

manufacturer has received any reports of this reaction.

- 1 Selvin BL. Systemic effects of topical ophthalmic medications. *South Med J* 1983;76:349-58.
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- 3 Pringle SD, MacEwen CJ. Severe bradycardia due to interaction of timolol eyedrops and verapamil. *Br Med J* 1987;294:155-6.
- 4 Falbe WJ, Boyd DL. Homatropine-associated confusion in an elderly patient. *J Am Geriatr Soc* 1988;36:649.

Depression associated with diltiazem

Ms CECILIA BIRIELL (WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden), Dr JOHN McEWEN (Adverse Drug Reactions Advisory Committee, Canberra, Australia), and Dr EMILIO SANZ (Swedish Adverse Drug Reactions Advisory Committee, Uppsala, Sweden) write: The World Health Organisation collaborative programme for international drug monitoring gathers details of suspected adverse drug reactions from 26 countries. We describe eight episodes of diltiazem associated depression identified in the programme's database.

Case 1—In 1985 a 52 year old Canadian man with angina, who was taking timolol 20 mg twice daily and isosorbide dinitrate 30 mg four times daily, started to take diltiazem 60 mg four times daily. After three days he developed "melancholia, weepiness, and general depression." These symptoms persisted for 14 days, when diltiazem was stopped. He then recovered.

Case 2—In 1987 a 56 year old man in the United Kingdom stopped taking nifedipine 10 mg capsules, which he had been taking for about 16 months for angina. On the same day he took 120 mg diltiazem. Six hours later he felt "unreal, depressed, and suicidal." These symptoms wore off. Two days later he again took 60 mg diltiazem and after six hours the symptoms returned. He continued to take diltiazem tablets 60 mg twice daily for three more days and the symptoms persisted. The symptoms resolved two days after he stopped taking diltiazem. He had been taking, and continued to take 200 mg metoprolol tartrate delayed release daily and up to 10 glyceryl trinitrate tablets sublingually daily.

Case 3—In 1987 a 64 year old Australian woman started to take diltiazem 30 mg three times a day for angina. After three days she developed insomnia and depression characterised by early morning waking and morbid thoughts. These symptoms persisted for 41 days, until she stopped taking diltiazem and recovered. She had been taking, and continued to take, one naproxen tablet daily for arthritis. About 10 days later she again started taking diltiazem, 90 mg daily, and the depression returned within two weeks. Recovery followed within a few days of stopping the drug.

Cases 4-9—Details are set out in the table.

Calcium channel blocking drugs are customarily classified in four groups, reflecting their chemical structures. The piperazine group, which includes cinnarizine and flunarizine, has adverse effects

strongly suggestive of a direct action on the central nervous system. Extrapyramidal symptoms and depression are well documented with flunarizine.^{1,2} Members of the other groups—phenylalkylamines (verapamil), dihydropyridines (nifedipine, felodipine, and nicardipine), and benzothiazepines (diltiazem)—have been used to treat neurological disorders including migraine,³ Gilles de la Tourette's syndrome,⁴ tardive dyskinesia and dystonia,⁵ and some psychiatric disorders. Verapamil, in particular, has been used to treat mania.^{6,7} However, evidence of direct adverse effects on the central nervous system is meagre. Single case reports have attributed akathisia⁸ and acute psychosis⁹ to diltiazem and acute psychosis to nifedipine.^{10,11} Recently four cases of substantial depression associated with nifedipine were reported.¹²

Spontaneous reports of suspected adverse reactions submitted to national centres often lack important information. None the less, we believe that these case reports show that diltiazem can cause depression. Cases 1 and 5 suggest that depression caused by diltiazem can be severe and may be accompanied by other symptoms. The latency of onset in these cases ranged from less than a day to one to two months. There was a positive rechallenge in two cases.^{2,3} In five of the eight cases the daily dose was 180 mg or more, and the pattern in case 4 suggested a dose related effect.

We thank the Committee on Safety of Medicines, United Kingdom, for details of cases 2, 6, and 7; Health and Welfare, Canada, for details of cases 1, 4, and 5; and the Food and Drug Administration, United States, for details of case 8.

