et al., 1973; Jollow et al., 1973). 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 (Dahlin et al., 1984; Holme et al., 1984). Initially, the reactive metabolite of paracetamol was believed to result from
oxidation of the drug to N-hydroxy-paracetamol followed by dehydration to NAPQI (Hinson et al., 1980; Holme et al., 1982). 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 (Dahlin et al., 1984; Potter & Hinson, 1987). NAPQI causes a depletion of both the mitochondrial and cytosolic pools of reduced glutathione (GSH) (Tirmenstein & Nelson, 1989). Once GSH is depleted, cellular proteins are directly arylated and oxidized by the reactive metabolite (Albano et al., 1985; Holme & Jacobsen, 1986), 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 (Tirmenstein & Nelson, 1990). 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\(^{2+}\) (Tsokos-Kuhn et al., 1988; Tirmenstein & Nelson, 1989), with large-scale calcium cycling by mitochondria resulting in oxidative stress and cell death (Thomas & Reed, 1988). 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 (Ray et al., 1990; Orrenius et al., 1991). 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 (Herman et al., 1992). Furthermore, secondary microcirculatory changes may exacerbate the original injury and extend the necrosis through ischaemic infarction of the periacinar region. Macrophages and neutrophils are attracted to the damaged areas and lead to additional protein thiol modification by releasing oxidants (Mitchell, 1988).

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 (Boobis et al., 1989). N-acetylcysteine may reduce the severity of liver necrosis by directly conjugating with and/or reducing the reactive metabolite NAPQI (Tee et al., 1986). In addition, N-acetylcysteine forms other nucleophiles, such as cysteine and GSH, that are also capable of detoxifying NAPQI (Corcoran et al., 1985; Boobis et al., 1989).

N-acetylcysteine is effective as an antidote when given some time after paracetamol exposure (Devalia et al., 1982). 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 (Boobis et al., 1989). 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 (Bruno et al., 1988; Rundgren et al., 1988).
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.

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).
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.

1.5 Factors influencing the toxicity of paracetamol

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).

1.5.1 Factors that may increase paracetamol toxicity

Of a number of purified rabbit hepatic isoenzymes of cytochrome P-450, P-4502E1 and P-4501A2 exhibit appreciable activity in the bioactivation of paracetamol (Morgan et al., 1983). Using monoclonal antibodies, isoenzymes P-4502E1 and P-4501A2 have been found to be approximately equally responsible for paracetamol bioactivation in human hepatic microsomes (Raucy et al., 1989). There are large human interindividual differences in the oxidative metabolism of paracetamol (Raucy et al., 1989). In animals cytochrome P-4502E1 is induced by pretreatment with ethanol (Morgan et al., 1982), and diabetes, acetone or fasting (Jeffery et al., 1991). Song et al. (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 (Perrot et al., 1989; Raucy et al., 1989).

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 (Zimmerman, 1986; Seeff et al., 1986; Floren et al., 1987). There is, however, some disagreement as to whether therapeutic doses of paracetamol produce liver injury in patients with chronic alcoholism (Prescott, 1986; Mitchell, 1988). Of interest is the fact that acute intake of ethanol at the time of paracetamol overdose is protective in animals and humans (Zimmerman, 1986). 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 et al. (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 diethylnmaleate will markedly augment paracetamol toxicity (Price & Jollow, 1983). Decreased concentrations of glutathione may also explain any increased susceptibility to paracetamol in alcoholics (Lauterburg & Velez, 1988; Smilkstein et al., 1988).

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

1.5.2 Factors that may reduce paracetamol toxicity

Many compounds, such as N-acetylcysteine and methionine (see section 1.4), 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 (Speeg et al., 1985). However, the effect of cimetidine in the prevention of liver damage in humans is uncertain (Critchley et al., 1983). Concomitant exposure to ethanol appears to reduce activation of paracetamol to reactive metabolites in rats (Wong et al., 1980). 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 (Mourelle et al., 1990). Ethanol given acutely appears to reduce the metabolic activation of paracetamol in humans (Critchley et al., 1983).

Calcium channel blocking agents such as nifedipine (Landan et al., 1985) and diltiazem (Deakin et al., 1991) 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 (Horton & Wood, 1989).

The hepatotoxic effect of paracetamol in female mice is reduced by feeding the animals a diet containing 0.75% butylated hydroxyanisol (Miranda et al., 1983), possibly by increasing the concentration of reduced glutathione in the liver (Miranda et al., 1985). Other antioxidants and inhibitors of lipid peroxidation such as diethylidithiocarbamate and anisyldithiolthione, may also protect against paracetamol-induced liver damage (Mansuy et al., 1986; Younes et al., 1988).

1.6 Diagnosis of paracetamol intoxication

Many methods have been described for the estimation of paracetamol in plasma. These include procedures based on ultraviolet
(UV) spectrophotometry (Routh et al., 1968), colorimetry, (Brodie & Axelrod, 1948a; Glynn & Kendal, 1975), gas liquid chromatography (Prescott, 1971) and high performance liquid chromatography with UV (Howie et al., 1977) or electrochemical detection (Riggin et al., 1975). More advanced techniques for the identification and estimation of paracetamol and its metabolites include fast atom bombardment mass spectrometry (Lay et al., 1987), thermospray liquid chromatography/mass spectrometry (Betowski et al., 1987) and proton nuclear magnetic resonance (Bales et al., 1988). 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 (Price et al., 1983) and immunoassay including techniques based on fluorescence polarisation (Hepler et al., 1984; Coxon et al., 1988).

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 be 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 (Weiner, 1978; Stewart & Watson, 1987). 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 (Stewart et al., 1979).

1.7 Management of severe paracetamol poisoning

Management of the patient with severe paracetamol poisoning can be considered under the headings of supportive care and specific antidotal therapy. The possible role of liver transplantation is also briefly discussed.

1.7.1 Supportive care

Supportive care is based on removal of unabsorbed drug, symptomatic treatment and the management of serious complications such as hepatic and renal failure. Gastric aspiration with lavage, or induction of emesis with syrup of ipecac (Ipecacuanha), is usually carried out in patients who are thought to have taken at least 100 mg paracetamol/kg within the previous 1-2 h. Activated charcoal has also been recommended. Unfortunately, paracetamol is normally absorbed very rapidly, and it is uncommon to obtain a good return of tablet material. Provided that more than 4 h have elapsed since the time of ingestion, a blood sample should be taken for the emergency estimation of the plasma paracetamol concentration and for baseline measurements of liver function tests, prothrombin time ratio, and plasma urea, creatinine and electrolytes. It will be found that most patients are not severely poisoned and so do not require specific treatment or further supportive care. In patients with protracted nausea and vomiting, maintenance of intravenous fluids and electrolytes may be required and a careful watch should be kept on the fluid balance;
hypophosphataemia has been reported (Jones et al., 1989). Because of the possibility of impending liver failure with gross impairment of drug metabolism, other drugs (including anti-emetics) should only be given if really necessary. The biochemical tests of hepatic and renal function should be monitored in patients at risk at least every 12 to 24 h, depending on the severity of intoxication and clinical state.

Acute oliguric renal failure during the first 24 to 48 h may be accompanied by severe back and loin pain. Fluid and electrolyte balance must be monitored carefully and dialysis is often necessary. The plasma urea and creatinine concentrations may rise slowly but progressively over a period of many days before renal function recovers.

The onset of acute, possibly fatal, hepatic failure is indicated by a rapid rise of the prothrombin time to a ratio of more than 5.0, gross elevation of the plasma alanine aminotransferase (ALAT) and appearance of mild jaundice within 36 to 48 h. In such circumstances vitamin K₁ is usually given parenterally and, depending on the results of serial clotting screens, the intravenous administration of clotting factor concentrate or fresh frozen plasma may be necessary to keep the prothrombin time ratio within a safe range. Careful attention must be given to fluid, electrolyte and acid-base balance, and it is important to avoid fluid overload as this will aggravate cerebral oedema. Neomycin (1 g every 4 to 6 h) and lactulose administration by nasogastric tube should be considered, as in the case of acute liver failure from other causes. Hypoglycaemia may occur at any time and should be prevented by intravenous administration of fluids containing glucose. Established acute liver failure should be treated by conventional methods (Williams, 1988) but the prognosis is very poor, even in specialist centres using measures such as orthotopic liver transplantation (O'Grady et al., 1988, 1991; Harrison et al., 1991).

1.7.1.1 Role of \(N\)-acetylcysteine in paracetamol-induced liver failure

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 (Prescott et al., 1977, 1979). Later, the prospective studies by Smilkstein et al. (1988, 1991) 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) (Keays et al., 1991). 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 (Keays et al., 1991).

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 (section 1.7.2), provided that serum paracetamol concentrations fall above the so-called treatment line, and in established paracetamol liver failure.

The role of N-acetylcysteine in other types of acute liver failure has not been studied, nor has the effect of methionine on paracetamol-induced liver failure been studied.

1.7.1.2 Role of liver transplantation

It is very difficult to perform, at the right moment, an adequate triage, based on clinical and biochemical parameters, of patients at significant risk of dying from hepatic failure in paracetamol poisoning. The correct time for doing this is early enough to provide the potential recipient with a donor organ at a time where he/she is still in an operable condition. Many studies over the years have indicated that the prothrombin time is the most reliable parameter in evaluating the risk of dying from liver failure following paracetamol overdose (Harrison et al., 1990). Patients with a continuous increase in prothrombin time on day 4 after overdose and a peak prothrombin time of > 180 seconds appear to have a less than 8% chance of survival (Harrison et al., 1990).

Recently O'Grady et al. (1991) performed a prospective study of 66 cases of severe paracetamol poisoning transferred to their Liver Unit in London. Of these, 37 patients (of whom 30 survived) were considered to have a reasonable prognosis with intensive care. Of 14 out of 29 patients considered to have a very poor prognosis and registered for urgent liver transplantation, six received liver transplants, four of whom survived, while seven died and one survived without a transplant. Three out of 15 patients who had poor prognostic indicators but were not selected for transplantation survived.

These results indicate that liver transplantation may have a definite, but very limited role in the treatment of paracetamol poisoning. Among arguments against liver transplantation are the fact that some patients recover completely while waiting in vain for their donor liver, and that liver transplantation in this acute stage is not without complications. Even a successful transplantation implies life-long immunosuppressive therapy.

1.7.2 Specific antidotal therapy

1.7.2.1 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 line 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 (Smilkstein et al., 1988, 1991). 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 et al. (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 et al. (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 (Mant et al., 1984), while in others the drug was not indicated in the first place and should never have been given (Ho & Beilin, 1983; Dawson et al., 1989). 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 (Bateman et al., 1984; Prescott et al., 1989; Smilkstein et al., 1991).

1.7.2.2 Oral \( N \)-acetylcysteine

\( N \)-acetylcysteine is given orally in the USA and there have been several reports of the results of a National Multicentre Study (Rumack & Peterson, 1978; Rumack et al., 1981; Smilkstein et al., 1988). 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 (Smilkstein et al., 1988). 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 et al. (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 (Rumack & Peterson, 1978). Intravenous therapy should be considered in patients who are vomiting and in those who have been given emetics or oral activated charcoal.

1.7.2.3 Oral methionine

Treatment with oral methionine is indicated in patients who present within 15 h of taking paracetamol in overdose and who have plasma paracetamol concentrations above the treatment line defined in section 1.3. Oral methionine is very safe, and although the plasma paracetamol concentration should always be measured if possible, treatment should never be delayed while awaiting the laboratory result. The dose of methionine is 2.5 g (10 x 250 mg tablets) orally repeated 4 hourly to a total dose of 10 g over 12 h. There have been two reports of the use of oral methionine in the treatment of paracetamol poisoning, and overall the results are similar to those obtained with \(N\)-acetylcysteine.

One study involved a comparison of patients in London and Newcastle-upon-Tyne, United Kingdom, treated within 10 h with oral methionine (13 patients), intravenous cysteamine (14 patients) or supportive therapy only (13 patients). Both active agents gave significant protection against liver damage but there were no important differences between them (Hamlyn et al., 1981). In the other study, the results of treating 132 patients in London with oral methionine were compared with those of similarly poisoned control patients who had previously received supportive therapy in Edinburgh (Vale et al., 1981). As before, oral methionine was found to be very effective in preventing liver damage when given within 10 h. It was much less effective when treatment was delayed to 10-24 h. Oral methionine may therefore be used to treat patients with paracetamol poisoning who are at significant risk of liver damage. There are no
recommendations at present for the use of oral methionine more than 15 h after ingestion of an overdose of paracetamol. Side-effects to oral methionine have not been reported in patients with paracetamol poisoning. Intravenous N-acetylcysteine should be considered in those who are vomiting and in patients who have been given emetics or oral activated charcoal.

1.7.2.4 Intravenous methionine

In the study by Prescott et al. (1976), 3 out of 15 patients at risk of liver damage from paracetamol and treated within 10 h developed severe liver damage. All three were given intravenous methionine 9-10 h following the ingestion of paracetamol (see section 2.10 for further details).

Centres in other countries (such as in Oslo, Norway) also have experience with the use of intravenous methionine (10 g over 12 h) and none of about 50 patients at risk of liver damage suffered such damage or side effects provided that methionine was given within 10 h following paracetamol ingestion (E. Enger, personal communication). Methionine is no longer given intravenously, there being no pharmaceutical preparation available.

1.7.2.5 Oral versus intravenous therapy

There is controversy concerning the optimal route of administration of N-acetyl-cysteine and methionine. The obvious advantage of the oral route is that most of the absorbed dose passes directly to the sites of action in the liver. Oral therapy is also simpler and cheaper, and can be given by non-medical health care workers in developing countries. Since systemic adverse effects have not been reported following oral therapy with either N-acetylcysteine or methionine, it is not so important to identify patients requiring treatment by prior measurement of the plasma paracetamol concentration.

On the other hand, the efficacy of oral treatment may be compromised if absorption is delayed or incomplete as a result of nausea and vomiting. A substantial proportion of severely poisoned patients develop nausea and vomiting within a few hours and it is in these circumstances that effective reliable treatment is most needed. Oral therapy must be given by nasogastric tube in unconscious patients and this route is inappropriate in patients who have been given emetics or oral activated charcoal. Although one route of administration does not appear to have any striking advantage over the other, prospective comparative studies in patients admitted at the critical time of about 8 h after ingestion of paracetamol have not been carried out.

1.7.2.6 Comparative efficacy of N-acetylcysteine and methionine

On the limited data available, it is not possible to state whether N-acetylcysteine is superior to methionine. The comparisons which have been made so far are only valid up to a point because of the lack of proper controls. As discussed above, there are theoretical reasons why N-acetylcysteine may be more effective than methionine in preventing liver damage under certain circumstances; there are also few data on the use of methionine in children and no clinical data on its use in established paracetamol-induced liver
failure. There is also an indication of a beneficial effect of N-acetylcysteine in patients admitted 10-24 h after the overdose (Smilkstein et al., 1988). Lack of such an indication in methionine-treated patients may, however, be related to the fact that this compound has not been studied in as much detail as N-acetylcysteine. This question can only be answered by careful prospective comparative studies in large numbers of properly matched patients with appropriate controls.

1.7.3 Summary of treatment recommendations

Paracetamol poisoning is not an immediate threat to life, and little can be achieved in the way of first aid outside the hospital. The most that can be done is to induce vomiting by pharyngeal stimulation, and to arrange transport to hospital. Definitive hospital treatment is based on early administration of sulfhydryl donors such as N-acetylcysteine and methionine, and supportive care. The latter includes removal of unabsorbed drug and management of complications such as hepatic and renal failure. N-acetylcysteine also has a documented therapeutic effect in established paracetamol-induced liver failure.

Intravenous and oral N-acetylcysteine and oral methionine are normally indicated in patients who are thought to have taken more than 100 mg paracetamol/kg in the preceding 24 h, or who have plasma paracetamol concentrations above a treatment line joining plots on a semilogarithmic graph of 200 mg/l at 4 h after ingestion and 30 mg/l at 15 h. Every effort must be made to start therapy within 8 h as their efficacy declines progressively after this time. Treatment is required in only a small proportion of unselected patients and measurement of the plasma paracetamol concentration should be determined first if time and circumstances allow.

The recommended dosage regimens are given in detail in sections 2.13.2 and 3.13.2.

