Drug points

Fluorouracil and angina

Drs CARLO SPONZILLI, WILLIAM TOFF, and others (Departments of Cardiology and Radiotherapy, St Bartholomew's Hospital, London EC1A 7BE) write: Angina, electrocardiographic abnormalities, and myocardial infarction have occasionally been observed after treatment with fluorouracil.¹⁻¹² A clear causal relation has not, however, been established, as coronary artery disease was either present or not excluded or the subjects had received thoracic radiotherapy, raising the possibility of small vessel thrombosis.

We saw a 48 year old woman who developed repeated episodes of severe chest pain and electrocardiographic changes during the fourth day of an intravenous infusion of fluorouracil (1.25 g (1 g/m²) in 1500 ml 5% dextrose daily) being given for treatment of a squamous carcinoma of the anal canal. A single intravenous bolus of 18.5 mg (1 g/m²) of mitomycin C was given on the first day only and radiotherapy was also given but was confined to the pelvis. After a prolonged episode of pain the electrocardiogram showed ST segment elevation of 1.5-3.0 mm in leads I, II, III, aVF, and V3-6. The fluorouracil was discontinued and an infusion of nitrates was started with rapid relief of the symptoms. An electrocardiogram 12 hours later was normal and no rise in cardiac enzymes was detected.

In view of the severity of the symptoms and a strong family history of ischaemic heart disease cardiac catheterisation was performed. This revealed normal coronary arteries and normal left ventricular function. No further fluorouracil has been given to date. The absence of a history of chest pain, the nature of the electrocardiographic changes, the swift response to nitrates and cessation of the drug, and the angiographic findings strongly support a diagnosis of coronary artery spasm induced by fluorouracil. Since coronary artery spasm may be an initiating event in myocardial infarction,¹³ we suggest that in patients who develop cardiotoxicity associated with fluorouracil further treatment if necessary should be accompanied by vasodilator therapy.

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- 3 Kaye SB, Ikram H. Acute cardiac pain and electrocardiographic changes following cytotoxic treatment for metastatic carcinoma. *Clin Oncol* 1976;2:215-8.
- 4 Stevenson DL, Mikhailidis DP, Gillett DS. Cardiotoxicity of 5-fluorouracil. *Lancet* 1977;ii:406-7.
- 5 Pottage A, Holt S, Ludgate S, Langlands AO. Fluorouracil cardiotoxicity. *Br Med J* 1978;ii:547.
- 6 Villani F, Guindani A, Pagnoni A. 5-fluorouracil cardiotoxicity. *Tumori* 1979;65:487-95.
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- 8 Gamucci T, Zampa G. Cardiotoxicity of 5-fluorouracil. *Tumori* 1980;66:635-6.
- 9 Manente P, Buchberger R, Valmachino G, et al. Cardiotoxicita' da 5-fluorouracile: descrizione di un caso clinico. *Tumori* 1980;66:255-60.
- 10 Spiers ASD, Kasimis BS, Janis MG. High-dose intravenous infusion of 5-fluorouracil for refractory solid tumours—the HI-FU regimen. *Clin Oncol* 1980;6:63-9.
- 11 Sanani S, Spaulding MB, Masud AR, Canty R. 5-FU cardiotoxicity. *Cancer Treat Rep* 1981;65:1123-5.
- 12 Blijham GH. Angina pectoris associated with infusions of 5FU and vindesine. *Cancer Treat Rep* 1986;70:314-5.
- 13 Maseri A, L'Abbate A, Baroldi G, et al. Coronary vasospasm as a possible cause of MI: Conclusion derived from the study of "preinfarction" angina. *N Engl J Med* 1978;299:1271-7.

