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Early prediction of the outcome of a paracetamol overdose based on an analysis of 163 patients

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Summary

Clinical and biochemical data obtained from 163 patients who had taken an overdose of paracetamol were examined to determine which factors or measurements were of value in predicting the severity of ensuing liver damage early after ingestion of tablets. Although the overall severity of hepatic necrosis was found to increase with the dose of paracetamol ingested, correlation was not sufficiently close to provide an accurate prognostic index in individuals. Severe hepatic damage was less likely if the patient had vomited or had a stomach wash-out within 6 hr of overdose. The plasma concentrations of paracetamol, measured at known times after overdose, distinguished those who developed hepatic dysfunction from those who did not, but there was a poor correlation, particularly in the first 6 hr after ingestion of tablets, between these values and the severity of ensuing liver damage. Estimates of early plasma paracetamol half-lives from three or more samples taken within 4 hr of admission showed that all patients developing moderate or severe liver damage had half-lives greater than 4 hr, but this was also the case in nearly one-third of those with minimal liver lesions only.

It is concluded that there is no completely reliable early prognostic test for individual patients with paracetamol overdose. If each patient is selected for treatment with cysteamine (mercaptamine) or other agents on the basis of plasma paracetamol levels, up to 30% may receive this agent who are at risk from trivial hepatic damage only.

Introduction

The number of attempted suicides with overdoses of paracetamol (acetaminophen; *N*-acetyl-*p*-aminophenol) has considerably increased in this country since 1966 when hepatic damage from this drug was first reported (Davidson and Eastham, 1966; Thompson and Prescott, 1966). In 1973 alone there were sixty-six deaths from fulminant hepatic failure in England and Wales caused by self-poisoning with paracetamol (Office of Population Census, 1975). Unlike most other drugs taken in overdose, the toxic effects of paracetamol may not be observed for several days (Clark *et al.*, 1973).

Jollow and his colleagues (Jollow *et al.*, 1973) were the first to show that damage to the liver was produced by a reactive intermediate of paracetamol, and it was then shown that this could be prevented by agents containing sulphydryl groups (Mitchell *et al.*, 1974). Prescott and his colleagues (Prescott *et al.*, 1974) subsequently reported that one such substance cysteamine (mercaptamine) was of value in man, although its use is accompanied by abdominal cramps, vomiting, and drowsiness. As the compound has to be given as soon as possible after the overdose (Mitchell *et al.*, 1974), it is important to discriminate at an early stage between the patient likely to develop severe hepatic damage requiring treatment with mercaptamine, and the one who is not at risk from the hepatotoxic effects of paracetamol.

The present study was therefore undertaken to determine whether any information was available shortly after the tablets had been taken that would be of value in predicting the outcome.

Patients and methods

The 163 patients included in this study were admitted to King's College Hospital between January 1971 and January 1974. All of them received conservative treatment to restore normal fluid and electrolyte balance, and to maintain an adequate

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calorie intake, but no patient received any specific antidotal therapy, such as mercaptamine.

Plasma levels of unconjugated paracetamol were estimated in 102 of these patients when they first arrived in the casualty department or were transferred there from other hospitals within 12 hr of taking an overdose. Seventeen patients were first seen between 12 and 24 hr after taking the tablets, and the remaining forty-four were transferred later when liver damage had developed. All those patients who presented within 24 hr had a stomach wash-out. Seemingly accurate drug histories were taken in 117 patients and, wherever possible, an estimate of the number of tablets taken was also obtained from a relative. In addition to paracetamol, thirty-five patients had taken additional drugs (diazepam in eight; nitrazepam, five; barbiturates, five; amitriptyline, two; propranolol, two; ampicillin, one; chlordiazepoxide, one; chlorpromazine, one). An additional ten patients had ingested alcohol with their paracetamol overdose, but in neither these nor those who had taken sedative or hypnotic drugs had sufficient been taken to produce clouding of consciousness.

A needle liver biopsy was performed on fifty-six patients between 4 and 10 days after ingestion of the tablets. The surviving number of hepatocytes was estimated by examining sections of liver with the high power lens of a microscope with a Weibel graticule fitted to the eyepiece (Weibel, Kistler and Scherle, 1966). The number of points on the graticule which coincided with a viable hepatocyte were counted in sixty high power fields. The fraction of the total area occupied by liver cells could then be calculated, and this was proportional to the hepatocyte volume fraction (HVF).

