

The spectrum of paracetamol (acetaminophen) overdose: clinical and epidemiological studies

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Summary

In a regional survey of paracetamol overdose, 201 patients were admitted to hospital over 12 months. Chronic alcoholism was present in 10% of cases. Over 25% of patients were females aged 20 years or less. Initial blood paracetamol levels were in the toxic range in 16% and histologically severe liver damage eventually found in 20% of those biopsied. This finding corresponded to a serum aspartate aminotransferase of 600 i.u./l or more. Renal failure severe enough to require peritoneal dialysis developed in 1%. Elevated serum amylase was recorded in 22% of a 108-patient subset. Evidence of myocardial damage was found in 11.6% of an eighty-six patient subset. An unfavourable prognosis was indicated by a prothrombin ratio of 20% or less and hepatic coma, the overall mortality being 3.5%.

The apparent safety of this useful analgesic is compromised by its widespread employment in parasuicide. This, the insidious and delayed onset of toxicity in overdose and ineffectiveness of late treatment argues for controlling availability to the general public.

Introduction

Overdose from paracetamol (acetaminophen) has been an increasing problem of North-East England in recent years.

In November, 1974, the Regional Paracetamol Overdose Survey was instituted at the Royal Victoria Infirmary, Newcastle upon Tyne. Adult and adolescent patients were referred from a wide area containing a large population centre, the Newcastle-Tyneside conurbation.

The purpose of the survey was to answer the following questions:

- (1) How prevalent was paracetamol overdose, what sections of the population chose this as a method of attempted suicide and why?
- (2) How far did liver, renal and other organ damage contribute to mortality and morbidity?
- (3) To what extent might the outcome be altered by treatment?

This paper describes the spectrum of paracetamol overdose in 201 consecutive cases seen in the 12-month period November 1974–November 1975.

Methods

Plasma paracetamol was estimated by spectrophotometry at the time of hospital admission (Routh *et al.*, 1968).

Liver function was tested daily by measurement of serum bilirubin, aspartate aminotransferase (AST, SGOT) (normal range 4–20 u./l and alkaline phosphatase (normal range 20–90 u./l) together with Quick prothrombin ratio.

Liver biopsy was performed on the fourth day after admission or as soon as the prothrombin time and patient's condition allowed. In seven patients, liver tissue was obtained just after death. The processing of biopsies and histological gradings of liver damage is as previously described (James *et al.*, 1975).

Serial serum amylase (normal range <300 i.u./l), creatinine kinase (CK) (normal range <50 i.u./l), and lactate dehydrogenase (LDH) isoenzymes were also measured for 4 days. The patient was interviewed, whenever possible, by a psychiatrist.

Treatment

No oral intake was initially allowed. Each patient received an intravenous infusion of 5% dextrose 2–3 litres daily together with phytomenadione* 10 mg, folic acid 15 mg and Parentrovite (vitamins B and C) twin ampoules. Potassium was added to the infusion as required. If liver function was normal 48 hr after admission clear fluids were given by mouth and the infusion was discontinued after a further 24 hr. Normal diet was then resumed. Where significant abnormalities were observed in liver function tests, the infusion was continued and lactulose 10 ml 6-hourly was given. If hepatic encephalopathy then developed, the full conventional treatment for acute hepatic failure was given.

* Konakion (Roche).

