as lofepramine), have caused neuropathies of a predominantly motor type.[1,2] Casarino has described a case of reversible motor neuropathy, manifested as bilateral footdrop, after three weeks of amitriptyline therapy.[3] The manufacturers of lofepramine (E Merck) are not aware of any cases of motor neuropathy with the drug. This case has been reported to the Committee on Safety of Medicines, which knows of only a few reports of lofepramine causing adverse effects on the peripheral nervous system. Although it is difficult to attribute this woman's motor neuropathy directly to lofepramine, we draw attention to a previously unreported potential side effect of this drug.

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Cyclosporin decreases nifedipine metabolism

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write: In common with several other drugs nifedipine is metabolised by a glucocorticoid inducible cytochrome P450 enzyme, P450pcn. This same P450 isozyme has recently been shown to be the major cyclosporin metabolising enzyme in human liver.[1] In our psoriasis clinic we have observed reactions to nifedipine among patients taking cyclosprin. A 44 year old woman, who developed hypertension while taking cyclosporin for psoriasis (4 mg/kg/day), was started on nifedipine 40 mg/day. At follow up two weeks later she complained of unpleasant "burning" sensations two hours after taking the nifedipine. The nifedipine was stopped, with abatement of the symptoms, but on restarting treatment she complained of severe flushing reactions, which again stopped after the drug was withdrawn. Another patient, a 54 year old woman taking cyclosporin (2 mg/kg/day) for psoriasis, developed a rash while taking nifedipine 20 mg twice daily, which cleared after stopping the drug. Data from the Committee on Safety of Medicines reveal that symptoms of paraesthesia, flushing, and rash are all common adverse effects of nifedipine. To assess the possible interaction of cyclosporin and nifedipine at a metabolic level we performed a study to assess the effect of cyclosporin on P450pcn enzyme activity.

Eight psoriatic patients (three men, five women; mean age 49 (range 32-64) years) were tested for P450pcn enzyme activity while taking cyclosporin (3 mg/kg in seven subjects, 4 mg/kg in one) and one week after cessation of the drug. All were given an oral 5 mg dose of nifedipine (Adalat, Bayer) after an overnight fast and voiding of the bladder. All urine collected in the eight hours after the dose was bulked and an aliquot stored at −20°C. Analysis of the urine for the principal metabolite of nifedipine MII was by automated capillary gas chromatography.[2] P450pcn activity was assessed by measuring the excretion of MII, expressed as percentage recovery (MII excreted over eight hours divided by the dose given and multiplied by 100).

The mean percentage recovery while patients were not taking cyclosporin was 51·75 (SD 13·59)% compared with a mean of 34·58 (10·14)% while taking cyclosporin ($p<0·05$). Thus cyclosporin in vivo decreased P450pcn availability, the metabolism of nifedipine presumably being reduced through direct competition with cyclosporin.

Nifedipine is an effective, relatively safe antihypertensive agent; it has been claimed to be nephroprotective in subjects treated with cyclosporin,[3] although further studies are required to substantiate this.[4] Our study, however, implies that it may be unwise for nifedipine to be prescribed in conjunction with cyclosporin without careful monitoring for side effects. The basis of their interaction would be competition for metabolism by cytochrome P450pcn.

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Peripheral neuropathy and mesalazine

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writes: Peripheral neuropathy is a well documented effect of treatment with sulphasalazine[1,2] (Pharmacia Ltd, personal communication) but rarely appears to have been reported in association with mesalazine (enteric coated 5-aminosalicylic acid) (Smith, Kline and French Laboratories, personal communication). I describe a patient with ulcerative colitis who developed neuropathy after starting treatment with mesalazine, which resolved when the drug was discontinued.

A 38 year old woman developed symptoms of ulcerative colitis in November 1986 and was prescribed mesalazine 400 mg three times a day by her general practitioner. She was admitted for rectal biopsy in December 1986, which confirmed non-specific colitis. At this time she complained of numbness of her feet at night. She was changed to sulphasalazine 1 g three times a day but could not tolerate it because of gastrointestinal side effects and so started taking mesalazine again, 400 mg three times a day, in January 1987. In April 1988 she was referred to the medical outpatient department, complaining of poor concentration, forgetfulness, numb feet, and tiredness in her leg muscles. Nerve conduction studies confirmed a mixed sensorimotor neuropathy, predominantly affecting the legs. Further investigation (including biochemical profile, glucose tolerance test, vitamin B_{12} and folate concentrations, serum and urine protein electrophoresis, and urine porphyria screen) showed no apparent underlying cause for her symptoms. Mesalazine was suspected and discontinued in September 1988. By November 1988 her symptoms had largely resolved, correlating with improvement in repeat nerve conduction studies.

Sulphasalazine is metabolised by colonic bacteria into sulphapyridine and 5-aminosalicyclic acid moieties. About 20% of patients taking sulphasalazine develop adverse reactions,[3,4] principally fever, rashes, vomiting, and reversible blood dyscrasias, usually related to the sulphonamide component.[5] Hepatitis, encephalitis, and neuropathy have also been reported.[1,6,7] The mechanism of the neurological complications is obscure; the 5-aminosalicylic acid moiety is thought to be an unlikely cause because of the very low plasma and central nervous system concentrations achieved after oral or rectal administration.[1,8]

Despite the poor absorption of mesalazine, however, systemic side effects such as deteriorating renal function have been observed.[9] In this patient neuropathy was associated with mesalazine; at the time of writing the Committee on Safety of Medicines had received three reports of neuropathy and one each of sensory disturbance, hyperaesthesia, paraesthesia, and neuralgia (personal communication).[10] These observations suggest that sulphasalazine associated neuropathy cannot be assumed to be sulphonamide toxicity, as is usually thought. Caution is necessary when considering replacing sulphasalazine with mesalazine in a patient who has developed neuropathy.

I thank Dr Shaw for allowing me to report on this patient.

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Identification of toga-like virus in fulminant hepatitis attributed to minocycline therapy

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write: Drs M G Davies and P J W Kersey described fulminant hepatitis and exfoliative dermatitis associated with minocycline therapy.[1] We would like to add the virological findings in case 2, which were not reported by the authors and have now been published.[2]

Liver transplantation was carried out on 16 May 1988, which was three days after this patient's admission to the liver failure unit, King's College Hospital, because of deteriorating liver function and progressive hepatic encephalopathy (grade III-IV coma). Regrafting was carried out 48 hours later because of mechanical obstruction of venous return. The serum aspartate aminotransferase value rapidly rose to 5810 IU/l (prothrombin time 21 s prolonged) on 23 May. She was transplanted for the third time (26 May) but died 24 hours later from gastrointestinal haemorrhage.

Electron microscopic studies of the original liver and the two successive grafts showed virus-like particles (60-70 nm) with spiked surfaces budding into cell vacuoles. Rod shaped inclusions were seen in the nuclei of the hepatocytes. Ultrastructural features resembled those of the RNA containing arboviruses, the Togaviridae.

We cannot exclude minocycline as the cause of the rash and the hepatic dysfunction, but the clinical course and similar virus-like particles have been found in two other patients with fulminant hepatitis who never received minocycline.[1,2,3] Also an RNA containing virus of similar size and resembling the Togaviridae has recently been isolated in parenteral chronic non-A, non-B hepatitis.[4]

These findings have been reported to the Committee on Safety of Medicines.

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