Predicting outcome of paracetamol poisoning by using ^{14}C-aminopyrine breath test

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Summary and conclusions

The ^{14}C-aminopyrine (^{14}C-amidopyrine) breath test, carried out within 24-36 hours of an overdosage of paracetamol, was used to predict the extent of liver damage in 30 seriously poisoned patients. Mean $^{14}CO_2$ excretion was 4·4% in 20 healthy control subjects; 5·5% in six patients who escaped injury; and 2·9%, 1·5%, and 0·2% in those with mild to moderate (12 patients), severe (eight patients), and fatal (four patients) liver damage respectively.

This test proved to be a more reliable predictor of the extent of liver damage than plasma paracetamol concentration or half life or the results of conventional liver function tests and may enable treatment of hepatic failure to be started at an early stage.

Introduction

A depressing feature of paracetamol poisoning is that the patient may be quite well when first seen yet die later of overwhelming liver damage. There is no satisfactory way of predicting the outcome. Single plasma paracetamol concentrations correlate only roughly with the degree of liver damage,[1 2] and the half life of plasma paracetamol, reportedly a better guide,[1] is affected by continuing absorption of the drug and the onset of liver damage. Furthermore, hepatic injury is caused by an intermediate metabolite of paracetamol,[3 4] and alcoholics and patients taking enzyme-inducing drugs are particularly at risk of developing liver damage because a greater proportion of paracetamol is converted to the toxic metabolite.[5 6] Conversely, treatment with drugs such as mercaptamine (cysteamine) reduces the risk of injury.[7] Plasma concentrations of unchanged paracetamol, therefore, might not be expected reliably to indicate prognosis.

The ^{14}C-aminopyrine (^{14}C-amidopyrine) breath test[8] measures the functional capacity of the hepatic microsomal enzymes, which are the site of maximal injury after paracetamol overdose.[9] We thought that this test might provide an early indication of the extent of liver damage.

Patients and methods

We studied 19 women and 11 men (aged 16-86 years) who had allegedly taken at least 10 g paracetamol. All had actual or extrapolated plasma paracetamol concentrations over 120 mg/l four hours after overdose. Most of the patients had taken only paracetamol, but two had also taken dextropropoxyphene (as Distalgesic), three dihydrocodeine (as Paramol-118), and two aspirin. One patient was a chronic alcoholic who habitually drank over 80 g alcohol daily.

Gastric lavage was performed when patients were seen within 24 hours of overdose, and mercaptamine administered to 15 of the 21 patients who were seen within 12 hours. A high-energy, low-protein diet, lactulose, and vitamin K were prescribed for patients who were thought likely to develop liver failure.

Routine haematological and biochemical tests were performed daily. Plasma paracetamol concentrations were determined by ultraviolet spectrophotometry, and the half life of plasma paracetamol was calculated from serial measurements obtained four to 36 hours after overdose by using the least squares method, assuming first-order kinetics of elimination.[1]

The ^{14}C-aminopyrine breath test[8] was performed 24-36 hours after overdose and then repeated every two to three days. An oral dose of 1·5 μCi ^{14}C-aminopyrine (Radiochemical Centre, Amersham) was given in 100 ml water, without previous fasting, and the patient asked to rest quietly. Two hours later a breath sample was collected by the patient's blowing into a scintillation phial containing 4 ml Hyamine hydroxide-ethanol 1 mol/l until the thymolphthalein indicator suddenly changed from blue to colourless, which indicated that 2 mmol CO_2 had been collected. After adding scintillation cocktail the $^{14}CO_2$ was measured and specific activity calculated. Cumulative excretion of $^{14}CO_2$ in the two-hour period was then calculated by multiplying the mean specific activity (specific activity at two hours ÷ 2) by the endogenous output of CO_2 (9 mmol/kg/h)[10] and was expressed as a percentage of the administered dose of ^{14}C label. Permission to use radiolabelled aminopyrine was granted by the Medical Research Council, and informed consent was obtained from the patients.

The severity of liver damage was assessed as follows. *None* (six patients): normal prothrombin time ratio (⩽1·2), serum bilirubin concentrations (⩽21 μmol/l; 1·22 mg/100 ml), and serum aspartate aminotransferase (AST) activity (⩽45 IU/l) throughout admission. *Mild to moderate* (12 patients): peak prothrombin time ratio ⩽2·0, bilirubin concentration ⩽45 μmol/l (⩽2·63 mg/100 ml), and AST activity ⩽4000 IU/l. *Severe* (eight patients): peak prothrombin time ratio >2·0, bilirubin concentration >45 μmol/l (>2·63 mg/100 ml), and AST activity >4000 IU/l, with clinical jaundice and tender hepatomegaly but no signs of liver failure. *Fatal* (four patients): death from hepatic failure.

Results

Plasma paracetamol concentrations in the four groups overlapped considerably at any time after the overdose. The highest concentrations were usually found in patients who developed severe or fatal liver damage, but two patients who developed severe damage had plasma paracetamol concentrations below 50 mg/l at 12 hours and undetectable concentrations at 24 hours; one of these was a chronic alcoholic. Conversely, one patient who had a concentration of 205 mg/l at 12 hours and was treated with mercaptamine did not develop liver damage.

