pyrexia. This abated over 48 hours of treatment, which included tobramycin, and repeat endoscopic retrograde cholangiography showed a biliary tree free of stones. She made an uneventful recovery, and subsequently eight consecutive stool samples over a period of three months showed clearance of the salmonella.

Comment

This patient was a chronic carrier of *S eastbourne* despite a cholecystectomy 18 years previously. This appeared to be resistant to appropriate antibiotics until a common bile duct stone was removed. Salmonella carriage was probably perpetuated by biliary stasis analogous to that caused by a stone filled gall bladder.

We thank Dr J Partridge for his help in arranging analysis of stool samples.

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Monitoring effects of oral anticoagulants during treatment with heparin

Patients' sensitivities to warfarin vary considerably.¹ Thus it would be useful to identify those who are sensitive to warfarin as early as possible during treatment by monitoring the British corrected ratios before the first dose and daily for the next four days. Because many patients receive heparin by intravenous infusion while they are receiving warfarin we examined the effects of heparin on the British corrected ratio.

Patients, methods, and results

Blood from 25 patients receiving both heparin and warfarin was collected into plastic tubes containing sodium citrate 3.1% (one part to nine parts blood), and the plasma was separated for estimation of clotting times. Heparin activity was measured as the kaolin cephalin clotting time with a platelet substitute (Diagen; Bell and Alton) (control kaolin cephalin clotting time roughly 40 seconds).² Heparin was neutralised by addition of 40 µl protamine sulphate solution (concentration 10 µg/ml) to 1 ml plasma to achieve a final plasma protamine concentration of 0.4 µg/ml. Oral anticoagulant activity was measured by the one stage method of Quick³ with British comparative thromboplastin (control time roughly 12 seconds).

British corrected ratios in plasma from patients receiving warfarin alone to which heparin was added in vitro. Numbers in parentheses are the ratios after subsequent neutralisation with protamine sulphate (1.0 µg/ml plasma in cases 1 and 8; 0.4 µg/ml plasma in all other cases)

Case No	Heparin concentration (U/ml)					
	0	0.2	0.4	0.6	0.8	1.0
1	1.2 (1.3)*	1.2 (1.3)*	1.3 (1.3)*	1.3 (1.3)*	1.4 (1.3)	1.5 (1.3)
2	1.2 (1.3)*	1.3 (1.2)*	1.4 (1.2)*	1.5 (1.2)	1.5 (1.2)	1.7 (1.3)
3	1.3 (1.3)*	1.3 (1.3)*	1.3 (1.3)*	1.4 (1.3)	1.5 (1.3)	1.7 (1.3)
4	2.4 (2.5)*	2.3 (2.3)*	2.7 (2.4)	2.8 (2.3)	3.2 (2.4)	3.5 (2.6)
5	2.9 (3.0)*	3.0 (2.8)*	3.2 (2.9)	3.5 (3.1)	3.8 (3.0)	4.4 (3.3)
6	3.4 (3.7)*	3.5 (3.4)*	3.9 (3.5)	4.4 (3.5)	5.3 (3.6)	6.6 (3.9)
7	3.5 (3.7)*	3.6 (3.6)*	3.9 (3.6)	4.3 (3.7)	5.0 (3.7)	6.1 (3.8)
8	3.5 (4.0)*	3.6 (3.9)*	4.0 (3.9)	4.3 (3.8)	4.8 (3.8)	5.6 (3.6)
9	5.4 (5.6)*	5.6 (5.7)	6.2 (5.4)	7.3 (5.5)	8.7 (5.9)	11.2 (6.1)

*Kaolin cephalin clotting time within or below therapeutic range (<2.5 times control).

Plasma was also collected from nine patients receiving warfarin alone. Heparin sulphate was added to achieve plasma heparin concentrations of between 0.1 and 1.0 U/ml. Heparin was neutralised with protamine as described above. The table shows the effect of in vitro addition of heparin on the prothrombin time of plasma from the nine patients, whose initial British corrected ratios were between 1.2 and 5.4. The percentage increase in prothrombin time induced by heparin (1.0 U/ml) was greater the higher the initial British corrected ratio ($r=0.916$, $p<0.001$). In those samples in which the corresponding kaolin cephalin clotting time was within or below the therapeutic range (1.5-2.5 times control) the median maximum percentage increase in British corrected ratio was only 3% (range -4 to +17%).

The table also shows (in parentheses) the British corrected ratios in samples from the nine patients after addition of protamine. Protamine brought the British corrected ratio close to the control value in all samples except at the highest heparin concentration (1.0 U/ml). Addition of protamine (0.4 µg/ml) to the control samples caused only a slight increase in British corrected ratio.

In the 25 patients receiving both heparin and warfarin addition of protamine reduced the British corrected ratio, the percentage reduction being directly related to the initial kaolin cephalin clotting time of the sample ($r=0.756$, $n=25$, $p<0.001$). In those patients whose kaolin cephalin clotting time was in the therapeutic range, however, the median reduction in British corrected ratio was only 4% (range 0-11%).

Comment

At present the recommendation for treatment with warfarin is to give 10 mg daily for three days and measure prothrombin time from the fourth day of treatment.³ Unfortunately, this loading dose regimen results in up to 70% of the patients being outside the range for anticoagulation by the fourth day.⁴ Half may have received too little anticoagulation and the other half too much and, therefore, be at greater risk of haemorrhage.⁴ Patients should, therefore, be monitored daily from the first dose of warfarin and subsequent doses should be tailored according to the British corrected ratio. Presumably this is not recommended at present because concomitant treatment with heparin might affect the British corrected ratio. This only occurs, however, when heparin is given by intravenous bolus; heparin infusions do not substantially interfere with prothrombin time when measured by Thrombotest.⁵ We have shown that this also holds for the British comparative reagent, provided that the kaolin cephalin clotting time is within the therapeutic range. If the kaolin cephalin clotting time is abnormally long the effect of heparin on the British corrected ratio can be neutralised by protamine in vitro. As heparin is normally given now by infusion with adjustment of dose rate according to the kaolin cephalin clotting time, however, neutralisation of samples with protamine should rarely be necessary. If the British corrected ratio is measured daily from the start of treatment with oral anticoagulants patients sensitive to these may be more rapidly identified and their dosages reduced accordingly.

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