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The effects of hepatic and renal damage on paracetamol metabolism and excretion following overdosage. A pharmacokinetic study.

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Summary

1. The kinetics of paracetamol metabolism and excretion were studied in 41 patients following overdosage. Acute hepatic necrosis developed in 23 patients and in 3 of these acute renal failure also occurred. Two patients died in hepatic failure.

2. Paracetamol metabolism was impaired in the patients with liver damage. The plasma half-life of the unchanged drug was significantly prolonged, and the ratio of the plasma concentrations of unchanged to conjugated paracetamol was significantly higher than in the patients without liver damage.

3. Paracetamol and its conjugates were rapidly excreted in the urine. However, excretion was slower in patients with liver damage and a higher proportion was excreted unchanged.

4. The renal clearance of unchanged (but not conjugated) paracetamol was related to the urine flow rate. However, forced diuresis is of no practical value and is contraindicated on clinical grounds. There was no correlation between urine pH and clearance of unchanged or conjugated drug.

5. In patients with hepatic necrosis there was a marked decrease in the overall elimination rate constant which could be accounted for by decreased metabolite formation. Except in patients with acute renal failure, the urinary excretion rate constants were similar to those observed in patients without liver damage.

Introduction

Paracetamol (*N*-acetyl-*p*-aminophenol, acetaminophen) is a widely used antipyretic analgesic which is remarkably safe when taken in therapeutic doses. It is normally extensively metabolized to glucuronide and sulphate conjugates and only 3–4% of a therapeutic dose is excreted unchanged in the urine (Cummings, King & Martin, 1967; Levy & Yamada, 1971). In overdosage, however, paracetamol often causes acute hepatic necrosis (Proudfoot & Wright, 1970) and the subsequent rate at which paracetamol is eliminated depends on the severity of the liver damage. Thus elevation of serum enzyme activity, bilirubin concentration and prothrombin time are all closely related to the plasma paracetamol half-life (Prescott, Wright, Roscoe & Brown, 1971). In addition, a minority of patients develop renal failure after paracetamol overdosage.

Previously reported pharmacokinetic studies of paracetamol have been restricted to healthy subjects taking therapeutic doses under ideal conditions (Nelson & Morioka, 1963; Cummings *et al.*, 1967; Levy & Yamada, 1971). In the present study a detailed clinical pharmacokinetic analysis has been carried out in patients taking paracetamol in overdosage since abnormal drug metabolism and elimination is inevitable in the presence of acute hepatic or renal damage.

Methods

Patients

Thirty females and 11 males aged 16–72 years (mean 32 years) with admission plasma paracetamol concentrations exceeding 30 μg/ml after overdosage were studied. The mean interval between the ingestion of paracetamol and admission was 6·0 h (range 1·75 to 16 hours). The management of patients and serial biochemical monitoring of liver and renal function have been described previously (Prescott *et al.*, 1971). All the patients with liver damage had serum alanine and aspartate aminotransferase (SGPT, SGOT) activities exceeding 200 and 100 i.u./l respectively. The mean maximum SGPT and SGOT values were 1,114 and 3,245 i.u./litre. Two patients with liver damage and two without received 6 l of fluid intravenously in 3 h to produce a forced diuresis as described by Lawson, Proudfoot, Brown, Macdonald, Fraser, Cameron & Matthew (1969) for the treatment of salicylate intoxication.

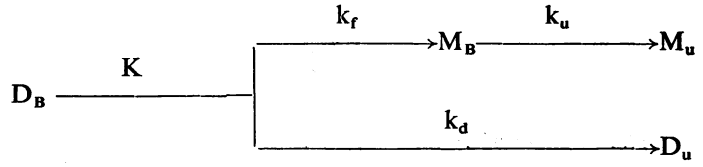
Samples

From 4 to 30 venous blood samples were obtained from each patient at intervals up to 90 h after ingestion. The plasma paracetamol half-life was calculated in each patient from data obtained during the period 4 to 36 h after ingestion. Urine was passed spontaneously and where possible consecutive samples were collected for up to 7 days. The time interval between urine collections was variable and some samples were lost due to incontinence or non-cooperation by the patient.

