

Linezolid-induced neuropathy

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TO THE EDITOR: Linezolid is the first of a new class of oxazolidinone antibacterials which was first registered in Australia in September 2001. It represents an important advance in the treatment of infections caused by some enterococci resistant to vancomycin and staphylococci resistant to methicillin.¹ In clinical trials, the most commonly reported drug-related adverse events which led to discontinuation of linezolid therapy were headache, diarrhoea, nausea and vomiting.² We describe a patient who developed peripheral and optic neuropathy while being treated with linezolid.

A 76-year-old man was hospitalised in November 2000 for the third revision of a left total hip joint prosthesis. This was complicated by infection with methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from hip joint washout. The organism was sensitive to vancomycin, teicoplanin, rifampicin and fusidic acid, and resistant to ciprofloxacin. Vancomycin therapy was commenced, but had to be replaced by rifampicin and fusidic acid when the patient developed fever (40°C), rigors, rash and eosinophilia. However, the patient developed severe, generalised pruritus. Therapy with rifampicin and fusidic acid was ceased and oral linezolid (600 mg twice daily) was given.

Linezolid was initially well tolerated. However, about six months after starting treatment with the antibiotic, the patient presented to his general practitioner with numbness of his hands, feet and legs below the knee, intermittent sharp pain in both feet and blurred vision. He was hospitalised and linezolid therapy ceased. On admission, peripheral sensory loss in a glove-and-stocking distribution was noted. Nerve-conduction studies showed severe sensory-motor axonal neuropathy, more severe in

the lower limbs than the upper limbs. Formal visual field testing showed patchy field damage, suggestive of drug-induced toxicity.

The patient declined further ophthalmological review. Five months after he stopped taking linezolid, he reported subjective resolution of visual impairment, but the peripheral neuropathy persists. The patient's alcohol intake had been negligible. Ongoing medications include digoxin, irbesartan, frusemide, omeprazole, piroxicam and diazepam.

We are not aware of any published articles describing peripheral or optic neuropathy associated with linezolid therapy. This information was not included in the original product information, but has been added to the revised version under the heading "Post-marketing surveillance".³

Up to June 2002 there had been only 13 reports of adverse reactions to linezolid to the Australian Adverse Drug Reactions Advisory Committee (ADRAC). Four of these, including our report, describe peripheral neuropathy and involve adult males who had received 1.2 g of linezolid daily for six to nine months. No patient's neuropathy had resolved at the time of reporting. Moreover, linezolid was the sole suspected drug in all four reports. It is important to note that the maximum duration of treatment with linezolid in clinical trials has been 28 days. Reports of neuropathy received by the manufacturer have primarily involved patients treated for longer than 28 days.³

Our report highlights the importance of postmarketing surveillance and reporting of adverse drug reactions, especially when a drug is used outside original indications or duration.

1. Hussar DA. New drugs of 2000. *J Am Pharm Assoc (Wash)* 2001; 41: 229-272.

2. Zyvox (linezolid) product information. Rydalmere, New South Wales: Pharmacia Australia Pty Limited, 24 August 2001.

3. Zyvox (linezolid) product information. Rydalmere, New South Wales: Pharmacia Australia Pty Limited, 21 February 2002. □

Cervical screening: time to change the policy

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TO THE EDITOR: I read with interest the article on cervical screening by Dickinson.¹ Cervical screening has been the most successful public health measure introduced for the prevention of cancer, and the Pap test has been highly effective in reducing cervical cancer mortality and morbidity.

In New South Wales, between 1972 and 1999, the age-standardised incidence and mortality of cervical cancer fell by 49% and 66.6%, respectively.² The overseas experience is similar, with the best screening programs reporting a 70% reduction in mortality rates, with slight annual mortality increases since 1986.³

That women continue to die from this potentially preventable disease emphasises the limitations of the current screening method and highlights the need for new directions. The conventional Pap test is "yesterday's tool for today's world", let alone tomorrow's! The Pap test is prone to errors at all levels, but, most importantly, at specimen collection and cytological interpretation. Consequently, relatively high numbers of false negative results are associated with the test. Further, the Pap test is only partially successful in predicting the biological behaviour of the cytological abnormality.

As Dickinson states, minor abnormalities that come and go are unimportant, and can cause unnecessary alarm. These minor and transient abnormalities often lead to colposcopy, biopsy, surgical treatment and subsequent cytological and clinical or colposcopic follow-up, at a considerable cost to individual women, the screening program and taxpayers.⁴

Recent developments in cervical cytology and molecular biology have opened up new horizons.⁵ Liquid-based cytology, human papillomavirus (HPV) DNA testing and new molecular markers will help us to accurately select the patients who are likely to have biologically aggressive disease with a high probability of progression.^{4,5} With refinements, these new technologies will not only dramatically reduce the frequency of Pap test screening, but they may postpone the age for starting screening from 18 years to perhaps 25 or even 30 years.

These new technologies come at a price. Liquid-based cytology costs about \$30 and HPV DNA testing is about \$90, and no

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There should be no more than 5 references. The reference list should not include anything that has not been published or accepted for publication. Reference details must be complete, including: names and initials for up to 4 authors, or 3 authors et al if there are more than 4 (see mja.com.au/public/information/uniform.html#refs for how to cite references other than journal articles).

Medicare rebates are currently available for these tests.