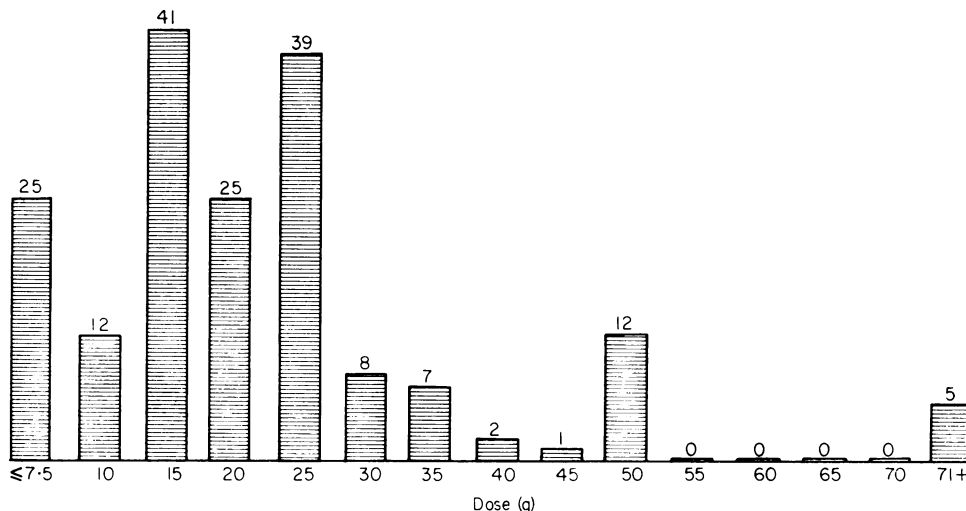


FIG. 1. Paracetamol overdose: amount stated to have been taken by age in 177 cases. Modal values correspond with commonly retailed quantities.

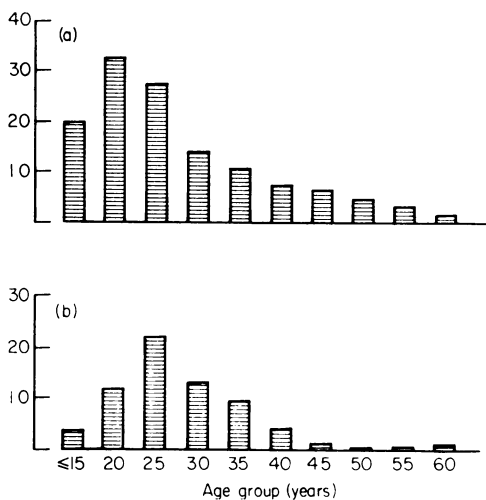


FIG. 2. Paracetamol overdose: age at presentation by sex (a) females (b) males. Over 25% are females of 20 years or less.

Cysteamine

Twenty-one patients whose initial plasma paracetamol level was considered to be high were given cysteamine as part of a controlled trial (Douglas, Hamlyn and James, 1976). The management of this group was otherwise no different from that of the other.

Results

Paracetamol dose ingested

The amount stated by patient or relatives to have been ingested varied widely (Fig. 1). The majority

were in the range 7.5–150 g with modal values at 25 and 50 g. The lowest stated dose associated with transaminase elevation was 6 g.

Age and sex ratio

The modal age for female patients was in the range 16–20 years and for males 21–25 years. At all ages females exceeded males and the highest ratio was found in the under-16s (Fig. 2). Females of 20 years of less comprised 26% of the series.

Psychiatric aspects

The principal factor in precipitating overdose was elicited by psychiatric interview in 124 cases. These are summarized in Fig. 3. In 4% of patients

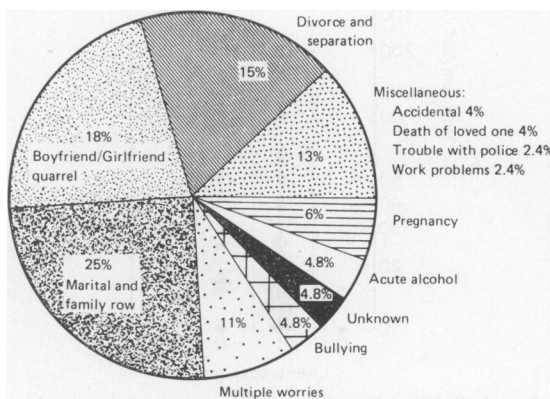


FIG. 3. Principal factor stated to precipitate overdose: psychiatrist's assessment in 124 patients. Marital or family discord account for the majority.

('accidental'), the overdose seems to have been taken in the innocent belief that the tablets should be taken successively until relief was obtained. An example of this was a patient, devoid of suicidal intention who, because of sinusitis, took an overdose of 20 g over several hours. Vomiting and malaise resulted in his eventually seeking medical attention.

