Opiate related collapse in an octogenarian

Drs J RADEMAKER and M SEVERS (Queen Alexander Hospital, Portsmouth) write: We report a case of reversible opiate toxicity to Tylex not previously described.

An 86 year old woman with chronic lung disease collapsed and was brought to the casualty department. She was unresponsive, cyanosed with minimal respiratory effort, and hypotensive. She displayed small pupils with no other abnormal neurological signs and had bilateral basal respiratory crackles. Her electrocardiogram and chest radiograph showed nothing abnormal, and blood gas measurement confirmed she was acidotic ([H^+] 56·6 nmol/l), hypercapnic (P_{CO_2} 10·6 kPa), and hypoxic (P_{O_2} 5·1 kPa). Initial resuscitation produced no improvement, and she remained unresponsive and hypotensive, requiring assisted ventilation. Her daughter then informed us that her mother had fallen that morning and was prescribed Tylex (paracetamol and codeine) two tablets six hourly for possible fractured ribs by her doctor.

Her regular medication included a salbutamol inhaler and amitriptyline 25 mg. The patient made a rapid recovery after she was given naloxone 400 μg intravenously, and within a few minutes was spontaneously breathing, normotensive, and talking.

Opiate toxicity is a well recognised problem in the elderly[1] and in patients with chronic lung disease, but has not been reported with codeine. Indeed, codeine has been reported to be safe in patients with chronic lung disease[2] and has been shown to improve their exercise tolerance.[3]

The risk of drug toxicity in the elderly is high because of the combination of increased sensitivity, altered metabolism, and reduced cardiopulmonary reserve. Pharmacokinetic studies suggest that opiate clearance may be reduced in the elderly,[4] and amitriptyline has been reported to increase the bioavailability and half life of morphine.[5]

Considerable dilemmas face doctors presented with a critically ill octogenarian. However, simple reversible adverse drug reactions should always be considered in the elderly, who may have coexisting disease and be taking other drugs. Tylex contains 30 mg of codeine, equivalent to 5 mg of morphine,[6] and should be prescribed with caution in the elderly with chronic lung disease. Any patient who presents collapsed with small pupils—irrespective of age—should be given a therapeutic trial of naloxone.

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3 Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effect of dihydrocodeine, alcohol, and caffeine of breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N Engl J Med* 1981;305:1611-6.
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Erythema multiforme following substitution of amlodipine for nifedipine

Drs A P BEWLEY, M D FEHER, and R C D STAUGHTON (Westminster Hospital, London SW10 9TH) write: A 62 year old man with longstanding hypertension and hypercholesterolaemia was admitted for treatment of chronic plaque psoriasis. His hypertension had been treated for two years with oral nifedipine capsules 10 mg twice daily. During admission his blood pressure varied between 160-190 mm Hg (systolic) and 90-110 mm Hg (diastolic). In view of this, and to reduce the number of tablets taken, antihypertensive medication was changed to the once daily amlodipine. His only other medications were topical preparations which he had received on three previous occasions without adverse effect. Three days after the change from nifedipine to amlodipine he developed a cutaneous eruption mainly affecting the acral areas. Erythema multiforme was diagnosed and confirmed histologically, after which the amlodipine was stopped and nifedipine started.

Amlodipine, a dihydropyridine derivative structurally related to nifedipine, is used in single doses and has been reported to have fewer side effects and better tolerability than other twice daily calcium channel blockers.[1,2] Single dose antihypertensive treatment is increasingly used to encourage long term compliance. To our knowledge erythema multiforme has not been reported in association with dihydropyridines, although the Committee on Safety of Medicines has received 12 reports of erythema multiforme associated with nifedipine. Two cases of erythema multiforme have been reported two weeks after starting amlodipine treatment.

Erythema multiforme is a rare[3] but potentially life threatening condition. In this case a severe cutaneous eruption was precipitated by one drug but not the other of the same class. Possibly amlodipine on substitution is more able to form a sensitising hapten than nifedipine.

1 Murdoch D, Rennie CH. Amlodipine, a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs* 1991;41:478-505.
2 Hosie J, Bremner AD, James IGV, Saul PA, Taylor SH. Comparison of early side effects with amlodipine and nifedipine retard in hypertension. *Cardiology* 1992;80(suppl 1): 54-9.
3 Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, *et al.* The incidence of erythema multiforme Stevens-Johnson syndrome and toxic epidermal necrolysis. A population based study with particular reference to reactions caused by drugs among outpatients. *Archives of Dermatology* 1990;126: 43-7.