The additional cost of these new technologies should be considered in the context of the cost of diagnosis, treatment and subsequent cytological and clinical follow-up of biologically insignificant disease. The money saved from improved patient selection for treatment and reduced frequency and late commencement of screening would allow more resources to be allocated to enrolling women (who are currently under-screened) and to funding these new technologies.

1. Dickinson JA. Cervical screening: time to change the policy. *Med J Aust* 2002; 176: 547-550.
2. Cervical cancer screening in New South Wales. Annual statistical report 2000. Sydney: NSW Cervical Screening Program, NSW Pap Test Register, 2000.
3. Larsen NS. Invasive cervical cancer rising in young white females. *J Natl Cancer Inst* 1994; 86: 6-7.
4. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomised trial. *J Natl Cancer Inst* 2001; 93: 293-299.
5. Williams GH, Romanowski P, Morris L, et al. Improved cervical smear assessment using antibodies against proteins that regulate DNA replication. *Proc Natl Acad Sci USA* 1998; 95: 14932-14937. □

Screening mammography and mortality

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TO THE EDITOR: Life expectancy in developed countries increased by an average of about 20 years during the 20th century. An editorial in the *Journal* by Rodger referred to mortality in populations having screening mammography.¹ Data quoted indicated that there had been only slight changes in breast-cancer mortality in Australia up to 1996.

Data for 1999 are available in the report of the Australian Bureau of Statistics *Causes of death*, published in December 2000.² The standardised all-causes death rate per 100 000 for all persons in 1989 was 758.9 and in 1999 was 584.2, a reduction of 23.0%. For women, the standardised death rate attributable to breast cancer in 1989 was 27.2 and in 1999 was 22.1, a reduction of 18.75%. Recent decreases in breast cancer mortality of similar magnitude have also been observed in the United Kingdom and the United States.³ However, screening mammography could only be responsible for a small portion of these changes, because population screening has been in place for little more than a decade and the benefits of earlier detection and treatment

would take more than five years to become evident. The causes of these dramatic reductions in death rates are not yet understood.

Regarding the effect of population screening mammography on mortality rates, this is limited to breast-cancer-specific mortality and cannot be expected to translate into a reduction in overall mortality. In a recent overview of the situation in Sweden,⁴ breast-cancer-specific mortality in the screened group was 22% lower than in the non-screened group. However, the age-adjusted relative risk for total mortality was 1.00 (95% CI, 0.98-1.02). In other words, the mammographically screened population died less frequently from breast cancer, but nevertheless died at the same rate as the non-screened population (from other causes such as heart disease and other cancers). If we consider that, in the age group 40-79 years, breast cancer accounts for about 3% of total mortality, a reduction in breast cancer mortality of 25% would be 25% of 3%, or 0.75%. This change is so small that it would probably never be possible to show an effect of breast-cancer screening on overall population mortality.

It is therefore realistic to regard the benefits of screening mammography as limited to early detection and treatment (possibly with improved quality of survival) and a reduction in breast-cancer-specific mortality.

1. Rodger A. Is it worth screening women over 70 for breast cancer — or indeed any women? [editorial] *Med J Aust* 2002; 176: 247-248. http://www.mja.com.au/public/issues/176_06_180302/rod10045_fm.html
2. Australian Bureau of Statistics. Causes of death, Australia, 1999. Canberra: ABS, 2000: 91 pp. (Catalogue No. 3303.0.)
3. Peto R, Boreham J, Clarke M, et al. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. *Lancet* 2000; 355: 1822.
4. Nyström L. Assessment of population screening: the case of mammography. Monograph. Umeå, Sweden: Department of Public Health and Clinical Medicine, 2000: 106 pp. □

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IN REPLY: I agree with Gough and welcome the more recent data showing up to an 18.75% reduction in breast cancer mortality in Australia in the 10 years from 1989.

Obviously, this cannot be attributed solely to the now 10-year-old National Mammographic Screening Program, but it may result from a combination of the screening program, ad-hoc screening before the program, and the more rigorous use of adjuvant therapies based on the results of clinical trials. That breast screening is

unlikely to have an impact on overall population mortality gives the lie to the conclusions of Olsen and Göttsche's overview,¹ which are based only on overall mortality.

Nevertheless, Gough and I agree that screening mammography is likely to deliver other benefits through detection of earlier-stage disease and a reduction in deaths from breast cancer.

1. Olsen O, Göttsche PC. Screening for breast cancer with mammography. In: Cochrane Library, issue 4. Oxford: Update Software, October 2001. □

Communication loads on clinical staff in the emergency department

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TO THE EDITOR: I would like to compliment Coiera et al for their very interesting article about communication in an emergency department.¹ Nearly a third of communication events were classified as interruptions, thus having an adverse effect on communication within the department.

In trying to reduce this level of interruption, perhaps it is time to rethink the role of the on-call emergency physician in an emergency department. In most large Australian emergency departments, the emergency physician is also the admitting officer, who is responsible for coordinating the non-elective admissions of the day. This involves being readily available for external and internal phone calls, usually by mobile phone. Thus, as well as the normal clinical workload of an emergency physician, he or she needs to respond immediately to the summons of a mobile phone — a recipe for interruptions and less efficient communication.

It is not optimal for the person who has clinical responsibility for the emergency department to also be the person through whom most of the communication is channelled. One possible solution is to channel calls about patients whom the referring doctor considers definitely need assessment in the emergency department to non-medical clerical staff. They could enter the details in a computerised "expected patients" database, which would be available for viewing by emergency department staff. Only calls about patients where there is some uncertainty, and advice calls, would be channelled to the emergency physician on call. This would