Paracetamol

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Summary

Paracetamol is an analgesic and antipyretic agent which was first marketed for use as a drug in the U.K. in 1956. It has since become popular with the medical profession and the general public as an alternative to aspirin.

History and usage of paracetamol

Aspirin was introduced into clinical practice in 1899 and, although paracetamol had already been synthesized by this time, its medicinal properties remained unrecognized. Quite by chance, acetanilide, a derivative of aniline, was found to possess antipyretic activity and this substance was introduced for the treatment of fever in 1866. It soon proved to be toxic, however, and attention became directed towards other derivatives of aniline such as phenacetin and paracetamol. Phenacetin was marketed in 1887 but this too was found to possess serious side effects which included haemolytic anaemia and methaemoglobin formation. Paracetamol was assumed to be similar in this respect and little interest was shown in the drug until 1949. Flinn and Brodie (1948) demonstrated that paracetamol was the metabolite of phenacetin and acetanilide responsible for the analgesic and antipyretic properties of these 2 compounds (Fig. 1). The methaemoglobinaemia was

later shown to be due to a compound derived from another metabolite of phenacetin, *p*-phenetidine (Brodie and Axelrod, 1949).

Paracetamol has steadily gained in popularity since its introduction in 1956 to the United Kingdom. In 1974, the equivalent of nearly 3000 million 500-mg tablets of paracetamol were consumed and 1800 million of these were purchased 'across the counter' without a prescription. Whilst the sales of paracetamol have risen, those of aspirin have fallen, so that the total number of analgesic tablets sold in this country has remained almost constant for more than 10 years.

The history of paracetamol in America is essentially similar to that in Great Britain. The drug was marketed in 1950 as a substitute for phenacetin in an analgesic mixture. After a few case reports of blood dyscrasias the manufacturer recalled the drug in 1951, but it was again made available the following year, although this time only on prescription. However, paracetamol has been freely available without prescription since 1955.

Paracetamol is also commonly prescribed both in Great Britain and America in the form of proprietary preparations which contain dextropropoxyphene as well as paracetamol. The acute toxicity of these combinations presents quite differently from that due to paracetamol alone, and this subject will be considered separately later.

Pharmacology

Paracetamol possesses antipyretic properties similar to those of aspirin although, unlike aspirin, it does not have anti-inflammatory activity. The possession of antipyretic activity by aspirin and paracetamol is the result of their ability to inhibit the biosynthesis of prostaglandins and other substances from arachidonic acid. The production of fever in man (Dinarello and Wolff, 1978) involves the synthesis of endogenous pyrogen by phagocytic leucocytes in response to exogenous pyrogens (toxic, immunological and infectious agents). Endogenous pyrogen, a low molecular weight protein, is released from phagocytic leucocytes and enters the circulation after new messenger RNA and protein have been synthesized (Dinarello, 1979). Fever is due to the interaction of endogenous pyrogen with receptors in

Fig. 1. The metabolism of phenacetin.

that part of the anterior hypothalamus concerned with thermoregulatory control of the body. This interaction involves the local production of prostaglandin E, monoamines and cyclic AMP. Information is transmitted from the anterior hypothalamus to the vasomotor centre which in turn directs sympathetic nerve fibres to constrict peripheral vessels and thereby decrease loss of heat from the body. Aspirin and paracetamol do not affect the release of endogenous pyrogen from leucocytes (Clark and Moyer, 1972) but they do interfere with the synthesis and release of prostaglandins from the anterior hypothalamus (Feldberg *et al.*, 1972). Recent experiments, though, suggest that compounds other than prostaglandins but also derived from arachidonic acid may be important in the development of fever (Cranston, 1979).

Unlike aspirin, the analgesic effect of paracetamol does not appear to be associated with anti-inflammatory activity and this seems to be due to the different sensitivities of central and peripheral prostaglandin synthetase systems to the drug. Paracetamol is a potent inhibitor of the prostaglandin synthetase found in the brains of the dog and the rabbit (Flower and Vane, 1972) and it is this action which is presumably primarily responsible for its effectiveness as an analgesic. However, when used in therapeutic concentrations, paracetamol has no action on the prostaglandin synthetase found in dog spleen. Aspirin and indomethacin differ from paracetamol in this respect because they inhibit both peripheral and central prostaglandin synthetase systems and as a consequence possess intrinsic anti-inflammatory activity.

Pharmacokinetics

Paracetamol is rapidly absorbed from the gastrointestinal tract (Gwilt *et al.*, 1963) and peak levels of 10–20 mg/l are achieved within one to 2 hr after the administration of a 1000-mg dose orally. Absorption is influenced by the presence of food (Mattok and McGilveray, 1973), and also by the rate of gastric emptying (Nimmo *et al.*, 1973).

Paracetamol is widely distributed throughout most body fluids. Although protein binding appears to be insignificant at therapeutic concentrations it does increase to about 20% when the drug is present in toxic concentrations (Gazzard *et al.*, 1973).

The half-life of elimination of paracetamol ranges between one and 4 hr and it is removed from the circulation mainly by microsomal liver enzymes by conjugation with glucuronic and sulphuric acids and approximately 80% of the drug is metabolized in this way. These conjugated metabolites lack biological activity. Although the half-life of elimination of paracetamol in children is similar, rather more paracetamol is excreted in the form of sulphate

conjugates than as glucuronide conjugates (Miller, Roberts and Fischer, 1976).

The half-life of unchanged paracetamol is increased in liver failure. The conjugated metabolites accumulate in renal failure as the glomerular filtration rate falls, but there is no significant increase in the concentration of the free drug (Lowenthal *et al.*, 1976).

