Case Study

Elisa, a 62-year-old woman on long-term Nitrofurantoin treatment for recurrent bladder infections, presented to her general practitioner (GP) with ongoing shortness of breath, cough and recurrent chest infections.

A known diabetic and hypertensive with benign positional vertigo and primary hyperthyroidism, Elisa had problems with recurrent urinary tract infections (UTIs) for about two years. Initially she had been treated with several courses of Nitrofurantoin for UTIs before being prescribed 50mg of Nitrofurantoin daily for three months as a prophylactic treatment to prevent UTI.

The GP examined Elisa and queried chest infection or heart failure as a cause of the symptoms. After examination, a chest X-ray was ordered. The chest X-ray showed extensive pulmonary abnormalities with bronchial wall thickening, patchy lesions and extensive bilateral-infiltration – suggestive of atypical infection. Elisa had no known drug allergies and no history of smoking. She was referred to a respiratory physician for further evaluation.

The respiratory physician considered that the abnormal clinical signs were suggestive of some inflammatory process. A high-resolution chest CT scan confirmed the opinion that the pattern and distribution of the lesions were consistent with the changes suggesting interstitial fibrosis secondary to Nitrofurantoin treatment. Elisa’s Nitrofurantoin therapy was discontinued and corticosteroid therapy was commenced for symptomatic treatment. She was advised to avoid Nitrofurantoin in the future.

A treatment injury claim was lodged for pulmonary toxicity as a result of prolonged Nitrofurantoin use. ACC received advice from a respiratory specialist that, while a recognised complication of Nitrofurantoin use, interstitial fibrosis was not an ordinary consequence of Elisa’s treatment. ACC accepted her treatment injury claim and contributed to the costs of Elisa’s treatment and loss of wages.

Expert Commentary

Dr Peter Martin, MB ChB, FRACP

Nitrofurantoin is mainly prescribed for chronic or recurrent UTIs. Pulmonary reactions were first reported in 1957, within a few years of its introduction. The drug and its metabolites are excreted by the kidney, and adverse reactions are more likely if there is renal impairment. As it is often prescribed for elderly people, this is frequently an issue and an alternative agent should be considered if renal function is abnormal.

Reactions may be acute, occurring within hours or days of starting the drug, and occur most commonly in women aged 40–50 years of age. They are usually a form of hypersensitivity and recur if the drug is used again. Sub-acute reactions, occurring after one to six months, and chronic reactions, occurring after six months, may cause pulmonary fibrosis, cryptogenic organising pneumonia (bronchiolitis obliterans organising pneumonia – BOOP), alveolar haemorrhage, collagen vascular disease and interstitial pneumonitis.

Pulmonary toxicity has been reported in 1 in 5,000 courses of the drug, and acute reactions are said to be 10–20 times more common than the other types of reaction. However, the experience of many pulmonary physicians would be that it is more common than this, presumably because it is not always reported. The most common presentation is the chronic form, usually found in elderly women.
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The most useful monitoring in a patient on Nitrofurantoin is a careful enquiry about symptoms such as shortness of breath or cough, and a search for physical signs such as fine or medium inspiratory crackles. These indicate the need for a chest X-ray or high-resolution CT scan and spirometry. Because of the differential diagnosis, most cases will need assessment by a respiratory physician.

The symptoms of Nitrofurantoin pulmonary toxicity, especially the sub-acute and chronic forms, are non-specific. As in the case of Elisa, they are frequently mistaken for other conditions that are common in the elderly. Heart failure, chronic obstructive pulmonary disease and other forms of interstitial lung disease are often misdiagnosed. As the Nitrofurantoin may have been used for years, it is easily overlooked as a cause of the problem.

Once a presumptive diagnosis has been made, the drug must be stopped. The case for using corticosteroids is not clear, but many clinicians would use prednisone if there is not a quick improvement after stopping the drug. Most patients improve, but recovery may be incomplete, especially if symptoms have been developing for a long time. Some radiological changes are likely to persist. Mortality has been reported at 10 percent in both acute and chronic forms of lung reaction.

