Centrolobular liver cell necrosis, myocardial infarction, and hyperamylasaemia after high dose corticosteroids

Drs R OLSSON, C LINDBERG, and O ANDERSEN (Sahlgrenska Hospital, S413 45 Gothenburg, Sweden) write: Wald and Farr recently described increased aminotransferase values in patients with asthma receiving prednisone ≥ 10 mg/day.¹ We describe a 69 year old patient with myasthenia who, while receiving pyridostigmine 420 mg and hyoscyamine 1.6 mg daily, was given methylprednisolone 2 g/day for two days at intervals of four to six weeks. His aminotransferase values were normal before and after the first two courses, but from the third course he showed a slight increase after each treatment (fig).

Aspartate aminotransferase values after four separate courses of methylprednisolone

Hyoscyamine was discontinued after the seventh course, with no effect on the aminotransferase reaction. Liver biopsies after the seventh and ninth courses showed centrolobular necroses, with extravasation of red blood cells and sparse infiltration of polymorphonuclear leucocytes. There was no clinical evidence of cardiac dysfunction, and blood pressure recordings after treatment, electrocardiography, lung radiography, and ultrasound investigation of the hepatic veins all gave normal results. Tests for hepatitis A and B (tests for hepatitis C were not available at that time), cytomegalovirus, Epstein-Barr virus, morbilli, rubella, mumps, herpes simplex, and mycoplasma were negative. The patient was not taking other drugs such as paracetamol or acetylsalicylic acid. Methylprednisolone was stopped after the 11th course, and aspartate aminotransferase values returned to normal within three months.

Among 52 patients given 550 courses of intravenous methylprednisolone 2 mg/day or oral prednisolone 1 g/day for three days for myasthenia, multiple sclerosis, or Behçet's disease, four patients (one

male) showed increases in aminotransferase values to a maximum of 1.3-2.2 µkat/l (reference limit ≤ 0.7) after four to eight courses. No other reports on liver damage have been submitted to the Swedish Adverse Drug Reactions Advisory Committee or the manufacturer.

1 Wald JA, Farr S. Abnormal liver-function tests associated with long-term systemic corticosteroid use in subjects with asthma. *Journal of Allergy and Clinical Immunology* 1991;88: 277-8.

Fixed drug eruption with fluconazole

Drs J M MORGAN and A J CARMICHAEL (South Cleveland Hospital, Middlesbrough TS4 3BW) write: A 27 year old man was referred with an 18 month history of a recurrent rash on the extensor surfaces of his elbows. He had suffered 15 episodes, each lasting three days and resolving spontaneously to leave residual bluish-grey macules (1 cm²). The patient had taken minocycline 50 mg daily for three years for acne and occasionally took Migrave (paracetamol 500 mg, codeine phosphate 8 mg), aspirin, and paracetamol. There was no temporal relation between his intermittent medication and the rash. A drug reaction was suspected and erythromycin 500 mg twice a day was substituted for minocycline. Six weeks later the patient had a further attack which prompted self referral. Clearly demarcated dusky red plaques with violaceous centres had developed at the sites of residual pigmentation over the elbows. A skin biopsy specimen showed appearances consistent with a fixed drug eruption; spongiosis, hydropic degeneration of the basal layer, a predominantly lymphocytic perivascular infiltrate, and dermal melanophages. On close questioning the patient recalled having taken fluconazole 150 mg two hours before the onset of the rash. It was later established that he had taken fluconazole 22 times over the previous three years as a single dose treatment for recurrent candidal balanitis. Challenge with fluconazole 150 mg four weeks later provoked identical signs within an hour.

The morphology and histology of the lesions, with residual post inflammatory pigmentation and recurrence at identical sites on challenge, are diagnostic of a fixed drug eruption.¹ Fluconazole is a systemic triazole antifungal agent. There are no previous published reports of fixed drug eruptions following this drug. The Committee on Safety of Medicines has received one other report (personal communication). Fixed drug eruptions have not been associated with itraconazole, the only other systemic

Rash induced by fluconazole on extensor surfaces of elbows

triazole, although maculopapular rashes have been reported.²

- 1 Breathnach SM, Hintner H. *Adverse drug reactions and the skin*. Oxford: Blackwell Scientific, 1992:72-8.
- 2 Tucker RM, Haq Y, Denning DW, Stevens DA. Adverse events associated with itraconazole in 189 patients on chronic therapy. *Journal of Antimicrobial Chemotherapy* 1990; 26:561-6.

Hyperkalaemia and non-oliguric renal failure associated with trimethoprim

Drs G W SMITH and S B COHEN (Fazakerley Hospital, Liverpool L9 7AL) write: A 79 year old woman was admitted with urinary frequency and suprapubic pain. Her usual treatment was mesalazine, diphenoxylate, prednisolone, cimetidine, and diclofenac for Crohn's disease and osteoarthritis. Trimethoprim 200 mg twice daily was started to treat a urinary tract infection.

On admission her serum urea and electrolyte concentrations were normal. Four days later they were deranged: potassium concentration was 7.0 mmol/l, urea concentration 16.0 mmol/l, serum creatinine concentration 225 µmol/l. Arterial blood gases showed mild metabolic acidosis. An electrocardiogram appeared normal. All drugs were stopped and standard measures taken to lower serum potassium concentration. Trimethoprim was replaced by ampicillin in reduced dose. Urine output was 1.5 l/day and kidneys were of normal size on ultrasonography. Seventy two hours later potassium concentration was 4.3 mmol/l, urea concentration 8.5 mmol/l, and serum creatinine concentration 85 µmol/l. Mesalazine and diphenoxylate were not given again, and she was discharged taking prednisolone and diclofenac. Her renal function remains normal.

Renal failure is not a recognised side effect of trimethoprim, although manufacturers advise caution when

treating elderly people and people with impaired renal function. Our patient developed hyperkalaemia shortly after starting trimethoprim. After stopping the drug and treating the hyperkalaemia the results of serum biochemistry returned to normal.

Renal failure has been reported with trimethoprim in combination with sulphamethoxazole (co-trimoxazole). Trimethoprim can also reversibly increase serum creatinine concentration and reduce creatinine clearance without decreasing glomerular filtration rate both in people with normal renal function and in those with renal allografts.^{1,2} Trimethoprim alone can cause an important but reversible increase in serum creatinine concentration in acute uncomplicated cystitis and in chronic renal failure.^{3,4} The mechanism is probably competitive inhibition of tubular secretion of creatinine and does not signify a deterioration in renal function. Non-steroidal inflammatory drugs including diclofenac can cause both renal failure and hyperkalaemia, but in this case timing strongly implicated trimethoprim. Indeed, renal function remained stable when diclofenac was given again.

Three cases of renal failure and one of deterioration in renal function associated with trimethoprim have been reported to the Committee on Safety of Medicines (personal communication).

- 1 Berglund K, Killander J, Pompeius R. Effect of trimethoprim-sulphamethoxazole on the renal excretion of creatinine in man. *J Urol* 1975;114:802-8.
- 2 Dijkman BAC, van Hooff JP, de Wolff FA, Mattie H. The effect of co-trimoxazole on serum creatinine. *Br J Clin Pharmacol* 1981; 12:701-3.
- 3 Sanberg T, Trollfors B. Effect of trimethoprim on serum creatinine in patients with acute cystitis. *J Antimicrobial Chemother* 1986;17: 123-4.
- 4 Myre SA, McCann J, First MR, Cluxton RJ Jr. Effect of trimethoprim on serum creatinine in healthy and chronic renal failure volunteers. *Ther Drug Monit* 1987;9:161-5.