The plasma concentrations of unconjugated paracetamol were estimated, using the absorbence of the drug at 250 nm after its extraction into ether (Dordoni *et al.*, 1973). The samples were all analysed within 1 hr of being taken. An absorption spectrum between 200 and 350 nm was also obtained in most of the patients using a Pye Unicam SP 800 spectrophotometer. In thirty-three patients plasma levels of paracetamol were also determined by gas liquid chromatography (Prescott, 1971). In fifty-six patients three or more samples were obtained at timed intervals over a period of 4 hr after admission. The initial plasma disappearance time for paracetamol was estimated from the results plotted on semi-logarithmic graph paper.

Plasma solutions of a number of other drugs commonly taken in overdose, with similar absorption spectra to paracetamol which are extracted into ether and therefore could potentially interfere with the spectrophotometric assay, were made up in the maximum concentrations found in the plasma of patients after overdose, and the pH was adjusted to 7·4. These were then extracted into ether in the same way as for the paracetamol estimation, and the ultraviolet absorption spectrum was obtained by scanning between wavelengths 200 and 350 nm using the SP 800 spectrophotometer. In addition, the optical density was measured for each drug at 250 nm. The degree of interference with the paracetamol assay was expressed as the 'apparent paracetamol concentration' obtained by relating the absorbence to the standard curve for paracetamol.

Results

The patients were separated into three categories according to the severity of the ensuing liver damage, on the basis of the maximum serum bilirubin levels described by Clark *et al.* (1973). There were forty patients in the 'severe' group (serum bilirubin levels >69 μmol/l), forty-eight patients in the 'moderate' group (levels of 17–60 μmol/l, and nineteen patients with minimal liver damage (minor changes in the serum aminotransferases and prothrombin time; no rise in plasma bilirubin levels). The remaining fifty-six patients had normal serum bilirubin levels and other standard liver function tests but without a liver biopsy, hepatic damage could not be excluded, and for statistical analysis they were included in group three. Comparison of the prolongation in prothrombin time showed these to be significantly different in each of the three groups (Table 1). The aspartate aminotransferase levels were significantly higher in the moderate and severe groups than in those with minimal damage, but a comparison between the former two groups was not possible as enzyme levels were recorded on occasions as 'greater than 1000 i.u./l' without absolute values being given. However, the percentage of surviving liver cells, estimated as the hepatocyte volume fraction, was significantly different in these two groups (Table 1).

The twenty patients in this series who died were all from amongst those considered to have severe liver damage (Table 2). When the outcome was considered in relation to the dose of paracetamol claimed to have been ingested, some correlation with the severity of liver damage could be detected. The chances of developing severe liver damage was less in those patients who had vomited or had a stomach wash-out within 6 hr of drug ingestion (twelve of seventy-one) than in those who had not (seventeen of forty-six, $\chi^2 = 6{\cdot}91$, $P < 0{\cdot}05$).

The investigation into the potential interference of other drugs commonly taken in overdose with the spectrophotometric assay for paracetamol showed that only high plasma concentrations of dichloralphenazone and, to a much lesser extent, phenobarbital, were likely to interfere significantly (Table

TABLE 1. Liver function tests and hepatocyte volume fraction (HVF) in patients developing minimal, moderate, or severe abnormalities in liver function tests. Mean values for the maximum abnormality recorded as shown ± 1 s.d. *P* values compare levels of significance between minimal and moderate or moderate and severe liver damage

Liver damage	Number of patients	Bilirubin (μmol/l)	Prothrombin time (sec prolonged)	Number with aspartate amino transferase > 100 i.u./l	HVF (%)
Minimal	19	14±3	3±2	0	80±10
		$P < 0.001$*	$P < 0.001$*	$P < 0.01$†	$P < 0.001$‡
Moderate	48	34±31	13±12	31	54±15
		$P < 0.001$*	$P < 0.001$*	P n.s.†	$P < 0.001$‡
Severe	40	137±68	75±64	35	38±20

* Using Student's *t*-test; † using χ^2 test; ‡ Mann-Whitney U test; n.s., not significant.