1.8 Areas for future research

1.8.1 Choice of antidote

Multicentre studies are the only practical way to compare the relative efficacy and safety of N-acetylcysteine and methionine. Appropriate controls will be necessary with stratification according to factors such as age, sex, severity of poisoning, use of ethanol and other drugs, and the ingestion-to-treatment interval. It is possible that for optimal results, different drugs and different routes may be indicated for different clinical circumstances. Since both antidotes are effective and safe, however, a very large number of patients will be necessary to document what is likely to be a marginal effect. Such a study may be difficult to justify when health resources globally are limited.

1.8.2 Optimum dose and route of administration

Work is also required to define optimal dosage regimens and routes of administration. The regimens in current use were chosen arbitrarily and there seems little doubt that some could be changed with benefit. For example, the total dose and duration of treatment with oral methionine (10 g over 12 h) is much less that the total dose and duration of treatment with oral N-acetylcysteine (100 g over...
72 h) yet their efficacy is comparable. The dose of oral N-acetylcysteine may therefore be unnecessarily large.

The initial rapid intravenous infusion of N-acetylcysteine produces very high plasma concentrations in the range of 300 to 900 mg/l, which may be more than is necessary. Most adverse reactions to intravenous N-acetylcysteine occur early when concentrations are highest, and they could probably be avoided without loss of efficacy by modifying the infusion rates according to predictions based on the kinetics of N-acetylcysteine in patients with severe paracetamol poisoning (Prescott et al., 1989). Information is also required concerning the bioavailability and plasma concentrations of oral N-acetylcysteine and methionine in patients with paracetamol poisoning. The proper characterization of the action of these agents depends on the full definition of the dose- or concentration-response curves, but this would be a formidable task. However, further useful information could be obtained about the concentration-time-response relationships of the antidotes in relation to the severity of poisoning and the time since ingestion.

1.8.3 Role of N-acetylcysteine in liver failure

The effect of N-acetylcysteine on paracetamol-induced fulminant liver failure should be studied further, if possible in a double-blinded manner. The mechanisms behind this effect also warrant further study. A similar study to investigate a possible therapeutic effect of methionine could be considered, perhaps in comparison with N-acetylcysteine, in a double-blind design.

The possible role of N-acetylcysteine in other types of liver failure might also be justified if the effect on paracetamol-induced liver failure was reproduced in a double-blind study.

1.8.4 Role of N-acetylcysteine 24-50 h after the overdose

In the studies of Smilkstein et al. (1988, 1991), an antidotal effect of N-acetylcysteine was demonstrated up to 24 h after the ingestion of paracetamol. As seen from Fig. 1 the treatment line is only useful up to 24 h post-ingestion. In the study by Keays et al. (1991), the average time from ingestion to inclusion in the study was 53 (36-80) h in the N-acetylcysteine-treated group. Thus we are left with a time period from 24 to 50 h after ingestion where there are no scientific data as to whether N-acetylcysteine is beneficial or not. Until such data become available, it may be reasonable to give N-acetylcysteine to patients admitted 24-50 h after ingestion of paracetamol if they are considered to be at risk of developing liver failure.

1.8.5 New approaches to the treatment of paracetamol poisoning

There seems little doubt that a large number of sulfhydryl compounds may be effective in preventing liver damage after paracetamol overdosage. Given that antidotes such as N-acetylcysteine and methionine act indirectly via glutathione, it is difficult to envisage other precursors with the same mechanisms of protection that would be safer and more effective. At present, the greatest need is for a new approach to the prevention of severe hepatotoxicity in patients who present too late for effective treatment with existing antidotes. Such treatment would have to be
based on mechanisms other than inhibition of the metabolic activation of paracetamol or stimulation of glutathione synthesis.

Future research may also find a role for cytochrome P-450 inhibitors, such as ethanol, in reducing the severity of paracetamol-induced liver toxicity. There is experimental evidence of efficacy but clinical data are scarce. The effects of different agents on the metabolism and toxicity of paracetamol could be better predicted if the specific isoenzymes of cytochrome P-450 that are involved in the metabolic activation of paracetamol in man were characterized.

1.8.6 Treatment failure

Patients occasionally suffer liver damage despite apparently adequate treatment started well within the critical time of 8 to 10 h. In such cases it is easy to assume that the patient's history is inaccurate, or that failure of oral therapy is due to delayed or incomplete absorption. However, similar problems have been encountered following intravenous administration of antidote, and further studies are needed to establish the reasons for treatment failure.

1.8.7 The treatment line

The line on a semilogarithmic graph joining plots of 200 mg/l at 4 h after ingestion of paracetamol and 30 mg/l at 15 h is used to determine the need for antidotal therapy in most countries (Fig. 1). The decision to treat only those patients with paracetamol concentrations above this line represents a compromise between the unnecessary treatment of the majority of poisoned patients on the one hand and failure to treat a very small minority who will suffer liver damage at concentrations below the line on the other. With N-acetylcysteine it is important to ensure that treatment really is necessary, although the position of the established treatment line is probably about right. It is also a useful guide for treatment with methionine, but, as this is so cheap and safe, unnecessary treatment is of less consequence and the line could probably be lowered to correspond to 150 mg/l at 4 h.

1.8.8 The role of ethanol

It is important to know whether acute or chronic heavy consumption of ethanol has significant effects on susceptibility to the hepatotoxicity of paracetamol following overdosage. To this end, the outcome of poisoning should be compared in a sufficiently large number of chronic alcoholics and appropriate control patients matched for severity of poisoning and delay in treatment. A similar approach might be used to determine whether early acute administration of ethanol influences the outcome of paracetamol poisoning.

1.8.9 Paracetamol poisoning in pregnancy

Limited information is available concerning the effects of an overdose of paracetamol at different times during the course of pregnancy but serious problems for mother and child seem to be uncommon (MacElhatton et al., 1990). National registers of patients who take an overdose of paracetamol during pregnancy should be kept with proper follow-up, so that the outcome and effects of different treatments can be compared.
1.9 References


Boyd EM & Hogan SE (1968) The chronic oral toxicity of paracetamol at the range of the \(LD_{50}\) (100 days) in albino rats. Can J Physiol Pharmacol, 46: 239-245.


Potter WZ, Davis DC, Mitchell JR, Jollow DJ, Gillette JR, & Brodie BB (1973) Acetaminophen-induced hepatic necrosis. III. Cytochrome P-450-


Ray SD, Sorge CL, Raucy JL, & Corcoran GB (1990) Early loss of large genomic DNA in vivo with accumulation of calcium in the nucleus during acetaminophen-induced liver injury. Toxicol Appl Pharmacol,


2. METHIONINE

2.1 Introduction

The amino acid methionine is indicated for the treatment of acute paracetamol (acetaminophen) poisoning provided that patients present sufficiently early to benefit from therapy (see below, and Meredith et al., 1978; Vale et al., 1981; Meredith, 1987).

Methionine acts as a glutathione precursor (McLean & Day, 1975; Vina et al., 1978; Vina et al., 1980) and protects against paracetamol-induced hepatic and renal toxicity provided that it is administered within 8-10 h of ingestion of the overdose (Meredith et al., 1978; Vale et al., 1981; Meredith, 1987). Some protection is afforded even when methionine is administered later than this, and the point at which methionine treatment becomes "ineffective" has not been determined with certainty (Vale et al., 1981; Meredith, 1987). However, no significant benefits have been documented in cases where more than 10 h has elapsed after a paracetamol overdose (Prescott et al., 1979; Meredith et al., 1986). The need for specific protective therapy with methionine in cases of paracetamol overdose may be judged by measurement of plasma paracetamol concentrations in relation to the time elapsed since ingestion (Vale et al., 1981). However, methionine is usually administered orally and it is therefore unsuitable for use in patients who are vomiting and for those in coma.

2.2 Name and chemical formula

It should be noted that L-methionine is the physiologically active enantiomorph but the pharmaceutical preparation is usually the racemic mixture.

International non-proprietary name: methionine

Synonyms: DL-methionine, Racemethionine, DL-2-amino-4-(methylthio)butyric acid, alpha-amino-gamma-methylmercaptobutyric acid, 2-amino-4-methylthiobutanoic acid, gamma-methylthio-alpha-aminobutyric acid

IUPAC-name: 2-amino-4-(methylthio)butyric acid

CAS Number: L-methionine 63-68-3
DL-methionine 59-51-8

EINECS Number: L-methionine 2005629
DL-methionine 2004321

NIOSH Number: L-methionine PD0457000
DL-methionine PD0456000

Empirical formula: C₅H₁₁NO₂S

Chemical structure: \( \text{CH₃-S-CH₂-CH₂-CH-COOH} \)
Relative molecular mass: 149.2

Conversion table:
- 1 mmol = 149.2 mg
- 1 g = 6.7 mmol
- 1 µmol = 149.2 µg
- 1 mg = 6.7 µmol

Manufacturers:

The major manufacturers of DL-methionine worldwide are Rhone-Poulenc and Degussa (Goldfarb et al., 1981). Pharmaceutical grade methionine is produced by the following companies:

Degussa Ltd, Earl Road, Stanley Green, Handforth, Wilmslow, Cheshire SK9 3RL, United Kingdom (tel: +44 (0)61-486-6211; fax: +44 (0)61-485-6445)

Degussa AG, Anwendungstechnik Av, Rodenbacher Chausee 4, Postfach 1345, D-6450 Hanau, Germany (tel: (01049) 59-35-54; telex: 415200-0 dw d)

Rhone Poulenc, 217 High St, Uxbridge, Middlesex UB8 1LQ, United Kingdom (tel: +44 (0)895-74080; fax: +44 (0)895-39323)

Walton Pharmaceuticals Ltd, Bowes House, 17 Bowes Road, Walton-on-Thames, Surrey KT12 3HS, United Kingdom (tel: +44 (0)932-241032; fax: +44 (0)932-255461)

2.3 Physico-chemical properties

2.3.1 Melting point (decomposition)

266-267 °C (Degussa AG, 1985)

2.3.2 Solubility in vehicle of administration

Methionine is usually given orally in a solid dose formulation, although in animal studies and in trials in humans, it has been administered parenterally (Prescott et al., 1976; Solomon et al., 1977).

The solubility in water at 20 °C is 29.1 g/l; it is also soluble in dilute acids and dilute solutions of alkaline hydroxides. Methionine is very slightly soluble in ethanol and practically insoluble in ether (Degussa AG, 1985; Budavari, 1989; Martindale, 1989).

2.3.3 Optical properties

DL-methionine has no significant optical properties.

2.3.4 pH

The pH of a 1% aqueous solution is 5.6-6.1 (Martindale, 1989).

2.3.5 $pK_a$

DL-methionine has two ionizable groups and it therefore possesses
two pK\textsubscript{a} values. The pK\textsubscript{a} of the carboxyl group is 2.28, and that of the amino group, 9.21 (Weast & Astle, 1978).

2.3.6 Stability in light

Methionine should be stored in the dark.

2.3.7 Thermal stability/flammability

DL-methionine decomposes at about 267 °C (Degussa AG, 1985), emitting fumes of sulfur and nitrogen oxides (Sax, 1989).

2.3.8 Loss of weight on drying

The loss of weight is < 0.3% on drying at 105 °C for 3 h (Degussa AG, 1985).

2.3.9 Excipients and pharmaceutical aids

An intravenous preparation may be made by dissolving methionine in 5% dextrose immediately before use and sterilizing by passage through a biological filter (Prescott et al., 1976).

2.3.10 Pharmaceutical incompatibilities

Methionine has been shown to be adsorbed by activated charcoal. Klein-Schwartz & Oderda (1981) added 10-ml aliquots (n=4) of a methionine solution (25 mg/ml) to 3, 6 and 10 g samples of activated charcoal in 50 ml of 0.1N hydrochloric acid. The 3 g charcoal-methionine mixtures were agitated for 30 seconds, 10 min, 30 min and 60 min, and then suction filtered. Based on the results of this time-course study, the 6- and 10-g samples were studied after 30 seconds of agitation. The binding of methionine by activated charcoal was found to occur rapidly (46.9% within 30 seconds). A tendency towards desorption was noted over the 60-min observation period (37.2% at 60 min), but did not achieve statistical significance. As the amount of charcoal was increased, and therefore as the ratio of charcoal to methionine increased, the percentage of methionine adsorbed increased. The percentages adsorbed by 3, 6, and 10 g of charcoal were 46.9 ± 4.0% (mean ± 1.96 SE), 76.8 ± 1.4%, and 89.5 ± 1.5%, respectively. A statistically significant difference was found between all three groups (P < 0.01).

2.4 Pharmaceutical formulation and synthesis

The raw materials for synthesis of DL-methionine are acrolein, methanethiol (methyl mercaptan), hydrogen cyanide, and ammonia or ammonium carbonate. These compounds are utilised in a number of different processes to yield the amino acid.

The Strecker process involves the addition of methanethiol to acrolein to form \( \beta \)-methylthiopropionaldehyde, which is reacted with cyanide to give alpha-hydroxy-gamma-methylthiobutyronitrile. This compound is treated with ammonia to produce alpha-amino-gamma-methylthiobutyronitrile, which is hydrolysed to DL-methionine (Goldfarb et al., 1981; Ullman, 1985).

A variation on this method involves the treatment of alpha-hydroxy-gamma-methyl-thiobutyronitrile with ammonia and carbon dioxide...
or ammonium carbonate to yield 5-(β-methylthioethyl)hydantoin. This product is subjected to alkaline hydrolysis at elevated temperature and pressure to yield sodium methionate. DL-methionine is isolated by acidification of the sodium methionate solution to the isoelectric point of the amino acid (pH = 5.7) (Goldfarb et al., 1981; Ullman, 1985).

L-methionine may be produced by the acylase-catalysed hydrolysis of N-acetyl-DL-methionine (Hoppe & Martens, 1984; Ullman, 1985).

Details of contaminants, excipients and pharmaceutical aids remain confidential to manufacturers.

Methionine is available as tablets of 250 mg (racemate).

The incorporation of methionine into tablets of paracetamol has been suggested as a means of protecting against hepatic and renal toxicity following paracetamol overdosage (McLean, 1974; McLean & Day, 1975). A preparation is now available commercially which contains paracetamol 500 mg and DL-methionine 250 mg (Pameton, Sterling Winthrop). Its use has been recommended in psychiatric wards in patients with depression who need a simple analgesic, and in families who are at risk (McLean, 1986). However, the formulation costs more than any other brand of paracetamol and its efficacy in preventing liver damage in humans following intentional paracetamol poisoning has not yet been established.

2.5 Analytical methods

2.5.1 Quality control of antidote

The preparation must contain not less than 99% and not more than the equivalent of 101% of DL-2-amino-4-(methylthio)butyric acid, calculated with reference to the dried substance (European Pharmacopoeia, 1989).

The European Pharmacopoeia (1989) describes the following assay method:

Dissolve 0.14 g of the substance in 3 ml of anhydrous formic acid. Add 30 ml of glacial acetic acid. Immediately after dissolution titrate with 0.1N perchloric acid, determining the end-point potentiometrically.

1 ml of 0.1N perchloric acid is equivalent to 14.92 mg DL-methionine.

2.5.2 Methods for identification of antidote

The European Pharmacopoeia (1989) stipulates that the preparation must be tested with either infrared absorption spectrophotometry or thin layer chromatography and the spectrum or chromatogram obtained compared with that for a reference sample of DL-methionine. In addition, one or both of the tests described below should be carried out. If the sample was tested spectrophotometrically then only test a) need be carried out; if chromatographically, then tests a) and b) should be carried out.

Additional tests:
a) Dissolve 2.5 g in 1N hydrochloric acid and dilute to 50 ml with the same acid. The angle of optical rotation is -0.05 ° to +0.05 °.

b) Dissolve 0.1 g of substance and 0.1 g of glycine in 4.5 ml of 2M sodium hydroxide. Add 1 ml of a 2.5% (w/v) solution of sodium nitroprusside. Heat to 40 °C for 10 min. Allow to cool and add 2 ml of a mixture of 1 volume of phosphoric acid and 9 volumes of hydrochloric acid. A deep red colour develops.

2.5.3 Methods for analysis of antidote in biological samples

Plasma methionine concentrations may be measured using ion exchange chromatography. There are several automated amino acids analysers available which utilize this technique. Before analysis it is necessary to deproteinise the plasma sample by mixing with sulfosalicylic acid. An equal volume of an external standard is added and the mixture centrifuged. The supernatant is injected into the analyser (Smolin et al., 1981).