Clinical efficacy

It is exceptionally difficult to assess the response of a fever to an antipyretic drug, and most published studies have been unsatisfactory in various respects. Perhaps because of these difficulties, aspirin has acquired a reputation for being a better antipyretic agent than paracetamol although, in fact, the 2 drugs have been shown to be equally effective. In one well designed study, febrile infants and children were observed for 4 hr before the administration of a single dose of either aspirin or paracetamol (Eden and Kaufman, 1967). Both drugs caused a similar fall in body temperature which lasted for 6 hr with a peak antipyretic effect at 3 hr.

Paracetamol is widely used as an analgesic for mild to moderate pain although unfortunately there are few adequately controlled trials. Those that do exist suggest that there is little difference between aspirin and paracetamol provided that the pain is not associated with local inflammation. Episiotomy pain and chronic cancer pain have, for example, been used as models. Moertel and his colleagues (1972) published a study of the use of mild analgesics in cancer pain. The study was double-blind and crossover in design. Analysis of the results from the 57 patients in the study showed that both aspirin and paracetamol were better than placebo when administered in similar doses. Although aspirin appeared to be better than paracetamol the difference was not statistically significant.

In contrast, when an anti-inflammatory rather than an analgesic effect is required, aspirin is considerably more effective than paracetamol. A study of patients with rheumatoid arthritis (Hajnal, Sharp and Propert, 1959) measured grip strength, pain and stiffness. Five grams of aspirin and 7.5 g of paracetamol were administered daily using a double-blind crossover trial design. Aspirin was shown to be far superior to paracetamol especially when assessed by changes in grip strength.

Side effects

Provided that paracetamol is taken in therapeutic doses (0.5–1.0 g orally 3–4 times/day as required) side effects of the drug are uncommon. Eczematous and urticarial skin rashes occur rarely and very rarely mucosal lesions, laryngeal oedema and drug fever are seen.

Five cases of thrombocytopenia have been reported (Heading, 1968; Eisner and Shahidi, 1972; Skokan, Hewlett and Hoffman, 1973; Kornberg and Polliack, 1978; Scheinberg, 1979) and one instance was due to an immune reaction to the sulphate conjugate of paracetamol (Eisner and Shahidi, 1972). Several patients have developed haemolytic anaemia (MacGibbon *et al.*, 1960; Manor *et al.*, 1976) and one patient simultaneously developed thrombocytopenia (Kornberg and Polliack, 1978).

Unlike aspirin, neither the bleeding time nor the platelet aggregation of normal subjects or haemophilic patients is affected when paracetamol is administered in single doses or chronically for up to 6 weeks (Mielke *et al.*, 1976). Paracetamol does not cause gastric erosions (Loebl *et al.*, 1977; Ivey, Silviso and Krause, 1978) or occult loss of blood from the gastrointestinal tract (Goulston and Skyring, 1964). Paracetamol, therefore, may safely be given to patients with bleeding disorders such as haemophilia. Antlitz, Mead and Tolentino (1968) noted that paracetamol may interact to a minor extent with oral anticoagulant therapy. Twelve patients who were maintained on approximately 5 mg/day of warfarin were given 2.6 g paracetamol daily in 4 divided doses, for 4 weeks. After 6 weeks, a mean increase of 3.7 sec in the prothrombin time was noted, which prompted a reduction in the anticoagulant dose. However, in a subsequent study (Antlitz and Awalt, 1969) the same authors were unable to demonstrate any effect on the prothrombin time of 2 doses of 650 mg of paracetamol given 4 hr apart.

Analgesic nephropathy was first reported from Switzerland and Scandinavia where analgesic powders were once regularly consumed in large quantities. The disease is common in Australia and Canada but occurs infrequently in the United States and Great Britain. Aspirin and phenacetin have been implicated as causes of analgesic nephropathy and because paracetamol is a major metabolite of phenacetin, there has been considerable concern about its possible role in the development of this form of nephropathy. There have, however, been only 4 reported cases of analgesic nephropathy associated with the chronic ingestion of large quantities of paracetamol (Krikler, 1967; Prescott, 1966; Kerr, 1970; Master and Krikler, 1973) and 3 of the patients had also ingested either aspirin or phenacetin. Furthermore, Edwards *et al.* (1971) assessed renal function in 18 rheumatology patients who had each consumed from 2 to 30 kg of paracetamol over varying periods of time. There was no significant impairment of renal function and no relation between any impairment and the quantity of paracetamol ingested. Thirteen of the patients showed no significant deterioration of renal function

during the following year when they each consumed an additional 2 kg of paracetamol.

Recently, there have been reports of chronic liver damage following the chronic ingestion of little more than therapeutic amounts of paracetamol. The evidence for this remains in doubt although it does seem probable that certain patients are more susceptible to the hepatotoxic effects of paracetamol. In some reports, the consumption of paracetamol was excessive (Barker, de Carle and Anuras, 1977; Ware *et al.*, 1978) and several patients were at special risk because of either chronic ethanol consumption or glutathione depletion caused by cachexia. Rosenberg *et al.* (1977) reported 2 patients who ingested paracetamol whilst suffering from infectious mononucleosis and who subsequently developed hepatitis. However, infectious mononucleosis itself may be complicated by hepatitis, and at least one of the patients concerned suffered from Gilbert's disease, a condition in which the metabolism of paracetamol is thought to be abnormal (Douglas *et al.*, 1978). In 2 well documented case reports (Johnson and Tolman, 1977; Bonkowsky, Mudge and McMurtry, 1978) there is no doubt that small doses of paracetamol did cause disturbance of liver function. The possibility of pre-existent or coincident chronic liver disease, however, cannot be excluded. It would seem sensible to use paracetamol with caution in patients with either probable or established liver disease where the half-life for elimination of paracetamol is known to be prolonged (Shamszad *et al.*, 1975; Forrest *et al.*, 1977; Andreassen and Hutters, 1979). Even so, there remains no definite evidence for a true variation in host susceptibility to paracetamol in either man or animal (Mitchell, 1977; Forrest *et al.*, 1979).

