Adverse drug reaction of the month

Nitrofurantoin rechallenge and recurrent toxicity

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There are a limited number of pathological responses to noxious stimuli, including drugs, and drug-induced (iatrogenic) disease may be difficult to distinguish from other causes. We describe the case of a woman who had two different serious reactions in association with two courses of the antibiotic nitrofurantoin given 16 years apart.

Case report

A 60-year-old woman was admitted as an emergency with progressive dyspnoea over the previous eight months becoming more rapid over the previous eight weeks. She was markedly dyspnoeic when walking more than 50 yards on level ground, had a nonproductive cough and complained of recent weight loss. She denied being on any medication or having had previous allergies and her only previous complaint had been of recurrent cystitis.

Examination revealed bilateral fine crackles in her mid-zones but she did not have finger clubbing. The rest of the examination was normal. Her chest X-ray was suggestive of interstitial fibrosis (figure (A)), her arterial $p\text{AO}_2$ at rest was 9.2 mmHg and her forced vital capacity (FVC) was 1.61 litres (predicted 3.27). Transfer factor for carbon monoxide (tCO) was reduced to 11.91 ml/min/mmHg (predicted 23.15). Liver function tests were also deranged with an aspartate transaminase of 93 IU/l (normal 12–30), gamma-glutamyl-transferase of 57 IU/l (5–35) and alkaline phosphatase 156 IU/l (40–110) but the bilirubin was normal and her erythrocyte sedimentation rate (ESR) was 23 mm/h. Renal function was normal.

On specific questioning about whether she might be taking any medications, particularly for prevention of cystitis, she recalled that she had been prescribed by her general practitioner a urinary, 'antiseptic' tablet which she had taken at night for more than a year but she had not considered it to be a drug. It was subsequently identified as nitrofurantoin 50 mg. A working diagnosis of nitrofurantoin-induced interstitial pulmonary fibrosis was made, the drug was stopped and she improved gradually such that eight weeks later her tCO had risen to 16.93 and her chest X-ray is shown in the figure (B). Seven months after drug withdrawal, her tCO was 21.9, FVC was 3.19 l and her liver function tests were normal. She could walk up to a mile on level ground without dyspnoea.

Subsequent examination of previous medical records from another hospital revealed that she had been referred to a consultant neurol-

ogist 16 years earlier with a history of numbness, pins and needles and tingling of the lower limbs up to mid thigh which occurred 14 days after a 10-day course of nitrofurantoin had been completed for an episode of cystitis. By the time she was seen by the neurologist three months later, there was possible diminished sensation of stocking distribution in the left leg (the right leg was in plaster after a fracture) but no other neurological abnormalities and liver and renal function was normal. Her ESR was 33 mm/h. The neurologist felt that the history indicated that her previous symptoms were likely to be drug-related and advised her general practitioner that she should 'never be prescribed nitrofurantoin again.'

Discussion

The adverse effects of nitrofurantoin on the lung have been widely described.¹ They are estimated to occur in approximately 1 in 10 000 courses of therapy. The Medicines Control Agency/Committee on Safety of Medicines have received 30 reports of suspected adverse reactions involving the lungs and in association with nitrofurantoin to November 1996. Patients can present acutely, subacutely, or chronically. In the latter case, they often present with the picture of a fibrosing alveolitis and occasionally pulmonary fibrosis, although the majority of such patients do show some improvement if the drug is withdrawn.² In a review of 49 cases of nitrofurantoin-induced interstitial pulmonary fibrosis, most patients were, like ours, older than 60 (mean age 66 years) and more often female (71%). The duration of therapy was often long (mean 31 months) and steroid therapy did not appear to favourably influence the outcome.²

Hepatic reactions are also described and are also rare but said to be more common in women,³ especially in older patients. They range from granulomatous hepatitis to chronic active hepatitis and even cirrhosis and end-stage liver disease requiring transplantation.⁴ Early discontinuation of the drug usually results in recovery. A recent case report concerned a recurrence of severe hepatitis in a 56-year-old woman with brief low-dose administration of nitrofurantoin 17 years after an initial hepatitis-like illness associated with administration of the same agent, indicating a long-term memory for hypersensitivity.⁵

Nitrofurantoin-induced neuropathy occurs with similar frequency to the pulmonary toxicity,¹ is usually mixed motor and sensory, and was initially thought to be related to the

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Figure Chest X-ray on presentation (A), and eight weeks after discontinuation of nitrofurantoin (B)

use of prolonged high doses in patients with poor renal function. Four cases have been described in elderly women where rapidly progressive neuropathy developed within two to eight weeks of initiating therapy or even after therapy was discontinued.⁶ The presence and severity of the neuropathy was not related to the dose or renal function and sural nerve histology revealed severe acute axonal degeneration, sometimes with almost complete loss of myelinated fibres.

We recommend that that patients' hospital and general practice records have an eye-catching label on the outside indicating previous serious adverse drug reactions and that they be given a card to show the previous drug reaction history to all practitioners whom they consult subsequently. None of these occurred in this case.

Learning points

- iatrogenic disease can be difficult to distinguish from disease of other (or unknown) causes and diagnosis is often crucially dependent upon a careful (and possibly repeated) history, a high index of suspicion and subsequent evidence of improvement after drug withdrawal
- drug toxicity may present with different patterns at different times after exposure and there may be a delay between exposure and appearance of the adverse reaction
- spontaneous reporting of serious suspected adverse reactions is an important part of the assessment of drug safety. Even though nitrofurantoin-induced pulmonary fibrosis and peripheral neuropathy are well-recognised adverse drug reactions, it is important to report all episodes as this helps to define risk and to identify other risk factors

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2 Robinson BW. Nitrofurantoin-induced interstitial pulmonary fibrosis. Presentation and outcome. *Med J Aust* 1983; **1**: 72–6.

3 Iwarson S Lindberg J, Lundin P. Nitrofurantoin-induced chronic liver disease. Clinical course and outcome of 5 cases. *Scand J Gastroenterol* 1979; **14**: 497–502.

4 Hebert MF, Roberts JP. Endstage liver disease associated with nitrofurantoin requiring transplantation. *Ann Pharmacother* 1993; **27**: 1193–4.

5 Paiva LA, Wright PJ, Koff RS. Long-term memory for hypersensitivity to nitrofurantoin. *Am J Gastroenterol* 1992; **87**: 891–3.

6 Yiannikas C, Pollard JD, Mcleod JG. Nitrofurantoin neuropathy. *Aust NZ J Med* 1981; **11**: 400–5.