References

- 1 Wormsley KG. Short-term treatment of duodenal ulceration. In: Baron JH, ed. *Cimetidine in the 80s*. Edinburgh: Churchill Livingstone, 1981:3-8.
- 2 Colin-Jones DG. Ranitidine in the treatment of peptic ulceration. In: Riley AJ, Salmon PR, eds. *Ranitidine: proceedings of an international symposium held in the context of the seventh world congress of gastroenterology*. Amsterdam: Excerpta Medica, 1982:16-29.
- 3 Robert A, Lancaster C, Davis JP, Field SO, Sinha AJW, Thornburgh BA. Cytoprotection by prostaglandin occurs in spite of penetration of absolute ethanol into the gastric mucosa. *Gastroenterology* 1985;88:328-33.
- 4 Davis GR, Walsh JH, Santa Ana CA, Morawski SG, Fordtran JS. Effect of cimetidine and enprostil (a Syntex investigational prostaglandin E_2) on gastric acidity and serum gastrin concentrations in normal subjects [Abstract]. *Gastroenterology* 1984;86:1058.
- 5 Mahachai V, Walker K, Sevelius H, Thomson ABR. Enprostil, a dehydro-prostaglandin E_2 , has potent antisecretory and antagastrin properties in patients with duodenal ulcer disease [Abstract]. *Gastroenterology* 1984;86:1171.
- 6 Santana IA, Sharma BK, Orchard K, Pounder RE. Twenty-four hour intragastric acidity before and during treatment with enprostil [Abstract]. *Gut* 1985;26:A545.
- 7 Deakin M, Ramage JK, Paul A, Gray S, Billings J, Williams JG. Effect of enprostil on 24 hour intragastric acidity and nocturnal acid and pepsin output [Abstract]. *Gut* 1985;26:A545.
- 8 Cohen MM, McCready DR, Clark L, Sevelius H. Protection against aspirin-induced antral and duodenal damage with enprostil. A double-blind endoscopic study. *Gastroenterology* 1985;88:382-6.
- 9 Lauritsen K, Bytzer P, Hansen J, Bekker C, Rask-Madsen J. Comparison of ranitidine and high-dose antacid in the treatment of prepyloric or duodenal ulcer. A double-blind controlled trial. *Scand J Gastroenterol* 1985;20:123-8.
- 10 Fleiss JL. *Statistical methods for rates and proportions*. New York: John Wiley & Sons, 1981.
- 11 Ireland A, Colin-Jones DG, Gear P, et al. Ranitidine 150 mg twice daily vs 300 mg nightly in the treatment of duodenal ulcers. *Lancet* 1984;ii:274-6.
- 12 Classen M, Dammann HG, Domschke W, et al. Short-duration treatment of duodenal ulcer with omeprazole and ranitidine: results of a multi-centre trial in Germany. *Dtsch Med Wochenschr* 1985;110:210-5.
- 13 Lauritsen K, Rune SJ, Bytzer P, et al. Effect of omeprazole and cimetidine on duodenal ulcer. A double-blind comparative trial. *N Engl J Med* 1985;312:958-61.
- 14 Walt RP, Gomes M de FA, Word EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24 hour intragastric acidity. *Br Med J* 1983;287:12-4.
- 15 Levine BA, Sirinek KR, Gaskill HV. Topical prostaglandin E_2 in the treatment of acute upper gastrointestinal tract hemorrhage. A prospective, randomized, double-blind study. *Arch Surg* 1985;120:600-4.
- 16 Lauritsen K, Laursen LS, Havelund T, Bytzer P, Rask-Madsen J. Controlled trial of arbutoprostil in bleeding peptic ulcer. *Br Med J* 1985;291:1093.

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SHORT REPORTS

Cholestatic jaundice caused by ethambutol

Jaundice is a well recognised adverse reaction in patients receiving antituberculous chemotherapy and is usually ascribed to rifampicin, isoniazid, or pyrazinamide. Ethambutol is thought not to cause any hepatotoxic side effects. We report on a patient who developed jaundice during treatment with ethambutol.