The urine pH was measured by a Pye Model 107 pH meter and plasma and urine samples were stored frozen. Unchanged and conjugated paracetamol was estimated by gas liquid chromatographic methods (Prescott, 1971a, 1971b).

Pharmacokinetic analysis

Patients were selected retrospectively for pharmacokinetic analysis on the basis of adequate data. The metabolism and excretion of paracetamol was assumed to conform to the scheme proposed by Cummings, Martin & Park (1967).



where D_B =amount of unchanged paracetamol in the body
M_B =amount of conjugated paracetamol in the body

M_u = amount of conjugated paracetamol excreted in the urine
D_u = amount of unchanged paracetamol excreted in the urine
K = overall paracetamol elimination rate constant
k_f = metabolite formation rate constant
k_d = unchanged paracetamol excretion rate constant
k_u = conjugated paracetamol excretion rate constant
D_o = estimated total amount of paracetamol absorbed
D_{co} = estimated plasma paracetamol concentration extrapolated back to the time of ingestion
t = time after ingestion
M_{CB} = plasma concentration of conjugated paracetamol
V_D = apparent volume of distribution of unchanged paracetamol
V_M = apparent volume of distribution of conjugated paracetamol

The following equations were derived by Cummings *et al.* (1967):

$$\ln D_B = \ln D_o - Kt \quad (1)$$

$$\ln \frac{dD_u}{dt} = \ln k_d D_o - Kt \quad (2)$$

$$\ln \frac{dM_u}{dt} = \ln \frac{k_u k_f D_o}{k_u - K} - \ln (e^{-Kt} - e^{-k_u t}) \quad (3)$$

$$\ln M_B = \ln \frac{k_f D_o}{k_u - K} - Kt \quad (4)$$

$$K = k_f + k_d \quad (5)$$

Dose absorbed

The dose absorbed could not be determined from the amount claimed to have been taken by the patients since the drug history in such circumstances is notoriously unreliable (Bloomer, Maddock, Sheehe & Adams, 1970). Furthermore, some patients vomited before admission, and the total urinary recovery of paracetamol could not be determined because collections were often incomplete. The amount of paracetamol absorbed was therefore estimated indirectly.

The assumption was made that the apparent volume of distribution of paracetamol (V_D) was the same in poisoned patients as that calculated in healthy volunteers given 12 mg/kg intravenously (0·85 ± 0·04 l/kg, unpublished observations) and the amount absorbed was calculated as the product of V_D, D_{co} and body weight. An alternative estimate was obtained by summing the areas beneath the plots of equations 2 and 3. The latter method probably gives a low estimate because only about 85% of a therapeutic dose of paracetamol can be recovered in the urine, but the results obtained by both methods were in good agreement (correlation coefficient r=0·97).

Overall elimination rate constant

The overall elimination constant (K) was determined from the slope of equation 1. The values were compared with those obtained from the slope of equation 2 and the terminal gradients of equations 3 and 4 when K is less than k_u.

Unchanged paracetamol excretion rate constant

The plot of equation 2 gives a value for $k_d D_o$ when t=o. Since D_o is known, k_d can be calculated.

Metabolite formation rate constant

The metabolite rate formation constant (k_f) was obtained directly from equation 5. It was assumed that the total amount absorbed is excreted either as free drug or conjugates which were detected by the assay techniques. The estimate of k_f will therefore probably be high.

Conjugated paracetamol excretion rate constant

When t is large and k_u is greater than K equation 3 reduces to

$$\ln\frac{dM_u}{dt}=\ln\frac{k_u\,k_fD_o}{k_u-K}-Kt$$

Thus k_u may be calculated if K, k_f and D_o are known.

