We believe that the potential for psychotropic effects of dextromethorphan because they experienced increased perceptual awareness, altered mood, and hallucinations. We believe that the potential for psychotropic effects of this drug is not fully appreciated and that its abuse may be more widespread than previously recognised.


Excessive blinking associated with combined antidepressants

Drs M A Cooper and T R Denig (Fulbourn Hospital, Cambridge CB1 5EF) write: A 47 year old man with resistant endogenous depression received trazodone with clomipramine, responding well to 100 mg of both. Three months later, although well, he complained of excessive blinking. Changing the doses of antidepressants greatly affected this. When the milligram proportion exceeded on equalization of that of clomipramine blinking increased. When trazodone was withdrawn (clomipramine was continued throughout) blinking became normal within three days. Concomitantly, trazodone 100 mg was reintroduced, clearing the depression. After three days blepharospasm reappeared and was swiftly abolished by extra clomipramine (150 mg). Withdrawal of trazodone only two months later left him well, blinking normally. Psychiatric illness and psychological elicitation of this effect, was probably through dopaminergic. The mechanism here is obscure. Possibly excessive blinking was induced by trazodone with some protection conferred by clomipramine. Only one study mentions eyelid spasm as a side effect of clomipramine. Neither drug manufacturer nor the Committee on Safety of Medicines has received any reports of excessive blinking after trazodone or clomipramine used either separately or together.


Fixed drug eruption associated with mefenamic acid

Drs C L Wilson and A Otter (Stande Vine deale Hospital, Aylesbury, Bucks) write: We report two cases of idiosyncratic reactions associated with mefenamic acid. The Committee on Safety of Medicines has a number of reports of other adverse reactions and rashes caused by mefenamic acid but not of fixed drug eruptions, thought the manufacturer, Parke Davis Laboratories, does have one report of a fixed drug eruption on the knees. There are also reports of fixed drug eruption with other non-steroidal anti-inflammatory drugs,1 including meclofenamic acid, which is available in the USA.

An 18 year old woman presented after eruption of a large bullous lesion on her left foot; over the next 24 hours she developed macular lesions on her hands and facial erythema. These settled over a few days, though they recurred in the same positions on several occasions, resulting in a well demarcated papular area on her foot. On further questioning she said she had used mefenamic acid for about the same time and had been started on mefenamic acid (500 mg) and Stemetil. These lesions ceased to occur when migraine treatment with aspirin was commenced. She developed a conjunctival and recurrent after relapse, with the patient's consent, with mefenamic acid. A 17 year old woman admitted with large pigmented patch on her anterior abdominal wall which had been present for three years. It was noticed to flare up monthly at the start of menstruation. She was treated with mefenamic acid, which cleared and in subsequent treatment achieved satisfactory control. The lesions swelled and became more erythematous.

Amphotericin B hepatotoxicity

Drs F Abril, A J Caro and others (Unidad de Farmacólômico, Clínico San Pedro, Medicina Interna, Hospital de la S L Paz, Madrid, Spain) write: A 29 year old man with the acquired immune deficiency syndrome (AIDS) and a history of intravenous drug abuse was admitted with oesophageal candidiasis. On admission the routine liver function tests were completely normal. Treatment with amphotericin B was initiated in an upward schedule. Fever and chills occurred but were prevented with oral paracetamol (600 mg) and chlorpheniramine (6 mg). Bromazepam (15 mg) was given at night. Six days after reaching the dose of 1 mg/kg/day (50 mg/day; cumulative dose 825 mg) an increase in serum creatinine (300 U/l (normal 30-115 U/l)), especially due to heptosioenzymes and y-gluathionyltranspeptidase (133 U/l (normal 5-65 U/l)) activities was noted. There was no rash, arthralgia, pruritus, eosinophilia, or other clinical manifestation. Ultrasound showed only a discrete hepatomegaly. A liver biopsy was proposed but the patient died before it was performed. On the death record the dose of amphotericin B was progressively diminished (but the concomitant medication continued) and a parallel decrease of side effects was observed; they reached normal levels days later, when the dose had been reduced to 0.5 mg/kg/day.