2.5.4 Methods for analysis of toxic agent

Section 1.6 gives details of analytical techniques available for measuring plasma or serum paracetamol concentrations.

2.6 Shelf-life

DL-methionine should be stored in closed containers in cool, dry, dark conditions. Degussa AG (1985) recommended that the time limit for storage is two years.

2.7 General properties

2.7.1 Mode of antidotal activity

Methionine acts as a glutathione precursor and replenishes glutathione stores depleted as a consequence of paracetamol overdose (McLean & Day, 1975). Glutathione is a naturally occurring tripeptide, composed of glycine, glutamic acid and cysteine, which inactivates the reactive intermediate metabolite of paracetamol, N-acetyl- p-benzoquinoneimine (NAPQI), by conjugation, resulting in the formation of mercapturate and cysteine conjugates (Jagenburg & Toczko, 1964), which are then excreted in the urine (see section 1.4 for details). Although, methionine acts as a glutathione precursor (McLean & Day, 1975; Vina et al., 1978; Stramentinoli et al., 1979; Vina et al., 1980), it must first undergo demethylation and then transulfuration to produce cysteine (see section 2.8.2.1 for further details of methionine metabolism).

2.7.2 Other properties

L-methionine has been administered to patients with Parkinson's disease with differing results. Pearce & Waterbury (1974) found that patients on levodopa or other antiparkinsonian therapy deteriorated
when given supplementary methionine. The patients were placed on a low methionine diet (0.5 g/day; 3.35 mmol/day) and were given either 1.5 g (10.05 mmol) of L-methionine or placebo daily on a randomized, double-blind basis. Clinical deterioration was noted from the fifth day of the trial and was reversed after discontinuation of the methionine. In a longer term, open study Smythies & Halsey (1984) gave patients, whose parkinsonism was maximally controlled by drug therapy, doses of L-methionine starting at 1 g/day (6.7 mmol/day) and rising to 5 g/day (33.5 mmol/day). After a total of eleven weeks, there was subjective improvement in 10 of 15 patients.

Oral administration of a large amount of methionine to schizophrenic patients treated with a monoamine oxidase inhibitor has been reported to produce either an intensification of schizophrenic symptoms or superimposed toxic symptoms (Pollin et al., 1961; Brune & Himwich, 1962; Park et al., 1965; Berlet et al., 1965). The reason for this observation has not been established, but Kakimoto et al. (1967) found evidence of amino acid imbalance (increased urinary excretion of serine, threonine, glutamine and histidine) in eight schizophrenic patients given isocarboxazid (1 mg/kg per day) and oral L-methionine (0.3 g/kg per day; 2 mmol/kg per day) together, but not when given isocarboxazid alone.

DL-methionine has been given in doses of 200 mg three or four times daily to lower the pH of the urine and thus reduce odour and irritation due to ammoniacal urine (Martindale, 1989). DL-methionine is also used as a dietary supplement, as is L-methionine which is also used in amino acid solutions given parenterally (Martindale, 1989).

2.8 Animal studies

2.8.1 Pharmacodynamics

There is considerable species difference in susceptibility to paracetamol-induced liver damage, which correlates with differences in the activity of the oxidative pathway in these species. Thus, while doses of 750 mg/kg (4.96 mmol/kg) are sufficient to cause severe hepatic necrosis in mice, doses of 1250-1500 mg/kg (8.3-9.9 mmol/kg) cause very little hepatic necrosis in rats, despite being lethal (Mitchell et al., 1973). In animal experiments to test the efficacy of methionine, therefore, rats are usually sensitized to paracetamol by pretreatment with phenobarbitone or other microsomal enzyme-inducing compounds.

The time-scale for the development of liver damage in laboratory animals is shorter than in humans. The results of animal studies investigating the efficacy of methionine in relation to the time of administration of paracetamol overdose cannot, therefore, readily be extrapolated to humans. Nonetheless, in view of the rapidity of glutathione depletion and the onset of covalent binding and consequent liver damage, preventative treatment would seem to be needed soon after paracetamol overdose in order to be maximally effective. Animal studies investigating the efficacy of methionine in the prevention of liver damage have largely involved its prior or simultaneous administration with paracetamol.

When methionine was given to mice 5 min before, and 20 min after, a toxic intraperitoneal dose (710 mg/kg; 4.7 mmol/kg) of paracetamol, mortality was reduced from 43 to 16.7%. Methionine was administered intramuscularly at a concentration of 7.5 mg/kg (0.05 mmol/kg)
It is not clear from the report of this study whether this represented the total dose of methionine given or if the total dose was, in fact, 15 mg/kg (0.1 mmol/kg) (Stramentinoli et al., 1979). The effective dose of methionine represented either 1 or 2% (w/w) of the dose of paracetamol.

The development of liver damage in mice, as indicated by elevation of alanine aminotransferase (ALAT) activity, was prevented completely by the intraperitoneal administration of L-methionine (1000 mg/kg; 6.7 mmol/kg) at the same time as oral administration of paracetamol (300 mg/kg; 1.98 mmol/kg) (Miners et al., 1984). In the control group, given no antidotal therapy, ALAT activity rose above 16 000 U/l, whereas in the group given methionine the ALAT activity remained within the normal range. The LD$_{50}$ of paracetamol was increased more than three-fold, from 295 mg/kg (1.95 mmol/kg) to 910 mg/kg (6 mmol/kg). However, the co-administration of methionine did not completely prevent depletion of hepatic glutathione content, which dropped by about one third.

That the protective effect of methionine was due to facilitation of glutathione synthesis was suggested by two findings in this study. Firstly, the co-administration of methionine resulted in an increased proportion of the dose of paracetamol being excreted as glutathione-derived and sulfate conjugates. There was no significant change in the amount excreted as glucuronide conjugates or as unchanged paracetamol. Secondly, the protective effect of methionine was removed by pretreating the animals with buthionine sulfoximine. This compound specifically inhibits glutathione synthesis without affecting any of the other enzyme systems pertinent to the mechanism of paracetamol toxicity (Miners et al., 1984).

In another study where the toxin and protective agent were given simultaneously, McLean & Day (1975) compared the efficacy of different doses of methionine. They used rats sensitized by pretreatment with phenobarbitone and gave the drugs orally. When the test animals were given paracetamol (1 g/kg; 6.6 mmol/kg), 90% showed histological evidence of liver damage and 16.7% died. When methionine was given at a concentration of 300 mg/kg (2 mmol/kg), i.e. 30% (w/w), liver damage was prevented completely. A 25% dose of methionine increased the LD$_{50}$ of paracetamol more than three-fold, from 2 g/kg (13.2 mmol/kg) to more than 7.5 g/kg (49.6 mmol/kg). Neuvonen et al. (1985) also found that the simultaneous oral administration of L-methionine was effective in reducing the toxicity of paracetamol. In their studies on mice, a 20% dose of L-methionine increased the LD$_{50}$ of paracetamol from a mean of 610 mg/kg (4 mmol/kg) to a mean of 1096 mg/kg (7.2 mmol/kg). Methionine has also been shown to be effective in reducing mortality in dogs (Maxwell et al., 1975). When paracetamol (750 mg/kg; 4.95 mmol/kg) and methionine (150 mg/kg; 1 mmol/kg) were given orally, mortality was reduced from 67% in controls to zero.

These studies confirm the usefulness of methionine in preventing or reducing paracetamol-induced liver damage when it is given at the same time as the toxin. Other animal work has shown that methionine is effective when given after paracetamol.

Legros (1976) treated mice given an oral lethal dose of paracetamol (875 mg/kg; 5.78 mmol/kg) with intraperitoneal methionine administered 2 and 6 h later. The lowest dose tested was 25 mg/kg
(0.17 mmol/kg) given twice, the total representing 5.7% of the dose of paracetamol. This dose significantly reduced the mortality of the animals from 75% in the untreated group to 20%. Mortality decreased with increasing dose of methionine. The optimal dose was found to be 200 mg/kg (1.34 mmol/kg), the total representing 45.7% of the dose of paracetamol, which reduced mortality to 3%.

In the same study an attempt was made to define the time-limit for the efficacy of methionine. Using the dosage of 200 mg/kg (1.34 mmol/kg), the optimal time was found to be within 2 h of paracetamol administration. At this time interval, mortality was reduced to 10% compared with 65% in control animals. As the delay before administering methionine increased so its efficacy decreased, so that by 6 h after administration of paracetamol the antidote was ineffective. Even after 8 h, however, when the animals would have sustained some liver damage, the administration of methionine did not increase mortality above control levels (Legros, 1976).

2.8.2 Pharmacokinetics

Animal studies describing the rate of absorption or elimination of orally or parenterally administered methionine have not been found in the literature (except as below).

When rats were given intraperitoneal L-methionine in a dose of 149.2 mg/kg (1 mmol/kg), peak concentrations in the liver were reached 1 h after the injection and concentrations fell to less than twice normal by 3 h. In rats fed a low protein diet, the rate of decline of hepatic methionine was slower, so that the 3 h level was 700% of control (Finkelstein et al., 1982).

2.8.2.1 Metabolism

The liver is the main site of methionine metabolism; as much as 48% of methionine metabolism occurs here (Zeisel & Poole, 1979). The mechanism is well understood and has been reviewed extensively by Stipanuk (1986), Mato et al. (1990) and Pisi & Marchesini (1990). It is illustrated diagrammatically in Fig. 2.

The main pathway of methionine metabolism involves transmethylation and transulfuration, but there is increasing evidence for the importance of a transamination pathway (Benevenga, 1984).

The first step in the metabolism of methionine involves its activation to the high energy sulfonium compound, S-adenosyl-L-methionine. This is achieved by the transfer of the adenosyl moiety of ATP to the sulfur atom of methionine. Thus one mole of ATP is required for each mole of methionine metabolized in this system. S-adenosyl-L-methionine synthetase (also called methionine adenosyl transferase) catalyses this reaction.

S-adenosyl-L-methionine is then demethylated to produce S-adenosyl-L-homo-cysteine, which is hydrolysed in a reversible reaction to yield homocysteine and adenosine.

The formation of homocysteine marks a branch point in this pathway of methionine metabolism. Homocysteine may either be remethylated to methionine, used for the resynthesis of S-adenosyl-L-homocysteine by reversal of hydrolysis, or irreversibly converted to cystathionine.
The final stage in the transulfuration pathway is the cleavage of cystathionine to produce cysteine and alpha-ketobutyrate. This is catalysed by the enzyme cystathionine-ß-synthase, which is deficient in individuals with homocystinuria. Homozygotes would be unable to utilize DL-methionine as a glutathione precursor; obligate heterozygotes also demonstrate an impaired ability to form cystathionine (Boers et al., 1985).

Another metabolic pathway for methionine involves decarboxylation of S-adenosyl-L-methionine and synthesis of polyamines and also, possibly, the synthesis of methylthio compounds.

An alternative pathway for methionine metabolism that is independent of the formation of S-adenosyl-L-methionine has been suggested (Benevenga, 1984). It is thought that methionine is transaminated to alpha-keto-gamma-methylbutyrate which is then decarboxylated to 3-methylthiopropionate. In vitro experiments suggest that this compound may be further metabolized to yield methanethiol and hydrogen sulfide. It is possible that the toxicity (see below) of methionine may be due, at least in part, to the formation of these compounds via the transamination pathway (Benevenga, 1984; Finkelstein & Benevenga, 1986).

Methionine transamination takes place in several tissues including heart, brain and spleen. Mitchell & Benevenga (1978) have calculated, however, that 48% of transamination may occur in the muscle and 40% in the liver.

The Cystathionine Pathway;V03AN02.BMP

2.8.3  Toxicology

2.8.3.1  Acute toxicity

Although L-methionine is an essential amino acid, it has been shown to be toxic in excess. D-methionine is thought to be less toxic, presumably because it is not metabolically active itself but only after it has been converted by deamination and reamination to the L-form. The rate of conversion may limit the cellular concentration of L-methionine (Benevenga, 1974; Bowman & Rand, 1980).

In the rat the oral LD<sub>50</sub> of L-methionine is 36 g/kg (241 mmol/kg) and the intraperitoneal LD<sub>50</sub> is 4.3 g/kg (29 mmol/kg) (NIOSH, 1992). For DL-methionine in the rat the lowest published intraperitoneal lethal dose is 2 g/kg (13.4 mmol/kg) (NIOSH, 1992). In mice the lowest published lethal doses of DL-methionine are: oral - 4 g/kg (26.8 mmol/kg); intraperitoneal - 1.5 g/kg (10 mmol/kg); and intravenous - 300 mg/kg (2 mmol/kg) (NIOSH, 1992).

The effects of excess methionine have been investigated in a number of animal species and differential toxicity has been noted (Hardwick et al., 1970).

Loss of appetite and death was found in guinea-pigs given large doses of L-methionine (Hardwick et al., 1970). These animals were fasted for 18 h and then given methionine doses of 492 mg/kg (3.3 mmol/kg) by gavage at 8-h intervals. The animals stopped eating and died at an average of 42 h (maximum 65 h) after initiation of the experiment, i.e. after a total dose of 2.5 g/kg (16.5 mmol/kg).
were no deaths among the control group of fasted animals.

Terminally, the experimental animals were found to be hypothermic, immobile and opisthotonic. They had severe hypoglycaemia (blood sugar averaged 207 mg/l compared with 1295 mg/l in controls) with significantly depressed hepatic glycogen stores and generalised aminoacidaemia. On postmortem examination, the liver was found to be fatty; lipid was concentrated in the periportal hepatocytes with a little present around the central veins. Hepatic lipid appeared as early as 16 h into the experiment, after a total dose of 584 mg/kg (6.6 mmol/kg). No hepatic lipid was found in control animals. Hepatic ATP concentrations were only one-third that of the control guinea-pigs. Even after a single dose of L-methionine (492 mg/kg; 3.3 mmol/kg), both blood sugar and hepatic glycogen were significantly lower than in the controls. The administration of adenine at the same time as L-methionine prevented a decrease in blood sugar and hepatic ATP concentration (Hardwick et al., 1970).

The fall in hepatic ATP concentration was accompanied by a comparable increase in the concentration of adenosyl thionium compounds. This suggested that the reduction in ATP was, at least partly, due to its utilization in the activation of methionine to S-adenosyl-L-methionine (Hardwick et al., 1970).

The same dose fed to rats had no adverse effect; none of the animals were ill at 21 days when the study terminated (Hardwick et al., 1970).

2.8.3.2 Subacute and chronic toxicity

Although less relevant to acute treatment with methionine in humans, the following observations have been made in long-term animal studies.

Excessive dietary L-methionine has been shown to depress hepatic cytochrome oxidase activity in rats fed 3% methionine for seven days, compared with animals fed 0.3% (Finkelstein & Benevenga, 1986).

Suppression of growth was shown in another, longer term feeding study (Stekol & Szaran, 1962). This study examined the D- and L-enantiomorphs separately. D-and L-methionine supplements were fed to 30-day-old rats in four different proportions: 0.5%, 1.0%, 2.0% and 4.0% for periods of 1, 2, 3, 4 and 9 months. Both the 2% and 4% supplements of both enantiomorphs suppressed weight gain, D-methionine more so than L-methionine. After one month the rats given these supplements were found to have enlarged livers and spleens, while the pancreas was smaller and softer than normal. Some rats exhibited hydronephrosis. On microscopic examination these organs showed moderate to severe degenerative changes, although there were also signs of regeneration in the liver. At this time there was no increase in hepatic fat. The gonads, heart and other organs showed no changes. L-methionine caused greater damage than D-methionine. Rats fed 1% methionine for 1 month showed milder changes and those given 0.5% methionine showed no changes. After 3 months of feeding the 1-4% supplements, the tissues were normal except for an increase in droplet fat in the liver with each subsequent month (Stekol & Szaran, 1962).

In a study of the ability of rats of different ages to utilize L-methionine, it was found that 30-day-old animals utilized far less
methionine in the production of phospholipids, choline and creatine than those older than 90 days. This reduction in methionine utilization may partly account for the organ damage seen in these animals, as adult rats fed 4% methionine suffered no organ damage (Stekol & Szaran, 1962).

