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Liver function in patients on long-term paracetamol (co-proxamol) analgesia

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Eleven patients on long term co-proxamol therapy for pain, in general practice, showed no abnormalities of liver or renal function, as assessed by serum prealbumin concentrations and blood enzyme and electrolyte activities. This indicates that although the preparation is hepatotoxic when taken acutely in overdose, in chronic therapeutic dosage it appears to be free from this hazard.

The analgesic preparation co-proxamol (Distalgesic: paracetamol 325 mg plus dextropropoxyphene HCl 32·5 mg) is widely prescribed in the United Kingdom. Despite the fact that some patients take up to eight tablets daily for many years, addiction to it seems uncommon although occasional cases have been reported (Whittington 1979). When taken in overdose, the preparation is a potent CNS-depressant and hepatotoxin and has been reported to cause severe liver damage or psychosis (Harris & Harper 1979; Hutchinson et al 1980). In the assessment of drug-induced hepatotoxicity the usual plasma enzyme parameters have occasionally been found to be unreliable (Hutchinson et al 1980) and isocitrate dehydrogenase and other plasma enzymes have been proposed as being more suitable (Hutchinson et al 1981). Serum prealbumin, a carrier protein of short half-life synthesized in the liver (Kohn et al 1978), has also been described as a highly specific and reliable index of liver function in drug toxicity and in hepatic disease (Hutchinson et al 1980; Kohn et al 1978; Helen et al 1975; Hutchinson 1980).

In view of the current concern about the safety of long-term paracetamol analgesia, especially co-proxamol, a number of patients taking this drug at medium to high dosage, for a long period of time, were investigated. For the assessment of liver function in these patients, the usual plasma enzymes were determined together with isocitrate dehydrogenase activity and plasma prealbumin concentration.

Patients and methods

Eleven consenting patients in general practice who had been taking the preparation for some 6 months at moderate to high doses were studied. Four patients were rheumatoid arthritics, one patient (V) had Paget's disease, and the remaining six patients suffered from general orthopaedic pains. The dose of co-proxamol each patient had been taking was determined from prescription records and checked with the patient; the estimated total annual intake of paracetamol was calculated from the daily intake and length of time on the drug. Concomitant medication, alcohol intake, and history of hepato-biliary disease were also assessed, and none of the patients were found to be taking additional medication or alcohol in quantities likely to cause or to potentiate hepatotoxity.

A serum and plasma sample was collected from each patient. Prealbumin concentration and isocitrate dehydrogenase activity were determined on the serum, and routine Vickers Automatic analysis (Na^+, K^+, HCO_3^-, urea, creatinine, albumin, total protein, alkaline phosphatase, bilirubin, aspartate, aminotransferase) was performed on the plasma sample. Liver and renal functions were assessed from the established normal ranges for the enzymes and other parameters with the methods used.

Results

The results are in Table 1. The eleven patients had been taking the preparation for periods of 5 to 39 months, and for an average of 20 months. All patients had normal serum prealbumin concentrations and normal isocitrate dehydrogenase and aspartate aminotransferase activities. The normal values and values for long-term treatment with co-proxamol were respectively: for serum prealbumin, 20 ± 6 and 23 ± 5 μg/100 ml; for isocitrate dehydrogenase, <4 and 2 ± 1 iu; and for aspartate aminotransferase, <40 and 25 ± 7 iu (±s.d.). One patient (V) had moderately raised alkaline phosphatase activity, which is characteristic of Paget's disease, but otherwise routine blood biochemistry was normal and showed no evidence of hepatic or renal abnormality. No patient experienced any epigastric discomfort, jaundice or history of hepatic disease.

Discussion

The results show that no significant abnormality in renal or liver function occurred in eleven patients taking paracetamol as co-proxamol for long period of time. In particular, the highly specific and sensitive indices of liver function, namely, serum prealbumin and isocitrate dehydrogenase, showed normal values in all patients. This investigation provides evidence for the long-term safety of administration of paracetamol and of the preparation, and confirms the findings of Neuberger et al (1980) that long term ingestion of paracetamol does not result in hepatitis, as was suggested by Bankowsky et al (1978).

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Table 1. Serum prealbumin concentration and plasma aspartate aminotransferase activity of patients taking co-proxamol long term.

Patient	Age	Sex	History of taking drug (months)	Dose of co-proxamol (tablets/month)	Estimated total annual paracetamol intake (g)	Serum prealbumin concentration (mg/100 ml)	Aspartate aminotransferase (iu)
I	72	F	17	112	440	17	40
II*	68	F	24	56	220	25	20
III	32	M	12	180	700	30	23
IV	58	F	24	100	390	29	26
V†	78	F	15	100	390	23	27
VI	82	M	39	40	160	14	24
VII*	66	F	20	65	250	22	24
VIII*	—	F	27	100	390	27	21
IX*	63	F	30	150	585	18	24
X	78	F	9	56	220	20	19
XI	72	F	5	100	390	21	23

* Rheumatoid arthritics.
† Paget's disease.

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