Paracetamol poisoning

The first cases of fulminant hepatic failure due to paracetamol poisoning were reported in 1966 (Davidson and Eastham, 1966; Thomson and Prescott, 1966). Since then, the incidence of paracetamol poisoning has progressively increased (Fig. 2) and this condition is now responsible for more cases of hepatic failure in the United Kingdom than any other cause. In 1977, there were 473 deaths officially recorded in England, Wales and Scotland as being associated with an overdose of products containing paracetamol. One-hundred-and-sixty deaths are recorded as being due to paracetamol alone and 313 occurred when paracetamol was taken in combination with other drugs. The recorded number of deaths due to paracetamol alone, however, may exceed the real number which can be directly attributed to paracetamol (Hamlyn, 1978; Harvey and Spooner, 1978; Spooner and Harvey, 1978). It is likely that some of the deaths were due to the

concomitant ingestion of the respiratory depressant drug, dextropropoxyphene, which can be prescribed in fixed combination with paracetamol. Two-hundred-and-thirty-two of the 313 deaths associated with the ingestion of paracetamol and other drugs were recorded as being due to such a combination (Fig. 2).

FIG. 2. Deaths officially recorded as being due to paracetamol and paracetamol-containing compounds in England and Wales, 1969-1977 (see text). From statistics published by the Office of Population Censuses and Surveys. ▲, Paracetamol and all other drugs; ○, paracetamol and dextropropoxyphene only; ●, paracetamol alone.

Adults account for the majority of serious and fatal cases of paracetamol poisoning, although adolescents are occasionally involved (Wilson *et al.*, 1978). It is extremely rare for young children to ingest sufficient paracetamol to cause more than minimal liver damage (Meredith, Newman and Goulding, 1978) but a fatal iatrogenic overdose has been reported in a young child (Nogen and Bremner, 1978).

Clinical features of paracetamol poisoning

Symptoms are uncommon on the first day follow-

ing ingestion of a paracetamol overdose, although pallor, anorexia, nausea and vomiting may occur. The paucity of symptoms, however, does not adversely affect the time of attendance of these patients at hospital. Information concerning the time of arrival of 1644 patients over a 2-year period in England and Wales has been reported by Meredith, Vale and Goulding (1980). Eighty-five per cent. of these patients arrived within 12 hr of the overdose, and in fact a greater proportion of those without symptoms arrived within this period.

Ingestion of a paracetamol overdose is not immediately followed by disturbance in the level of consciousness unless a sedative drug has been taken in addition. If the liver damage which may occur is sufficiently severe, abdominal pain and hepatic tenderness appear on the second day. Liver function tests become abnormal 12 to 36 hr after ingestion of an overdose, with elevation of the serum aminotransferase and prolongation of the prothrombin time. These abnormalities may be preceded by an increase in the plasma unconjugated bilirubin due to early reduction in bilirubin glucuronyltransferase activity (Davidson *et al.*, 1976) and an even earlier inhibition of hepatic bilirubin conjugation by either paracetamol or a metabolite of paracetamol (Davis *et al.*, 1975). Peak disturbance of liver function occurs 4-6 days after the overdose and frank liver failure preceded by jaundice and hepatic encephalopathy may ensue.

Mild or moderate liver damage due to paracetamol overdose may be accompanied by transient glucose intolerance (Thomson and Prescott, 1960), but severe liver damage may be associated with hypoglycaemia (Clark *et al.*, 1973a). Disseminated intravascular coagulation (Clark *et al.*, 1973b) sometimes occurs in severe paracetamol overdose as may metabolic acidosis and acute renal failure, although this latter complication is most often preceded by hepatic failure. Cardiac arrhythmias and electrocardiographic abnormalities have been reported in severely affected patients as have necrosis and fatty infiltration of the myocardium at post-mortem (Pimstone and Uys, 1968; Sanerkin, 1971; Hamlyn, Douglas and James, 1978). However, cardiac arrhythmias and histological abnormalities of the myocardium are found commonly in patients with fulminant hepatic failure from any cause (Weston *et al.*, 1976) and it is unlikely that they occur specifically as a consequence of paracetamol overdose.

Before effective treatment became available, the overall mortality rate of patients admitted to hospital with paracetamol poisoning was 2-3% (Proudfoot and Prescott, 1977). In a series of 60 severely poisoned patients admitted to the Liver Unit at King's College Hospital, London, though, the mortality was 20% (Clark *et al.*, 1973a). Those

patients who do not succumb to the acute illness make a full recovery. Liver function tests return to normal within 3 to 6 months of the overdose (Hamlyn *et al.*, 1977) although rarely hepatic fibrosis may persist (Clark *et al.*, 1973a; Portmann *et al.*, 1975; Hamlyn *et al.*, 1977; Prescott, Oswald and Proudfoot, 1978b).

Histological changes similar to those which can be produced experimentally in animals are seen in the liver in man after paracetamol overdose (Boyd and Bereczky, 1966; Dixon, Nimmo and Prescott, 1971). Necrosis of hepatocytes in the centrilobular areas is seen in the less severely affected patients, but those cases which progress to fulminant hepatic failure develop wide areas of confluent necrosis, often with survival of only a few hepatocytes in the periportal areas (Portmann *et al.*, 1975).

