Long-term ingestion of paracetamol and liver disease[1]

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Summary: Of 45 patients with chronic active hepatitis, 17 had taken paracetamol before the onset of symptoms. There were no significant differences, however, between the two groups in abnormalities of liver function tests, nor in ease of control after paracetamol withdrawal and institution of immunosuppressive therapy. The patient who had taken more than 5 g/week was studied in greater detail, but after a challenge dose of 1 g paracetamol there was no rise in serum aminotransferases and the pattern of excretion of paracetamol metabolites was normal. A critical review of the previously published reports failed to uncover any convincing evidence that paracetamol is an initiating factor in the development of chronic active hepatitis, although it may, at therapeutic levels, cause a toxic hepatitis in those individuals at risk.

Introduction

Paracetamol is a widely used and safe analgesic, although when taken in overdose with suicidal intent it will produce hepatic necrosis and, depending on dosage, hepatic failure. While chronic ingestion of therapeutic doses of paracetamol has hitherto been considered safe, recent reports have suggested that this may result in either a toxic hepatitis or chronic active hepatitis (Bonkowsky *et al.* 1978, Johnson & Tolman 1977, Barker *et al.* 1977, Sacher & Thaler 1977). To investigate this possibility further, we carried out a survey of patients with chronic active hepatitis (CAH) attending the liver follow-up clinic, using a detailed questionnaire to assess the quantity of paracetamol and other drugs ingested presently and in the past. The clinical and biochemical patterns in those with a history of paracetamol ingestion before the onset of symptoms of the disease were compared with those in patients who had not taken paracetamol. Challenge studies were performed in one patient with a high level of paracetamol ingestion. The evidence of a causal association in previously reported cases has been critically reviewed.

Design of survey

The 45 patients (33 women and 12 men) had histologically confirmed chronic active hepatitis. Ages ranged from 15 to 74 years (median 45 years). All were negative for markers of hepatitis B infection. Each patient was interviewed with respect to the ingestion of drugs obtained either from their own doctor on prescription or as proprietary brands from chemists, supermarkets or their friends. Details of current drug intake were obtained at the time of interview as well as over the four-week period one month before the onset of symptoms attributable to CAH. At the end of the interview patients were shown a list of the commoner proprietary preparations containing paracetamol and asked directly whether they had taken any of these. Patients were also asked about their alcohol intake; none admitted to an intake greater than 20 g ethanol equivalents weekly, and no patient had a history of occupational or leisure exposure to known hepatotoxins.

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The results of standard liver function tests both at the time of diagnosis and at the interview were available for all patients (serum bilirubin, aspartate aminotransferase (AST), alkaline phosphatase and albumin) as well as serum immunoglobulins and autoantibodies (antinuclear, smooth muscle and mitochondrial antibodies). As a measure of the ease of control, the times taken for the serum AST to fall to one-half and to one-quarter of the presenting value were assessed after institution of prednisolone and azathioprine therapy.

Results

Seventeen of the 45 patients had taken paracetamol between four and eight weeks before the onset of symptoms. Doses varied from an average of 500 mg to 5 g weekly (median 750 mg), and only 4 had a weekly paracetamol ingestion greater than 1 g. Other drugs taken by patients in this group included aspirin by 9 patients (range 300 mg to 6 g weekly, median 1 g), dextropropoxyphene by 4 patients (range 10 mg to 300 mg, median 150 mg) and one patient was taking benorylate (an ester of paracetamol and salicylate). These analgesics were taken for headaches or nonspecific arthralgias. One each of the patients taking paracetamol was also taking digoxin, frusemide and salbutamol, and naproxen and practolol. Other diseases suffered by patients in this group included diabetes mellitus, ulcerative colitis, rheumatoid arthritis and fibrosing alveolitis. In contrast, at the time of interview, 8 patients were taking paracetamol, but in smaller doses so that only 2 were taking more than 1 g (median 325 mg) and 9 were not taking any paracetamol. Two of these were taking α-methyldopa, 2 spironolactone and 2 aspirin; one each was taking chlorpropamide, cholestyramine and dipyridamole.