TABLE 2. Relationship between dose of paracetamol and the occurrence of vomiting or stomach wash-out, and severity of subsequent liver damage

	Number and percentage of patients developing liver damage			
Dose of paracetamol (g)	Minimal ($n = 46$)	Moderate ($n = 42$)	Severe ($n = 29$)	Deaths
< 17·5	16 (76%)	1 (5%)	4 (19%)	—
17·5–45	27 (38%)	30 (42%)	14 (20%)	—
> 45	3 (12%)	11 (44%)	11 (44%)	20
Stomach wash-out or vomiting within 6 hr	33 (47%)	26 (37%)	12 (16%)	—
No stomach wash-out or vomiting	13 (30%)	16 (33%)	17 (37%)	—

TABLE 3. Interference by drugs commonly taken in overdose with the spectrophotomctric assay of paracetamol

Drug	E_{max} (nm)	Maximum overdose plasma concentration (μg/ml)	Apparent paracetamol concentration as determined by ether extraction technique at 250 nm (μg/ml)
Salicylates	300	1000	0
Phenobarbital	240	300	12
Amobarbital	240	60	0
Glutethimide	250	40	0
Methaqualone	263	40	3
Dichloralphenazone	230	325	40

3). A highly significant correlation was found between measurements of plasma unconjugated paracetamol levels by the ether extraction method and by gas liquid chromatography ($n = 33, r = 0.98$, $P < 0.001$).

When plasma paracetamol concentrations were plotted on a semi-logarithmic scale against time after ingestion of tablets, all patients who developed moderate or severe hepatic damage had levels falling on or above a line joining values of 180 μg/ml at 4 hr and 45 μg/ml at 12 hr (Fig. 1). However, although patients who developed moderate or severe liver damage generally had the highest plasma paracetamol levels, the correlation with the clinical outcome in individual subjects was poor. This was particularly so in those cases in which the values plotted had been obtained within 6 hr of overdose. Thus, of the sixty patients with values falling above this line, nineteen developed minimal hepatic lesions only. Figure 1 also shows the line used by Douglas, Hamlyn and James (1976) for the selection of patients for mercaptamine therapy. In the present study, eighteen of fifty-three patients with values above this line developed minimal hepatic damage only, but the values of one patient with severe hepatocellular necrosis fell below the line.

Similarly, although estimates of the initial plasma half-life of paracetamol were generally higher in patients who developed the more extensive liver damage, there was considerable overlap for individual values (Fig. 2). Thus, although plasma half-lives of 4 hr or longer were found in all patients who subsequently developed moderate or severe hepatic necrosis, such prolongation was also found in eight of the twenty-eight patients classified as having minimal liver lesions. Furthermore, of the twenty

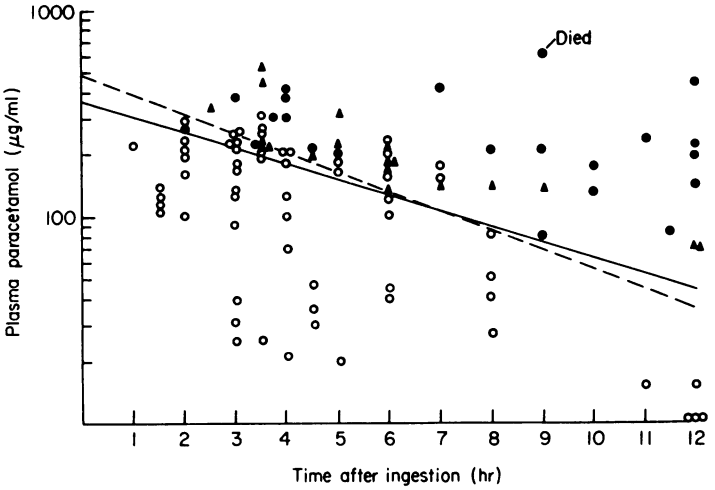

FIG. 1. Plasma paracetamol concentrations in patients developing minimal (○), moderate (▲), or severe (●) liver damage. —, Present study; – – –, Douglas *et al.* (1976).