Clear evidence of abnormal psychiatric state was obtained in eighty-two cases of the 177 interviewed. Long-standing depression existed in 66% of these and one-third of this group had taken at least one drug overdose before. Hysterical or immature personality with overdose as part of a pattern of manipulative behaviour was found in 17%. There was a background of chronic alcoholism in 10%, of psychopathy in 5% and severe psychosis in 2.5%. One case was classified as educationally subnormal.

Toxicity of paracetamol overdose; blood levels

The relationship of toxicity to blood paracetamol level has been previously described (James *et al.*, 1975; Prescott *et al.*, 1971). On this definition 16% of patients fell into the toxic range, 29% into the intermediate or equivocal range and 48% into the non-toxic range. In 7% of cases the level could not be determined or was of doubtful value, more than

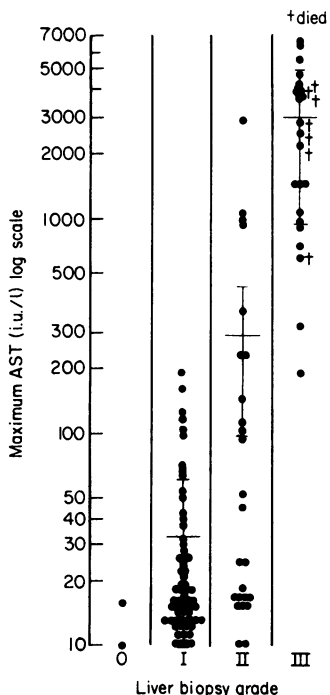


FIG. 4. Relationship of liver biopsy grade to maximal aspartate aminotransferase level. (Mean + s.d.). Histologically severe liver damage corresponds to a level of 600 i.u./l or more.

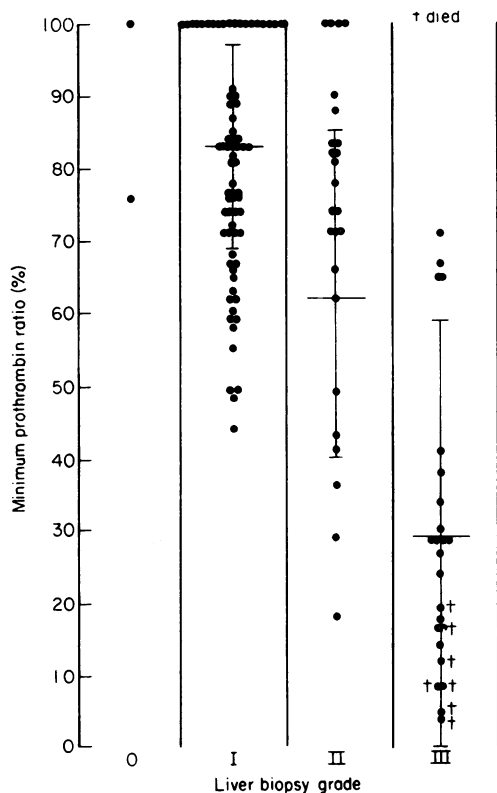


FIG. 5. Relationship of liver biopsy to minimal prothrombin time. (Mean + s.d.). A level over 20% or less implies survival.

24 hr having elapsed since the time of ingestion. The overall deaths were seven in number, a total mortality of 3.5%.

Greatly elevated serum aspartate aminotransferase levels (600–6,000 i.u./l) were seen in fourteen of those not receiving cysteamine. Nine patients developed hepatic encephalopathy; of these, seven died. Mild histological damage was seen in seventy-one (58%), moderate change in twenty-five (22%) and severe in twenty-seven (20%). The relationship between transaminase levels and liver damage is summarized in Fig. 4. Figure 5 shows the relationship between minimum prothrombin ratio and liver biopsy grade.

In no instance was elevated serum alkaline phosphatase seen.

Raised serum amylase

Daily serum amylase determinations were available in 108 patients in whom alcoholism and renal damage had been excluded.

Elevated serum amylase was seen in 9.4% of patients on admission but was eventually apparent

in 22%. Values ranged up to 1450 i.u./l, reverting to normal in all survivors. Of twenty-one patients exhibiting severe histological liver damage nine had raised serum amylase, of fifty-four with little or no histological liver damage seven had raised serum amylase. No symptom of pancreatitis was elicited from any conscious patient. No histological evidence of pancreatitis was found in three post-mortem cases exhibiting raised amylase levels. Despite the possibility of this amylase being liver-derived (Warshaw, Bellini and Lee, 1976) no relationship was established between liver biopsy grade and serum amylase level.