Dextropropoxyphene poisoning

Dextropropoxyphene, a substance chemically similar to methadone, was first synthesized in 1953 (Pohland and Sullivan, 1953) and its analgesic properties were described 2 years later (Robbins, 1955). It was said to resemble codeine in its potency and toxicity but to have fewer side effects (Lasagna, 1964). It was marketed in the United States as the hydrochloride salt under the proprietary names of 'Darvon' (Lilly), 'Dolene' (Lederle), 'Progesic' (Ulmer), and 'SK-65' (Smith Kline), and later as the napsylate salt in 'Darvon-N' and 'Darvocet-N'. In the United Kingdom, dextropropoxyphene is a constituent of a number of preparations. These include 'Depronol SA' (Warner), 'Napsalgesic' (Dista), and 'Cosalgesic' (Cox-Continental), all of which are available only on prescription. The most commonly prescribed preparation is 'Distalgesic': each tablet contains 325 mg of paracetamol and 32.5 mg of dextropropoxyphene.

The signs of overdosage with dextropropoxyphene are similar to those of morphine poisoning with early onset of pin-point pupils, depressed respiration and loss of consciousness. The respiratory depression may further lead to cardiac arrhythmias and convulsions. Respiratory arrest is the usual mode of death and this occurs typically within a few hours of the overdose. Ingestion of more than 20 to 30 tablets of Distalgesic is dangerous but 10 to 15 tablets may cause death if alcohol or other central depressants are taken at the same time (Carson and Carson, 1977). Early diagnosis of dextropropoxyphene poisoning is important because respiratory arrest and death may be averted by the use of the opiate antagonist, naloxone (Kersh, 1973; Tarala and Forrest, 1973).

Dextropropoxyphene is a potent inhibitor of microsomal mixed function oxidases *in vitro* (Peterson *et al.*, 1979), and theoretically this action

could reduce the formation of the toxic metabolite of paracetamol responsible for the development of hepatic damage (see below). In any event, liver failure is an uncommon cause of death in Distalgesic poisoning.

Metabolism of paracetamol

The principal metabolites of paracetamol are the glucuronide and sulphate derivatives, which are formed by conjugation with the phenolic group of the drug (Cummings, King and Martin, 1967). Small proportions are excreted in the urine as either free paracetamol, or as one of the products of microsomal oxidation. A proportion of the metabolite formed by microsomal oxidation is conjugated with glutathione (Fig. 3) and this is then subsequently excreted in the form of cysteine and mercapturate conjugates (Jagenburg and Toczko, 1964). However, a further proportion of the oxidized paracetamol is metabolized to other compounds before excretion (Mrochek *et al.*, 1974; Andrews *et al.*, 1976).

The chemical structure of the initial metabolite which is formed by oxidative metabolism remains obscure, although it has been deduced that this is most likely to be either an epoxide or an N-hydroxylamine derivative since both these types of compounds are known to be intermediates which can be formed in the conjugation of aryl compounds with glutathione (Boyland, 1971). Another possibility is that the intermediate could be a free radical (Tomaszewski, Jerina and Daly, 1975; Jerina *et al.*, 1967). Mitchell and his colleagues, using a range of model compounds, have produced both *in vivo* and *in vitro* evidence that the N-hydroxylamine derivative is the most likely intermediate (Jollow *et al.*, 1973; Potter *et al.*, 1973; Jollow *et al.*, 1974).

The relative proportions of paracetamol metabolites excreted in urine by man after therapeutic doses have been measured by a number of workers. Nevertheless, the results obtained independently are consistent and are summarized in Table 1.

Mechanism of hepatic toxicity

Much of the basic work on the mechanisms of toxicity of paracetamol has been carried out by Mitchell and his associates (Mitchell *et al.*, 1973a; Jollow *et al.*, 1973; Potter *et al.*, 1973; Mitchell *et al.*, 1973b). They showed that in mice and rats the development of liver necrosis was not directly related to the presence of unchanged paracetamol, but appeared to be due to a metabolite of the drug (Mitchell *et al.*, 1973a). Phenobarbitone and 3-methylcholanthrene which both stimulate the mixed function oxidase (cytochrome P₄₅₀) enzyme system, were found to accelerate the disappearance of paracetamol from the tissues although they markedly potentiated the hepatic necrosis. Piperonyl

FIG. 3. The metabolism and detoxification of paracetamol.

butoxide and cobalt chloride, which inhibit mixed function oxidases, were used to inhibit the metabolism and to delay the disappearance of paracetamol from the tissues. These compounds were found to protect the liver from necrosis. Piperonyl butoxide combines with cytochrome P_{450} and thereby inactivates the enzyme, whereas cobalt chloride blocks the synthesis of cytochrome P_{450} . It therefore seemed reasonable to suppose that the hepatic necrosis was due to a metabolite of paracetamol rather than to paracetamol itself.

Covalent binding was found to occur during the

TABLE 1. The relative proportions of the metabolites excreted in the urine after a therapeutic dose of paracetamol in man (from Mrochek *et al.*, 1974; Jagenburg, Nagy and Rodjer, 1968; Jagenburg and Toczko, 1964; Cummings *et al.*, 1967)

Urinary product	% of paracetamol excreted
Free paracetamol	1-4
Simple conjugates	
Paracetamol glucuronide	40-60
Paracetamol sulphate	20-30
Oxidation metabolites	
Sulphur conjugates	5-10
Paracetamol-3-cysteine	
Paracetamol-3-mercapturate	
Catechol derivatives	5-10
3-hydroxy paracetamol sulphate	
3-methoxy paracetamol sulphate	
3-methoxy paracetamol glucuronide	

development of liver necrosis suggesting that reactive metabolite was formed because paracetamol itself is a stable compound. Tritium-labelled paracetamol was used to determine the amount of covalently bound material with respect to time and the severity of liver necrosis (Jollow *et al.*, 1973). Pre-treatment with phenobarbitone was found to increase covalent binding, and cobalt chloride and piperonyl butoxide were found to decrease binding. The extent of covalent binding paralleled the degree of liver necrosis. Little material became bound outside the liver.

