Drug points

Cardiac side effects of pentamidine

Dr B J BOUGHTON (Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH) writes: *Pneumocystis carinii* pneumonitis is a well recognised complication in patients who are immunosuppressed because of the acquired immune deficiency syndrome (AIDS) or cancer chemotherapy. Co-trimoxazole is used widely to treat this condition, but up to 35% of patients do not respond, and in these patients pentamidine may be the only effective drug.[1] In contrast to co-trimoxazole, pentamidine has serious side effects, including renal impairment, pancreatic islet cell toxicity, and severe hypotension.[2] We used pentamidine to treat a patient with pneumonitis resistant to co-trimoxazole, and our observations help to explain its hypotensive effects. A 22 year old man underwent remission induction treatment for acute lymphoblastic leukaemia and entered remission. After five months of oral maintenance chemotherapy he developed a dry cough and shortness of breath. Blood pressure on admission was 120/70 mm Hg and the pulse rate 60 beats/min. Arterial Pao_2 was 6·7 kPa, and chest radiography showed evidence of widespread interstitial pneumonitis. *P carinii* was not detected in sputum, but antibody titres for *P carinii* rose over the next three weeks from <1/16 to 1/64. Five days of treatment with intravenous co-trimoxazole (640 mg trimethoprin, 3200 mg sulphamethoxazole) was ineffective, and treatment with pentamidine mesylate 240 mg daily was started. Because of thrombocytopenia this was given intravenously as an eight hour infusion. The patient's fever subsided on the second day, and over the next two weeks his respiratory symptoms resolved and radiography showed that the pneumonitis had cleared. On the sixth day of treatment with pentamidine he could not sit upright or stand without faintness, and his blood pressure was 70/50 mm Hg supine and 60/0 mm Hg erect. This was associated with a sinus bradycardia (40 beats/min), which did not vary with posture. Tests of cardiac autonomic function showed 0% variation in the pulse rate during respiration (normal >10%) and only 7% variation during a Valsalva manoeuvre (normal >10%). Electrocardiography showed no evidence of intracardiac conduction defects, and the short tetracosactrin test yielded normal results. His blood pressure did not respond to intravenous colloids, graded compression stockings, or fludrocortisone, but the bradycardia and hypotension resolved within four days of stopping treatment with pentamidine. Hypotension did not recur during four subsequent courses of leukaemia chemotherapy with vincristine. Pentamidine probably induces hypoglycaemia because of its biguanide like structure, but the hypotensive side effects are poorly documented. Only three similar episodes have been notified to the Committee on Safety of Medicines, and one case of a reaction after rapid intravenous infusion of the drug has been reported.[3] The present evidence strongly suggests, however, that hypotension induced by pentamidine is caused by autonomic neuropathy and sinoatrial node dysfunction. Pentamidine will probably be used increasingly to treat *P carinii* infections in patients with AIDS, and if it is administered intravenously patients should be monitored for cardiac side effects.

1 Haverkos HW. Assessment of therapy for Pneumocystis carinii pneumonia. *Am J Med* 1984;76:501-8.
2 Tester-Dalderup CBM. Antiprotozoal drugs. In: Dukes H, ed. *Meyler's side effects of drugs*. 10th ed. Amsterdam: Elsevier, 1984:536.
3 Stark R, Crust F, Clemmer T, Ramirez R. Fatal Herxheimer reaction after pentamidine in pneumocystis pneumonia. *Lancet* 1976;i:1193-4.

Severe cholestasis associated with stanozolol

Dr D A GREER (University of Edinburgh, Edinburgh EH3 9EW) and colleagues write: Dr R S Evely and colleagues (7 March, p 612) reported severe cholestasis associated with stanozolol in patients with no history of liver disease. As stanozolol is C17 substituted testosterone such a complication is to be expected, though it is fairly rare. The authors, however, did not comment on the effects of stanozolol on liver function in patients with pre-existing liver function abnormalities. Chronic abnormalities of liver function often occur in haemophiliacs as a result of the use of blood products.[1] Though this is usually subclinical, these patients have chronically raised serum aminotransferase activities. We have studied the effect of stanozolol on the coagulation and fibrinolytic systems in haemophiliacs with such abnormalities of liver function, including several with a history of viral hepatitis.[2] Though we showed no beneficial effects on the coagulation system, we noted a pronounced improvement in liver function during the study. Ten patients with severe haemophilia were studied. Each received 10 mg stanozolol a day for 28 days. A significant reduction in alkaline phosphatase and serum alanine aminotransferase activities occurred within a week of starting treatment, and this was maintained throughout the study. When treatment with stanozolol was stopped activities of both alkaline phosphatase and alanine aminotransferase returned to pretreatment levels within seven days. Other studies have also shown stanozolol to have beneficial effects on liver function. Improvement in serum bilirubin concentration in a patient with Gilbert's disease has been reported,[3] and a controlled study of treatment with stanozolol in children with hepatitis showed a more rapid return to normal serum transaminase activity (Sterling Research Laboratories, on file). The mechanism of these changes is unclear, but the effect seems somewhat paradoxical in view of the report by Dr Evely and others. The clinical importance of these improvements in liver function remains to be established, but stanozolol may be beneficial in patients with chronic liver disease.

1 Forbes CD. Clinical aspects of haemophilias and their treatment. In: Ratnoff OD, Forbes CD, eds. *Disorders of haemostasis*. New York: Grune and Stratton, 1984:177-239.
2 Greer IA, Greaves M, Madhok R, *et al*. Effect of stanozolol on factors VIII and IX and serum aminotransferases in haemophilia. *Thromb Haemost* 1985;53:386-9.
3 Preston FE, Burakowski BK, Porters NR, Malia RG. The fibrinolytic response to stanozolol in normal subjects. *Thromb Res* 1981;22:543-51.