In the group who had not taken paracetamol during the period before onset of symptoms, 7 had taken aspirin (25 mg to 5 g weekly, median 150 mg) and one had taken codeine phosphate. Other drugs taken by this group included salazopyrine, thyroxine, metformin and Moduretic (amiloride hydrochloride + hydrochlorothiazide). Four patients had concomitant diseases (one each diabetes mellitus, ulcerative colitis, myxoedema and asthma). At the time of interview, 9 patients were taking paracetamol (500 mg to 4.5 g weekly, median 600 mg).

There was no significant difference between those patients taking paracetamol before the onset of disease and those without such drug ingestion with respect to age, sex and levels of liver function tests and serum autoantibodies (Table 1). No correlation was detected between

Table 1. Clinical and laboratory findings and paracetamol ingestion before onset of symptoms in 45 patients with chronic active hepatitis. (Results expressed as median (range))

	Paracetamol	No paracetamol
Number (sex)	17 (3M, 14F)	28 (9M, 19F)
Age in years (mean ± s.d.)	48 ± 18	45 ± 17
Bilirubin (μmol/l)	73 (8–350)	88 (7–355)
Albumin (g/l)	31 (15–53)	29 (20–44)
Aspartate aminotransferase (iu/l)	620 (48–1700)	820 (52–2100)
Alkaline phosphatase (iu/l)	210 (40–1280)	180 (86–850)
Globulins (g/l)	28 (15–50)	34 (17–63)
Presence of autoantibodies	14 (82%)	26 (92%)

the weekly dose of paracetamol taken before the onset of symptoms and the levels on admission of serum bilirubin, albumin, AST or alkaline phosphatase ($r = -0.11$, -0.32, -0.21 and 0.28 respectively). The rate of fall of the serum AST after initiation of immunosuppressive drug therapy was less in those patients with a history of paracetamol ingestion although this did not reach statistical significance (Table 2). Again, there was no difference in liver function tests between those patients who were taking paracetamol at the time of interview and those who were not (Table 3).

Table 2. Time taken for serum aspartate aminotransferase to fall after institution of treatment in patients with and without paracetamol ingestion. (Results expressed as median (range))

	Paracetamol	No paracetamol
Time taken to fall to:		
Half initial value (days)	28 (4–160)	18 (5–140)
Quarter initial value (months)	1.1 (0.4–9)	1.3 (0.3–8.4)

Table 3. Liver function tests of patients taking and not taking paracetamol at time of interview. (Results expressed as median (range))

	Paracetamol	No paracetamol
Number	17	28
Bilirubin (μmol/l)	13 (6–53)	15 (5–95)
Albumin (g/l)	43 (25–49)	41 (28–46)
Aspartate aminotransferase (iu/l)	27 (10–298)	27 (5–232)
Alkaline phosphatase (iu/l)	110 (52–820)	101 (59–810)

The case history of the only patient with an ingestion greater than 3 g/week of paracetamol, together with the results of metabolic and challenge studies, are given below.

Case report

The patient, a 71-year-old man, underwent laparotomy after three months of deteriorating health, with weight loss and increasing jaundice, when the liver was found to be cirrhotic. Subsequently he was transferred to the Liver Unit of King's College Hospital. He has been taking paracetamol and Distalgesic (paracetamol 325 mg and dextropropoxyphene 32.5 mg) tablets for one year because of cervical spondylosis, together with frusemide 40 mg, Slow K 1200 mg and salbutamol 12 mg tablets for six years for cor pulmonale and emphysema. Investigations on admission showed bilirubin 87 μmol/1, albumin 15 g/1, alkaline phosphatase 126 iu/1 (>75% of hepatic origin), AST 45 iu/1 and γ-glutamyl transpeptidase 126 iu/1. Hepatitis B surface antigen, antibody and anticore antibody were negative; α-fetoprotein and α_1-antitrypsin were normal. Antinuclear antibodies were present in a titre of 1 in 320. Liver biopsy showed a cirrhosis with piecemeal necrosis and a marked inflammatory cell infiltrate consistent with chronic active hepatitis.