The overall elimination rate constant K, became greater than k_u in the patients who developed renal failure and equation 3 could then be reduced to:

$$\ln\frac{dM_u}{dt}=\ln\frac{k_u\,k_f\,D_o}{k_u-K}-k_ut$$

Thus k_u could be obtained directly from the terminal slope of the semilogarithmic plot of the excretion rate of conjugated paracetamol against time.

Renal clearance

The renal clearances of unchanged and conjugated paracetamol were calculated as UV/P where U is the urine concentration, P is the plasma concentration, and V is the urine volume (ml/minute). The correlation of clearance with urine flow rate and pH was determined by multiple regression analysis.

Volume of distribution

The apparent volume of distribution was obtained from the following relationship:

$$\text{Volume of distribution}=\frac{\text{renal clearance}}{\text{excretion rate constant}}$$

Results

Liver damage and plasma paracetamol concentrations

Twenty-three of the 41 patients developed liver damage and three of these also developed acute renal failure. There was no consistent relationship between the D_o values and the presence or absence of liver damage. However, mean plasma concentrations of unchanged paracetamol at 4 and 12 h after ingestion were significantly higher in patients with liver damage than in those without (Table 1).

TABLE 1. *Mean (±S.E.M.) plasma concentrations and half-life of unchanged paracetamol in patients with and without liver damage*

Patients	Plasma paracetamol half-life (h)	Plasma paracetamol concentrations (hours after ingestion)	
		4 h	12 h
No liver damage (n=18)	2·9±0·3	163±20	29·5± 6
Liver damage (n=23)	7·2±0·7	296±26	124±22

The mean plasma half-life of paracetamol was greatly prolonged in the patients with liver damage and the difference between the two groups was statistically significant ($P<0{\cdot}001$). In the patients without liver damage the plasma concentrations of the conjugated paracetamol were higher after 6 h than the concentrations of unchanged drug. However, conjugation was impaired in patients with liver damage since concentrations of paracetamol conjugates were always lower than those of unchanged drug (Figure 1). The mean ratio of the concentrations of unchanged to conjugated paracetamol in plasma differed markedly in the two groups (Figure 2).

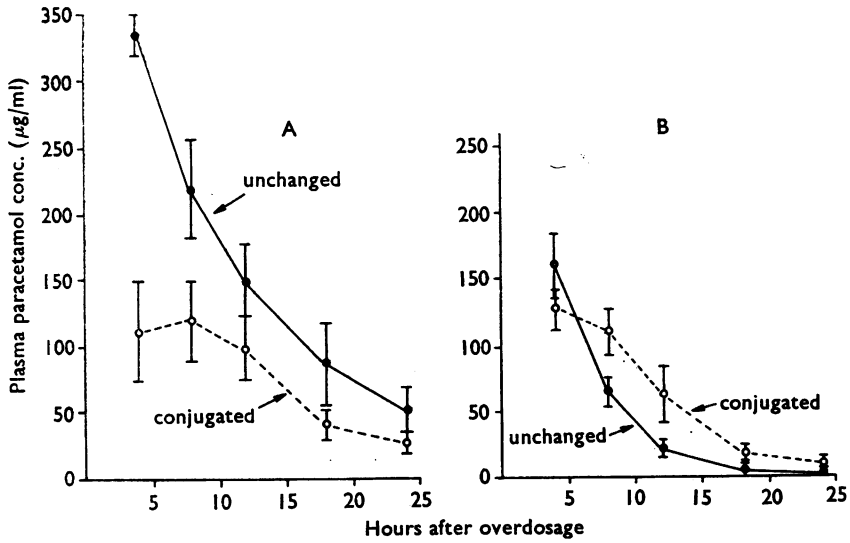


FIG. 1. Plasma concentrations of unchanged and conjugated paracetamol in 9 patients with liver damage (A) and 9 patients without liver damage (B) following overdosage. Vertical bars represent S.E.M.