These findings suggested that a metabolite of paracetamol was formed by the mixed function oxidase enzyme system and that this became covalently bound to liver tissue to cause liver cell death and damage. The concept of an intervening metabolic process was supported by the fact that the covalent binding lagged behind the peak level of paracetamol and *in vitro* studies confirmed that the covalently bound protein was a metabolite of the cytochrome P_{450} system (Potter *et al.*, 1973).

Finally, Mitchell and his colleagues (1973b) demonstrated in mice the crucial role of glutathione. Pretreatment with diethyl maleate depleted hepatic glutathione and potentiated paracetamol-induced necrosis. Pretreatment with cysteine, a glutathione precursor, prevented hepatic damage. Paracetamol caused a dose-dependent depletion of hepatic glutathione and this depletion was found to be

enhanced by treatments that potentiated hepatic necrosis and inhibited by treatments that protected against liver damage. Covalent binding and hepatic necrosis did not occur until glutathione stores in the liver were depleted by more than 70%.

In summary, the theory which emerged was that a small fraction of paracetamol is oxidized by the mixed function oxidase enzyme (cytochrome P₄₅₀) system in the liver to a reactive product which is normally detoxified by reaction with glutathione mediated by microsomal and cytosol enzymes (Rollins and Buckpitt, 1979). However, if paracetamol is ingested in sufficiently large quantities, the hepatic glutathione stores become depleted below a certain critical level and the metabolite becomes free to react with nucleophilic cell macromolecules to cause cell death and hepatic necrosis. Further evidence for this hypothesis is provided by the pattern of metabolites excreted in the urine of different animal species. If non-toxic doses of paracetamol are administered to animals such that hepatic glutathione stores are not depleted (Davis *et al.*, 1974; Jollow *et al.*, 1974) the more susceptible species (mice and hamsters) excrete a higher proportion of glutathione-derived metabolites than the resistant species (rats). Similar results have been obtained using isolated hepatocytes from rats and mice (Moldeus, 1978), and the future use of this model may provide much useful information concerning the mechanism of toxicity of paracetamol.

The evidence for a similar mechanism in humans is less clearly defined, although Wright and Prescott (1973) reported an increased susceptibility to paracetamol-induced liver damage in patients with a history of drug ingestion likely to cause liver enzyme induction. Moreover, Mitchell, Thorgeirsson and Potter (1974) have shown that prestimulation of microsomal enzymes with phenobarbitone in man leads to an increase in mercapturic acid excretion after therapeutic doses of paracetamol. Furthermore, Davis *et al.* (1976) examined the urinary excretion of paracetamol and its conjugates firstly in volunteers taking therapeutic doses of the drug, and secondly in patients admitted early after an overdose of the drug. In the latter group, there was a greatly increased production of the cysteine and mercapturic acid conjugates of paracetamol. Pharmacokinetic analysis of these data suggests that diversion of paracetamol to this route occurs after the sulphate and glucuronide pathways have become saturated (Slattery and Levy, 1979). Similar findings have been reported by Andrews *et al.* (1976) and Howie, Adriaenssens and Prescott (1977). Since glucuronide formation accounts for 50% of paracetamol metabolism, inhibition of this route could lead to diversion of extra paracetamol to the oxidative pathway. It is interesting to speculate that individuals

with Gilbert's syndrome, who have deficient glucuronyl transferase activity, may be more susceptible to the effects of paracetamol taken in overdose. However, only 2 cases have been so far reported in the literature (Hamlyn *et al.*, 1977; Rosenberg *et al.*, 1977).

Renal toxicity of paracetamol

Acute tubular necrosis occasionally occurs in patients following the ingestion of an overdose of paracetamol. This most often occurs in the context of fulminant liver failure (Clark *et al.*, 1973a) but it can nevertheless be due to a toxic effect of paracetamol itself and can occur in the absence of significant liver damage (Prescott *et al.*, 1971; Prescott, 1979).

The kidney possesses cytochrome P₄₅₀ enzyme systems similar to those in the liver and, using the rat as an experimental model, Mitchell and his colleagues have extended their studies to the kidney (Mitchell *et al.*, 1977; McMurtry, Snodgrass and Mitchell, 1978). They demonstrated dose-dependent proximal tubular damage in paracetamol overdose, and the use of tritium-labelled paracetamol showed covalent binding of large amounts of metabolite. Significant covalent binding and renal necrosis occurred only when total renal glutathione stores were depleted by 45% or more. Pretreatment with cobalt chloride decreased glutathione depletion and binding of the metabolite, whilst concomitantly protecting against tissue damage in both the liver and kidney. Pretreatment of animals with methyl-cholanthrene, which induces certain enzymes in the liver but not in the kidney, markedly potentiated hepatic necrosis without significant effect on the renal lesion. Results similar to these have been published recently by Mudge, Gemborys and Duggin (1978). *In vitro* studies have confirmed that the formation of the toxic metabolite occurs *in situ* and does not arise in the liver (Mitchell *et al.*, 1977; McMurtry *et al.*, 1978). Furthermore, the development of acute renal failure due to paracetamol poisoning in man may be prevented by the use of those same agents (see below) which protect against hepatic toxicity (Prescott, 1979).