Another study, in which different age groups of mice were fed supplementary L-methionine for 42 days, did not show such a clear age-related difference (Massie & Aiello, 1984). When 42-day-old mice were fed methionine in their drinking-water at a concentration of 0.05 mol/litre, they did not show any reduction in weight gain but did have a significantly shorter life-span than control mice. Older mice (581 days) given the same regimen had a similar life-span to that of the young mice. Their life-span was not significantly different from that of their control group, although the control group was considered to have an unusually short life-span. The cause of death was not investigated. The estimated total daily intake of L-methionine by the mice in this study was 1.67 g/kg (11.2 mmol/kg), i.e. 1.03% of the animals' total solid intake. This concentration was found to cause only minor organ changes (Massie & Aiello, 1984).

2.8.3.3 Toxicity in experimental liver damage

Although the study by Legros (1976) (section 2.8.1) showed no increase in mortality in mice with paracetamol-induced liver damage who were given methionine, a study in rats with liver damage has shown that oral methionine may cause hepatic encephalopathy when administered in combination with ammonia. Higashi (1982b) induced liver damage in rats by administering carbon tetrachloride. Intragastric methionine 3.4 g/kg (23 mmol/kg) was then given, followed an hour later by an intraperitoneal dose of ammonium acetate (5 mmol/kg). While rats given methionine or ammonium acetate alone did not develop hepatic encephalopathy, those given the two agents in combination did so. Encephalopathy did not develop when glycine or leucine was substituted for methionine.

When the interval between administration of methionine and ammonium acetate was varied, the severity of encephalopathy was also found to vary. Only mild and brief encephalopathy developed if the ammonium compound was given either immediately or 30 min after methionine. The most severe encephalopathy developed in rats given ammonium acetate 120 min after methionine. This suggests that methionine metabolites may be responsible for enhancement of the encephalopathic effect of ammonia in rats with liver damage (Higashi, 1982b).

2.8.4 Effect in pregnancy

As described above, excessive dietary methionine reduces weight gain, and in pregnant rats this may adversely affect fetal development. When rats were given a diet containing 4% methionine from day one of pregnancy, their food intake, and thus their weight gain compared to control animals, was reduced. Fewer rats were able to maintain their pregnancy and both average fetal weight and placental weight were abnormally low. It is possible that some of this adverse effect was due to impaired secretion of ovarian hormones (Viau & Leathem, 1973).

2.9 Volunteer studies
Volunteer studies to investigate the pharmacokinetics of methionine following therapeutic doses (or overdoses) of paracetamol have not been undertaken. However, Stegink et al. (1986) studied the ability of adult volunteers to utilize L-methionine and D-methionine for nutritional purposes. The data indicate that adult humans do not utilize D-methionine efficiently as a methionine source.

In a study to investigate methionine metabolism in patients with liver disease, Higashi (1982a) measured serum methionine concentrations in 20 healthy control subjects; values of 19 ± 12 µmol/l (2.8 ± 1.8 mg/l) were obtained. An intravenous methionine loading test was performed in five of the control subjects to obtain elimination constants. Serum methionine concentrations were 19 ± 4 µmol/l (2.8 ± 0.6 mg/l) prior to the administration of 10 mg methionine per kg body weight; the mean elimination constant was 24.0 ± 6.3 x 10^{-3} min^{-1}.

Plasma concentrations achieved after an oral loading dose of methionine have been measured in two studies. In both cases L-methionine in a dose of 0.1 g (0.7 mmol) per kg body weight was given to male volunteers. In the study by Murphy-Chutorian et al. (1985), the subjects were a group of 138 men, aged 31 to 65 years (mean 53 years), referred for cardiac catheterization. Plasma methionine concentrations were measured before, and 6 h after, dosing with L-methionine; the concentrations in 39 subjects found to have normal coronary arteries were 20.25 ± 4.68 µmol/l (3.02 ± 0.7 mg/l) before, and 483.3 ± 141.9 µmol/l (72.1 ± 21.2 mg/l) after loading; the corresponding concentrations in the remaining 99 subjects were 20.53 ± 7.53 µmol/l (3.06 ± 1.12 mg/l) and 537.5 ± 165.0 µmol/l (80.2 ± 24.6 mg/l), respectively. The differences in plasma methionine concentrations were not statistically significant.

By comparison, Boers et al. (1985) examined a group of 20 men aged 22–61 years (mean 42 years) and found a considerably higher mean peak methionine concentration of 1063 ± 65 µmol/l (158.6 ± 9.7 mg/l) between 1 and 8 h after dosing. The fasting methionine concentration was slightly higher than in the study of Murphy-Chutorian et al. (1985), i.e. 28 ± 2 µmol/l (4.2 ± 0.3 mg/l). Boers et al. (1983) also measured methionine concentrations in pre- and post-menopausal women given the same dose of methionine. In 10 pre-menopausal women (aged 14–42, mean 25 years) the fasting concentration of methionine was 26 ± 2 µmol/l (3.9 ± 0.3 mg/l) and the peak concentration after the oral loading dose was 1033 ± 60 µmol/l (154 ± 9 mg/l). In 10 post-menopausal women (aged 45–59, mean 54 years) the corresponding figures were 21 ± 1 µmol/l (3 ± 0.15 mg/l) and 1107 ± 53 µmol/l (165 ± 8 mg/l).

Elimination values for methionine after the loading dose were 0.1 ± 0.03 l/h per kg for men and 0.08 ± 0.02 l/h per kg for both groups of women (Boers et al., 1983).

2.9.1 Methionine in patients with hepatic dysfunction

Phear et al. (1956) studied the effects of DL-methionine administered orally to 17 patients with liver disease. Nine patients suffered from cirrhosis of the liver and had previously experienced episodes of impending hepatic coma (chronic portal systemic...
encephalopathy). Electroencephalograms were compatible with this diagnosis. In eight of the patients, the extent of the portal venous collateral circulation was assessed by transsplenic portal venography and a very extensive collateral circulation was demonstrated. In the ninth patient, disturbance of blood clotting prohibited this investigation. Enteric-coated tablets containing 250 mg DL-methionine were given in divided doses between 6 am and 9 pm; the total daily dose, usually 10 g, varied between 8 and 20 g. During the administration of methionine, neurological deterioration occurred in seven patients, and in two this effect was reproduced when the drug was administered a second time. This occurred from 1 to 4 days after commencing methionine administration and after total doses of 11 to 46 g methionine.

Two of the nine patients tolerated 80 and 99 g methionine without neurological change. A further seven patients with portal cirrhosis who had never exhibited neurological complications, tolerated 50-102 g methionine without neurological change. Liver function was considered to be less severely impaired than in the patients who were sensitive to the drug and an extensive collateral circulation was demonstrated in only three. A patient with extra-hepatic portal vein obstruction also showed no change.

In four patients who deteriorated after methionine administration, the control blood methionine concentrations were normal in two (9 and 18 mg/l; normal < 20 mg/l) and elevated in two (26 and 39 mg/l). The concentration was increased in two (24 and 27 mg/l) and normal (13, 12, 20, 15 and 15 mg/l) in five of the patients who were unaffected by methionine feeding. In both groups, the rise in blood methionine concentrations after methionine administration was comparable. Moreover, neurological deterioration occurred without significant change in blood ammonium, blood pH or serum bilirubin levels.

In summary, this study showed that oral methionine caused neurological deterioration in patients with large collateral channels between the portal and systemic venous systems with chronic portal systemic encephalopathy. Clearly, this situation is very different from that which obtains in the early stages following acute paracetamol overdosage.

2.10 Clinical studies - clinical trials

Only one controlled trial of oral DL-methionine therapy in paracetamol poisoning has been undertaken (Hamlyn et al., 1980, 1981; Meredith, 1987). However, there have been two studies of the intravenous use of methionine in paracetamol poisoning (Prescott et al., 1976; Solomon et al., 1977).

2.10.1 Study by Prescott et al. (1976)

Prescott et al. (1976) reported 60 patients with paracetamol poisoning that were treated with intravenous cysteamine, L-methionine, or D-penicillamine and in whom the incidence and severity of hepatic necrosis were compared with those in 70 patients who received supportive therapy only.

2.10.1.1 Patients and treatment

The admission plasma paracetamol concentration, related to the
time after ingestion, was used as a guide to the severity of intoxication and the need for treatment. Gastric aspiration and lavage were carried out on all patients admitted within 4 h of overdosage. Patients with nausea and vomiting were given maintenance intravenous fluids and cyclizine intramuscularly if necessary. Vitamin K and fresh-frozen plasma or clotting factor concentrates were given if the prothrombin time ratio exceeded 3.0. Once specific treatment became available, it was given to all patients with plasma paracetamol concentrations above the line in Fig. 3.

Twenty patients (mean age 27 years) received methionine, and three were thought to be at particular risk. Methionine was given intravenously in an initial loading dose of 5 g injected over 10 min followed by an infusion of a further 15 g over 20 h. The methionine was stored in vials, dissolved in 5% dextrose immediately before use and sterilized by passage through a bacterial filter.

2.10.1.2 Investigations

The following investigations were carried out daily for 5 days in most patients: haemoglobin, total and differential white blood cell count, platelet count, plasma urea, electrolytes, creatinine, bilirubin, alkaline phosphatase, aspartate and alanine aminotransferases (ASAT, ALAT), blood glucose level, prothrombin time ratio and electrocardiogram. The plasma paracetamol concentration on admission was estimated by a rapid spectrophotometric method (Routh et al., 1968). Additional blood samples were taken 4-8 hourly for up to 72 h and the plasma concentrations of unchanged paracetamol in these and the admission sample were subsequently determined by gas-liquid chromatography (Prescott, 1971a). Urine was collected for 3-5 days for estimation of paracetamol and its sulfate and glucuronide conjugates to determine the minimum amount of paracetamol absorbed (Prescott, 1971a,b). Many collections were incomplete.
2.10.1.3 Results of treatment

The actual or extrapolated plasma paracetamol concentration 4 h after ingestion was used as a guide to the risk of liver damage. To assess the effects of treatment within 10 h, patients were placed into four groups of increasing risk according to the 4-h plasma paracetamol concentration (<150, 150-250, 250-300, and > 300 mg/l). In these four groups the mean plasma paracetamol concentrations on admission and at 4 h after ingestion did not differ significantly among different treatment regimens (Table 1). The severity of intoxication and the risk of liver damage could therefore be regarded as similar, allowing direct comparisons of the results of early treatment. The incidence and severity of hepatic necrosis were assessed using standard liver function tests, together with a "liver damage score" which was calculated for each patient as the sum of the minimum values of prothrombin time ratio, plasma bilirubin, and ASAT + ALAT/1000. Thus with upper normal limits of 1.3, 1.0 mg/dl, 40 and 40 U/l,
respectively, the liver damage score would be 2.38. Liver damage was defined as "severe" if the ASAT or ALAT activity exceeded 1000 U/l. Tests of statistical significance were carried out with Student's t-test, chi$^2$, and Fisher's exact test as appropriate.

a) **Supportive therapy only:** The results of laboratory investigations in patients receiving supportive therapy only are set out in Table 1. The incidence and severity of hepatic necrosis rose progressively with increasing 4-h plasma paracetamol concentrations. With one exception, liver damage was insignificant in the patients with 4-h values less than 150 mg/l, whereas every patient with a paracetamol concentration greater than 300 mg/l developed severe liver damage. In the latter group the mean maximum values for ASAT, ALAT, bilirubin, and prothrombin time ratio were 5293 and 3751 U/l, 7.3 mg/dl and 2.4, respectively. The same pattern of increasing liver damage was reflected in the liver damage scores. Three patients died in hepatic failure and four developed acute renal failure.

b) **Methionine:** None of the 15 patients treated with methionine within 10 h of ingestion died or developed acute renal failure, and in 12 liver damage was absent or trivial. However, three patients sustained severe damage with mean values of ASAT, ALAT, bilirubin, prothrombin time ratio and liver damage score of 8133 and 6867 U/l, 3.3 mg/dl, 2.8 and 21.2, respectively. The ingestion-treatment intervals were 8.8, 9.5 and 9.7 h, and the 4-h paracetamol concentrations were 357, 252 and 353 mg/l. Only one patient was thought to be at particular risk. The inclusion of these three patients is largely responsible for the high mean values in Table 1. The incidence of severe liver damage in the methionine group with a 4-h paracetamol concentration greater than 300 mg/l was significantly less than in the corresponding group receiving supportive therapy only ($p < 0.01$), but in all other comparisons of treatment with methionine and supportive therapy the differences were not statistically significant.

Liver-function tests were only mildly disturbed in five patients receiving methionine 10-12 h after overdosage (see Table 1).

2.10.1.4 Toxicity of methionine

There were no adverse effects on haemoglobin, white blood cell count, platelet count, or plasma urea, creatinine, electrolyte, and calcium and blood glucose concentrations that could be attributed to treatment with methionine.

2.10.1.5 Likelihood of benefit due to antidote

Intravenous methionine appeared to be effective in most patients. However, three patients treated within 10 h suffered severe liver damage, including one, who was apparently not at great risk with a 4-h plasma paracetamol concentration of 252 mg/l. The results of treatment with cysteamine and D-penicillamine in this study have not been presented in detail, but none of 23 patients given cysteamine within 10 h of ingestion suffered severe liver damage or renal failure, and none died.

Cysteamine was partially effective at 10-12 h, but ineffective 12 h or more after ingestion. Of five patients treated with
D-penicillamine, one developed severe liver damage with acute renal failure.

2.10.2 Study by Solomon et al. (1977)

Solomon et al. (1977) reported 12 patients with paracetamol poisoning, half of whom were treated with cysteamine and half with intravenous amino acid preparations (Aminosol 10%, Aminoplex 14) containing methionine and cysteine.

2.10.2.1 Results of treatment

In only one patient in the cysteamine-treated group was the ALAT activity raised, and the bilirubin concentration was not raised above normal in any patient. In the amino acid-treated group, two patients showed a mild rise in ALAT activity, and serum bilirubin concentrations remained normal in all patients.

2.10.2.2 Toxicity of methionine

No side effects attributable to therapy occurred in the amino acid-treated group, but nausea, vomiting and muscle twitching variably occurred in all the patients treated with cysteamine.

Table 1. Results (mean ± SEM) of investigations in patients receiving either supportive therapy or methionine

<table>
<thead>
<tr>
<th>No. of patients (n=95)</th>
<th>4-h Plasma paracetamol concentration (mg/l)</th>
<th>Mean 4-h plasma paracetamol (mg/l)</th>
<th>Mean minimum urinary recovery of paracetamol (g)</th>
<th>Mean ingestion-treatment interval (h)</th>
<th>No. of patients with severe liver damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive therapy only (n=70)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 &lt; 150</td>
<td>92 ± 11</td>
<td>7.4 ± 0.7</td>
<td>-</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>23 150-250</td>
<td>199 ± 5</td>
<td>9.5 ± 1.3</td>
<td>-</td>
<td>6 (26)</td>
<td></td>
</tr>
<tr>
<td>15 250-300</td>
<td>275 ± 15</td>
<td>12.1 ± 1.2</td>
<td>-</td>
<td>6 (40)</td>
<td></td>
</tr>
<tr>
<td>16 &gt; 300</td>
<td>404 ± 26</td>
<td>15.6 ± 3.2</td>
<td>-</td>
<td>16 (100)</td>
<td></td>
</tr>
<tr>
<td>Methionine &lt; 10 h (n=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 150-250</td>
<td>219 ± 4</td>
<td>13.5 ± 0.7</td>
<td>5.7 ± 0.8</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>3 250-300</td>
<td>277 ± 13</td>
<td>12.6 ± 0.7</td>
<td>8.7 ± 0.6</td>
<td>1 (33)</td>
<td></td>
</tr>
<tr>
<td>7 &gt; 300</td>
<td>379 ± 27</td>
<td>15.7 ± 1.7</td>
<td>7.7 ± 0.5</td>
<td>2 (29)</td>
<td></td>
</tr>
<tr>
<td>Methionine &gt; 10 h (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>314 ± 30</td>
<td>-</td>
<td>11.1 ± 0.2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

a From: Prescott et al. (1976)
b ASAT or ALAT > 1000 U/l
Unfortunately, it is impossible to determine whether methionine had any beneficial effect in these patients, for the reasons set out below.