Case report

A 78 year old woman, a retired pottery worker, presented with a history of weight loss, night sweats, cough, and haemoptysis. Chest x ray films showed simple pneumoconiosis with some recently developed soft shadowing in the right upper lobe. Cultures of sputum samples contained *Mycobacterium tuberculosis*, which was fully sensitive to first line drugs. She did not have a history of adverse drug reactions or excessive consumption of alcohol, and results of biochemical liver function tests were normal.

She was treated initially with streptomycin 0.5 g intramuscularly twice weekly, isoniazid 300 mg daily, and ethambutol 750 mg (15 mg/kg) daily by mouth beginning on 17 November 1983. After two months she developed painless jaundice with pale stools and dark urine. Serum bilirubin was 201 $\mu\text{mol/l}$ (11.8 mg/100 ml), alkaline phosphatase 976 U/l, γ -glutamyltransferase 616 U/l, and aspartate transaminase 264 U/l. Treatment was stopped on 20 January 1984. Tests for hepatitis B surface antigen, hepatitis A IgM antibodies, cytomegalovirus antibodies, smooth muscle antibodies, and antimitochondrial antibodies and the Paul Bunnell test yielded negative results. Two ultrasound scans showed that the structure of the liver was normal with no evidence of dilatation of the biliary tree; a liver biopsy specimen showed cholestasis.

Serial changes in hepatic enzyme activities during treatment with ethambutol.

Her jaundice was thought to be due to isoniazid, and treatment was restarted on 1 February with ethambutol (700 mg daily) alone to test whether isoniazid was the offending drug. During six days' treatment the alkaline phosphatase activity increased from 767 U/l to 1225 U/l and aspartate transaminase activity from 144 U/l to 356 U/l (figure). Treatment was stopped on 6 February for 11 days, during which time the results of liver function tests improved. On 17 February ethambutol was again started together with streptomycin 0.5 g twice weekly. Within four days there was a further increase in the alkaline phosphatase activity, from 812 U/l to 1128 U/l, and in aspartate transaminase activity, from 76 U/l to 228 U/l (figure). When the drugs were stopped the results of liver function tests slowly returned to normal. Subsequent treatment with isoniazid and streptomycin was uneventful.

Comment

Hepatic problems are well described in patients receiving rifampicin, isoniazid, or pyrazinamide and often limit options for treatment, particularly in the elderly.¹ The risk of jaundice induced by drugs increases with age and the presence of pre-existing liver disease. In our case the initial drug regimen was chosen because of the high risk of hepatotoxicity from rifampicin in the elderly.

Among first line drugs in current use streptomycin is usually considered to be free from hepatotoxic effects while possible hepatotoxicity due to ethambutol is poorly documented. A single case of jaundice during treatment with ethambutol has been noted but not documented.² In other cases jaundice has occurred during treatment with rifampicin, isoniazid, and pyrazinamide and has been considered to have been due to these drugs.³⁻⁵ The Committee on Safety of Medicines has received one report of hepatitis and one of hepatic cirrhosis during treatment with ethambutol, but the cause of these cases was uncertain. The manufacturers are not aware of any hepatotoxicity thought to be due to ethambutol, but the possibility of such reactions should be considered in patients receiving chemotherapy for tuberculosis.

- 1 Mackay AD, Cole RB. The problems of tuberculosis in the elderly. *Q J Med* 1984;53:497-510.
- 2 Fandos E, Guallar J. Results obtained with ethambutol in the treatment of chronic pulmonary tuberculosis in medical institutions. *Rev Clin Esp* 1968;110:319-28.
- 3 Lees AW, Allan GW, Smith J, et al. Rifampicin plus isoniazid in initial therapy of pulmonary tuberculosis and rifampicin and ethambutol in retreatment cases. *Chest* 1972;61:579-82.
- 4 Segarra FO, Lorian V, Sherman DS. Ethambutol treatment of tuberculosis in a controlled trial. *Scandinavian Journal of Respiratory Disease* 1968;49:202-6.
- 5 British Thoracic Association. A controlled trial of six months' chemotherapy in pulmonary tuberculosis. *Br J Dis Chest* 1981;75:141-53.

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