After treatment with prednisolone 40 mg/day, he improved rapidly but because of the possibility that his intake of paracetamol could be related to his deterioration over the past year, the corticosteroids were gradually withdrawn and he remained off all paracetamol-containing drugs. The liver function tests remained stable and his serum AST stayed within the normal range. Three months later he was given a challenge dose of 1 g paracetamol. There was no change in his serum AST over the next three days. His urine excretion of paracetamol metabolites showed a normal pattern (sulphate 42%, glucuronide 38%, cysteine conjugate 5% and mercapturic acid conjugate 10% of excreted dose). After a further three months off prednisolone and without paracetamol ingestion, another liver biopsy was performed. This showed piecemeal necrosis and extensive rosette formation. His liver function tests remained normal. Although he was in good health, because of continued histological activity he was restarted on corticosteroids.

Analysis of previously reported cases

There have been two reported cases of patients developing symptoms of chronic active hepatitis whilst taking therapeutic doses of paracetamol (Table 4). That of Bonkowsky *et al.* (1978) was a 53-year-old man who was treated for shoulder and hip pain with paracetamol 325 mg 12 times daily. Initially his serum AST was within the normal range. Thirteen months

Table 4. Details of previously reported cases of liver damage after chronic ingestion of paracetamol

Reference	Cases		Paracetamol ingestion (dose and duration)	Liver histology	Challenge	Other contributing factors
	Age	Sex				
Bonkowsky *et al.* 1978	53	M	3.9 g/day, 13 months	CAH+cirrhosis	Slight rise in enzymes	Past history of hepatitis; progression after stopping paracetamol
Johnson & Tolman 1977	59	F	2.9 g/day, 1 year	CAH+cirrhosis	Positive	1 year arthralgia ? due to underlying liver disease
Barker *et al.* 1977	59	M	up to 3 g/day, 'years'	Toxic hepatitis	NT	1 pint vodka/day for years
	67	F	1.2–2.6 g/day, 3 weeks	Toxic hepatitis	Positive	Bronchial carcinoma
	50	F	5.2–6.5 g/day, 3 weeks	Toxic hepatitis	NT	Serum paracetamol at 40 h 15 μg/ml, suggesting previous toxic dose
Sacher & Thaler 1977	13	F	Benorylate 948 g in 21 weeks	Toxic hepatitis	NT	Also taking salicylate and penicillamine
Present report	71	M	5 g/week, 1 year	CAH+cirrhosis	Negative	Progression after stopping drug

NT, not tested; CAH, chronic active hepatitis

later he was found to have hepatomegaly and his serum AST had risen to 190 mu/ml. Paracetamol was discontinued and his serum AST fell towards normal levels (70 mu/ml). Two months after restarting paracetamol 3.9 g/day, the serum AST rose again to 170 mu/ml and fell to normal after the drug was discontinued. Three weeks later he was challenged with 1 g paracetamol and the serum AST rose from 48 mu/ml to 70 mu/ml and a liver biopsy showed changes consistent with diffuse central necrosis and portal inflammation. He remained off paracetamol and the serum AST returned to normal. A further liver biopsy four months later revealed more portal inflammation and fibrosis so he was started on prednisolone and azathioprine. A third liver biopsy six months later showed histological improvement. A portion of that biopsy specimen was assayed for reduced glutathione, which was increased. A further five months later he was again given a challenge dose of 1.3 g paracetamol which produced no change in serum AST and plasma and urine profiles of the metabolites were normal.

The second case is that of Johnson & Tolman (1977) who reported a 59-year-old woman who had been taking paracetamol 2.9 g daily for nonspecific arthralgia. One month before admission she developed anorexia and easy fatiguability. There was no history of a previous liver disease or exposure to known hepatotoxins. Serum analysis showed a raised AST of 600 iu/ml; six weeks later it was still raised at 470 iu/ml. A liver biopsy showed features of chronic active hepatitis and a cirrhosis. After stopping all medication, the AST fell rapidly to normal. One week later she was challenged with paracetamol 2.9 g daily for two weeks and the AST rose to 1150 iu/ml. A repeat liver biopsy showed similar changes. The paracetamol was stopped and the AST fell to normal over the next fourteen weeks, and she has remained asymptomatic and with normal liver function tests.