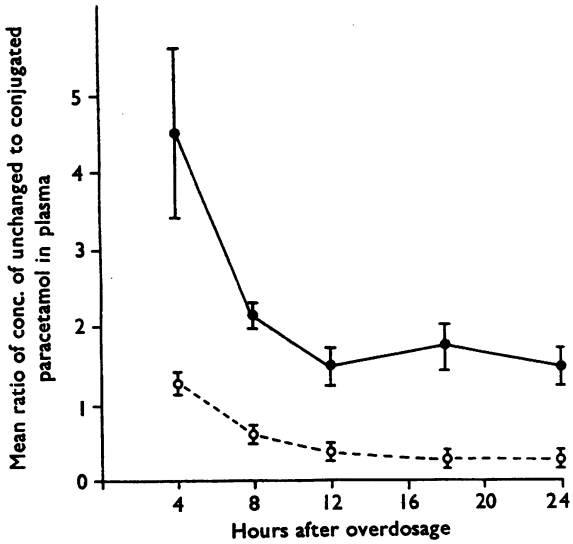


FIG. 2. Mean ratio of concentrations of unchanged to conjugated paracetamol in 8 patients with hepatic necrosis (●——●) and 9 patients without liver damage (○- - -○) following overdosage. Vertical bars represent S.E.M.

Urinary excretion of paracetamol

Paracetamol and its conjugates were excreted very rapidly in the patients without liver damage. Thus about 70% of the amount recovered appeared in the urine within 10 h of ingestion (Figure 3). In patients with liver damage, excretion was slower and proportionately less was present as conjugates than in patients with normal hepatic function. During the first 6 h after ingestion 15–25% of the total drug was excreted by both groups as unchanged paracetamol. After 12 h, the proportion excreted unchanged fell to less than 5% in the patients without liver damage, but continued at about 15% in those with liver damage.

Renal clearance values are shown in Table 2. There was a statistically significant positive correlation between the renal clearance of unchanged drug and the urine flow rate ($P<0{\cdot}01$). No such relationship could be demonstrated for conjugated paracetamol and there was no significant correlation between urine pH and the clearance of either unchanged or conjugated drug. The correlation between the clearance of unchanged drug and urine flow is of little practical significance since the mean clearance only rose from 12·3 to 23·9 ml/min when the urine flow increased 8-fold. Liver damage did not appear to influence the renal clearance of unchanged or conjugated paracetamol.

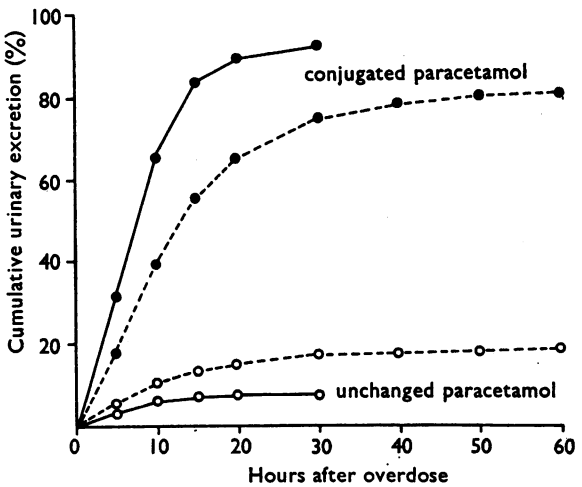


FIG. 3. Mean cumulative urinary excretion of paracetamol and its conjugates in 5 patients with liver damage (- - - -) and 4 without liver damage (——).

TABLE 2. *Effects of liver damage and forced diuresis on the renal clearance of paracetamol*

	No. of patients	No. of observations	Urine flow (ml/min)	Renal clearance of paracetamol Unchanged (ml/min)	Conjugated (ml/min)
No liver damage	4	25	10·8±2·7	20·0±2·2	124±14
Liver damage	5	38	6·4±1·6	17·8±2·3	149±16
No forced diuresis	5	29	1·6±0·3	12·3±1·6	132±15
Forced diuresis*	4	34	13·7±2·1	23·9±2·3	146±15

* Forced diuresis was carried out in 2 patients with and 2 patients without liver damage. Values given are means±S.E.M.

