products and fibrinogen, dysfibrinogenaemia may be detected by a prolongation of the reptilase clotting time.[2] Barr *et al* have suggested that the reptilase time may prove to be a sensitive screening procedure in patients with cirrhosis, who have an increased risk of developing hepatocellular carcinoma. Nevertheless, a prolongation of the reptilase time (due to a delay in the production of fibrin monomer) has also been reported in some cases of cirrhosis alone.[3] In the present study we have measured coagulation factors, including reptilase and thrombin clotting times and fibrinogen concentrations, in 22 patients with hepatocellular carcinoma, 40 with cirrhosis alone, 14 with secondary carcinoma of the liver, and 45 normal controls.

Patients, methods, and results

The 22 patients with hepatocellular carcinoma came from Britain (14), Eastern Europe (4), Africa (2), Greece (1), and Italy (1). Fourteen of them had underlying cirrhosis. In the 40 patients with cirrhosis the underlying aetiology was alcoholic (15), chronic active hepatitis (8), haemochromatosis (7), and cryptogenic (10). Hepatocellular carcinoma was confirmed histologically in 15 patients and diagnosed on the basis of arteriography and α-fetoprotein (>1000 μg/l) in seven. The reptilase time was measured by the standard technique using 0·2 ml plasma and 0·1 ml reptilase, and was considered abnormal when greater than 20 s.

The patients with cirrhosis, whether or not they had developed a tumour, had significantly prolonged thrombin and reptilase times when compared with controls. A total of 16 patients with cirrhosis and 8 with cirrhosis complicated by hepatocellular carcinoma had prolonged reptilase times, but there was no significant difference between these two groups ($P < 0.5$). In the eight cases of hepatocellular carcinoma without cirrhosis, the reptilase time was within the normal range (figure). The striking difference in this group was the raised fibrinogen concentrations of 3·95 g/l, as compared with mean values of 2·42 g/l in controls ($P < 0.001$). This was also found in patients with secondary carcinoma in whom the mean value was 4·14 g/l. Fibrinogen concentrations in patients with cirrhosis with or without tumour development (mean values 2·8 g/l and 2·3 g/l, respectively) were within the normal range.

Discussion

The lower fibrinogen concentrations in patients with hepatocellular carcinoma in cirrhosis may be accounted for by the well-documented increase in the catabolism of fibrinogen,[4] which may counteract the anti-fibrinolytic activity reported in patients with hepatocellular carcinoma.[5]

Our results would imply that the prolonged reptilase time found in patients with hepatocellular carcinoma is usually a consequence of the underlying cirrhosis rather than directly related to the tumour and, in our experience, it is of no value for screening for hepatocellular carcinoma.

[1] Barr, R D, *et al*, *Quarterly Journal of Medicine*, 1976, **180**, 647.
[2] Funk, C, *et al*, *British Journal of Haematology*, 1971, **21**, 43.
[3] Green, S L, *et al*, *British Journal of Haematology*, 1976, **34**, 427.
[4] Clark, R D, *et al*, *British Journal of Haematology*, 1975, **30**, 95.
[5] Kwaan, H C, *et al*, *Clinical Science*, 1959, **18**, 251.

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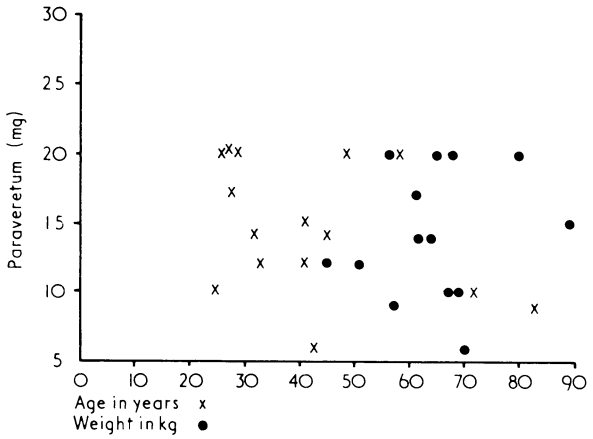
Postoperative analgesia by titration of papaveretum

"No, you cannot have 'something' for at least seven hours" is still too often the response to the plea, "Can I have something for my pain, nurse?"[1 2] Papaveretum 10 mg is an overdose for some, but there are others, not easily recognisable, for whom 20 mg is not enough. This study is designed to show that doses of analgesic drugs vary so much that no set scheme of postoperative analgesia is practicable, but that the patient's initial requirement should be determined by intravenous titration.

Patients, methods, and results

Sixty-one patients anaesthetised by us for laparotomy were studied. They were given diazepam as premedicant, induced with althesin, and maintained with nitrous oxide, oxygen, halothane, pancuronium, and pentazocine, 30 mg. The patients were admitted to the intensive care unit for titration by senior house officers who did not know the purpose of the procedure. They were the first patients anaesthetised by us who consented to be studied when there were vacancies on the unit.



Papaveretum requirements of 14 women who had undergone hysterectomy. Mean dose (±SD) 14·2±4·66 mg (range 6–20 mg). Correlation of age to dose −0·32, slope −1·18. Correlation of weight to dose −0·16, slope 0·39.

When the patient required analgesia papaveretum diluted in physiological saline solution, 1 mg/1 ml, was injected intravenously in 2-mg boluses up to 8 mg, and then in 1-mg boluses until the patient said that the pain was relieved and could cough comfortably and effectively. The dose of papaveretum was correlated with the age and weight of the patients. There were 17 men, mean dose 17·2 mg, range 9–30 mg, standard deviation 4·98, coefficient of correlation between dose and age 0·03, slope of least squares line 0·09, coefficient of correlation with weight 0·65, slope 0·43. There were 44 women, mean dose 13·6 mg, range 6–25 mg, standard deviation 4·66, coefficient of correlation with age −0·29, slope of least squares line −1·19, coefficient of correlation with weight 0·37, slope 1·09. Fourteen of the women had hysterectomy performed by one surgeon using a transverse incision. The papaveretum requirements of these are shown in the figure.

Comment

The variation of the titrated dose and poor correlation with age or weight explain why drug regimens based on these factors are unsuitable for many patients and indicates that the only safe and effective relief of severe pain is intravenous titration of a potent analgesic drug.

After the titration, analgesia was maintained by three intramuscular injections of the same dose of papaveretum. When spaced six-hourly the first injection was too delayed. Most patients required further analgesia after four and a half hours. Forty patients were treated by repeating the titrated dose of papaveretum intramuscularly at intervals of four, six, and eight hours. This regimen gives safe, effective analgesia after abdominal operations. We now give the first titrated dose in the recovery ward with the intramuscular injections given by nursing staff on the wards.

[1] *British Medical Journal*, 1976, **3**, 664.
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