Other reports have suggested that therapeutic doses of paracetamol may cause a toxic hepatitis. Barker *et al.* (1977) described 3 such patients. The first patient was a 59-year-old man admitted because of haematemesis. For years he had drunk more than a pint of vodka and taken up to ten 300 mg paracetamol tablets daily. Four days before admission he stopped alcohol but took 100 tablets of paracetamol over that period. His serum AST was 6200 iu and fell rapidly. A needle biopsy showed a toxic hepatitis. Subsequently he has stopped both alcohol and paracetamol and his liver function tests have remained normal. The second case

was a 67-year-old woman who was cachectic due to a squamous cell carcinoma of the lung. The serum AST was normal but because of persistent pyrexia she was started on paracetamol, up to 5.2 g/day, and three weeks later serum AST had risen to 1040 iu. Aspirin was substituted for paracetamol and over the next four days her serum AST fell to 45 iu. Two weeks later paracetamol was reintroduced and after seven days her serum AST had risen to 121 iu. After discontinuing paracetamol, the AST fell to 27 iu and a liver biopsy showed toxic hepatitis. Twenty-four hours after stopping the drug, the serum paracetamol was 37 μg/ml. The third patient was a 50-year-old woman who had taken up to 6.5 g of paracetamol daily for postprandial epigastric pain for three weeks before admission. As the serum AST was 410 iu, a liver biopsy was taken which showed mild pericentral necrosis. The serum paracetamol was 15 μg/ml 40 hours after stopping the drug. The serum AST fell to normal in 5 days.

Sacher & Thaler (1977) reported a 13-year-old girl was was treated for rheumatoid arthritis with D-penicillamine and benorylate (a paracetamol and acetylsalicylic acid ester). At 20 weeks she was jaundiced and this improved after she stopped taking both drugs. She had received a total of 948 g benorylate and 72 g penicillamine. Nine weeks later a liver biopsy specimen showed haemorrhagic central necrosis and six months later the liver biopsy was repeated and showed complete resolution. The authors postulated that the liver damage was due to increased hepatic sensitivity caused by cysteine depletion resulting from its excretion with penicillamine as L-cysteine-D-penicillamine disulphide.

Discussion

The results of this survey have shown no difference in the biochemical and immunological markers of chronic active hepatitis in those patients who had taken paracetamol before the onset of symptoms compared with those who had not. The two groups were well matched for age and sex-distribution; furthermore, there was no significant difference in the ease of control as measured by the rate of fall of serum AST after institution of immunosuppressive therapy and with cessation of paracetamol ingestion. If the drug had been a trigger or an aggravating factor, it might have been expected that the withdrawal of paracetamol would result in a more rapid improvement, as has been found with oxyphenisatin-related chronic active hepatitis (Reynolds *et al.* 1971). It is possible, however, that any such effect was masked by administration of corticosteroids. The results of this survey also failed to show any difference in the standard liver function tests between those taking and those not taking paracetamol at the time of interview, suggesting that paracetamol does not, at these doses, have a direct hepatotoxic effect.

One way in which paracetamol could act as a trigger to the development of chronic active hepatitis is by the drug, or a metabolite, altering a liver cell membrane component. This could then stimulate an immunologically mediated attack upon the hepatocyte in a manner analogous to that which has been postulated for halothane (Vergani *et al.* 1980). With an induced cytotoxicity assay, however, we were unable to find any evidence of such a mechanism in patients with fulminant hepatic failure after much larger doses of paracetamol taken with suicidal intent. Eisner & Shahidi (1972) reported the presence of a circulating antibody to the paracetamol sulphate conjugate in a patient who developed thrombocytopenia associated with paracetamol ingestion. This indicates that in some circumstances paracetamol ingestion can be followed by the development of antibodies.