Prediction of liver damage

By extrapolating from animal data it is possible to calculate the dose of paracetamol in man that would deplete the liver of more than 70% of its glutathione content and thus cause liver damage. In normal individuals this amounts to 15 g of paracetamol in a single dose, and in those whose enzymes are 'induced' by previous alcohol or drug consumption the calculated hepatotoxic dose of paracetamol would be about 10 g (Mitchell *et al.*, 1974). These

amounts correspond well with those found clinically to cause hepatic necrosis in adults.

Nevertheless, it is unwise to rely upon an estimate (particularly one made by the patient) of the dose of paracetamol ingested. A more reliable indicator of the likelihood of liver damage is the plasma level of paracetamol. Prescott and his colleagues (1974) in Edinburgh showed that significant liver damage is likely to occur if the level at 4 hr exceeds 200 mg/l and at 12 hr exceeds 50 mg/l (Fig. 4). This finding was substantiated by 2 subsequent studies (Douglas, Hamlyn and James, 1976; Gazzard *et al.*, 1977). It is apparent from the latter study, however, that some patients with high paracetamol levels in the early hours after overdose may subsequently develop only minimal liver damage. This is particularly likely to occur if the level is determined within 6 hr of ingestion of the overdose.

An even more reliable predictor of liver damage should be the half-life of elimination of unchanged paracetamol which is normally of the order of 2 to 3 hr. However, in overdose complicated by liver damage the half-life of paracetamol exceeds 4 hr (Prescott *et al.*, 1971). This prolongation of the half-life for elimination has been shown to be due to saturation of the sulphation and glucuronidation processes rather than being due to liver damage itself (Siegers, Strubelt and Schutt, 1978; Slattery and Levy, 1979). Unfortunately, calculation of the half-life requires 2 plasma paracetamol estimations separated by a reasonable period of time, and by the time the second value is available it may be too late to offer effective treatment to the patient (see below).

Furthermore, Gazzard *et al.* (1977) found that although severe liver damage did not occur in patients with a paracetamol half-life of less than 4 hr, the reverse of this situation was not necessarily true. Indeed, the paracetamol half-life was greater than 4 hr in nearly one third of those patients who developed minimal liver damage only.

Despite the limitations and individual variations detailed above, the most reliable way to determine those patients who need specific treatment is measurement of the plasma paracetamol level. This may be performed accurately within minutes in the casualty department or at the bedside with the aid of a blood paracetamol estimation kit (Kendal, Lloyd-Jones and Smith, 1976; Widdop, 1976).

Treatment of paracetamol poisoning

Gastric lavage has been shown to be of value for up to 6 hr after ingestion of a paracetamol overdose (Gazzard *et al.*, 1977). However, because small children of less than 5 years old tend to swallow only small amounts of paracetamol (Meredith *et al.*, 1978), gastric lavage is unnecessary and syrup of ipecacuanha is all that is usually required for them.

Activated charcoal has been advocated as an additional means of preventing absorption of paracetamol from the stomach. Levy and Gwilt (1972) reported that 10 g of charcoal administered immediately after ingestion of 1 g paracetamol will reduce absorption by 69–77%. Dordoni *et al.* (1973) found that absorption of a therapeutic dose of paracetamol (2 g) was reduced by about 60% when either activated charcoal or cholestyramine

FIG. 4. The likelihood of liver damage occurring after an overdose of paracetamol may be predicted by measurement of the plasma paracetamol level.

was administered immediately after the paracetamol. However, when the cholestyramine was given 60 min after ingestion of the paracetamol there was only a 16% reduction in absorption. It therefore seems unlikely that either activated charcoal or cholestyramine would be of value more than a few hours after ingestion of an overdose of paracetamol. Even then, because the ideal charcoal : paracetamol ratio is 10 : 1, patients would be required to ingest substantial quantities of charcoal, and 0.5 kg of charcoal, for example, would be needed to adsorb 50 g of paracetamol.

Further general treatment may include parenteral fluid replacement for the first one to 2 days because of nausea and vomiting that may occur. Respiratory depression and coma due to Distalgesic (or other dextropropoxyphene-containing compounds) may be reversed with the use of naloxone (0.4 mg i.v. repeated as necessary at 2- to 3-min intervals). The response to this antidote may be assessed by the change in the level of consciousness, dilatation of the pupils and improvement in the tidal volume of respiration. Intravenous vitamin K (10 mg daily for 3 days) may be given to severely poisoned patients although it is unlikely to be very effective. Fresh frozen plasma or clotting factor concentrate may be used to maintain the prothrombin time within safe limits, although such treatment does not appear to influence either the morbidity or mortality (Gazzard, Henderson and Williams, 1975). The further management of hepatic failure has recently been reviewed elsewhere (Murray-Lyon and Trewby, 1977).

Forced diuresis has been advocated for paracetamol poisoning because excretion of the unchanged drug is related to urine flow (Maclean *et al.*, 1968). The use of early forced diuresis, however, does not prevent liver damage (Prescott and Wright, 1973) and may even be dangerous because of the anti-diuretic effect of paracetamol (Nusynowitz and Forsham, 1966).

Haemodialysis and haemoperfusion have both been used in the treatment of paracetamol poisoning. Free paracetamol as well as the non-toxic glucuronide and sulphate conjugates are removed by haemodialysis (Oie *et al.*, 1976). However, the early use of this procedure does not influence the prognosis of these patients (Farid, Glynn and Kerr, 1972; Prescott, 1972) as would be expected from consideration of the hepatotoxic mechanism of paracetamol.