Firstly, the amino acid solutions contained cysteine as well as methionine. Cysteine alone has been shown to protect against paracetamol toxicity in mice (Strubelt et al., 1974) and it is thought to act as a glutathione precursor (Reed & Beatty, 1980). Indeed, N-acetylcysteine is first converted to cysteine by deacetylation before it acts as a glutathione precursor (Lauterberg et al., 1983). Cysteine may also act as a source of sulfate for conjugation with unchanged paracetamol (Glazenberg et al., 1984). Secondly, in six patients plasma paracetamol concentrations were measured within 4 h of ingestion of the overdose and are therefore uninterpretable. Only five of the six remaining patients were at risk when judged by the criterion now applied before considering specific therapy [a plasma paracetamol concentration falling above a line joining 200 mg/l (1.32 mmol/l) at 4 h and 50 mg/l (0.33 mmol/l) at 12 h after ingestion of the overdose when plotted on a semi-logarithmic paracetamol concentration time scale (Meredith et al., 1986)]. Only one of these five patients was treated with an amino acid solution and she developed minor disturbance of hepatic function with a peak ALAT activity of 67 U/l.

Hamlyn et al. (1981) were stimulated by case reports (Crome et al., 1976) of the successful use of oral methionine in the treatment of paracetamol poisoning to undertake a collaborative, controlled trial.

In total, 40 patients at risk from hepatic and renal toxicity due to serious paracetamol overdose were studied. Hepatic necrosis, as judged by "blind" histological assessment, occurred significantly less often in actively treated patients (methionine p < 0.02, cysteamine p < 0.01). Significant differences in peak serum ASAT activity were seen, the geometric means being 1046 U/l in the supportive group, 96 U/l in the cysteamine group, and 139 U/l following methionine treatment (Wilcoxon sum of ranks p < 0.01 in favour of methionine, p < 0.002 in favour of cysteamine). These differences in favour of cysteamine and methionine were also reflected in peak serum bilirubin concentrations and prothrombin time ratios.

This trial is the only controlled study of the use of oral methionine in the treatment of paracetamol poisoning, although it was not truly prospective because four patients had been included in an earlier trial and had been reported previously (Douglas et al., 1976). A convincing hepatoprotective effect of early intravenous cysteamine and oral methionine was demonstrated. However, no clear difference in efficacy of the two protective agents was shown, although early methionine administration was associated with few, if any, undesirable
side-effects.

2.11 Clinical studies - case reports

The London Centre of the National Poisons Information Service in the United Kingdom recommended the use of oral methionine from 1974 (Crome et al., 1976) in patients thought to be at risk of paracetamol-induced liver damage. Initially, this was as an alternative to intravenous cysteamine and then later to intravenous N-acetylcysteine (Meredith, 1987).

2.11.1 Study by Vale et al. (1981)

Vale et al. (1981) reported on the efficacy of oral methionine therapy in 132 patients at risk of paracetamol-induced hepatic and renal toxicity. Some of these patients had been reported previously (Crome et al., 1976; Meredith et al., 1978; Vale et al., 1979); because of the retrospective nature of the study, it does not constitute a formal clinical trial.

2.11.1.1 Patients and treatment

This study included 132 adult patients who were initially seen within 24 h of their overdose, which occurred between 1974 and 1979. These patients had plasma paracetamol concentrations falling above a line joining plots of 200 mg/l (1.32 mmol/l) at 4 h and 70 mg/l (0.46 mmol/l) at 12 h. More severely poisoned patients, with plasma paracetamol concentrations above a line joining 300 mg/l (1.98 mmol/l) at 4 h and 75 mg/l (0.50 mmol/l) at 12 h, were classified as a high-risk group. Where necessary, the plasma paracetamol plots were extended to 24 h.

Of the 132 patients, 88 patients claimed to have taken only paracetamol, 16 took ethanol in addition, eight took benzodiazepines, three took dextropropoxyphene hydrochloride in combination with paracetamol (Distalgesic), and 17 ingested other drugs (including aspirin, tricyclic antidepressants, and orphenadrine hydrochloride). The mean age of the 132 patients was 26 years (range, 14 to 73 years); 48 were male and 84 were female.

All patients underwent gastric lavage within 6 h of ingestion of the overdose. Patients with persistent nausea and vomiting were also given intravenous fluid replacement and anti-emetics. Each patient received methionine orally in a dose of 2.5 g, which was then repeated on three subsequent occasions at 4-hourly intervals (i.e. 10 g during 12 h).

2.11.1.2 Investigations

All patients had plasma paracetamol levels measured on admission and at least once subsequently. Haematological and biochemical tests were performed on admission and daily thereafter for at least 7 days. Severe liver damage was defined as an increase in serum ASAT activity to a level above 1000 U/l, and renal impairment as a serum creatinine concentration greater than 300 µmol/l.

2.11.1.3 Results of treatment

The efficacy of methionine was assessed by comparing it with the results of supportive therapy alone (when given to 57 similarly
poisoned patients treated at the Royal Infirmary, Edinburgh (Prescott et al., 1979)]. Chi-square statistics were used for this purpose, with Yates' correction for continuity. Comparisons were also made with patients treated with oral (Rumack & Peterson, 1978) and intravenous (Prescott et al., 1979) N-acetylcysteine. It should be noted, however, that in these two other studies (Rumack & Peterson, 1978; Prescott et al., 1979), the "treatment" lines adopted joined plots of 200 mg/l (1.32 mmol/l) at 4 h and 50 mg/l (0.33 mmol/l) at 12 h, and that they cannot therefore be compared directly.

The patients were divided into two main groups depending on whether oral methionine was given either within, or later than, 10 h after paracetamol ingestion. These two groups of patients were further subdivided into those who were at moderate risk and those who were at high risk of severe liver damage on the basis of their plasma paracetamol concentrations (Table 2).

2.11.1.4 Liver damage

a) Oral methionine given within 10 h: Only seven of the 96 patients given methionine within ten hours had severe liver damage, as compared with 33 (58%) of the 57 patients given supportive treatment (Table 3).

Patients given methionine showed an increase in mean maximum serum ASAT activity to 294 U/l, compared to a mean maximum level of more than 2000 U/l in those treated supportively. (Between 1969 and 1973, the liver enzyme test results at the Royal Infirmary, Edinburgh, were reported as more than 850 or 1000 U/l; therefore, a precise figure cannot be given.)

Table 2. Severity of poisoning and time of methionine administration in 132 patients at risk of paracetamol-induced hepatorenal toxicity

<table>
<thead>
<tr>
<th>Commencement of treatment (hours after overdose)</th>
<th>&lt; 10</th>
<th>10-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients&lt;sup&gt;a&lt;/sup&gt; (n = 132)</td>
<td>96</td>
<td>36</td>
</tr>
<tr>
<td>High-risk patients&lt;sup&gt;b&lt;/sup&gt; (n = 74)</td>
<td>43</td>
<td>31</td>
</tr>
</tbody>
</table>

<sup>a</sup> Plasma paracetamol concentration > 200 mg/l (1.32 mmol/l) at 4 h and > 70 mg/l (0.46 mmol/l) at 12 h

<sup>b</sup> Plasma paracetamol concentration > 300 mg/l (1.98 mmol/l) at 4 h and > 75 mg/l (0.50 mmol/l) at 12 h

Of the seven patients in whom severe liver damage developed, six were severely poisoned (high-risk cases), but only one had transient hepatic failure; none of these patients died. All seven patients underwent gastric lavage within 5 h of ingestion of the overdose, and all received methionine within 8 h, although two vomited the first dose.

The incidence of severe liver damage in patients given methionine
was significantly less than that found in those treated supportively (chi² corrected for continuity, 44.8; p < 0.0001).

b) Oral methionine given within 10-24 h

In 36 cases, methionine was given 10-24 h after ingestion (Table 3). Severe liver damage occurred in 17 (47%), and the mean maximum ASAT activity was 1464 U/l. These results were not statistically different from those found in patients given supportive treatment only.

2.11.1.5 High-risk patients

Severe hepatic damage occurred in 89% of high-risk patients treated supportively (Table 4), whereas only 14% of those treated with oral methionine within 10 h of ingestion had severe liver damage (chi² corrected for continuity, 36.1; p < 0.0001). In patients treated between 10 and 24 h after ingestion, those in whom severe liver damage developed numbered half those of the group receiving supportive treatment alone (chi² corrected for continuity, 10.9; p < 0.0001).

2.11.1.6 Renal impairment

One patient given oral methionine within 10 h had transient renal failure (even though his maximum ASAT activity was only 160 U/l). Renal impairment occurred in two other patients (6%) treated between 10 and 24 h after ingestion, whereas six (11%) of 57 patients in the group treated supportively suffered the same complication.

2.11.1.7 Deaths

None of the patients given oral methionine within 10 h died of hepatic failure, but two high-risk patients, both treated later than 10 h after ingestion, died.

2.11.1.8 Toxicity of methionine

Methionine did not produce any serious side effects. Twenty-two (17%) of the 132 patients vomited before treatment with methionine, but only seven (5%) vomited afterwards.

2.11.1.9 Likelihood of benefit due to antidote

Comparative data for oral and intravenous acetylcysteine are shown in Tables 3-4. When given within 10 h, both methionine and N-acetylcysteine protected against death caused by hepatic failure. The incidence of severe liver damage was not significantly different in the three treatment groups; similar results were seen for those patients treated between 10 and 24 h. In this retrospective study, oral methionine was clearly effective in protecting against severe liver damage, renal failure and death after paracetamol overdose when given within 10 h of ingestion.

2.12 Summary of evaluation

2.12.1 Indications

Oral methionine is indicated for the treatment of acute
paracetamol (acetaminophen) poisoning. When 4 h or more have elapsed after ingestion of an overdose the plasma concentration of paracetamol should be measured. Specific treatment with methionine is required if the plasma paracetamol concentration falls above a line which on a semilog graph joins plots of 200 mg/l (1.32 mmol/l) at 4 h and 30 mg/l (0.33 mmol/l) at 15 h after the overdose (see Fig. 1 in section 1.3). In cases where plasma concentrations of methionine are not available, methionine should be given if more than 100 mg paracetamol/kg is taken in a single dose.

Table 3. Hepatic and renal damage in patients poisoned with paracetamol given oral methionine or intravenous N-acetylcysteine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>No. (%) with severe liver damage (ASAT &gt; 1000 U/l)</th>
<th>Mean ASAT (U/l)</th>
<th>No. (%) with acute renal failure</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral methionine given within 10 h(^a)</td>
<td>96</td>
<td>7 (7)</td>
<td>294</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Oral N-acetylcysteine given within 10 h (Rumack &amp; Peterson, 1978)(^b)</td>
<td>49</td>
<td>8 (16)</td>
<td>210</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Intravenous N-acetylcysteine given within 10 h (Prescott et al., 1979)(^b)</td>
<td>62</td>
<td>1 (2)</td>
<td>113</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Oral methionine given within 10-24 h(^a)</td>
<td>36</td>
<td>17 (47)</td>
<td>1464</td>
<td></td>
<td>2 (6)</td>
</tr>
<tr>
<td>Oral N-acetylcysteine given within 10-24 h (Rumack &amp; Peterson, 1978)(^b)</td>
<td>51</td>
<td>23 (45)</td>
<td>2207</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Intravenous acetylcysteine given within 10-24 h (Prescott et al., 1979)(^b)</td>
<td>38</td>
<td>20 (53)</td>
<td>3814</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Supportive treatment only (Prescott et al., 1979)(^b)</td>
<td>57</td>
<td>33 (58)</td>
<td>&gt; 2022</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Plasma paracetamol concentration > 200 mg/l (1.32 mmol/l) at 4 h and > 70 mg/l.
\(^b\) Plasma paracetamol concentration > 200 mg/l (1.32 mmol/l) at 4 h and > 50 mg/l.

Table 4. Hepatic and renal damage in high-risk patients poisoned with paracetamol or intravenous N-acetylcysteine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>No. (%) with severe liver damage (ASAT &gt; 1000 U/l)</th>
<th>Mean ASAT (U/l)</th>
<th>No. (%) with acute renal failure</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive treatment only (Prescott et al., 1979)(^b)</td>
<td>57</td>
<td>33 (58)</td>
<td>&gt; 2022</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>
Oral methionine given within 10 h 43 6 (14) 464

Intravenous N-acetylcysteine given within 10 h (Prescott et al., 1979)\textsuperscript{b} 33 1 (3) 185

Oral methionine given within 10-24 h 31 14 (45) 1532

Intravenous acetylcysteine given within 10-24 h (Prescott et al., 1979) 27 18 (67) 4919 5

Supportive treatment only (Prescott et al., 1979) 28 25 (89) > 3186 6

\textsuperscript{a} Plasma paracetamol concentration > 300 mg/l at 4 h and > 75 mg/l at 12 h

\textsuperscript{b} Plasma creatinine concentration > 300 µmol/l

If the patient is either vomiting or unconscious (usually the result of taking another drug in addition to paracetamol), then it is more appropriate to give N-acetylcysteine by the intravenous route. Children aged less than 6 years tend to swallow only small amounts of paracetamol and specific treatment is rarely indicated (Meredith et al., 1978). Nevertheless, plasma paracetamol concentrations should be measured and interpreted as in adult patients (Meredith, 1987). Adolescents, who are more likely than younger children to take a hepatotoxic dose of paracetamol, should be dealt with similarly.

Certain special situations arise in adult patients. Firstly, some patients take repeated doses of paracetamol over a period of hours or days that either individually or in total are potentially hepatotoxic. The interpretation of single measurements of the plasma paracetamol concentration is therefore difficult or impossible in these circumstances, and immediate specific therapy is advised provided that liver dysfunction has not already developed, as shown, for example, by an elevated prothrombin time ratio. Secondly, a paracetamol overdose is sometimes taken in combination with drugs that delay gastric emptying (for example, dextropropoxy-phene or tricyclic antidepressants) and, therefore, gastrointestinal absorption. The so-called "treatment line" (which on a semilog graph joins plots of 200 mg/l at 4 h and 30 mg/l at 15 h after ingestion) will be shifted to the right as a consequence. The extent to which this will occur cannot easily be predicted and care must be taken to avoid under-treatment of this group of patients. If there is any doubt, specific treatment should be given.

2.12.2 Advised route and dosage

Methionine should be given orally in a dose of 2.5 g, followed by three further doses of 2.5 g at 4-hourly intervals. Adolescents at risk may be given the same doses, but children aged less than 6 years should be given 1 g orally followed by three further doses of 1 g at 4-hourly intervals. If a patient is vomiting and is unable to tolerate oral methionine, intravenous N-acetylcysteine should be given. The intravenous administration of methionine cannot be
recommended (see section 2.12.4).

2.12.3 Other consequential or supportive therapy

Patients who present to hospital within 1-2 h and who are thought to have ingested 100 mg paracetamol/kg body weight or more should undergo gastric lavage. As already mentioned, children aged less than six years tend to swallow only small amounts of paracetamol and gastric lavage is probably unnecessary. In neither adults nor children has the value of syrup of ipecacuanha or activated charcoal been established. In addition, the former may preclude the administration of methionine because of resultant persistent nausea and vomiting, and the latter is likely to adsorb (and therefore annul the effect of) methionine administered either beforehand or afterwards. For these reasons syrup of ipecacuanha should not be employed in the treatment of paracetamol overdosage, and the use of activated charcoal should be avoided unless intravenous therapy (with N-acetylcysteine) is to be employed.

2.12.4 Areas of use where there is insufficient information to make recommendations

The time after ingestion of a paracetamol overdose at which the oral administration of methionine ceases to provide protection against hepatic and renal damage has not been established with certainty. The evidence shows that the degree of protection afforded declines rapidly once more than 10 h has elapsed after the overdose. On present evidence, specific treatment should be given up to 15 h after the overdose provided that the International Normalized Ratio (prothrombin time) remains normal. There are insufficient data to make recommendations about methionine therapy for the period 10-24 h after a paracetamol overdose or thereafter.

There are insufficient published data on the clinical efficacy and safety in use of methionine administered intravenously (and neither is a pharmaceutical preparation available). For this reason, a recommendation concerning the use of methionine in this manner cannot be made.

2.12.5 Proposals for further studies

The dosage regimen for methionine was empirically based on its action as a glutathione precursor. Further information is needed about the optimal dosage, kinetics of absorption and treatment period. Different formulations of methionine should be studied in paracetamol overdose patients to define and obtain optimal absorption characteristics. Childhood dosage regimens should also be investigated because the dose employed currently may be more than is necessary, and the use of intravenous preparations of N-acetylcysteine may sometimes cause problems with fluid overload.