The half life of plasma paracetamol was under four hours in four of the six patients who did not develop liver damage (fig 1). It was over four hours in 21 of the 24 patients with liver damage, but again the values in the groups overlapped considerably. In one patient who developed severe damage the paracetamol half life was only 3·2 hours, and in another, who died, it was only 8·4 hours.

The mean value of the ^{14}C-aminopyrine breath test in a group of 20 healthy control subjects (aged 21-60 years) was 4·4% and the normal range (±2 SD from the mean) 3·2-5·6%. Figure 2 shows that in patients who did not develop liver damage the values were in or slightly above this range (mean value 5·5%). In those with mild to moderate damage the mean value (±1 SD) was 2·9±0·8% and in those with severe damage the mean value was 1·5±0·5%, the lowest value being 0·9%. The four patients who died had values between 0% and 0·4%.

The peak serum AST activity and peak prothrombin time ratio occurred between two and five days after overdose. We could not predict the eventual outcome with any consistency from values

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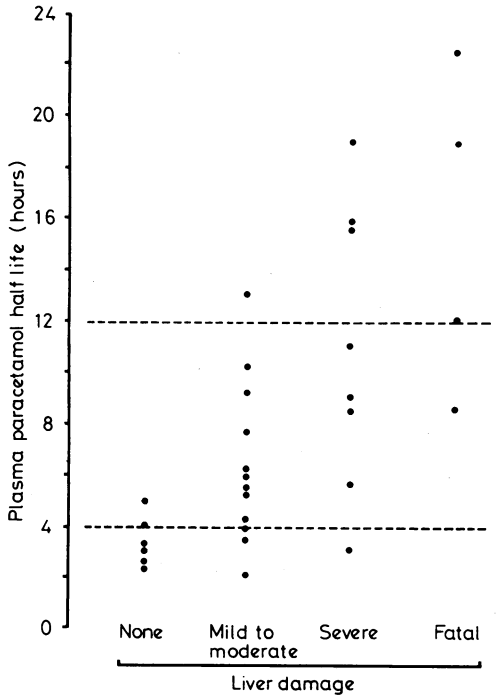

FIG 1—Half life of plasma paracetamol in 30 patients grouped according to severity of ensuing liver damage.

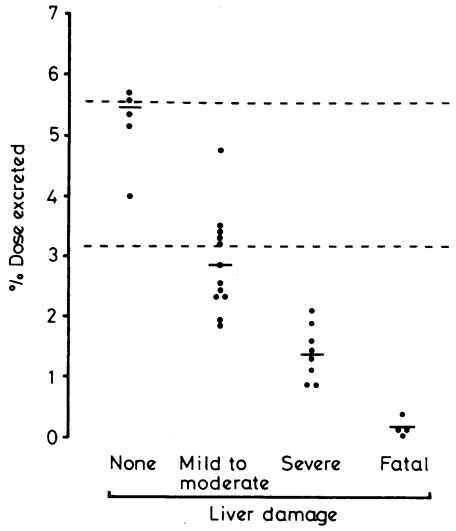

FIG 2—Values for aminopyrine breath test (expressed as percentage of administered ^{14}C label excreted) performed 24-36 hours after paracetamol overdose in 30 patients, grouped according to severity of ensuing liver damage. - - - = Limit of normal range in 20 healthy controls. Horizontal bars indicate mean value in each group.

obtained within the first 36 hours, and peak AST activity was sometimes higher in patients who survived than in those who died.

The results of sequential breath tests in patients with liver damage remained low for the first week after overdose and then gradually returned to normal. Results of conventional liver function tests reverted to normal within 14 days.

Discussion

Paracetamol causes liver damage because of its conversion by the microsomal mixed-function-oxidase system to a toxic, oxidative metabolite that binds covalently to cellular proteins.[3 4] Binding occurs preferentially to the microsomal fraction and is most pronounced in the centrilobular areas[3 4]; liver-cell necrosis follows.

Plasma paracetamol concentrations under 50 mg/l at 12 hours after overdose or a half life of under four hours are thought to indicate that the patient is safe, whereas concentrations above 50 mg/l at 12 hours or a half life of over four hours are regarded as harbingers of liver damage.[1] A half life of over 12 hours is thought to predict severe liver damage with a serious risk of hepatic coma.[1] Our results clearly show that these methods of assessing prognosis are unsatisfactory. Moreover, the results of conventional liver function tests, such as the prothrombin time ratio and measurement of serum AST activity, change too slowly to be helpful in the first 48 hours, and the time of maximal abnormality can be determined only retrospectively.

Aminopyrine is almost entirely metabolised by the hepatic, microsomal mixed-function-oxidase system, and urinary excretion of unchanged drug is minimal.[11] Measuring $^{14}CO_2$ in a single breath sample taken two hours after a dose of ^{14}C-aminopyrine provides a quantitative assessment of microsomal function.[8] We found that reduction in metabolism of aminopyrine occurred early after paracetamol overdose and was directly related to the severity of the subsequent illness. We do not know how soon this reduction occurs, but two patients who developed severe liver damage already showed substantial impairment of $^{14}CO_2$ excretion at 15 hours after overdose. Interestingly, those patients who died of liver failure could be distinguished from those who developed severe liver damage, but subsequently recovered, as early as 24 hours after overdose. This breath test may, therefore, enable treatment of hepatic failure to be started at an early stage rather than at the onset of encephalopathy, when the outlook is poor.

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A table showing clinical details and results of laboratory investigations in all patients is available from the authors on request.

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