Drug Points

Probable fatal interaction between ciprofloxacin and theophylline

Dr R HOLDEN (Edinburgh) writes: Thomson *et al* recently reported theophylline toxicity in an elderly patient concurrently taking ciprofloxacin.[1] The Committee on Safety of Medicines has been notified of several other cases (R D Mann, personal communication). We report a further probable interaction with a fatal outcome.

A 65 year old woman with a history of a left hemiplegia, atrial fibrillation, congestive cardiac failure, and inoperable carcinoma of the breast was admitted after collapsing. Five days before admission she had been prescribed ciprofloxacin 250 mg twice daily and slow release theophylline (Uniphyllin Continus) 600 mg daily for a chest infection. Her condition had been stable until the time of collapse. She had been taking digoxin 0·25 mg, bumetanide 1 mg, and tamoxifen 40 mg daily for more than a year.

On examination she was conscious but unable to communicate and had frequent epileptic seizures, involving the non-hemiplegic side. She had developed fast atrial fibrillation with a ventricular rate of 160 beats/minute and blood pressure of 120/60 mm Hg, but cardiovascular examination gave otherwise unremarkable results. Neurological examination showed features of a previous left hemiplegia and an equivocal right plantar response.

Radiography of the chest showed slight cardiomegaly, and electrocardiography showed atrial fibrillation with a heart rate of 160 beats/minute and widespread ST segment depression. Plasma concentrations of sodium were 133 mmol/l, potassium 2·8 mmol/l, and urea 4·1 mmol/l. Liver function was substantially altered: serum aspartate transaminase activity was 319 IU/l (normal range 12-42 IU/l) and alanine transferase activity was 660 IU/l (normal range 10-50 IU/l); alkaline phosphatase activity was 493 IU/l (normal range 90-300 IU/l); and serum total bilirubin concentration was 59 μmol/l (normal range <17 μmol/l) and albumin concentration 32 g/l (normal range 36-52 g/l). Haemoglobin concentration was 118 g/l and white cell count $17{\cdot}6\times10^9$/l with moderate neutrophilia. Serum concentration of digoxin was 1·3 nmol/l (reference range 1·3-2·5 nmol/l) and theophylline 188 μmol/l (55-110 μmol/l).

The patient was treated with intravenous digoxin 0·5 mg and subcutaneous diazepam 10 mg, but one hour later her heart rate was still the same, she continued to have frequent seizures, and she had become unconscious. Phenytoin 250 mg was given intravenously, abolishing the seizures. Over the next six hours the patient remained deeply unconscious, her heart rate remaining between 140 and 150 beats/minute, and she died seven hours after admission. Permission to perform a necropsy was not obtained.

In this case abnormal liver function due to metastatic disease could have contributed to theophylline toxicity. Alternatively, the hepatic abnormalities may have been due to uncontrolled atrial fibrillation with hepatic congestion induced by theophylline. Ciprofloxacin has been shown experimentally to have a minor effect on theophylline metabolism in normal subjects.[2] The effect may be clinically important in the elderly[3,4] and those with acute and chronic disturbance of liver function. Wijnands *et al* have shown that full body clearance of theophylline is reduced by 30% and that plasma theophylline concentration is increased by 23% in patients with chronic obstructive airways disease taking ciprofloxacin 500 mg twice daily and suggested that the 4-oxo metabolite common to several quinolones was responsible for the interaction.[5] This potentially common combination should be avoided in the elderly and in acutely ill patients, and the dosage of theophylline should be monitored carefully in hospital whenever the combination is used.

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Systemic symptoms associated with a rubefacient

Dr D A N FERGUSSON (Brook Lane Medical Mission, Bromley BR1 4PX) writes: Rubefacients are popular topical preparations, often bought without prescription, which by counterirritation bring comfort in painful lesions of muscles, tendons, and joints and in non-articular rheumatism. They are symptomatically effective and there are few reported problems. I describe a case where normal use may have produced unpleasant systemic sensations and fainting.

Twice an 18 year old girl used a popular proprietary preparation containing methyl nicotinate 1%, capsicin *BPC* 0·12% w/w, and preservatives in a cream base. She was otherwise fit, taking only a combined oral contraceptive, being a non-smoker, and having been discharged as fit after investigation for a symptomless systolic murmur, with electrocardiogram, chest *x* ray film, echocardiogram, and Doppler ultrasound all normal. On the first occasion she had rubbed about 2-3 g of the rubefacient on to her back. Ten minutes later she felt a curious burning sensation internally in her abdomen and felt faint but recovered after 10 minutes. About a month later she rubbed a larger quantity, at most 5 g, on to a painful knee and within five minutes felt nauseated, experienced the internal pain even more unpleasantly, and fainted. When seen some 20 minutes later she was conscious, pale but not shocked, and with a normal pulse and blood pressure. There was intense erythema over the area of application on her knee and lower thigh.

Neither the Committee on Safety of Medicines nor the manufacturer has any reports of such effects. The cream used was later tested by the manufacturers and found to be satisfactory. With the full cooperation of the manufacturer and the informed consent of the patient standard skin patch testing was performed to identify which ingredient might be responsible, and she reacted with erythema to the methyl nicotinate and to the whole preparation, but without any systemic effects as much smaller quantities were used.