Pharmacokinetic analysis

Sufficient data were available for analysis in 4 patients without liver damage, 4 with liver damage and 3 with both liver and renal damage. The results are summarized in Table 3. The mean overall elimination rate constant (K) was significantly reduced in patients with liver damage only as compared with those without liver damage (0·12 and 0·26 h^{-1} respectively, $P<0·001$). This difference can be attributed entirely to the reduced rate of metabolite formation since the rate constants for excretion of unchanged drug (k_d) were similar in the two groups. As expected, the mean metabolite formation rate constant (k_f) was significantly lower in patients with liver damage than in those without (0·10 and 0·24 h^{-1}, $P<0·001$). The conjugated paracetamol excretion rate constants (k_u) were similar in the two groups. In one patient, forced diuresis had no apparent influence on any of the rate constants.

The rate constants for overall elimination, metabolite formation and renal excretion of unchanged and conjugated paracetamol were all significantly lower in the 3 patients with both liver and renal damage. Acute renal failure developed during the period of study and in 2 of the 3 patients the rate of accumulation of metabolite in the body eventually equalled the rate of metabolite formation.

The reliability of the pharmacokinetic analysis was checked by independent calculation of the overall elimination rate constant (K) from equations 1, 2, 3 and 4 using plasma and urinary concentrations of unchanged and conjugated paracetamol. The results were in good agreement (Table 4).

TABLE 3. *Pharmacokinetic constants in patients without liver damage, with liver damage and with liver and renal damage*

Patient group	Age and sex	Overall elimination rate constant $K(h^{-1})$	Metabolite formation rate constant $k_f(h^{-1})$	Drug excretion rate constant $k_d(h^{-1})$	Metabolite excretion rate constant $k_u(h^{-1})$	Dose ingested D_o (g)†
No liver damage	23 M	0·24	0·22	0·02	0·40	15·1
	46* F	0·26	0·24	0·02	0·50	8·2
	32 F	0·27	0·26	0·01	0·45	15·3
	46 F	0·27	0·25	0·02	0·40	12·0
Mean±S.E.M.		0·26±0·007	0·24±0·008	0·02±0·003	0·43±0·024	12·7±1·7
Liver damage	16 F	0·09	0·07	0·02	0·66	6·2
	23 F	0·16	0·12	0·04	0·50	12·1
	52 F	0·10	0·09	0·01	0·44	34·9
	24 F	0·12	0·10	0·02	0·40	22·1
Mean±S.E.M.		0·12±0·02	0·10±0·01	0·02±0·006	0·5±0·06	18·8±6·3
Liver damage and renal failure	36 F	0·16	0·16	0·002	0·06	21·6
	54 F	0·06	0·06	0·003	0·008	31·9
	32 F	0·05	0·04	0·009	0·005	18·3
Mean±S.E.M.		0·09±0·04	0·09±0·04	0·005±0·002	0·024±0·018	23·9±4·1

* Forced diuresis; † Calculated from plasma concentration data.

TABLE 4. *Overall elimination rate constants calculated from equations* 1, 2, 3 *and* 4 (*means*±S.E.M.)

Patients	Equation 1	Equation 2	Equation 3	Equation 4
No liver damage	0·26±0·01	0·24±0·02	0·23±0·01	0·22±0·03
Liver damage	0·12±0·02	0·11±0·01	0·12±0·01	0·11±0·01
Liver and renal damage	0·09±0·06	0·09±0·01	0·10±0·04	0·11±0·02

Dose absorbed in relation to liver damage

The dose of paracetamol absorbed was calculated from the plasma concentration data for the patients without liver damage, with liver damage and with both liver and renal damage (Table 3). Although the mean dose absorbed was higher in the groups with liver damage than in those without, there was striking individual variation. Thus as little as 6·2 g caused a severe hepatic lesion in one patient (SGOT 2760 i.u./l) while 15.3 g did not produce liver damage in another. Similarly, one patient who absorbed 18·3 g died in hepato-renal failure, but another patient survived a dose of 34·9 grams.