Hypothyroidism after treatment with ketoconazole

Dr A R TANNER (North Tees General Hospital, Cleveland TS19 8PE) writes: Dr N H Kitching suggested a relationship between ketoconazole administration and the subsequent development of hypothyroidism in a father and son with chronic mucocutaneous candidiasis, a further child having chronic mucocutaneous candidiasis without any endocrine abnormality (18 October, p 994). Chronic mucocutaneous candidiasis is commonly associated with endocrine abnormalities, the so called candida endocrinopathy syndrome, and this can be inherited

in an autosomal dominant or recessive fashion.¹ Although the endocrinopathy is often associated with organ specific autoantibodies, their absence is not unusual. Rather than the hypothyroidism being attributed to ketoconazole administration, it is at least as likely that this family exhibited the candida endocrinopathy syndrome and that the drug administration was purely coincidental.

- 1 Jorizzo JL. Chronic mucocutaneous candidiasis: an update. *Arch Dermatol* 1982;118:963-5.

Psoriasis, cyclosporin A, and AIDS

Drs R C D STAUGHTON, A C S KEAT (Departments of Dermatology and Rheumatology, Westminster Hospital, London SW1P 2AP) and J I HARPER (Department of Immunology (Dermatology), Institute of Child Health, London WC1N 1EN) write: Cyclosporin A exerts a considerable influence on psoriasis.¹⁻³ Our own further experience confirms that psoriasis responds to low doses of the drug, and the report from Dr C E M Griffiths and colleagues (20 September, p 732) echoes this. However, it is premature to assume that because the drug has a considerable effect on the immune system (damping T helper cell activity), and because T helper cells are found in increased numbers beneath a psoriatic plaque, therefore psoriasis is an "immunological disease" and cyclosporin A ameliorates it by an immunological mechanism. Indeed, two pieces of clinical information argue against this. Epidemiological evidence does not suggest that people with psoriasis are prone to either immunodeficiency or hyperimmune or autoimmune conditions. Moreover, psoriasis with the acquired immune deficiency syndrome with extremely low T helper cell population and function, far from showing improvement, may show explosive worsening of their disease.^{4,5} The full range of pharmacological properties of cyclosporin A has yet to be investigated—for example, on the arachidonic acid pathway⁶ or the calmodulin/calcium system (4 October, p 882)—and it is premature to argue that benefit in psoriasis implies a purely immunological cause and effect.

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- 3 Harper JJ, Keat ACS, Staughton RCD. Cyclosporin for psoriasis. *Lancet* 1984;ii:981-2.
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- 5 Farthing CF, Brown SE, Staughton RCD, Cream JJ. *Acquired immunodeficiency syndrome*. London: Wolfe Medical Publications, Ltd, 1986.
- 6 Fan TPD, Lewis GP. Effect of cyclosporin A and inhibitors of arachidonic acid metabolism on blood flow and cyclo-oxygenase products in rat skin allografts. *Br J Pharmacol* 1984;81:361-71.

Alfacalcidol and hypercalcaemia

Dr MARK ARDRON (Selly Oak Hospital, Birmingham B29 6JD) writes: Dr C W H HAVARD (19 October, p 1018) mentions the use of 1 α -hydroxycholecalciferol (alfacalcidol) in the prevention of osteoporosis. Its use, especially in the elderly, is not without hazard. In the past year I have seen two cases of hypercalcaemia presenting as an acute confusional state; both patients were taking alfacalcidol in a dose of 1 μ g/day. The confusion cleared and the serum calcium concentration returned to normal when alfacalcidol was stopped. Treatment had been started by a general practitioner in one case and a consultant physician in the other. Neither patient had received biochemical follow up. Alfacalcidol can cause hypercalcaemia.¹ In Hoikka *et al*'s study of 19 patients with osteoporotic hip fractures treated with 1 μ g/day 6 developed hypercalcaemia, 2 requiring admission to hospital.²

Interpersonal variations in sensitivities to vitamin D may exist in the elderly.³ The case for the use of alfacalcidol in osteoporosis is by no means "cast iron." Hoikka *et al* failed to show any improvement in osteoporosis as judged by determination of bone mineral density and histomorphological analysis.² If this

powerful drug is used the need for careful biochemical follow up should be emphasised.

