Editorial

Gentamicin: a great way to start

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For many years, Therapeutic Guidelines: Antibiotic has recommended the use of gentamicin for therapy of serious infections possibly caused by Gram-negative organisms. This is because of its rapid bactericidal activity and comparatively low levels of resistance in most community- and hospital-associated Gram-negative pathogens. These properties make it a very useful empirical drug when rapid control of a serious infection is required.

However, gentamicin is both ototoxic and nephrotoxic. Ototoxicity is less frequently reported but, unlike nephrotoxicity, is much less commonly reversible.[1] Monitoring of plasma concentrations has been recommended to guide safe and effective dosing, but will not prevent the rare occurrence of sudden idiosyncratic deafness. Prolonged therapy is an independent risk factor for nephrotoxicity.[2] Conversely, short-term therapy (three days or less) has a very low incidence of nephrotoxicity.[3]

In this issue…

Spring is a time of change, so it is appropriate that some of the papers in this issue herald potential changes in practice. Rob Moulds and Melanie Jeyasingham propose abandoning routine monitoring of gentamicin concentrations during short-term use of the drug.

Routine self-monitoring of blood glucose (by some patients with type 2 diabetes) could also be unnecessary according to a Canadian paper reviewed by Julia Lowe. However, according to Peter Davoran and David McIntyre, testing is still recommended in gestational diabetes.

Tests for melanoma are becoming more widespread. Elizabeth Wurm and Peter Soyer review some of the non-invasive diagnostic tools now available.

There have been changes at the National Prescribing Service (NPS), with the closure of the Therapeutic Advice and Information Service, while at *Australian Prescriber* we are mourning the sudden death of Maureen Ryan, our editorial assistant. This issue is dedicated to the memory of Maureen.

Although gentamicin is primarily indicated for empirical therapy, in practice empirical use often continues beyond the time frame originally intended. Despite the best endeavours of all concerned to ensure appropriate monitoring, gentamicin toxicity remains an important clinical problem and many clinicians are reluctant to use it, even for short-term empirical therapy.[4]

This reluctance to use gentamicin has resulted in increasing use of alternative drugs, such as broad-spectrum cephalosporins, for empirical therapy against likely Gram-negative pathogens.[4] Widespread use of broad-spectrum antibiotics has been linked with the increasing prevalence of infections due to methicillin-resistant *Staphylococcus aureus*,[5] vancomycin-resistant enterococci,[6] multiresistant Gram-negative organisms,[7] and *Clostridium difficile*.[8] For empirical use, these drugs should therefore be reserved for situations where gentamicin is specifically contraindicated – previous vestibular or auditory toxicity or serious hypersensitivity reaction to an aminoglycoside.

To resolve the dilemma that concern about long-term toxicity is inhibiting its use as short-term empirical therapy, the expert writing group for version 14 of Therapeutic Guidelines: Antibiotic[9] has recommended some major changes to the way gentamicin is used. There are now clear distinctions between empirical and directed therapy.

These principles apply to use in both adults and children and to other intravenously administered aminoglycosides.

For **empirical therapy**, the recommended treatment duration with gentamicin is now limited to a maximum of 48 hours in all patients. The initial dose is based on the patient's age and weight, then the dose interval for either one or two further doses (or none at all) is determined by the patient's renal function. For example, a patient with normal renal function would receive a maximum of three empirical doses at 0, 24 and 48 hours. As dosing with gentamicin will not continue beyond 48 hours, monitoring of plasma concentrations is not required.

Susceptibility results should be used to guide ongoing therapy. If susceptibility results are not available by 72 hours and empirical intravenous therapy is still required, the gentamicin-containing regimen should be ceased and an alternative regimen used. The recommended alternative depends on the

indication, but broad-spectrum cephalosporins should not automatically replace gentamicin.