The patient's clinical state did not satisfactorily explain the transient liver dysfunction. This, and the time relation between the enzymatic disturbance and the amphotericin B dosage schedule, made us think that the drug was involved. Only twelve cases of amphotericin B related hepatotoxicity have been documented in the literature in relation with amphotericin B have been published,1 although the World Health Organization has recorded a few more (Spanish Centre for Drug Monitoring, personal communication). Recently, the manufacturer has also detected in a worldwide spontaneous report program some cases of liver dysfunction (Squibb, personal communication). As in the previous reports,1 hepatic damage appeared in our case when the daily dose was increased to 1.5 mg/kg/day, which suggests a dose dependent mechanism. However, a genetic or pathological predisposition may also be necessary. Amphotericin B seems to be rather new and recent reviews estimate that the evidence of hepatotoxicity is insufficient,2 we consider it prudent to check liver function in all patients on amphotericin B therapy is started, especially when a daily dose near or over 50 mg/kg/day is required. Reducing the dose may be enough to control a mild enzymatic disturbance.


Anergenonic oedema associated with two angiotensin converting enzyme inhibitors

Drs Donald R J Singer and Graham A MacGregor (Blood Pressure Unit, Charter Cross Hospital, London W6R8F) write: A 57 year old hypertensive man with moderate chronic renal impairment and concomitant cardiac failure was treated with captopril 12.5 mg every three days without significant hypotension. Captopril was increased to 25 mg three times a day, frusaemide 40 mg twice a day added, and renal function improved, with no evidence of overall hypertension treatment. Ten weeks later he developed acute neurogenic oedema with dysphagia and lip swelling. Captopril was stopped and he recovered over the next five days. There were no detectable antibodies to captopril of class IgG, IgM, or IgE, and the C4 complement was normal (0-18-0.26 mg/l). Over the initial six weeks of captopril and frusenide plasma creatinine concentrations rose from 320 μmol/l to 400 μmol/l, in association with the development of hypoalbuminaemia. There was therefore more marked acute on chronic renal impairment, the creatinine concentration rising to 550 μmol/l.

For the next three months he was treated with frusenide, ratanidine, and isosorbid nitrate. The cardiac failure became worse, however, and enalapril treatment was added, associated initially with more hypertensive hypotension. Twelve days later he developed angiotensin oedema with lip swelling and tongue and pharyngeal pain. During the next four months he developed frusenide, ratanidine and angiotensin oedema did not recur. In association with the enalapril, there was a more rapid and severe decline in renal function, creatinine rising from 410 to 690 μmol/l. In both cases, the decline in renal function was reversible on withdrawal of the angiotensin converting enzyme inhibitors. The aetiology of bilateral renal artery stenosis was considered. An intravenous pyelogram showed a normal sized right and small scarred left kidney. A dihydralazine test was negative. A biopsy of the right kidney was made following withdrawal of both captopril and enalapril, treatment and showed normal perfusion of the right kidney and poor perfusion of the left kidney.

There is one previous well documented report of angiotensin oedema with captopril.1 The Committee on Safety of Medicines has received six reports of non-fatal angiotensin oedema in association with captopril and 15 in association with enalapril. The manufacturer of captopril (Squibb) give an estimate of 1 to 4 cases of angio-oedema in the 52 830 patients in their United Kingdom postmarketing surveillance study. From their worldwide database of 11 041 hypertensive patients and 498 patients in heart failure, studied in clinical trials of captopril there have been eight reports of angio-oedema (0-07%) and two of laryngeal oedema (0-02%). Over the last 12 months, enalapril (Merck, Sharp and Dohme) suggest from their clinical database an incidence of angio-oedema of around 0.02-0.1% with enalapril in their postmarketing surveillance study of 11 710 patients two have developed angio-oedema.

The mechanism for this rare side effect of angiotensin converting enzyme inhibitors. The delay between starting captopril and the onset of angio-oedema, absence of detectable antibodies to captopril, suggestive of angiotensinergic oedema after enalapril make a biochemical rather than an immunological mechanism more likely. Angiotensin converting enzyme inhibitors convert angiotensin I to angiotensin II, which, at high dose, can cause lip swelling and tongue dysaesthesia. However, because captopril and enalapril share a proline analogue as a cross reacting angiotensin II receptor, the mechanism may be more complex. When the potentially serious but rare adverse reaction, angiotensin oedema, has occurred with one angiotensin converting enzyme inhibitor a structurally different converting enzyme inhibitor should be used with caution.


Correction

Drug induced parkinsonism

We regret that an error occurred in this letter by Ds J A Wilson and W R Primrose (11 October, p 957). The fourth sentence of the second paragraph should have read: ‘Of the 20 still alive, five (25%) had some degree of drug induced Parkinson’s disease, but subsequently developed idiopathic Parkinson’s disease . . .’ and not four, as stated in the journal.