Haemoperfusion is an efficient way of removing paracetamol from the circulation (Willson *et al.*, 1973; Winchester *et al.*, 1975). However, a controlled trial showed no benefit when 8 patients treated with haemoperfusion within 12 hr of ingestion of a paracetamol overdose were compared with 8 matched patients treated conservatively (Gazzard

et al., 1974a). Although this result is not surprising when one considers the mechanism of toxicity of paracetamol, the clearance of the drug achieved was rather poor. This may have been due to the unusually thick coating of the charcoal particles in the haemoperfusion columns with acrylic hydrogel (10 to 11% by weight).

The hepatic damage caused by paracetamol is due to the formation of an active metabolite, and treatments directed towards either the removal of this compound or inhibition of the enzymes responsible for its formation have been more successful than those already mentioned above. Experimental studies in animals have shown that glutathione penetrates poorly into cells and, to protect mice from liver damage, large doses are needed soon after administration of the paracetamol (Benedetti *et al.*, 1975). For this reason, agents other than glutathione have been investigated:

- (i) provision of sulphhydryl groups
 - dimercaprol
 - penicillamine
- (ii) inhibition of mixed function oxidase enzymes
 - cysteamine
- (iii) glutathione precursors
 - cysteine
 - acetylcysteine
 - methionine.

The active paracetamol metabolite becomes conjugated with cysteine or glutathione via sulphhydryl groups. Dimercaprol, which is used to provide sulphhydryl groups in other circumstances, was used in the treatment of patients by Prescott and Wright (1974) but no protection against liver damage was seen. Hughes *et al.* (1977) later compared dimercaprol and cysteamine in a controlled trial with 26 patients randomly allocated to each form of treatment. Cysteamine was found to afford better protection than dimercaprol and one death due to hepatic failure occurred in the dimercaprol group. An alternative form of provision of sulphhydryl groups was investigated by Prescott and his colleagues (1976b) who used penicillamine in 5 patients. Five grams of penicillamine were given over a period of 20 hr and 4 of 5 patients developed little or no liver damage. However, 2 patients developed acute renal failure, one of whom had had no preceding liver damage. Use of the drug was abandoned, therefore, because of suspected potentiation of the nephrotoxicity of paracetamol.

Cysteamine is a compound which has been found to protect against paracetamol-induced liver damage. It does contain sulphhydryl groups, but these are unlikely to account for its success because of the failure of both penicillamine and dimercaprol.

Cysteamine is rapidly oxidized to cystamine *in vivo* and these 2 compounds remain in equilibrium in the body. Both compounds strongly inhibit cytochrome P₄₅₀ activity (Castro *et al.*, 1973) and probably act therefore by reducing formation of the active paracetamol metabolite (Harvey and Goulding, 1974) (Fig. 5).

Cysteamine has been shown to protect rats from experimental paracetamol poisoning (Gazzard *et al.*, 1974b) and in mice it reduces covalent binding of tritium-labelled paracetamol to microsomal enzymes with a concomitant reduction in the development of liver necrosis (Mitchell *et al.*, 1974).

The first report of the use of cysteine in man came from Prescott *et al.* (1974) who reported on its use in 5 patients with high paracetamol levels. A total of 3.2 g of the base was given over 20 hr. All patients survived and developed only minimal liver damage. It was emphasized that, to be of value, cysteine should be given as soon as possible after ingestion, and certainly within 10 hr.

All subsequent reports of the use of cysteine in paracetamol poisoning have, with one exception (Douglas *et al.*, 1976), shown it to be effective in the prevention of hepatic damage, provided that it is administered within 10 hr of ingestion of the paracetamol (Prescott, Park and Proudfoot, 1976a; Prescott *et al.*, 1976b; Hughes, Trewby and Williams, 1976; Hughes *et al.*, 1977). Unfortunately, the use of cysteine is associated with a number of distressing

side effects. These include nausea, vomiting, abdominal cramps and a general feeling of misery. In rats, cysteine and cystamine predictably caused perforating ulcers of the duodenum by increasing gastric acid output and delaying gastric emptying (Szabo, 1977). Moreover, cardiac arrhythmias, including ventricular tachycardia, have been observed during the administration of cysteine in man. The drug is not available as a pharmaceutical preparation and it has in many cases to be made up and filtered immediately before use. The dose of cysteine, which is given *i.v.*, is shown in Table 2.

Consideration of the mechanism of hepatotoxicity of paracetamol would suggest that cysteine given 'late' (*i.e.* > 10 hr) after the ingestion of an overdose would have little value. At this stage the toxic metabolite will be formed and covalently bound to liver microsomal protein. Indeed, there is some experimental evidence to suggest that late cysteine enhances the toxicity of paracetamol (Davis, 1978).

However, Smith and her colleagues reported on the use of 'late' cysteine in 16 patients (Smith *et al.*, 1978). Eight patients developed severe liver damage and 4 developed mild liver damage. There was no control group, though, and the method of estimating plasma paracetamol was not specific in that paracetamol conjugates were measured as well as the unchanged drug. This makes comparison with other series difficult. Moreover, Prescott *et al.* (1976b) showed that late cysteine treatment for severe

FIG. 5. The mechanism of action of cysteine, methionine and acetylcysteine in the treatment of paracetamol poisoning.

paracetamol poisoning has the same incidence of morbidity and mortality as simple supportive treatment.