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- 4 Berg R. A case of Tourette syndrome treated with nifedipine. *Acta Psychiatr Scand* 1985;72:400-1.
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MMR and the nephrotic syndrome

Drs A S AHUJA and M WRIGHT (Paediatric Department, Royal Albert Edward Infirmary,

Wigan) write: In 1969 one of us (ASA) looked after a young child who developed the nephrotic syndrome two weeks after measles immunisation. In 1972 three cases of the nephrotic syndrome after measles vaccination were reported.¹ As yet none of the reports of adverse reactions to measles, mumps, and rubella (MMR) vaccination have included renal lesions (Committee on Safety of Medicines). It is of interest therefore that we have encountered a child who developed steroid responsive nephrotic syndrome after measles, mumps, and rubella vaccination.

A 13 month old girl received the vaccination in November 1988. She was well at the time and receiving no other medication. There was no history of contact with infectious disease. Six days later she became generally unwell and developed periorbital swelling. This proceeded to generalised swelling, in particular of the abdomen, hands, and feet. Her medical history was unremarkable. Her mother had asthma and hay fever, but the child showed no signs of atopy.

Examination showed an apyrexial child with periorbital, hand, and feet oedema and evidence of ascites. There was no lymphadenopathy and no rash. Examination of the respiratory and cardiovascular systems showed nothing abnormal, and in particular she was normotensive. Investigations showed: proteinuria 4+, midstream specimen of urine sterile, haemoglobin concentration 148 g/l, white cell count 14.5 × 10⁹/l, platelet count 462 × 10⁹/l, urea and electrolyte concentrations normal, total protein concentration 33.8 g/l, albumin concentration 17.3 g/l, aspartate aminotransferase activity <200 IU/ml, complement normal. She was treated with prednisolone (and penicillin). By the fifth day of treatment the proteinuria had diminished to 1+. The oedema settled by day 7 and she was discharged on the ninth day of treatment. Review 10 days later showed that the residual proteinuria had resolved and her albumin concentration had increased to 35.5 g/l (total protein concentration 60.9 g/l). Prednisolone was finally stopped in early March 1989, after which she remained well.

This case does not prove a causal relation between measles, mumps, and rubella vaccination and the nephrotic syndrome. We report it as an observation which may in future be substantiated by the observations of others and lead to further investigations.

- 1 Kuzemko JA. Measles vaccination and the nephrotic syndrome. *Br Med J* 1972;iv:665-6.

Correction

Evaluation of a call programme for cervical cytology screening

An error occurred in a letter with this title by Dr Katy J Shroff (26 August, p 567). In the last sentence the findings emphasise the need for accurate family practitioner committee registers and not family planning clinic registers as printed.

Case No	Age, sex	Daily dose (mg)	Latency of onset	Reported symptoms	Concomitant therapy	Outcome	Comment
4	55 F	240	36	Hallucinations at night, agitation, depression	Insulin, timolol maleate, glyceryl trinitrate	Recovered	Symptoms occurred after dose increased from 120 mg day, taken previously for 3 months
5	28 M	240	48-56	Slow onset of episodes of amnesia, general depression, despondency, violent verbal expressions	None	Recovered	Symptoms reported by patient after about 5 months' therapy; referred for psychiatric assessment and hospital admission
6	45 F	180	1	Light headed, impaired concentration, "talked gibberish," depressed, "odd sensations in chest"	Atenolol	Not recovered*	Symptoms did not resolve when dose lowered to 60 mg/day; symptoms persisted when atenolol stopped for 3 days
7	54 M	180	10	Arthralgia, depression	Enalapril, bendrofluazide, hydroxocobalamin	Recovered	Depression lifted within 24 hours of stopping treatment
8	60 M	90	1-14	Depression, severe fatigue, photosensitivity (after 3 months' treatment), nightmares (after 18 months' treatment)	Dipyridamol, aspirin	Recovered	Symptoms persisted during 20 months' therapy; nightmares ceased immediately and other symptoms within two weeks of stopping diltiazem

*At time of reporting.