If a susceptible Gram-negative organism is identified, gentamicin should only be continued if the patient has one of the following indications for **directed therapy**:

- infections when resistance to other safer antimicrobials has been shown
- combination therapy for serious *Pseudomonas aeruginosa* infections and brucellosis
- low doses as synergistic treatment for streptococcal and enterococcal endocarditis.

The first dose of directed therapy is based on the patient's age and weight, as for empirical therapy. Monitoring of plasma concentrations is essential and should commence with this first dose of directed therapy to guide subsequent dosing.

Computerised methods can be successfully used for gentamicin monitoring. They estimate the 24-hour area under the curve (AUC) of concentration against time and recommend dose adjustment to achieve the target AUC. These methods are the most sophisticated as they automatically adjust for significant individual variation in volume of distribution and elimination. The timing of the blood sample will depend on the specific program used.[1]

The nomograms for plasma concentration monitoring that appeared in previous versions of the guidelines have been deleted. These graphical methods had significant limitations as they were based on population pharmacokinetics and had only been validated in adult patients with normal renal function.[1] They were included in previous versions of the guidelines because it was recognised that not all hospitals had access to the more sophisticated computerised methods.

As there are now only a few specific and uncommon indications where directed therapy with gentamicin is recommended, the expert group decided that the more accurate computerised methods of monitoring should be used. This is to discourage long-term use except in these circumstances, in which case patients should be in a facility that has access to a computerised monitoring program and skilled personnel to interpret the information.

For ongoing directed gentamicin therapy, other monitoring recommendations remain unchanged.

The expert writing group recognises that these changes, and in particular the intentional omission of the monitoring nomograms, might surprise users of the guidelines. However, it is hoped that the changes will lead to better patient care by striking a practical balance between the benefits of the breadth of activity of gentamicin and its rapid bactericidal activity, especially in bloodstream infections, versus the limitations of toxicity with prolonged use.

References

1. Turnidge J. Pharmacodynamics and dosing of aminoglycosides. Infect Dis Clin North Am 2003;17:503-28.
2. Bertino JS Jr, Booker LA, Franck PA, Jenkins PL, Franck KR, Nafziger AN. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. J Infect Dis 1993;167:173-9.
3. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995;39:650-5.
4. Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A. Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis 2007;45:753-60.
5. Aldeyab MA, Monnet DL, Lopez-Lozano JM, Hughes CM, Scott MG, Kearney MP, et al. Modelling the impact of antibiotic use and infection control practices on the incidence of hospital-acquired methicillin-resistant Staphylococcus aureus: a time-series analysis. J Antimicrob Chemother 2008;62:593-600.
6. Tokars JI, Satake S, Rimland D, Carson L, Miller ER, Killum E, et al. The prevalence of colonization with vancomycin-resistant Enterococcus at a Veterans' Affairs institution. Infect Control Hosp Epidemiol 1999;20:171-5.
7. Lopez-Lozano JM, Monnet DL, Yague A, Burgos A, Gonzalo N, Campillos P, et al. Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: a time series analysis. Int J Antimicrob Agents 2000;14:21-31.
8. Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired Clostridium difficile-associated diarrhoea: a systematic review. J Antimicrob Chemother 2003;51:1339-50.
9. Antibiotic Expert Group. Therapeutic Guidelines: Antibiotic. Version 14. Melbourne: Therapeutic Guidelines Limited; 2010.

Professor Moulds was chair, and Ms Jeyasingham was editor, of the expert writing group for the Antibiotic Guidelines version 14.

Dr John Dowden and Professor John Tiller from the Editorial Executive Committee of Australian Prescriber are directors of Therapeutic Guidelines Limited.

RADAR

The latest edition of NPS RADAR reviews sitagliptin and vildagliptin, two drugs from a new class of dipeptidyl peptidase-4 (DPP-4) inhibitors – or 'gliptins' – for type 2 diabetes mellitus. RADAR also reviews an adrenaline autoinjector for acute allergic anaphylaxis.

To read the full reviews go to www.nps.org.au/radar