Psoriasiform eruptions associated with penicillamine

Drs JOHN C FORGIE and ALLAN S HIGHET (York District Hospital, York YO3 7HE) write: A 60 year old woman with a 35 year history of seropositive rheumatoid arthritis complicated by Felty's syndrome developed a psoriasiform eruption seven months after the introduction of treatment with pencillamine. The initial dose was 125 mg daily, which was gradually increased to 500 mg daily. Six weeks after the higher dose had been introduced the eruption appeared. A well defined scaly plaque developed on the left shin, with scaling of the soles of the feet. Typical psoriatic nail changes developed, including pitting and onycholysis. Finally, discrete, small, scaly eruptions appeared on the arms. Treatment with penicillamine was stopped and the eruption settled with topical clobetasone butyrate ointment (Eumovate). There was still some scaling of the soles of the feet, which slowly improved with the application of betamethasone dipropionate 0·05% and salicylic acid 3% (Diprosalic).

Her other medications at the time of onset included triazolam, naproxen, frusemide, spironolactone, and prednisolone (12·5 mg daily), but she had taken these for several years, and they were continued while the eruption settled.

A 58 year old woman with a two year history of seropositive rheumatoid arthritis developed a psoriasiform eruption of red, scaly, itchy, well demarcated plaques on the hands six weeks after starting treatment with penicillamine 125 mg daily. She had been taking 9 mg prednisolone daily for over a year but had stopped taking it by mistake when treatment with penicillamine was started. Prednisolone was subsequently restarted (5 mg daily). She had been taking ketoprofen 200 mg daily for two months before the onset of the eruption and continued to do so. Treatment with penicillamine was stopped one month after the onset of the eruption, which was resolving when she was seen 10 days later. Treatment with penicillamine was then restarted and the psoriasiform eruption worsened. Treatment was thus stopped again, and two months later the eruption had cleared without any topical treatment.

The development of these psoriasiform eruptions after treatment with penicillamine and their improvement after the treatment was stopped strongly suggest a causal relation. In the second patient the abrupt cessation of treatment with the systemic steroid was a possible cause of the onset of psoriasis, but the eruption deteriorated when penicillamine was later reintroduced, the dose of prednisolone remaining unchanged. Neither patient had a personal or family history of psoriasis. An exacerbation of pre-existing psoriasis after treatment with penicillamine and recurrence on subsequent rechallenge with the drug has been reported.[1] Two other cases of psoriasis after treatment with penicillamine are known to the manufacturer, and five cases, including one exacerbation of pre-existing psoriasis, have been reported to the Committee on Safety of Medicines.

1 Daunt SON, Cawley MID, Robertson JC, Cox NL. A placebo controlled trial of D-penicillamine in psoriatic arthritis: interim report of benefit. *British Journal of Rheumatology* 1986;25:74.

Hypertension in association with buserelin

Drs J F R BARRETT and M E DALTON (Department of Obstetrics and Gynaecology, St James's University Hospital, Leeds LS9 7TF) write: We describe here a case of hypertension occurring in a patient treated with the gonadotrophin releasing hormone agonist buserelin. Neither the manufacturer nor the Committee on Safety of Medicines knows of any other cases of this association.

The patient was a 39 year old unmarried woman (nulliparous) being treated for endometriosis. Initial therapy with danazol and dydrogesterone was ineffective and accompanied by intolerable side effects. There was no personal or family history of hypertension or renal disease. Her blood pressure during and after her hospital admission, when the condition was diagnosed by laparoscopy, was normal. She did not smoke. Buserelin (Suprefact) 900 µg/day was administered by two intranasal puffs, each delivering a metered dose of 150 µg/puff, three times a day for three months. Amenorrhoea was achieved and she was pain free, but her blood pressure at the clinic was 160/120 mm Hg. Measurements were repeated at half hour intervals with the patient lying supine for two hours and were unchanged over this period. The buserelin was stopped and other possible causes for the hypertension investigated. All investigations, including blood electrolytes, urinary vanillylmandelic acid excretion, creatinine clearance, chest radiograph, and a renal diethylene triamine penta-acetic acid scan were normal. Her blood pressure gradually fell over the following four weeks to 130/80 mm Hg, but over the next six months it once again rose and seemed to be permanently raised.

Correction

Dangers in treating hyponatraemia

We regret that the table from this letter by Mr A N Ghanem and others (28 March, p 837) was accidentally omitted.

Biochemical abnormalities of the transurethral reaction syndrome in case 1

	Normal	Before operation	End of operation (1050)*	Day after operation 1030†	1130†	1300	1700	Day 2
Serum sodium (mmol/l)	135-145	144	107	109	122	126	138	145
Potassium (mmol/l)	3·5-5·1	3·0	6·1	5·7	5·9	4·9	4·4	4
Urea (mmol/l)	2·5-6·5	9·5	12·2	19·9	20·2	20	19·7	14·1
Osmolality (mmol/l)	275-295		249	251	273	280	302	304
Albumin (g/l)	30-50	34			28	26	26	26
Vasopressin (ADH) (pg/ml)				4·6	5·5	2·2	9·4	
Ammonia (µmol/l)	<76			83	126	62	52	
Glycine (µmol/l)	<422			6741	5872	4900	2872	

*Frusemide 80 mg × 2. †500 ml of 5% sodium chloride given in one hour.