Volume of distribution

The apparent volumes of distribution of unchanged and conjugated paracetamol were calculated excluding data from the 3 patients with renal failure. The mean values for V_D and V_M were $0{\cdot}77 \pm 0{\cdot}03$ l/kg and $0{\cdot}24 \pm 0{\cdot}03$ l/kg respectively.

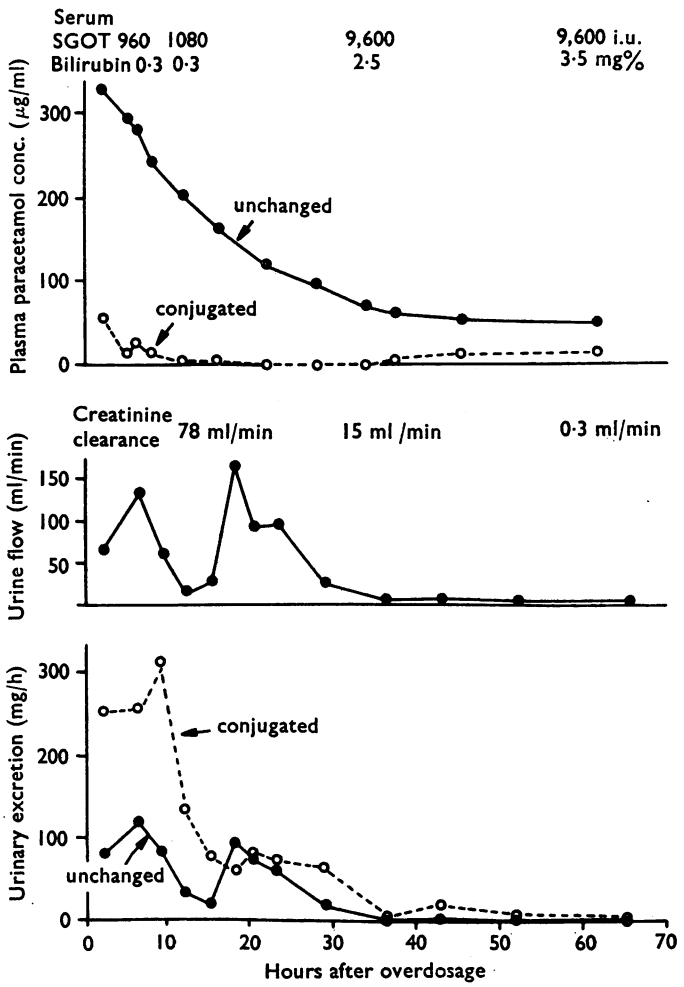


FIG. 4. Clinical and pharmacokinetic data in a 32-year-old woman with fatal hepatic necrosis following paracetamol overdosage.

Patients dying with hepatic failure

The results of serial liver function tests together with plasma and urine concentrations of unchanged and concentrated paracetamol in 2 patients who died in hepatic failure are shown in Figs. 4 and 5. Severe liver damage occurred very early, and there was virtually complete failure of paracetamol conjugation in one patient (Figure 4). The initial plasma paracetamol concentration was only 320 μg/ml, and higher concentrations were observed in many other patients who survived. Initially, the plasma paracetamol half-life was 15 h, but after 36 h it gradually increased to about 60 hours. In the other fatal case, the initial plasma paracetamol concentration was 697 μg/ml, but conjugation was not markedly impaired until about 12 h after ingestion. The paracetamol half-life eventually increased from 10 to about 25 hours. Oliguria and renal failure developed in