Prospective studies comparing oral methionine and intravenous N-acetylcysteine therapy should be performed because: (a) those undertaken so far have used historical controls; and (b) the use of methionine in developing countries may have wider applicability than N-acetylcysteine (because of the greater cost of the latter and difficulties with the cold chain in relation to transportation and storage). The efficacy of treatment should be assessed during successive periods of time between 10 and 24 h, or even later, after
paracetamol overdosage to determine the latest point at which it may be employed effectively. (Unfortunately, the safety in use and established clinical efficacy of N-acetylcysteine reduces the likelihood of such studies being undertaken.)

There is no evidence as yet, from the use of methionine in humans, as to whether protection against paracetamol-induced toxicity results in retardation of fetal growth or even teratogenicity. Epidemiological studies are therefore indicated. Finally, it would be desirable to determine the efficacy of methionine as a protective agent for paracetamol poisoning in heterozygotes for homocystinuria (see section 2.8.2.1), but there is the obvious practical difficulty of being able to study a sufficient number of individuals with this condition who have taken a paracetamol overdose.

2.12.6 Adverse effects

Oral methionine therapy in the dosage used for paracetamol poisoning has not been associated in practice with any adverse effects in patients with or without paracetamol-induced liver failure. There is, however, evidence of neurological deterioration associated with methionine administration to patients with chronic hepatic dysfunction from causes other than paracetamol.

There is also evidence of increased hepatotoxicity when methionine is given to mice with liver failure induced experimentally by carbon tetrachloride, but not if induced by paracetamol.

2.12.7 Restrictions of use

On theoretical grounds, methionine is likely to be ineffective in patients with homocystinuria and N-acetylcysteine should be given instead following paracetamol overdose.

If patients are vomiting or unconscious, intravenous N-acetylcysteine should be given in preference to methionine. N-acetylcysteine is also the preferred agent in patients with chronic hepatic failure who have taken paracetamol in overdose.

2.13 Model information sheet

2.13.1 Uses

Methionine is indicated for the treatment of acute paracetamol (acetaminophen) poisoning if a patient is at risk of developing hepatic or renal toxicity. The risk may be judged by measuring the plasma paracetamol concentration when more than 4 h have elapsed after the overdose. Oral methionine should be given if the plasma paracetamol concentration lies above a line which on a semilog graph joins plots of 200 mg/l (1.32 mmol/l) at 4 h and 30 mg/l (0.20 mmol/l) at 15 h after overdose (see Fig. 1 in section 1.3).

Methionine is also indicated if more than 100 mg paracetamol/kg has been ingested in a single dose and plasma paracetamol concentrations are not available.

2.13.2 Dosage and route

The dose for adults and adolescents is 2.5 g orally, followed by a further three doses of 2.5 g at 4-hourly intervals (10 g in total).
Children aged less than 6 years tend to swallow only small amounts of paracetamol and specific treatment is rarely indicated but, if necessary, the dose is 1 g orally, followed by a further three doses of 1 g at 4-hourly intervals.

2.13.3 Precautions/contraindications

If a patient is vomiting or unconscious (usually the result of taking another drug), then alternative specific treatment should be administered. Special attention should be given to the need for treatment in patients who present 10-24 h after the overdose and in patients who have taken repeated doses of paracetamol. In patients who have taken other drugs that might delay gastric emptying (for example, opiates or tricyclic antidepressants) and who present more than 10 h after the overdose, an intravenous protective agent (N-acetylcysteine) may be preferred because the kinetics of absorption of methionine are likely to be disturbed.

N-acetylcysteine, rather than methionine, should be used as protective therapy in patients with homocystinuria and chronic liver failure.

2.13.4 Adverse effects

Oral methionine therapy in the dosage used for paracetamol poisoning has not been associated in practice with any adverse effects. Early concerns that methionine might contribute to hepatic encephalopathy in paracetamol-induced liver failure have not been substantiated, and review of the data suggests that it is unlikely to occur.

2.13.5 Use in pregnancy and lactation

Animal studies, in which large amounts of methionine (up to 4% of the total diet) were given orally, have shown suppression of growth, but there is no evidence in humans that methionine is a hazard in pregnancy or during lactation. If the mother is at risk of paracetamol-induced hepatic and renal toxicity, then treatment should not be withheld. Moreover, it should be remembered that the unborn fetus is itself at risk of paracetamol-induced hepatotoxicity.

2.13.6 Storage

Methionine should be stored in closed containers in cool, dry, dark conditions. The recommended time-limit for storage is 2 years.

2.14 References


Park LC, Baldessarini MJ, & Kety SS (1965) Methionine effects on chronic schizophrenics. Patients treated with monoamine oxidase inhibitors. Arch Gen Psychiatr, 12: 346-351.


3. **N-ACETYLCYSTEINE**

3.1 **Introduction**

*N*-acetylcysteine is the *N*-acetyl derivative of L-cysteine, a naturally occurring amino acid. It was originally introduced into clinical medicine as a mucolytic agent in the 1960s but is now widely used in the management of paracetamol poisoning, initially having been used as an alternative to the more toxic agent cysteamine (Prescott et al., 1977).

*N*-acetylcysteine has been shown to protect against paracetamol-induced liver damage and has been used both intravenously and orally for this purpose. It is given intravenously in a number of countries, including the United Kingdom and Australia, whereas in the USA its use has principally been by the oral route. It protects against paracetamol-induced liver damage when given by both routes (Prescott et al., 1979; Smilkstein et al., 1988) if given within 8 h of intoxication. Use of *N*-acetylcysteine should be guided by plasma concentrations of paracetamol taken in conjunction with the time of the overdose (Prescott et al., 1979; Rumack et al., 1981). It is clear that the efficacy of *N*-acetylcysteine is reduced with increasing time after administration of paracetamol and there is no evidence of antidotal efficacy if given more than 24 h after poisoning. The intravenous and oral regimens are essentially empirical and no controlled studies have been performed of the optimal dose or duration of therapy.

*N*-acetylcysteine has also been investigated in a number of other clinical situations in which reactive metabolites are believed to be important in the toxicity of the poison. In animals, *N*-acetylcysteine may protect against hepatotoxicity of halothane (Keaney & Cocking, 1981). *N*-acetylcysteine has also been shown in animals to be protective against heavy metals, alkylating agents and radiation, and in man to haemorrhagic cystitis secondary to...
cyclophosphamide (Flanagan, 1987). The only formal clinical trials in this situation have been conducted on cyclophosphamide- and isophosphamide-induced haemorrhagic cystitis. N-acetyl-cysteine is effective in the management of cystine stones in cystinuria (Martindale, 1988a).

Recently it has also been shown that N-acetylcysteine reduces mortality in patients with acute paracetamol-induced liver failure (Keays et al., 1991). Thus N-acetylcysteine may have two effects in paracetamol poisoning: firstly, it prevents liver damage from occurring and secondly, if that does occur, N-acetylcysteine may significantly reduce mortality in such patients.

3.2 Name and chemical formula

International non-
proprietary name: N-acetylcysteine

Synonyms: Acetylcysteine; N-acetyl-L-cysteine; NSC-11180; L-alpha-acetamido-beta-mercaptropropionic acid

IUPAC name: N-acetyl-3-mercaptoalanine

CAS number: 616-91-1

Empirical formula: C₅H₉NO₃S

Chemical structure:
\[
\text{HSCH₂CHCOOH} \\
\text{NHCOCH₃}
\]

N-acetylcysteine

Relative molecular mass: 163.2

Conversion table:
1 g = 6.1 mmol
1 mg = 6.1 µmol
1 mmol = 163.2 mg
1 µmol = 163.2 µg

3.3 Physico-chemical properties

3.3.1 Melting point

109-110 °C

3.3.2 Physical state

N-acetylcysteine consists of a white crystalline powder with a slightly acetic odour. In its liquid formulation for drug use, it has an odour common to sulfhydryl-containing compounds, i.e. an odour similar to that of hydrogen sulfide ("rotten eggs").

3.3.3 Solubility

Solubility values in water of 1 part in 8 (British Pharmacopoeia, 1993) and 1 part in 5 (United States Pharmacopeia, 1990) and in
ethanol of 1 part in 2 (British Pharmacopoeia, 1993) and 1 part in 4 (United States Pharmacopoeia, 1990) have been reported.

\( \text{N-acetylcysteine is practically insoluble in chloroform and ether (Martindale, 1988b).} \)

3.3.4 Optical properties

\( \text{N-acetylcysteine has no significant optical properties.} \)

3.3.5 \( \text{pK}_a \)

The \( \text{pK}_a \) value is 9.5 (Clarke, 1986).

3.3.6 \( \text{pH} \)

A 1% solution has a \( \text{pH} \) of 2.0 to 2.8. Sterile solution is buffered with sodium hydroxide to a \( \text{pH} \) of 7.

3.3.7 Stability

\( \text{N-acetylcysteine should be stored in airtight containers at a temperature below 15 °C and protected from light (Martindale, 1988b).} \)

3.3.8 Incompatibilities

\( \text{N-acetylcysteine is incompatible with many metals, with rubber, and with oxygen and oxidizing substances. Some antibiotics including amphotericin, ampicillin sodium, erythromycin lactobionate and some tetracyclines are either physically incompatible with, or may be inactivated on mixture with, \( \text{N-acetylcysteine}. \) A change in colour of solutions of \( \text{N-acetylcysteine} \) to light purple does not indicate significant impairment of safety or efficacy.} \)

3.3.9 Proprietary names and manufacturers

Many preparations of \( \text{N-acetylcysteine} \) are marketed, most as mucolytics. The proprietary names, manufacturers and countries include:

Airbron (Allen & Hanburys, Canada; Duncan Flockhart, United Kingdom); Brunac (Bruschettini, Italy); Eurespiran (Nicholas, Germany); Exomuc (Bouchara, France); Fabrol (Ciba, Denmark; Inphazam, Sweden; Zyma, United Kingdom); Fluimucil (Arsac, France; Inpharzam, Germany; Azmbom, Italy, Netherlands; Zambon, Spain; Inpharzam, Switzerland); Fluprowit (Thiemann, Germany); Granon (DAK, Denmark); Ilube (Duncan Flockhart, United Kingdom); Inspir (Sweden); L CIMexyl (Cimex, Switzerland); Lysomucil (Belgium); Muco Sanigen (Beecham-Wulfing, Germany); Mucocedyl (Kettelhack Riker, Germany); Mucofílil Sol (Japan); Mucolysin (Durascan, Denmark); Mucolysticum (Bristol, Germany); Mucomist (Bristol Italiana Sud, Italy); Mucomyst (Astra, Argentina, Australia, Belgium; Bristol, Canada; Astra, Denmark; Allard, France, Netherlands; Draco, Norway; Tika, Sweden, Switzerland;

Mead Johnson Pharmaceutical, USA); Mucosal (Dey, USA); Mucothiol (Ozotheine, France); Mucret (Astra, Germany); Nac (Canada);
Parvolex (Glaxo, Australia; Allen & Hanburys, Canada; Duncan, Flockhart, United Kingdom); Solmucol (Ibsa, Switzerland); Tixair (Valpan, France).
Preparations available for use in paracetamol poisoning include Parvolex (for intravenous use) and Mucomyst (for oral and intravenous administration).

It should be noted that in some parts of the world a similar compound $\text{S-carboxymethylcysteine}$ is available rather than $\text{N-acetylcysteine}$. Although its efficacy is not proven, animal data appear to be comparable to those for $\text{N-acetylcysteine}$ (Ioannides et al., 1983).

3.4 Pharmaceutical formulation and synthesis

A synthetic route has been described by Smith & Gorin (1961). Cysteine methyl ester hydrochloride and ethyl acetimidate hydrochloride are condensed to synthesize methyl 2-methyl-2-thiazoline-4-carboxylate hydrochloride. In the presence of hydrochloric acid, this compound is converted to $\text{N-acetylcysteine}$ and $\text{S-acetylcysteine}$.

Commercial products usually contain ethylenediaminetetraacetic acid (EDTA) to remove trace amounts of metals, such as copper, that will catalyse oxidation of $\text{N-acetylcysteine}$.

The available commercial preparations for oral use contain a 10-20% solution of $\text{N-acetylcysteine}$. This formulation needs to be diluted before administration to avoid gastrointestinal irritation. Dilution is best performed with water or a commercial carbonated or still flavoured drink.

3.5 Analytical methods

$\text{N-acetylcysteine}$ exists in biological systems in the oxidized or reduced form, and also in combination with thiol groups of, for example, proteins. Methods to measure these other forms have been described (Burgunder et al., 1989). As the levels necessary to protect the liver and kidney against paracetamol damage are unknown, it is inappropriate at present to measure levels of $\text{N-acetylcysteine}$ in blood or serum during treatment. The concentrations of $\text{N-acetylcysteine}$ that are toxic to man have not been established but there are indications of a relationship between adverse effects of $\text{N-acetylcysteine}$ and high plasma $\text{N-acetylcysteine}$ levels (> 300 mg/l) (Prescott et al., 1989).

3.5.1 Quality control of antidote

$\text{N-acetylcysteine}$ can be assayed in formulations by liquid chromatography (United States Pharmacopeia, 1990) or spectrophotometrically after reaction according to Ellman (1959) and Fontana & Toniolo (1974).

3.5.2 Methods for identification of the antidote

$\text{N-acetylcysteine}$ is identified by its infrared spectrum directly when dispersed in potassium bromide or, if in solution, after isolation by precipitation subsequent to saturation with sodium chloride at pH 2-3 (United States Pharmacopeia, 1990; personal communication from Astra Draco, Sweden).

3.5.3 Methods for analysis of the antidote in biological samples
Techniques for quantifying \( N \)-acetylcysteine in plasma and urine by high performance liquid chromatography have been developed and appear to be highly accurate (Kagedal et al., 1984; Lewis et al., 1984). Other similar methods have been described (Frank et al., 1984; Drummer et al., 1986; Johansson & Westerlund, 1986).

3.5.4 Methods for analysis of toxic agent

Methods for paracetamol analysis are discussed in section 1.6.

3.6 Shelf-life

3.6.1 Formulations for oral use

The shelf-life in the unopened commercial container appears to vary depending on the volume and concentration of the product. The average quoted shelf-life is 24 months (10-60 months) when the product is protected from light.

In the original opened container the shelf-life is 96 h but this shelf-life is reduced to one hour after dilution or preparation of \( N \)-acetylcysteine for administration.

3.6.2 Formulations for intravenous use

Duncan Flockhart state that \( N \)-acetylcysteine for intravenous use has a shelf-life of 3 years when stored at 25 \( ^\circ \)C and protected from light.

3.7 General properties

3.7.1 Mode of antidotal activity

The toxicity of paracetamol in overdose is thought to be mediated by its conversion to \( N \)-acetyl-\( p \)-benzoquinone imine (NAPQI) and the subsequent arylation and oxidation of critical thiol groups in the cell membrane (see section 1.4 for further details).

\( N \)-acetylcysteine could theoretically protect against paracetamol toxicity in a number of ways (see chapter 1). Commonly cited mechanism is that \( N \)-acetylcysteine can provide necessary sulfhydryl groups through synthesis of glutathione (GSH). In addition to acting as a conjugating agent, glutathione may have other effects including reduction of oxidized thiol groups such as those of the calcium translocases in cell membranes (Tee et al., 1986). The mode of antidotal action of \( N \)-acetylcysteine in the possible management of other forms of intoxication is likely to be similar to that in paracetamol poisoning (Flanagan, 1987).

3.7.2 Effect in paracetamol-induced liver failure

The mechanism of action of the protective effect of \( N \)-acetylcysteine on paracetamol-induced liver failure in humans has not been established. Most probably it is related to the ability of \( N \)-acetylcysteine to reverse tissue hypoxia through improved tissue microperfusion (Harrison et al., 1990; Keays et al., 1991).

3.7.3 Other therapeutic uses

The most common medical use of \( N \)-acetylcysteine is inhalation
therapy to reduce the viscosity of pulmonary secretions by reducing disulfide linkages of mucoproteins (Sheffner, 1983). It is also used to dissolve cystine stones in cystinuria (Martindale, 1988a). These properties are not relevant to its antidotal use.

The hypothesis that N-acetylcysteine might prevent nitrate tolerance has also been investigated on the basis that this tolerance was due to lack of reduced sulfhydryl groups in vascular smooth muscle. This has not been found to be the case (Parker et al., 1987; Hogan et al., 1990).

The suggestion that acetylcysteine may produce a reduction in lipoprotein a in patients with hyperlipidaemia and an associated risk of atherosclerosis (Gavish & Breslow, 1991) has been questioned by others (Stalenhoef et al., 1991).