In the two previously reported cases of chronic active hepatitis which may have been initiated by paracetamol ingestion, it is clear that in neither instance was pre-existing liver disease excluded. The patient described by Johnson & Tolman (1977) may have had underlying liver disease of which the arthralgia was an associated feature. Although the serum aminotransferases were normal initially, this does not necessarily indicate absence of histological activity, as shown both by the patient we describe and that of Bonkowsky *et al.* (1978), where histological progression and activity occurred in the presence of normal serum aminotransferase levels. Furthermore, if paracetamol had been the initiating factor in our case, then the cirrhosis would have developed within the relatively short period of one year.

Challenge tests were performed in both reported cases (Bonkowsky *et al.* 1978, Johnson & Tolman 1977), although the rise in AST was slight in the former. These may be misleading, however. The specificity of a positive challenge test has been questioned (Dykes 1977), and Reynolds (1975) has shown that patients with chronic active hepatitis show a rise in serum aminotransferase after challenge with oxyphenisatin, even if the drug was not implicated in the pathogenesis of the disease.

The three patients described by Barker *et al.* (1977) all had a toxic hepatitis. In normal subjects paracetamol is metabolized by glucuronidation and sulphation. As these pathways become saturated with increased doses, the parent compound is activated to a highly unstable intermediate which is complexed with glutathione and converted to the mercapturic acid and cysteine conjugates. Hepatic necrosis occurs after depletion of glutathione stores which allows the highly reactive metabolite to bind to hepatic macromolecules (Davis *et al.* 1976). The first patient described by Barker *et al.* (1977) had a high alcohol intake. It has been shown that following paracetamol overdosage, more serious liver function test abnormalities are seen in those taking alcohol (Wright & Prescott 1972, Teschke *et al.* 1979). Alcohol is an inducing agent and increased levels of cytochrome P_{450} will result in increased rates of paracetamol metabolism via toxic metabolite (Teschke *et al.* 1979). The second patient was suffering from a wasting disease, carcinoma of the bronchus, and was cachectic. This is likely to have been associated with a reduced level of glutathione (Leaf & Neuberger 1947), and so put the patient at greater risk of paracetamol toxicity. Furthermore, the plasma levels of paracetamol in both this and Barker's third patient were in the range associated with hepatotoxicity (Gazzard *et al.* 1977).

In addition to paracetamol, the patient of Sacher & Thaler (1977) was taking salicylate (as Benoral) and D-penicillamine. The former is hepatotoxic (Athreya *et al.* 1975) and there has been one report of penicillamine causing hepatotoxicity (Rau *et al.* 1972).

It is not yet fully established whether paracetamol metabolism, and thus its hepatotoxic potential, is altered in the presence of underlying liver disease. Rosenberg *et al.* (1977) reported a husband and wife who had taken paracetamol for symptoms of infectious mononucleosis and found that they both had levels of AST greater than are usually associated with this condition. Forrest *et al.* (1979) studied the metabolism of a single oral dose of 1.5 g paracetamol in patients with underlying liver disease, and found a prolonged serum paracetamol half-life but normal production of the cysteine and mercapturic acid conjugates of the drug, implying that these patients are not at increased risk of hepatoxicity when given a small, single dose of paracetamol. Nevertheless, it remains to be established whether the pattern remains normal in such patients taking larger amounts of the drug over a longer period. If the glutathione stores become depleted, then paracetamol is toxic at a lower dose (Mitchell *et al.* 1973).

From time to time patients with chronic active hepatitis need analgesia. Aspirin is usually best avoided as it may precipitate gastrointestinal bleeding and is also hepatotoxic. As yet there is no clear evidence to incriminate paracetamol as either initiating or exacerbating chronic active hepatitis when taken in amounts of less than 2.5 g/day. While paracetamol seems the drug of choice in patients with liver disease who require analgesia, it is prudent to monitor liver function carefully, especially in those who are at greater risk by virtue of malnutrition.

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