The maximum amount of methyl nicotinate applied in the second episode would have been 50 mg. Had this all been absorbed systemically the effect might have been similar to intravenous dosing. In 1975 Davidson *et al* gave 50 mg of nicotinic acid by slow intravenous injection over 30 seconds to 16 patients with Gilbert's syndrome and six controls, and the only side effects reported were mild flushing and a transient metallic taste.[1] Methyl nicotinate would be expected to have a similar effect to nicotinic acid, although there are no known data on intravenous dosing.

As many thousands of people use such preparations without untoward effects there is no obvious ready explanation in this case for the patient's symptoms, although the history of the two episodes suggests a clear cause and effect. Perhaps she had a local sensitivity to topical nicotinate which through vasodilatation would then enhance systemic absorption, and she may also have been abnormally sensitive systemically to pharmacological effects of nicotinate. As these popular treatments are usually obtained over the counter systemic effects may be underreported.

1 Davidson AR, Rojas-Bueno A, Thompson RPH, Williams R. Reduced caloric intake and nicotinic acid provocation tests in the diagnosis of Gilbert's syndrome. *Br Med J* 1975;ii:480.

Toxic interaction of lithium carbonate and mefenamic acid

Drs JOANNA MACDONALD and T JAMES NEALE (Hutt Regional Community Health Service and Department of Medicine, Wellington School of Medicine, Wellington, New Zealand) write: Lithium carbonate is an indispensable treatment for manic depressive illness which has predictable effects on renal tubular concentrating ability. It can also produce acute renal functional impairment, especially in hypovolaemic or dehydrated patients. Drug interactions and hypovolaemic states are associated with acute lithium toxicity, which may include renal functional impairment. We report here a serious acute drug interaction between lithium and the non-steroidal anti-inflammatory agent mefenamic acid, which was substantiated by withdrawal and rechallenge.

A 29 year old woman with a 10 year history of recurrent depression was referred with profound depression associated with severe biological symptoms. The patient admitted to "high" periods, and bipolar affective disorder was diagnosed. Lithium carbonate was started at a dose of 1000 mg/day after the symptoms were controlled with an increase in background tricyclic antidepressant therapy (doxepin 75 mg to 175 mg). Mefenamic acid, two 250 mg tablets three times daily, was her only other medication, taken for two weeks premenstrually. Fluid retention and relative oliguria had been noted perimenstrually in the past. Before the introduction of lithium renal function was normal (plasma creatinine 0·09 mmol/l, blood urea 3·8 mmol/l, and 24 hour creatinine clearance of 1·70 ml/s). Urine analysis gave a normal result. Free thyroxine was measured in the reference range at 11·5 pmol/l. While the patient was taking lithium 1000 mg the plasma lithium value was 0·4 mmol/l. An increase in the dose to 1250 mg daily was associated one week later with nausea and the plasma lithium concentration reached the toxic range at 1·7 mmol/l, leading to cessation of therapy. We assumed that the lithium toxicity had resulted from concomitant hypovolaemia, although this was not clinically evident. Renal function was normal.

Lithium was restarted, but a dose of only 250 mg/day produced symptoms of toxicity while she was also taking mefenamic acid. Serum creatinine concentration was 0·19 mmol/l and creatinine clearance 1·05 ml/s. Lithium and mefenamic acid were discontinued and the patient instructed to increase her fluid and salt intake. Creatinine clearance rose to normal at 1·67 ml/s. A further attempt was made to reintroduce lithium cautiously at a dose of 250 mg three times a day, and blood concentrations at weekly intervals were stable at 0·5 mmol/l over the next month. Mefenamic acid 250 mg tablets, two three times a day, were again added for dysmenorrhoea, and six days later the lithium concentration was 2·0 mmol/l, with symptoms of acute toxicity. Four days after cessation of lithium the blood value was 0·5 mmol/l, plasma creatinine 0·06 mmol/l, and creatinine clearance 2·0 ml/s.

This case was unique in two respects. Renal function was documented as normal before lithium treatment, deteriorated sharply when both therapeutic agents were used, and reverted to normal after their withdrawal. This sequence occurred after rechallenge with both agents. In the only previous report of their association renal function was impaired before treatment.[2] Blood lithium values were considerably raised in our patient, in association with clinical toxicity, but only equivocally so in the previous case.[2] On rechallenge with both agents renal function again deteriorated, although lithium alone did not produce a measurable change in renal function.

Mefenamic acid has been reported to produce a variety of renal syndromes,[3-5] and non-steroidal anti-inflammatory agents as a group may be responsible for acute and chronic renal syndromes, both predictable and idiosyncratic.[5-9] Impairment of concentrating ability occurs in over half of patients taking lithium.[1] Acute reversible renal functional impairment with associated lithium toxicity probably occurred in our patient because of the interaction of a reduction in renal blood flow and glomerular filtration rate induced by a non-steroidal anti-inflammatory drug concurrent with intravascular volume contraction produced by a natriuresis and diuresis initiated by lithium. Although reversible, this potentially dangerous interaction may become more common as use of both agents continues to increase.

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