Muscle damage

Eighty-six patients were assessed for muscle damage on the evidence of daily CK determination. Raised CK levels were noted in twenty-four patients (28%). Levels ranged from the upper limit of normal to 650 i.u./l. The greatest rise was generally seen 24 hr after admission. Of these patients the myocardial lactate dehydrogenase level (plasma LDH₁) was elevated in six, of whom four had an abnormal ECG. Abnormal ECGs were recorded in four with normal LDH₁, thus evidence of myocardial damage was found in 10 (11.6%) of this subset. The ECG changes comprised non-specific T wave changes in eight, bundle branch block in two, delayed onset sinus bradycardia in one and ST segment depression in one. No clinical evidence of toxic myocarditis was seen.

Renal damage

Of fourteen patients with toxic levels and to whom no cysteamine was given, two (1%) developed acute renal tubular necrosis, both recovering after peritoneal dialysis. Biochemical evidence of liver damage was apparent in both instances and preceded plasma creatinine rise by 3 days.

Paracetamol, cysteamine and pregnancy

Four overdoses coincided with pregnancy and one girl given cysteamine in early pregnancy produced a small for dates infant which subsequently failed to thrive.

Discussion

Paracetamol (acetaminophen in the U.S. literature) has become increasingly popular as a substitute for aspirin. In 1974 consumption had risen in England and Wales to the equivalent of 3000 million 500 mg tablets compared with 3050 million aspirin tablets (Spooner and Harvey, 1976) and by March 1976 no less than twenty-seven proprietary preparations containing it were on the U.K. market. This has led to its use in overdose as an agent of attempted suicide. According to one estimate, every year about 7000 such patients are admitted to

hospitals in England and Wales (Proudfoot and Wright, 1970).

Regional incidence

The annual incidence of paracetamol overdose in the North-East region of England is difficult to estimate from these figures. If a catchment area population of two million is assumed, it is 10/100,000. A number of trivial cases and those at great distance would not be so readily referred so that the incidence is perhaps higher. The regional figures correspond to a U.K. incidence of about 6000 cases annually.

Risk to life

Paracetamol overdose was hazardous when blood levels were in the toxic range as defined for hepatic damage. The risk of severe renal damage was more remote (1%) whilst pancreatitis and myocardial damage seemed to be insignificant contributors to morbidity and mortality. This is in agreement with other studies (Clark *et al.*, 1973; Portman *et al.*, 1975). Respiratory or cardiac depression (Dixop, 1975) as a cause of death did not occur in the authors' patients.

Approximately one in six experienced severe hepatic damage and three in every 100 died as a result. Hepatic necrosis is a dominant consequence of paracetamol overdose. Fortunately, survivors make a virtually complete recovery and prolonged follow-up is unnecessary (Hamlyn *et al.*, 1977).

Prevention

The cost of 5000–7000 annual paracetamol overdoses demands some form of control. Abandonment of paracetamol as an analgesic could, nevertheless, open the way possibly to some other and perhaps more dangerous substitute.

A suggested solution, from the evidence of Fig. 1, which shows a relationship between retail quantity and dose ingested, is the packaging of tablets into smaller quantities, perhaps in foil or bubble packs and restriction to pharmacists of over-counter sales. Education of vulnerable adolescents is also indicated.

Treatment of paracetamol overdose

A series of recommendations has been drawn up by a working party on the subject (Paracetamol Symposium, 1976). They emphasize the need for early treatment, including gastric lavage, determination of blood paracetamol levels and, if appropriate, administration of sulphhydryl group donors such as cysteamine or methionine.

It is clear that the solution to the problem of paracetamol overdose attempts lies not only in preventive measures but also the early treatment of those patients in danger of severe renal or hepatic injury. There is need for further controlled clinical

trials of antidotes in the treatment of this common, acute poisoning.

Acknowledgments

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