TABLE 2. The dosage regimes for the use of methionine, N-acetylcysteine and cysteamine in the treatment of paracetamol poisoning

METHIONINE 2.5 g orally stat., then 2.5 g 4-hourly for a further 3 doses. Total dose: 10 g methionine over 12 hr. or N-ACETYLCYSTEINE 150 mg/kg i.v. over 15 min, then 50 mg/kg in 500 ml of 5% dextrose i.v. in the next 4 hr and 100 mg/kg in 1000 ml of 5% dextrose i.v. over the ensuing 16 hr. Total dose: 300 mg/kg over 20 hr. Alternatively, the 20% solution may be diluted to a 5% solution in a soft drink for oral administration. A single loading dose of 140 mg/kg is given, followed by 17 doses of 70 mg/kg every 4 hr. or CYSTEAMINE 2 g (as the base) in 5% dextrose i.v. over 10 min, then 800 mg i.v. in the next 4 hr and 800 mg i.v. over the ensuing 16 hr. Total dose: 3.6 g cysteamine (base) over 20 hr.
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N.B. These protective agents should be administered only so long as no more than 10 hr have elapsed from the time of ingestion of the paracetamol overdose (see text).

The importance of the review of 163 paracetamol overdose patients made by Gazzard *et al.* (1977) lies in the implications that it has for the treatment of paracetamol overdose. A significant number of patients who on the basis of blood paracetamol levels would be expected to develop severe liver damage fail to do so without having received specific treatment. In other words, any treatment given to patients should not be toxic in itself, or those who might otherwise remain well could be harmed. For this reason methionine and acetylcysteine, which are remarkably free of side effects, are more satisfactory 'antidotes' than cysteamine. Methionine (Fig. 5) speeds the synthesis of liver glutathione (McLean and Day, 1975) and in the experimental situation effectively prevents liver damage. Prescott *et al.* (1976b) published results obtained with the use of i.v. methionine (20 g over 20 hr) in 20 patients. Three patients developed significant liver damage, one of whom had not been thought to be at special risk. There is good reason to believe, though, that, as a paracetamol 'antidote', methionine is more effective orally than when it is injected. Although results from a controlled trial are not available, the National Poisons Information Service has accumulated information from a large number of hospitals about paracetamol overdose patients treated with methionine (Vale, Meredith and Goulding, 1980). Information was collected on 132 patients with high plasma paracetamol levels who were treated orally with methionine. Ninety-six patients were given methionine within 10 hr of the overdose and had

serial liver function tests performed. Seven patients developed severe liver damage (aspartate aminotransferase (AAT) > 1000 i.u./l), but only one of these developed hepatic encephalopathy and one suffered transient renal failure (maximum AAT 160 i.u./l). There were no deaths from hepatic failure. Six of the patients who developed severe liver damage had very high plasma paracetamol levels (300 mg/l at 4 hr and 75 mg/l at 12 hr). It is emphasized that the administration of methionine should usually be started at less than 10 hr after ingestion of the overdose, because if hepatic function is disturbed methionine may precipitate hepatic encephalopathy (Phear *et al.*, 1956).

The use of oral methionine is not associated with any serious side effects. Sometimes, however, there is difficulty with the oral administration of the drug. This may be due to vomiting, which occurs uncommonly when paracetamol alone is ingested (Meredith *et al.*, 1979) but which may then be controlled with the use of an anti-emetic agent such as metoclopramide. More commonly, difficulties are encountered because the patient is unconscious as a result of ingestion of another drug. This is often due to dextropropoxyphene (in Distalgesic for example) and in these circumstances naloxone (see above) should be administered. Even if the patient remains unconscious, methionine may be given with the aid of a nasogastric tube, provided that the tablets are crushed beforehand. The dose of methionine is shown in Table 2. Young children rarely require the administration of anything other than an emetic because of their tendency to ingest only small quantities of paracetamol. Older children may be given the usual adult dose of oral methionine.

Cysteine (Fig. 5) acts as a precursor of glutathione. There is some evidence, however, that it does not reduce hepatic covalent binding (Gerber *et al.*, 1977) and it may act principally as a source of sulphate for conjugation with unchanged paracetamol (Slattery and Levy, 1977). It has been used to treat paracetamol toxicity in mice with good effect (Strubelt, Siegers and Schult, 1974). N-acetylcysteine (Fig. 5) is rapidly hydrolysed to cysteine *in vivo* and this, too, is effective experimentally in mice (Piperno and Berssenbruegge, 1976). It was first used for the treatment of patients by Prescott and his colleagues (1977) and in America by Rumack and Peterson (1978). Acetylcysteine has since proved to be as effective as cysteamine (Prescott, Stewart and Proudfoot, 1978a) but has fewer side effects. Acetylcysteine may be administered either by injection or orally and is available as 'Parvolex' (Duncan Flockhart), which is a 20% solution suitable for i.v. use. 'Airbron' (Duncan Flockhart) and 'Mucomyst' (McNeil Laboratories) are 20% solutions intended as mucolytic agents but they are

sterile and, although not necessarily pyrogen-free, they may be used in an emergency. Acetylcysteine may be used orally but requires dilution in a soft drink because of its unpleasant taste and even then is likely to cause vomiting in a considerable proportion of patients. Treatment with acetylcysteine has not been shown to be effective if administered more than 10 hr after ingestion of a paracetamol overdose. The dosage regime is shown in Table 2.

Conclusion

Paracetamol is a safe and effective analgesic and antipyretic agent when used in therapeutic doses. It is, however, predictably hepatotoxic in adults when ingested in single quantities of more than 10 to 15 g. Cysteamine effectively reduces the severity of paracetamol-induced liver damage, but has a number of unpleasant and dangerous side effects. The most effective and safe antidotes available at present are oral methionine and i.v. N-acetylcysteine, either of which should ideally be administered within 10 hr of ingestion of a paracetamol overdose.

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