- 1 Paterson CR. Hypercalcaemia in alphacalcidol therapy. *Postgrad Med J* 1981;57:431-2.
- 2 Hoikka V, Aihava EM, Aro A, Karjalainen P, Rehnberg V. Treatment of osteoporosis with 1-alpha-hydroxycholecalciferol and calcium. *Acta Med Scand* 1980;207:221-4.
- 3 Kemm JR, ed. *Vita.nin deficiency in the elderly*. Oxford: Blackwell, 1985:73.

Endoscopic removal of a pharmacobezoar of slow release theophylline

Dr W D F SMITH (Manchester M28 4JH) writes: Bezoar formation by agents such as slow release theophylline taken in overdose (1 November, p 1143) is more common than generally realised and has serious implications for morbidity and mortality. A review of toxic theophylline levels in Salford health district for a twelve month period ending in May 1985 (before the patient described by Dr Jean-Michel Cereda and others was admitted) showed that 11 patients had been admitted with an overdose. Seven patients made an uneventful recovery after gastric washout, one patient vomited a bezoar, two patients had bezoars removed at gastroscopy, and one patient was found to have a bezoar at necropsy. Gastroscopy should therefore be performed early in patients with clinical and laboratory evidence of serious poisoning, particularly if there are signs of deterioration. Charcoal haemoperfusion is another measure worth considering in addition to gastroscopic removal of the bezoar and has been shown to be effective in lowering theophylline concentrations.¹

- 1 Laggner AN, Kaik G, Lenz K, Druml W, Kleinberger G. Treatment of severe poisoning with slow release theophylline. *Br Med J* 1984;288:1497.

Dr T M E DAVIS and Mr J NICHOLLS (Endocrine Unit, Hammersmith Hospital, London W12 0HS) write: Dr J-M Cereda and coworkers (1 November, p 1143) describe a case of slow release theophylline overdose in which endoscopic removal of a pharmacobezoar followed gastric lavage, administration of activated charcoal, and intravenous infusion of physiological saline with potassium chloride. It is not clear whether the patient was asthmatic, but, as the tablets had been prescribed for someone else, this might be reasonably assumed. In similar cases intravenous propranolol has been shown to reverse attendant hypotension, hypokalaemia, and hyperglycaemia and to control tachycardia and life threatening arrhythmias.¹ The administration of intravenous propranolol to this patient may, through these effects, have made subsequent endoscopy a lot less hazardous.

There are several conditions in which endoscopic removal of unabsorbed theophylline might be inappropriate or unsafe—for example, in patients taking theophylline for reversible airways obstruction with toxic serum concentrations and when ingestion of only a small amount of the drug (1.5-4.0 g) has caused severe symptoms.² Propranolol administration may benefit these patients greatly despite the risk of bronchospasm.¹ Water soluble β blockers such as sotalol may be preferable to propranolol,³ which decreases the clearance rate of therapeutic doses of theophylline by an average of 36% in normal volunteers.⁴ However, there are no reports comparing the effectiveness of these longer acting agents with that of propranolol in the management of theophylline overdose. Also, the use of cardioselective agents such as atenolol may theoretically decrease the risk of bronchospasm in susceptible individuals, but no systematic evaluation has yet been published.

- 1 Amin DN, Henry JA. Propranolol administration in theophylline overdose. *Lancet* 1985;ii:520-1.
- 2 Anonymous. Self poisoning with theophylline. *Lancet* 1985;ii:146-7.
- 3 Farrar KT, Dunn AM. Beta-blockers in treatment of theophylline overdose. *Lancet* 1985;ii:983.
- 4 Conrad KA, Nyman DW. Effects of metoprolol and propranolol on theophylline metabolism. *Clin Pharmacol Ther* 1980;28:463-7.