3.8 Animal studies

3.8.1 Pharmacodynamics

Following a suggestion for the use of N-acetylcysteine by Prescott & Matthew (1974), studies in a number of animal species have shown that paracetamol-induced hepatic damage can be prevented. Piperno et al. (1978) reported that in the mouse N-acetylcysteine protected against paracetamol-induced liver damage and that this protective effect could be demonstrated even when administration was instituted 4 h after dosing with paracetamol. More recent studies have concentrated on the mechanism of this effect.

Lauterburg et al. (1983) studied the effects of N-acetylcysteine on rats in vivo. N-acetylcysteine was found not to form significant amounts of conjugate with the reactive intermediate, though it did result in increased glutathione synthesis. It was concluded that this mechanism is likely to be the most important one that operates in vivo. Studies by Corcoran et al. (1985) using mice did not support the hypothesis that N-acetylcysteine increases the proportion of paracetamol sulfated to a degree that would reduce the amount of toxic intermediate produced.

The pharmacodynamics of N-acetylcysteine as derived from studies on animals are discussed further in section 1.4.

3.8.2 Pharmacokinetics

Studies using radiolabelled N-acetylcysteine in rats showed moderately good absorption of the drug given by the oral route. The percentage of radioactivity recovered in the urine and faeces was 42, 33 and 20% by the intravenous, intramuscular and oral routes, respectively. A similar study in dogs dosed orally resulted in 36% recovery in the urine and faeces (Bonanomi & Gazzaniga, 1980). Distribution and elimination studies have only been performed with radio-labelled N-acetylcysteine and radioactivity measurements (Bonanomi & Gazzaniga, 1980). The results are difficult to interpret, but there is an indication of rapid distribution and elimination.

3.8.3 Toxicology

The LD$_{50}$ of N-acetylcysteine has been examined in a number of species and values range from 700 mg/kg intraperitoneally in the mouse to between 5100 and 6000 mg/kg orally in the rat (NIOSH, 1983;
Johnston et al., 1983).

The oral LD$_{50}$ in the mouse was found to be 7900 mg/kg compared to an intravenous LD$_{50}$ of 3800 mg/kg (NIOSH, 1983). The oral LD$_{50}$ in dogs was > 1000 mg/kg (Gosselin et al., 1984).

Respiratory failure is the usual terminal event in laboratory animals acutely poisoned with $N$-acetylcysteine (Johnston et al., 1983).

$N$-acetylcysteine has not been shown to be teratogenic in rats or rabbits (Bonanomi & Gazzaniga, 1980; USPCI, 1985). When administered to rabbits during the critical phase of embryogenesis, no malformation resulted (Johnston et al., 1983).

$N$-acetylcysteine is negative in the Ames mutagenicity test, and also reduces the mutagenic affect of chemical carcinogens in the same assay (Wilpart et al., 1985).

3.8.4 Studies with modified cytochrome P-450 activity

The important step in paracetamol metabolism is the formation of the reactive intermediate NAPQI by the cytochrome P-450 system. Inhibition or stimulation of activity of this enzyme group will therefore reduce or increase paracetamol toxicity, as discussed in section 1.5.

3.9 Volunteer studies

No studies on the efficacy of $N$-acetylcysteine in paracetamol poisoning have been carried out in volunteers. Studies on the pharmacokinetics of $N$-acetylcysteine, and effects of paracetamol on these, have however been performed.

From a pharmacokinetic point of view, one can look at $N$-acetylcysteine in two ways (Olsson et al., 1988). The reduced form can be considered as the parent drug and all other forms as metabolites. Alternatively, all $N$-acetylcysteine, irrespective of the fraction oxidized, may be regarded as the parent drug. The latter approach has been considered most logical from a clinical point of view (Olsson et al., 1988), although it is the reduced form that is the active form in paracetamol poisoning.

3.9.1 Absorption and bioavailability

Human studies that attempt to quantify $N$-acetylcysteine absorption have shown great variations in plasma area under the curve (AUC). Difficulties in clarifying this issue relate to the complicated pharmacokinetics and difficulties with the assay (reduced versus total $N$-acetylcysteine), and the possible contribution of a significant first-pass effect.

$N$-acetylcysteine appears to be absorbed rapidly when given as standard release preparations, the $T_{max}$ being around 40-45 min in the study of Borgstrom et al. (1986), and exists as the free reduced species in plasma for only a short time. It also causes an increase in protein and non-protein sulfhydryl concentrations (Maddock, 1980).

When given orally, as tablets or a solution, total
N-acetylcysteine was found to have a bioavailability as low as 6-10% (Borgstrom et al., 1986; Olsson et al., 1988). The bioavailability was lowest when a slow-release preparation was used.

The good absorption and low bioavailability is most probably due to an extensive first-pass elimination by the liver. However, the rather low hepatic extraction ratio (0.26) in one study argues against this theory (Borgstrom et al., 1986). Rapid uptake and deacetylation by tissues in the gut wall and liver, to form cysteine, glutathione, and inorganic sulfite, have been proposed to be the most probable explanation for the extensive first-pass effect (Borgstrom et al., 1986; Olsson et al., 1988). It is not clear whether this first-pass effect favours the administration of N-acetylcysteine by the oral route, as suggested by some authors (Borgstrom et al., 1986).

3.9.2 Distribution

The volume of distribution of total N-acetylcysteine in healthy volunteers receiving low doses (200-600 mg) was 0.33-0.47 litres/kg (Borgstrom et al., 1986; Olsson et al., 1988) compared to 0.54 litres/kg in patients receiving standard N-acetylcysteine treatment intravenously (Prescott et al., 1989). The volume of distribution of N-acetylcysteine therefore appears to be independent of dose. The volume of distribution of reduced N-acetylcysteine was 0.59 litres/kg in healthy volunteers (Olsson et al., 1988).

The mechanism of plasma protein binding of N-acetylcysteine is unlike that of other drugs. N-acetylcysteine is oxidized by reacting with thiol groups in plasma proteins to form mixed disulfides. In the study by Olsson et al. (1988), plasma proteins were precipitated with perchloric acid and dithiothreitol and the supernatant stored at -70 °C to prevent oxidation of reduced N-acetylcysteine. Reduced N-acetylcysteine was measured by chromatography of deproteinized plasma. The total plasma concentration of N-acetylcysteine, including protein-bound N-acetylcysteine, was assayed after initial reduction of disulfide bonds in plasma. With this technique, covalent protein binding of N-acetylcysteine in plasma increased with time after dosing to a maximum of about 50% 4 h after intravenous administration. This percentage fell to approximately 20% after 12 h.

3.9.3 Elimination

Borgstrom et al. (1986) studied the pharmacokinetics of N-acetylcysteine given intravenously and orally as three separate oral formulations to ten normal volunteers. Renal clearance accounted for about 30% of the total body clearance. Total body clearance was of the order of 0.2 litres/h per kg and the terminal elimination half-life of N-acetylcysteine, measured in this study by HPLC, was 2.27 h.

Other workers have measured both free N-acetylcysteine and total plasma sulphydryls. Thus Burgunder et al. (1989) noted that only a small proportion of the administered N-acetylcysteine was in its free form, the majority being present as disulfides. Administration of N-acetylcysteine increased free cysteine, but total cysteine and free and total glutathione in plasma were unchanged. Olsson et al. (1988) reported the terminal elimination half-life of total N-acetylcysteine, measured as free and disulfide, to be 6.25 h after oral administration and 5.15 h (range, 3.4-13)
after intravenous administration.

In patients receiving the standard intravenous N-acetylcysteine treatment, the half-life of total N-acetylcysteine was 5.7 h (Prescott et al., 1989).

3.9.4 Oral N-acetylcysteine and interaction with activated charcoal

Three in vitro studies have indicated effective adsorption of N-acetylcysteine by activated charcoal (Chinouth et al., 1980; Klein-Schwarz & Oerda, 1981; Rybolt et al., 1986). In studies on volunteers, the in vivo effects of charcoal have been contradictory. Two studies showed no statistical difference in plasma AUC between N-acetylcysteine alone and N-acetylcysteine plus charcoal (Krenzelok et al., 1980; Renzi et al., 1985). In contrast, Ekins et al. (1987) reported a decrease in the mean peak plasma N-acetylcysteine level of 29% and a decrease in mean plasma AUC of 39% in the activated charcoal group.

Although the clinical implication of an interaction between N-acetylcysteine and activated charcoal appears unclear, it is generally recommended that the use of activated charcoal should be avoided if N-acetylcysteine is being administered orally.

3.9.5 Pharmacodynamics

Burgunder et al. (1989) measured the effects of giving paracetamol in a dose of 2 g with 2 g N-acetylcysteine orally. In a control experiment, this dose of paracetamol alone resulted in a decrease in both plasma cysteine and glutathione levels. In contrast, administration of paracetamol with 2 g N-acetylcysteine resulted in an increase in cysteine and glutathione levels. The authors concluded that, in humans, N-acetylcysteine supports glutathione synthesis when demand for this is increased, as is the case after paracetamol administration.

3.10 Clinical studies - clinical trials

3.10.1 Efficacy of intravenous N-acetylcysteine

Prescott et al. (1977) first reported the effects of N-acetylcysteine given in a dose of 300 mg/kg body weight over 20 h to 15 patients whose plasma paracetamol concentrations (range 262-369 mg/l at 4 h) suggested the likelihood of subsequent hepatic dysfunction. In this study, 11 out of 12 patients treated within 10 h either suffered no liver dysfunction or developed only mild disturbance, as judged by liver function tests. The other patient, and three further patients treated more than 10 h after ingestion of paracetamol, developed liver damage.

In a subsequent report dealing with a hundred cases of severe paracetamol poisoning (Prescott et al., 1979), only 1 of 62 patients treated within 10 h developed severe liver damage. This was in comparison with a 58% incidence of severe liver damage in a retrospective series of patients who had received supportive treatment alone (33 of 57 patients). This study also showed that efficacy after 10 h diminishes and that treatment after 15 h with intravenous N-acetylcysteine is likely to be ineffective. Furthermore paracetamol-induced renal damage did not occur in patients treated less than 10 h after overdose. The incidence of renal impairment in
patients treated after this time (13%, 5/38) was similar to that in a group treated supportively (11%, 6/57). Only four patients with renal impairment required haemodialysis.

The dosage regimen used in both the studies of Prescott consisted of an initial loading dose of 150 mg/kg in 200 ml of 5% dextrose over 15 min followed by 50 mg/kg in 500 ml of 5% dextrose over 4 h and a final 100 mg/kg in one litre of 5% dextrose given over 16 h. The total dose was thus 300 mg/kg over 20 h. The basis for this dosage regimen was empirical and not based on experimental data. The treatment line was defined as a line joining the following plots on a semi-logarithmic graph of plasma paracetamol concentration: 200 mg/l at 4 h after ingestion and 30 mg/l at 15 h (Fig. 1). As a result of this study intravenous N-acetylcysteine was adopted as a treatment for paracetamol poisoning in the United Kingdom and in most countries worldwide.

Smilkstein et al. (1991) reported a non-randomized open multicentre trial of 179 patients with acute paracetamol overdose and plasma concentrations above the treatment line. All patients received a 48-h intravenous N-acetylcysteine dosage regimen consisting of a loading dose of 140 mg/kg, followed by 12 doses of 70 mg/kg every 4 h, giving a total dose of 980 mg/kg over 48 h. For patients classified as having a "probable risk", as defined in the Smilkstein et al. (1988) study, hepato-toxicity occurred in 5 out of 50 (10%) patients treated within 10 h of ingestion and in 23 of 85 (27%) patients treated 10 to 24 h after ingestion. Of the high-risk patients treated 16 to 24 h after ingestion, 11 of 19 (58%) developed hepatotoxicity. When compared with historical controls in the 20-h intravenous protocol (Prescott et al., 1979), these results were equivalent for patients treated within 10 h post-ingestion and superior for patients treated after 10 h (27 versus 53%). Smilkstein et al. (1991), however, used a treatment line that was 25% lower than that of Prescott et al. (1979), thus precluding valid comparison of data. However, when comparing the high-risk patients treated 16-24 h post-ingestion in the Smilkstein et al. (1991) study, i.e. patients with paracetamol concentrations above a treatment line between 300 mg/l at 4 h and 75 mg/l at 12 h (Fig. 1), there is some evidence for less hepatotoxicity resulting from use of the 48-h intravenous protocol (58 versus 82%).

3.10.2 Efficacy of oral N-acetylcysteine

Oral N-acetylcysteine is the most widely used antidote for paracetamol poisoning in the USA. Rumack and his colleagues have published a series of reports on their experience with N-acetylcysteine in cases of paracetamol poisoning. Rumack & Peterson (1978) reported on 100 patients who had ingested toxic doses and were treated with N-acetylcysteine. In this series, 17% of 49 patients beginning therapy within 10 h of paracetamol poisoning developed hepatotoxicity. Treatment between 10 and 24 h was less successful; 45% of patients treated at this time developed severe hepatotoxicity.

In a second report (Rumack et al., 1981) only 7% of 57 patients treated within 10 h after ingestion developed hepatotoxicity, 29% of 52 patients treated between 10 and 16 h developed hepatotoxicity and 63% of 39 patients beginning treatment at 16 to 24 h after ingestion developed hepatic dysfunction.
Smilstein et al. (1988) reported on their experience over a 10-year period (1976-1985) in a large prospective study involving 2540 patients treated orally with a loading dose of \( N \)-acetylcysteine of 140 mg/kg, followed by 17 oral maintenance doses of 70 mg/kg (i.e. a total of 18 doses). In this large series no deaths were directly related to paracetamol toxicity in patients in whom \( N \)-acetylcysteine therapy began within 16 h after ingestion. There was, however, a relationship between delay in treatment and the risk of hepatotoxicity, as judged by liver function tests in patients in whom plasma paracetamol concentrations indicated a likelihood of hepatotoxicity. In patients considered at high risk of hepatotoxicity, as judged by paracetamol concentrations, 8.3% \((17 \text{ out of } 206)\) of patients treated within 10 h developed hepatotoxicity, 34.4% \((199 \text{ of } 578)\) patients treated 10 to 16 h after presentation developed hepatotoxicity, and 41% \((116 \text{ of } 283)\) of patients treated 16 to 24 h after presentation developed hepatotoxicity. The 95% confidence intervals for the three groups were 5-13%, 31-37%, and 35-46%, respectively. High risk was defined as initial plasma paracetamol concentrations above the line intersecting 300 mg/l at 4 h and 75 mg/l at 12 h \((n=1067)\) (see Fig. 1).

3.10.3 Oral versus intravenous \( N \)-acetylcysteine

In summary, the frequency of severe liver damage in patients treated within 10 h was 2% in patients \((n=62)\) treated with intravenous \( N \)-acetylcysteine, compared to 17% \((n=49)\), 7% \((n=57)\) and 8% \((n=206)\) in patients treated with oral \( N \)-acetyl-cysteine (sections 3.10.1 and 3.10.2). However, there have been no studies published which allow a direct comparison of oral versus intravenous \( N \)-acetylcysteine treatment, nor has the optimal duration of either the oral or intravenous regimen been clearly established on the basis of comparative clinical trials.

3.10.4 Therapeutic drug monitoring during \( N \)-acetylcysteine treatment

The doses of \( N \)-acetylcysteine given in both the oral and intravenous dose regimen are empirical and are not based on studies of the plasma concentrations of \( N \)-acetylcysteine required for antidotal activity. Although there are pharmacokinetic data available for the standard intravenous dose regimen, there is no indication for measuring \( N \)-acetylcysteine in plasma during this treatment (Prescott et al., 1989).

3.10.5 \( N \)-acetylcysteine in paracetamol-induced liver failure

When \( N \)-acetylcysteine was introduced as an antidote in paracetamol poisoning, there was some concern that late administration (> 24 h post-ingestion) of \( N \)-acetyl-cysteine, and thereby amino and sulfhydryl-groups, could be potentially dangerous in the presence of failing liver function. Keays et al. (1991) performed an open randomized study of 50 consecutive patients with paracetamol-induced fulminant hepatic failure without previous \( N \)-acetylcysteine treatment. The study could not be performed blind because the \( N \)-acetylcysteine solution has an easily identifiable pungent aroma. The \( N \)-acetylcysteine dose given was the standard 20-h intravenous regimen. The rate of survival was significantly higher among the patients given \( N \)-acetylcysteine \( (48\%, \ 12/25)\) as compared to controls \( (20\%, \ 5/25)\). The \( N \)-acetyl-cysteine-treated patients also had a
significantly lower incidence of cerebral oedema and hypotension requiring inotropic support. The average time from paracetamol ingestion to inclusion in the study was 53 h (range 36-80) in the N-acetylcysteine-treated group as compared to 56 h (33-96) among controls.