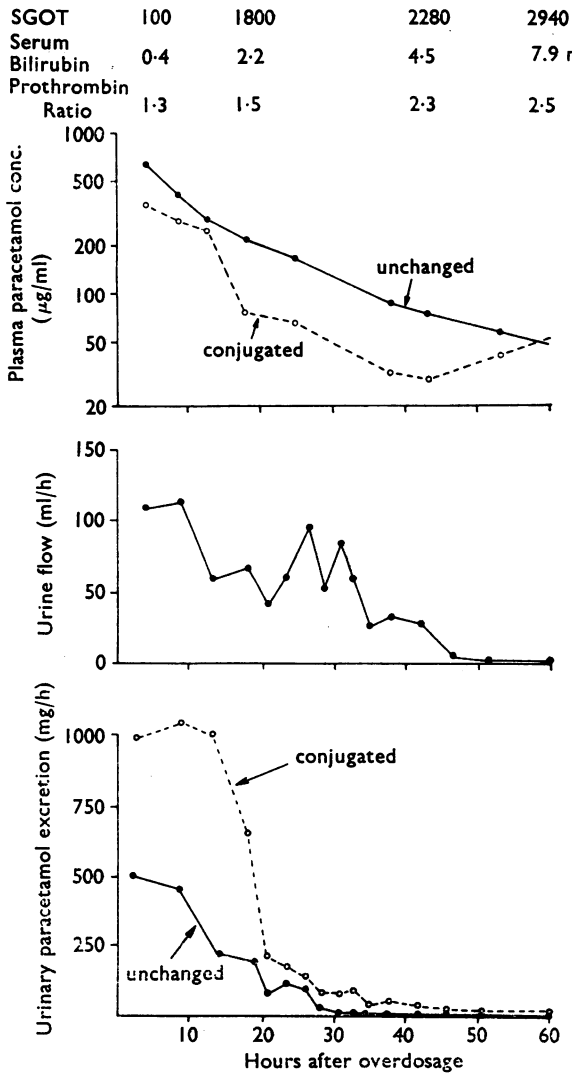


FIG. 5. Clinical and pharmacokinetic data in a 54-year-old woman who died in hepatic failure following paracetamol overdosage.

both patients 40–50 h after ingestion of paracetamol. Massive centrilobular hepatic necrosis was found at post-mortem examination in both patients.

Discussion

The present studies show that the conjugation of paracetamol is markedly impaired in patients who develop liver damage following overdosage. As judged by the early depression of paracetamol metabolism, liver damage occurs within 2–3 hours of ingestion, and the ratio of the plasma concentrations of unchanged to conjugated paracetamol provides a sensitive index of hepatic injury. It has previously been shown that the plasma paracetamol half-life is significantly correlated with biochemical abnormalities of liver function and the prognosis can be established within 12 h of admission (Prescott *et al.*, 1971). It is clearly unnecessary to wait 3–4 days for elevation of serum bilirubin and prothrombin time as suggested by Clark, Thompson, Borirakchanyavat, Widdop, Davidson, Goulding & Williams (1973). In the patients with fatal hepatic necrosis the rate of paracetamol metabolism was strikingly reduced, and the outcome is likely to be fatal if the paracetamol half-life exceeds 10–12 hours. The initial plasma concentrations of conjugated paracetamol in the patients with and without liver damage were similar (Fig. 1), and it could be argued that depression of conjugation in the former group was due to enzyme saturation or limited availability of glucuronic acid and sulphate rather than liver damage. Although this may apply in the case of sulphate conjugation (Levy & Yamada, 1971) the dominant glucuronide conjugation pathway could not have been saturated since there was an exponential decline in plasma paracetamol concentrations in all the patients except the two who died in hepatic failure. Further prolongation of the paracetamol half-life in these two patients could have been due to progressive hepatic necrosis or reduced renal excretion of unchanged drug because of acute renal failure. Further evidence of the reduced capacity of the acutely damaged liver to metabolize drugs is provided by the observation of marked depression of barbiturate and antipyrine metabolism in patients with paracetamol-induced hepatic necrosis (Prescott & Stevenson, 1973).