Fluoxetine-warfarin interaction

Dr S WOOLFREY, Mr N S GAMMACK, Dr M S DEWAR, and Dr P J E BROWN (Wansbeck General Hospital, Ashington, Northumberland NE63 9JJ) write: We report two cases where fluoxetine contributed to a loss of anticoagulant control.

A 47 year old man receiving atenolol and frusemide for hypertension started warfarin treatment in 1990. A routine international normalised ratio (INR) measurement was 8·0, although his anticoagulation had previously been stable. His general practitioner had started fluoxetine (20 mg daily) 10 days previously. Fluoxetine was stopped and the INR returned to normal. Other medication was occasional diazepam, and his low alcohol intake was unchanged.

A 72 year old woman with mild heart failure and previously stable anticoagulation was admitted with an INR of 6·9. Her usual medication was prochlorperazine (5 mg/day), frusemide (40 mg/day), potassium (24 mmol/day), ferrous sulphate (20 mg/day), folic acid (5 mg/day), temazepam (10 mg when required), and warfarin. Fluoxetine (20 mg daily) and lormetazepam (500 μg at night, had been started 10 days previously; these and warfarin were stopped on admission. The INR was 7·8 the next day and fell progressively to 1·9 on day 5.

Unlike fluoxetine fluvoxamine and paroxetine have been reported to enhance the anticoagulant effect of warfarin.[1,2] Although fluoxetine prolongs the half life of warfarin in animals, by inhibiting cytochrome P-450, this has not been reported in healthy individuals.[3] Benzodiazepines have been used extensively and safely with warfarin.[4] In the first case the loss of anticoagulant control was probably related to the introduction of fluoxetine. Although the second patient had heart failure and possible hepatic congestion, the temporal relation between the introduction of fluoxetine and loss of anticoagulant control suggests an interaction with warfarin. There has been one report of a possible, inconclusive, interaction between fluoxetine and warfarin,[5] and the Committee on Safety of Medicines has received six reports, including these two, of an increased INR with fluoxetine.

1 *British National Formulary Number 24.* London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1992.
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3 *AHFS Drug Information 92.* Bethesda: American Hospital Formulary Service, 1992.
4 Stockley IH. *Drug interactions: A source book of drug interactions, their mechanisms, clinical importance and management.* 2nd ed. Oxford: Blackwell Scientific, 1991.
5 Claire RJ, Servis ME, Cram DL. Potential interaction between warfarin sodium and fluoxetine. *Am J Psychiatry* 1991;148:1604.

Generalised seizure due to terfenadine

Dr P TIDSWELL and Ms A D'ASSIS-FONSECA (Pinderfields Hospital, Wakefield WF1 4DG) write: A 27 year old man had a tonic-clonic seizure, preceded by a brief aura of dizziness, while at home. A clear eyewitness account was given in the accident and emergency department, but there was no history of previous seizures, neurological disorder, or alcohol abuse. There were no precipitating factors and no family history of epilepsy. There were no physical signs. An electrocardiogram was normal (including QT interval).

He was seen in the neurology clinic three weeks later, when both electroencephalography and computed tomography produced normal results. He had been taking terfenadine 60 mg twice daily, as prescribed by his general practitioner, for a rash for six weeks before the seizure. He had stopped this after the fit. Nine weeks later there had been no further fits.

The Committee on Safety of Medicines have received 17 reports of convulsions possibly associated with terfenadine (personal communication). However, according to the manufacturer's data from five cases (personal communication), seizures have been reported in association with terfenadine only in patients with pre-existing epilepsy, after neurosurgery, or after excessive doses (over 120 mg/day).

Terfenadine is structurally unrelated to older antihistamines and has a lower incidence of central nervous system side effects, including drowsiness, because of poor penetration of the brain by the drug and its metabolites. A known side effect of terfenadine is ventricular tachyarrhythmia,[1] which might result in a secondary hypoxic seizure, but clinically this seems an unlikely mechanism in our patient. This case suggests that terfenadine taken at therapeutic doses may provoke seizures in neurologically normal individuals.

1 Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems (Committee on Safety of Medicines)* 1992;35:1.