The mechanism for the therapeutic effect of N-acetylcysteine in paracetamol-induced liver failure is not clear but may be related to increased tissue oxygen consumption and decreased oxidant stress, thereby reducing the oxidation of important protein thiol groups (Keays et al., 1991). Although this study was not placebo-controlled, it seems justified at present to give N-acetylcysteine to all patients with paracetamol-induced fulminant liver failure.

3.11 Clinical studies - case reports

Clinical studies of the use of oral and intravenous N-acetylcysteine have clearly documented its effect and have thus limited the need for efficacy information from case reports. However, case reports have provided valuable information about the adverse effects and toxicity of N-acetylcysteine in humans.

3.11.1 Adverse effects

The principal toxic effects of N-acetylcysteine when given intravenously consist of anaphylactoid reactions following therapeutic doses (Bateman et al., 1984a,b; Gervais et al., 1984; Mant et al., 1984; Tenenbein, 1984). This effect could be a pseudo-allergic reaction, since it appears to be due to histamine release (Bateman et al., 1984b). The most appropriate therapy for this adverse effect appears to be intravenous antihistamines. Flushing of the chest or face is common and usually begins 15 to 75 min after the initiation of the infusion, being associated with peak N-acetylcysteine concentrations of between 300 and 900 mg/l. These concentrations are considerably higher than peak levels obtained following the oral regimen (Prescott et al., 1989). Occasionally more severe anaphylactic reactions to intravenous N-acetylcysteine have been reported (Walton et al., 1979; Vale & Wheeler, 1982). Urticarial reactions may also follow the use of oral N-acetylcysteine (Charley et al., 1987).

Extravasation of a 20% N-acetylcysteine solution caused pain and inflammation (Casola & van Sonnenburg, 1984).

Nausea and vomiting are very common during oral N-acetylcysteine therapy in paracetamol overdose. Dilution to at least a 9% solution prior to oral administration is therefore recommended (Shaw, 1969). Granules of N-acetylcysteine (200 mg) given in sachets did not result in histopathological changes in the gastrointestinal mucosa (Marini et al., 1980). Diarrhoea may also occur following N-acetylcysteine administration (Ferrari, 1980). One report suggested that liver enzyme changes may have occurred in a 3-year-old male child with cystic fibrosis treated with both oral and rectal N-acetylcysteine for meconium ileus. Liver enzyme levels were elevated on two separate occasions, but the doses of N-acetylcysteine delivered were considerably larger than those recommended for antidotal use for paracetamol poisoning in a child of this age. Intrinsic hepatobiliary disease in the infant could not be ruled out (Bailey & Andres, 1987).
Bronchospasm, which may be part of the anaphylactoid reaction to intravenous N-acetylcysteine (Ho & Beilin, 1983; Mant et al., 1984), may occur after N-acetyl-cysteine inhalation in the management of pulmonary disease (Dano, 1971). Intracranial hypertension has also been reported following inhalational therapy (Venturelli & Tein, 1984).

Cardiovascular collapse and death was reported in a 4-year-old child who received 2.17 g N-acetylcysteine intravenously as a loading dose and intravenous infusion of 0.36 g/h (Anon, 1984). This dose is in excess of that recommended.

In another case reported by Mant et al. (1984), hepatorenal failure secondary to paracetamol overdose was associated with disseminated intravascular coagulation. This patient also received between 2 and 6 times the recommended loading dose of intravenous N-acetylcysteine, but a cause-and-effect relationship between N-acetyl-cysteine and disseminated intravascular coagulation cannot be established. Similarly, haemolysis developed in a patient with glucose-6-phosphate dehydrogenase deficiency who had received a 6-fold overdose of N-acetylcysteine, but this cannot be explained on the basis of oxidative haemolysis, and other mechanisms must, presumably, have been responsible.

In the study by Smilkstein et al. (1991), 980 mg N-acetylcysteine/kg was given intravenously over 48 h to 223 patients initially entering the study. Adverse reactions to N-acetylcysteine occurred in 32 out of 223 cases (14%), consisting in 29 out of 32 patients (91% of reactions) of transient, patchy skin erythema or mild urticaria during the loading dose (140 mg/kg) that did not require discontinuation of therapy. One patient suffered a potentially life-threatening reaction as 12 g (instead of 3.6 g) was given as the fifth dose. The patient developed oedema, diffuse rash, wheezing, throat tightness, and itching. All symptoms and signs responded to antihistamine administration.

3.11.2 Use in pregnancy

Experience in 59 pregnant patients suggested that use of N-acetylcysteine in pregnancy did not result in toxic effects on the fetus (Bronstein & Rumack, 1984). In practice, the risk to the mother and baby of paracetamol-induced liver damage probably far outweighs any potential risk of N-acetylcysteine, and pregnancy should not be considered a contraindication to the use of this agent.

3.12 Summary of evaluation

3.12.1 Indications

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 in this manner should be considered.

3.12.2 Advised route and dosage

3.12.2.1 Intravenous N-acetylcysteine

Intravenous N-acetylcysteine should be given as an initial loading dose of 150 mg/kg body weight in 200 ml of 5% dextrose over 15 min, followed by 50 mg/kg in 500 ml of 5% dextrose over 4 h and then 100 mg/kg in 1 litre of 5% dextrose over the next 16 h. The total dose by this route will be 300 mg/kg over 20 h.

There are indications that a dosage regimen of 980 mg/kg over 48 h may be more effective for patients admitted 10-24 h post-ingestion, especially those at "high risk". The fact that N-acetylcysteine also increases survival in patients with established acute paracetamol-induced liver failure (N-acetylcysteine being given in this instance at about 50 h post-ingestion) may support the use of a 48-h dosing regimen to "high risk" patients admitted late after ingestion of a paracetamol overdose.

3.12.2.2 Oral N-acetylcysteine

A 5% solution of N-acetylcysteine should be given as an oral loading dose of 140 mg/kg. The available commercial preparations of N-acetylcysteine are 10 and 20% solutions, and these need to be diluted. Seventeen further doses of 70 mg N-acetylcysteine/kg should be given as a 5% solution in diluent every 4 h. The total dose by this route will be 1330 mg/kg over 72 h.

The intravenous regimen is preferable to the oral one because of the predictable occurrence of vomiting in seriously poisoned patients.
when using the oral regimen. The relative efficacy of the two regimens in the prevention of paracetamol-induced hepatotoxicity cannot be judged on present evidence.

3.12.3 Other consequential or supportive therapy

Symptomatic treatment of ensuing complications should be according to conventional principles of intensive care. Special emphasis should be given to the treatment of liver failure and acute renal failure, as discussed in section 1.7. At present, liver transplantation has no clearly defined role in the treatment of acute liver failure due to paracetamol poisoning, although it may be useful in selected cases being treated at specialist centres (see section 1.7.1.2).

3.12.4 Controversial issues and areas where there is insufficient information to make recommendations

Studies to determine the relative efficacy of the oral and intravenous regimens have not been performed. Data exist suggesting that the 48-h intravenous infusion regimen and the 72-h oral regimen may be more effective than the 20-h intravenous regimen when the latter is used as the historical control. Direct comparison of the results from the 48 and 72-h studies with those from the 20-h study is not possible.

From a practical point of view, the shortest dosing regimen is desirable, provided that it is effective. One problem when comparing the different N-acetylcysteine studies is the efficacy parameter or end-point "severe liver damage", defined as an ALAT/ASAT activity of > 1000 U/l. Firstly, this is a measurement of hepatic necrosis and not of liver function/protein synthesis. Secondly, clinical experience shows that more than 99% of patients suffering from paracetamol-induced hepatotoxicity where ALAT/ASAT activity is > 1000 U/l will recover completely without long-term sequelae provided that appropriate therapy is given. This parameter was arbitrarily chosen in early studies of paracetamol poisoning. However, in view of the marginal differences in outcome when different dosage regimens are employed, the need for a new efficacy parameter should be considered by clinical toxicologists and hepatologists.

When comparing the results obtained from use of the 20-h intravenous dosing regimens with those from the 48-h intravenous and 72-h oral dosing regimens, no differences are observed when end-points such as mortality or permanent sequelae are considered.

Possible benefit from the use of N-acetylcysteine in patients admitted late and at risk of developing fulminant liver failure has not been proven and remains controversial (see section 3.12.1).

3.12.5 Proposals for further studies

Future studies on intravenous N-acetylcysteine should be performed with the 20-and 48-h regimens in such a way as to make the data obtained comparable. Such studies should concentrate on patients in the high-risk group admitted late (10-24 h post-ingestion). The use of firmer end-points than an ALAT/ASAT activity > 1000 U/l should be considered.
It would be useful to investigate whether side-effects of N-acetylcysteine might be avoided and antidotal efficacy maintained if the initial intravenous bolus dose is given more slowly.

The possible benefit of N-acetylcysteine treatment in patients admitted late (24-50 h after poisoning), and at particular risk of developing liver failure, needs further study. Since the treatment nomogram does not extend beyond 24 h, it would be useful to study correlations between ingested dose and the risk of liver failure and whether there is a dose threshold for this risk.

3.12.6 Adverse effects

N-acetylcysteine appears to have a good therapeutic index and side-effects are few, consisting mainly of mild flushing. These side-effects are more common following intravenous administration and are considered to be dose-dependent. The incidence and severity of side-effects may therefore be reduced by giving the initial bolus dose more slowly. There have been some reports of serious side-effects associated with the intravenous administration of N-acetylcysteine.

These appear to be anaphylactoid and have generally been reported when more than the recommended dose has been given in error; at least one death has resulted. Antihistamines appear to be effective.

Oral N-acetylcysteine may cause gastrointestinal irritation; dilution to a solution of 9% or less is recommended to reduce the incidence and severity of this side-effect.

3.12.7 Restrictions of use

If a patient has previously experienced a severe anaphylactoid reaction to N-acetylcysteine, oral methionine should be given in preference. Otherwise there are no contraindications to the use of N-acetylcysteine following the ingestion of paracetamol. If the time of ingestion is difficult to assess, current evidence indicates that no harm will come if N-acetylcysteine is given later than 24 h after ingestion of paracetamol.

3.13 Model information sheet

3.13.1 Uses

N-acetylcysteine is indicated in the treatment of paracetamol poisoning if:

a) plasma paracetamol levels taken between 4 and 8 h post-ingestion fall above "the treatment line" indicated in Fig. 1;

b) more than 100 mg paracetamol/kg has been ingested in a single dose and plasma paracetamol concentrations are not available;

c) acute paracetamol-induced liver failure has developed or is likely to develop (see 3.13.1.1).

N-acetylcysteine treatment should be started as soon as possible if the criteria above are fulfilled, as its antidotal efficacy rapidly declines once more than 8 h have elapsed from the time of ingestion of paracetamol. No antidotal effect has been
documented when \( N \)-acetylcysteine has been given later than 24 h post-ingestion. However, harm is unlikely if \( N \)-acetylcysteine is given later than this, e.g., in the event of an incomplete or uncertain case history.

In the event of an unreliable case history, where the time of ingestion and/or amount of paracetamol ingested is not known, it is reasonable to adopt a low threshold for the use of \( N \)-acetylcysteine, i.e. if in doubt, \( N \)-acetylcysteine should be administered.

If a plasma sample taken later than 8 h post-ingestion shows that the plasma paracetamol concentration is definitely below the treatment line, \( N \)-acetylcysteine treatment should be stopped.

3.13.1.1 Use in liver failure

\( N \)-acetylcysteine significantly increases survival in patients with acute paracetamol-induced fulminant liver failure when given according to the 20-h intravenous dosing regimen indicated in section 3.13.2.1. There appear to be no contraindications to this therapy, which should be instituted as soon as possible in patients admitted in this late stage of poisoning or who for some other reason have not received \( N \)-acetylcysteine previously.

In patients admitted more than 24 h post-ingestion who are not suffering from liver failure but who are at particular risk of developing it (> 150-200 mg paracetamol/kg ingested), it would seem reasonable to give \( N \)-acetylcysteine intravenously according to the dosage regimen given in section 3.13.2.1.

3.13.2 Dosage and route

3.13.2.1 Intravenous \( N \)-acetylcysteine

Intravenous \( N \)-acetylcysteine should be given as an initial loading dose of 150 mg/kg body weight in 200 ml of 5% dextrose over 15 min, followed by 50 mg/kg in 500 ml of 5% dextrose over 4 h and then 100 mg/kg in 1 litre of 5% dextrose over the next 16 h. The total dose given by this route will be 300 mg/kg over 20 h.

In patients admitted 10-24 h after ingestion of paracetamol, and especially if large amounts are ingested, one may consider using the 48-h intravenous dosage regimen instead: an initial loading dose of 140 mg \( N \)-acetylcysteine/kg, followed by 12 doses of 70 mg/kg every 4 h, i.e. a total of 980 mg/kg over 48 h (in 5% dextrose).

3.13.2.2 Oral \( N \)-acetylcysteine

A 5% solution of \( N \)-acetylcysteine should be given as an oral loading dose of 140 mg/kg. The available commercial preparations of \( N \)-acetylcysteine are 10 and 20% solutions and need to be diluted. This can be done using water or a commercial carbonated or still flavoured drink. Seventeen further doses of 70 mg \( N \)-acetylcysteine/kg should be given as a 5% solution in diluent every 4 h. The total dose given by this route will be 1330 mg/kg over 72 h.

The intravenous treatment regimen is preferred to the oral one (see sections 3.12.2 and 3.12.4) unless the intravenous \( N \)-acetylcysteine formulation is unavailable or there is lack of
expertise/equipment for such treatment.

3.13.3 Precautions/contraindications

Previous severe anaphylactoid reactions to $N$-acetylcysteine should be considered an absolute contraindication if methionine is available as an alternative antidote. But in the case of a potentially severe paracetamol intoxication where methionine is unavailable, a history of such a reaction is a relative contraindication.

3.13.4 Pharmaceutical incompatibilities and drug interactions

$N$-acetylcysteine is incompatible with solutions containing certain antibiotics, including ampicillin sodium, amphotericin, erythromycin lactobionate and some tetracyclines. Activated charcoal should not be given if oral $N$-acetylcysteine is administered.

3.13.5 Adverse effects

In about 15% of patients given $N$-acetylcysteine intravenously, mild urticaria is seen during infusion of the bolus dose. This does not usually require discontinuation of infusion, although a slower infusion rate of the bolus dose (1-2 h) may be advisable. If more pronounced skin erythema or urticaria develops, an antihistamine should be given.

Patients should be monitored for possible anaphylactoid reactions including bronchospasm, hypotension and urticaria; such reactions are more common with intravenous $N$-acetylcysteine. Management of these reactions involves the following measures:

a) stop the $N$-acetylcysteine infusion, at least temporarily;
b) administer an antihistamine intravenously;
c) in the rare event of severe bronchospasm consider using nebulized salbutamol or, in severe cases, parenteral adrenaline. If the reaction is mild, $N$-acetylcysteine may be restarted cautiously. As an alternative, especially in the case of a severe reaction, the use of oral methionine is advisable.

Other adverse reactions to oral $N$-acetylcysteine include vomiting and diarrhoea.

3.13.6 Use in pregnancy and lactation

There is no evidence of toxic effects on the fetus arising from the use of standard oral doses of $N$-acetylcysteine in pregnant women poisoned by paracetamol. The risk to the mother and baby of paracetamol-induced liver damage is likely to far outweigh any potential risk of $N$-acetylcysteine administration.

3.13.7 Storage

The shelf-life of the intravenous preparation (Parvolex) is stated by the manufacturer, Duncan Flockart, to be 3 years at room temperature.

The shelf-life of oral $N$-acetylcysteine is usually 2 years.
A change in colour of solutions of $N$-acetylcysteine to light purple does not indicate significant impairment of safety or efficacy.

3.14 References


United States Pharmacopeia (1990) 22nd ed. Rockville, Maryland, United States Pharmacopeial Convention, Inc.


Vale JA & Wheeler DC (1982) Anaphylactoid reactions to acetylcysteine