The results of the pharmacokinetic analysis indicate a mean reduction of about 60% in the rate of conjugation of paracetamol in the patients with liver damage. The reduction in the overall rate of elimination of paracetamol could be attributed entirely to impaired conjugation since the urinary excretion rate constants were the same as in patients without hepatic and renal damage. As expected, the urinary excretion rate constants were grossly reduced in the patients who developed renal failure.

A number of assumptions had to be made in the calculation of the pharmacokinetic constants in the present study. The amount of paracetamol absorbed could not be determined directly and with the indirect method used, serious errors could have occurred if the stated time of drug ingestion was incorrect. Furthermore, with the analytical methods used only about 85% of an intravenous dose of paracetamol can be accounted for in the urine. Unknown and minor metabolites such as cysteine and mercapturic acid conjugates (Jagenburg, Nagy & Rödjer, 1968) were presumably not detected.

Despite these limitations, the derived rate constants in the patients without liver

damage were in good agreement with those obtained in healthy volunteers receiving 12 mg/kg of paracetamol intravenously. Similarly, when the data of Cummings *et al.* (1967), was recalculated to obtain total metabolite formation and excretion rate constants the values were comparable to those observed in the present study. Thus, the corrected rate constants for overall elimination, metabolite formation, and excretion of unchanged and conjugated drug in 4 volunteers given therapeutic doses of paracetamol orally were 0·31, 0·23, 0·01 and 0·62 per hour respectively (compare with Table 3).

In the absence of impaired renal function, the excretion of unchanged and conjugated paracetamol was rapid, even in patients with liver damage. A relatively large proportion of the drug was excreted in the urine unchanged during the first few hours after ingestion, reflecting high plasma concentrations. Normal individuals excrete only 3–4% of a therapeutic dose of paracetamol unchanged in the urine, but in the patients without liver damage following overdosage the corresponding fraction was 5–10%. This difference may be explained by saturation of the sulphate conjugation mechanism as proposed by Levy & Yamada (1971). Paracetamol conjugates are apparently excreted by active tubular secretion since their overall renal clearance was much higher than that of the unchanged drug, and often exceeded 125 ml/minute. According to Milne (1965), the renal excretion of acidic drugs with pKa values between 3·0 and 7·5 is pH-dependent. Paracetamol is a weak acid with a pKa value of 9·5, and physiological changes in urine pH would not be expected to influence its renal clearance. Although the clearance of unchanged paracetamol showed a statistically significant correlation with urine flow rate, forced diuresis had no obvious effect on any of the rate constants and would have no therapeutic value. Furthermore, in our experience, early forced diuresis does not prevent liver damage and is potentially dangerous because paracetamol has an antidiuretic effect (Nusynowitz & Forsham, 1966).

The mechanism of paracetamol-induced hepatic necrosis has been elucidated by Mitchell, Jollow, Potter, Davis, Gillette & Brodie (1973) and Jollow, Mitchell, Potter, Davis, Gillette & Brodie (1973). The lesion is caused by covalent binding of active intermediate metabolites of paracetamol to liver cell proteins and toxicity in animals is enhanced by pretreatment with microsomal enzyme inducers and reduced by inhibitors such as piperonyl butoxide and SKF 525A (Mitchell *et al.*, 1973 ; Prescott, 1973). In man, the hepatotoxicity of paracetamol is also increased by previous consumption of drugs likely to cause microsomal enzyme induction (Wright & Prescott, 1973). There is a rather poor correlation between the calculated dose of paracetamol absorbed and the severity of subsequent liver damage. It is clearly impossible to establish a minimum hepatotoxic or a minimum lethal dose in view of the obvious individual variation in susceptibility to the hepatotoxic effects of paracetamol.

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