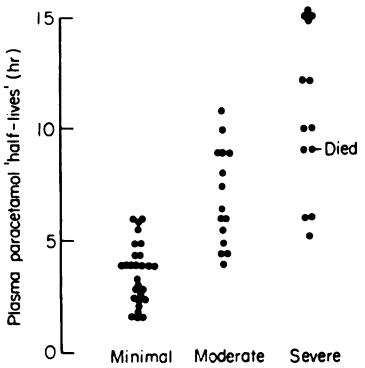

FIG. 2. Early plasma paracetamol half-lives in patients developing minimal, moderate, and severe liver damage.

patients in this series who died the only one who was admitted early enough for determination of paracetamol half-life had a value well below the maximum recorded for the severe group (Fig. 2).

Discussion

Experimental studies in animals have shown paracetamol to be a dose-related hepatotoxin (Mitchell *et al.*, 1973). and this is also probably true in man (Davis *et al.*, 1976). In the present series there was an overall correlation between the number of tablets ingested and the degree of ensuing liver damage, but this was not sufficiently precise to be of prognostic value in individual cases. One likely reason for this is that estimates of drug ingestion by acutely distressed self-poisoned patients are not always accurate (Matthew, 1971) despite careful history taking. Indeed, in one-third of the patients in the present series, this information could not be obtained. Furthermore, the quantity of drug absorbed from the gastrointestinal tract must vary widely from individual to individual (Rowland *et al.*, 1972) depending on whether the patient vomits or has a stomach wash-out early after the overdose, and certainly, in the present study, either of these two events significantly reduced the degree of liver damage. This is likely to complicate interpretation of the results of treatment with mercaptamine, although in neither of the trials reported with this drug to date has the possible influence of early vomiting or gastric lavage been acknowledged (Prescott *et al.*, 1974; Douglas *et al.*, 1976).

If plasma levels of paracetamol are to be of early prognostic help a rapid technique for measuring the drug is clearly essential. The method of ultra-violet absorption after ether extraction from plasma used in the present study provides results within 15 min and, although the technique is not specific for paracetamol, the results correlated well with the more time-consuming gas liquid chromatographic method. The possible interference in the assay by other compounds with similar absorption spectra was investigated because in 25% of suicidal overdoses more than one drug is involved (Chambers, 1976). Some, such as amitriptyline and chlordiazepoxide, are present in the plasma only in very low concentrations, even when taken as an overdose. Others, such as phenothiazines and the benzodiazepines, are completely ionized at physiological pH, and will therefore not be extracted by ether. However, the present authors' findings have shown that the concomitant presence of dichloralphenazone or phenobarbital in the plasma would produce

spuriously high estimates of plasma paracetamol concentration. For this reason, the more specific, but equally rapid, test kit which has been developed recently for the estimation of paracetamol (Kendal, Lloyd-Jones and Smith, 1976; Widdop, 1976) is to be preferred.

Previous studies by Prescott *et al.* (1971) have demonstrated that measurement of the half-life of paracetamol correlates well with the severity of ensuing hepatic necrosis. However, these workers used plasma samples taken up to 36 hr after ingestion of tablets to calculate these values, and clearly this technique would not give the early prognostic information required to select patients for treatment with mercaptamine or other agents, which likewise should be given as soon as possible, and not later than 10 hr after overdose. The authors' estimates of paracetamol half-life early after the overdose from three or more samples taken within 4 hr, may not accurately reflect the overall rate of clearance of the drug from the plasma, owing to continuing gastrointestinal absorption. Although severe liver damage was not found in the patients with a half-life of less than 4 hr, the reverse did not apply, and if mercaptamine had been given to all those with such values, over 20% (those shown to develop minimal damage only) would have received this unpleasant form of therapy unnecessarily.

In all published reports of the use of mercaptamine, patients have been selected for treatment on the basis of single estimates of the plasma paracetamol levels (Prescott *et al.*, 1974; Douglas *et al.*, 1976). The difficulty is that patients may not accurately recall the exact time they took the overdose, particularly when sedative drugs or large quantities of alcohol have also been ingested. Furthermore, in the present series, plasma paracetamol concentrations correlated poorly with the degree of ensuing hepatocellular damage for individual subjects and the prognostic value of these estimates was particularly poor when measurements were made within 6 hr of overdose. Thus, as the results of the present study indicate, about 25% of patients selected for mercaptamine treatment on the basis of a single plasma paracetamol level will be at risk from trivial hepatic damage only, and if cases seen within 6 hr are considered, up to one third may be treated unnecessarily.

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