Adverse Event Notification Feedback
Dr Kylie Morse, BMBS, FRACGP, DCH

Dr Morse has been involved in a Nitrofurantoin case that was notified to the Ministry of Health and Medsafe. She has kindly agreed to describe this experience and the learnings she has since shared with her colleagues.

“One of the difficult parts of my experience, and possibly Elisa’s GP, was the arrival of an ADR notification letter from the acting Chief Medical Officer for the Ministry of Health, about an ACC treatment injury event ‘that it believes represents a degree of risk to the public’. It arrived with an ACC Treatment Injury Medication Event Notification report, which specified the date of injury as the date of my consult in January. This felt personal and anxiety-provoking as the practice was required to complete a Notification of Harm Report Provider Feedback Form listing causal factors, actions taken to reduce the risk of recurrence and system lessons.”

“MY patient had a history of long-term Nitrofurantoin treatment and a one-week history of cough, with bibasal creps on examination. Her chest X-ray was suggestive of atypical infection and she had a two-week course of amoxicillin and erythromycin, during which time she improved. I had stopped her Nitrofurantoin whilst she was on the other antibiotics, however, on restarting the Nitrofurantoin her cough returned and she was admitted within a week. A CT scan showed pulmonary fibrosis, Nitrofurantoin was stopped and she returned to near-normal respiratory function by March.”

“A literature review by our local Pharmacist found that pulmonary reactions are idiosyncratic and unpredictable. The Nitrofurantoin Medsafe data sheet (2004) states that the ‘severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. The risk is greater when chronic pulmonary reactions are not recognised early’. There were two deaths reported to Centre for Adverse Drug Reactions Monitoring between January 2000 and July 2012; only one with information reported and that was associated with continuing Nitrofurantoin six months after she developed pulmonary symptoms (NZMJ Oct 2007, vol 20, no. 1263).”

“Prescriber Update June 2012 states that Nitrofurantoin use should not be prescribed beyond six months because of the risk of pulmonary toxicity unless the benefits clearly outweigh the risks. PHARMAC data suggests up to 5% of patients on Nitrofurantoin take it for longer than this.”

“Following our significant event and literature reviews the practice has identified all patients on Nitrofurantoin prophylaxis with the aim of cessation at six months if possible, and put an alert on to discuss and monitor potential pulmonary side effects.”

Dr Morse has discussed the event with ACC, which clarified that the intent of the notification was to highlight to Medsafe an increase in Nitrofurantoin-related claims. The date of injury is determined to be the date the client first sought treatment for the symptoms of the injury.

References
- Prescriber Update, 2012; 33 (2) June
- www.nzma.org.nz/journal/120-1263/2149

Claims information
Between 1 July 2005 and 30 June 2012, ACC received 45 claims related to Nitrofurantoin pulmonary toxicity treatment injuries, of which 36 were accepted and nine were declined.

The most common reason for declining the claims was because no physical injury caused by treatment was able to be established, or there was no causal link between the treatment and the injury claimed.

How ACC can help your patients following treatment injury
Many patients may not require assistance following their treatment injury. However, for those who need help and have an accepted ACC claim, a range of assistance is available, depending on the specific nature of the injury and the person’s circumstances. Help may include things like:
- contributions towards treatment costs
- weekly compensation for lost income (if there’s an inability to work because of the injury)
- help at home, with things like housekeeping and childcare.

No help can be given until a claim is accepted, so it’s important to lodge a claim for a treatment injury as soon as possible after the incident, with relevant clinical information attached. This will ensure ACC is able to investigate, make a decision and, if covered, help your patient with their recovery.

About this case study
This case study is based on information amalgamated from a number of claims. The name given to the patient is therefore not a real one.

The cases are produced by ACC’s Treatment Injury Centre, to provide health professionals with:
- an overview of the factors leading to treatment injury
- expert commentary on how similar injuries might be avoided in the future.

The case studies are not intended as a guide to treatment injury cover. Send your feedback to: TI.info@acc.co.nz