CLINICAL PRACTICE

# Aminoglycoside monitoring: perspective on current trends in the Western Cape

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Therapeutic drug monitoring (TDM) of antibiotics is employed only for aminoglycosides, chloramphenicol and, arguably, vancomycin.[1-4]

Aminoglycosides are first-line antibiotics in treating infections of Gram-negative micro-organisms that are resistant to less toxic agents.[2] They have potent concentration-dependent bactericidal activity, a post-antibiotic effect (PAE), relatively predictable pharmacokinetics and act synergistically with many other antibiotics. With susceptible organisms, clinical responses are rapid and understanding their toxicity profiles has allayed fears relating to adverse effects of these drugs (principally nephro- and ototoxicity).

TDM of aminoglycosides is costly and some controversy exists with regard to its role in patients with adequate renal function.[2,3] The serum levels in such patients must be carefully interpreted, since pharmacokinetics may be altered by many factors other than renal function.[5,6]

Aminoglycosides are administered by traditional or pulse-dosing regimens, i.e. they may be given in divided doses thrice daily or as a bolus (total daily dose) 24-hourly.[2] With pulse-dosing, toxicity and costs (logistical and TDM) may decrease and higher plasma concentrations could improve their PAE.

Resistance to aminoglycosides may be due to decreased antibiotic uptake/accumulation and efflux from the organism, modification of the ribosomal target as well as enzymatic degradation of the drug.[7] Except for amikacin, the latter mechanism appears to be the primary cause of acquired resistance to these drugs.

In view of the above, it was the aim of this study to investigate the demands for blood level determinations of amikacin, gentamicin, netilmicin and tobramycin over the past 13 years in the Western Cape, to compare these results with resistance patterns and to discuss the patterns in terms of changed dosing regimens, costs and published literature.

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## Methods and materials

The Pharmacology/Toxicology Laboratory of Stellenbosch University and Tygerberg Academic Hospital provides a 24-hour service, primarily to the Tygerberg Academic Hospital, but also an after-hours service to Groote Schuur, Victoria, Red Cross, 2 Military and a number of satellite hospitals. As a result, this laboratory processes the largest number of specimens by a single laboratory in the Western Cape. The total requests received for TDM of aminoglycosides, which in 1991 and 2004 numbered 8 585 and 2 204, respectively, are therefore probably the best available reflection of the demand for these analyses, and by extrapolation, the usage of aminoglycosides, in the Western Cape.

Laboratory records from the Pharmacology/Toxicology Laboratory of Stellenbosch University and Tygerberg Academic Hospital were examined, spanning the period 1991 - 2004. The number of requests for serum determinations of four aminoglycosides, i.e. amikacin, gentamicin, netilmicin and tobramycin, was extracted from these records. All routine serum determinations of the aminoglycosides are performed quantitatively by means of a fluorescence polarisation immunoassay (FPIA) technique. The data were transferred to an Excel spreadsheet (Microsoft Incorporated, Seattle, USA). Hereafter, the number of requests for determinations performed (totals per month and totals per year between 1991 and 2003) was plotted for each aminoglycoside using GraphPad Prism software (GraphPad Software Inc, San Diego, USA).

Similarly, laboratory records from the Department of Medical Microbiology of Stellenbosch University and Tygerberg Academic Hospital were examined, spanning the period October 2002 - September 2004. The number of organisms that were exposed to amikacin, gentamicin and tobramycin, excluding netilmicin, the latter being primarily used in the private sector, as well as their susceptibility profiles, was obtained from these records. *Acinetobacter* species was chosen as an example of a bacterium that demonstrated a relatively high level of resistance to aminoglycosides in comparison with other organisms of which fairly large numbers were also tested. *Acinetobacter* species, in particular *Acinetobacter baumannii*, has been associated with a number of clinically significant infections in Tygerberg Academic Hospital, Johannesburg Hospital and other hospitals worldwide.[8,9] The data were again

transferred to an Excel spreadsheet (Microsoft Incorporated, Seattle, USA). Hereafter, the percentage of *Acinetobacter* species, as well as *A. baumannii*, that was resistant to amikacin, gentamicin and tobramycin, was plotted (in 6-monthly intervals for the period October 2002 - September 2004) using GraphPad Prism software (GraphPad Software Inc, San Diego, USA).

## Results

The number of analyses for amikacin, gentamicin, netilmicin and tobramycin for the period 1991 - 2004 (requested per month and per year) are shown in Figs 1 and 2, respectively.

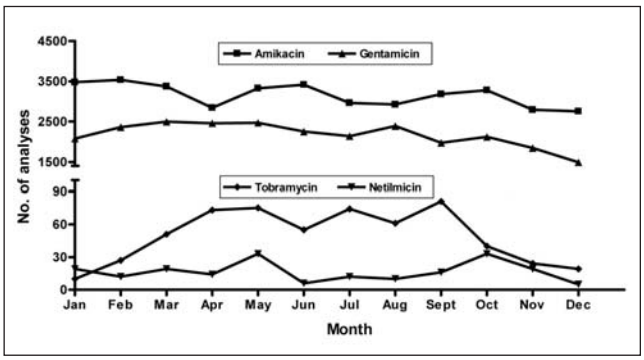


*Fig. 1. Total number of analyses for aminoglycosides requested per month (1991 - 2004).*

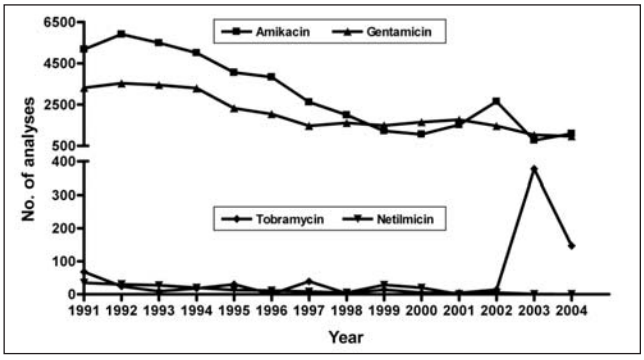


*Fig. 2. Total number of analyses for aminoglycosides requested per year (1999 - 2004).*

The percentage of *Acinetobacter* species and *A. baumannii* that were resistant to amikacin, gentamicin and tobramycin for the period October 2002 - September 2004 (divided into 6-monthly intervals) are shown in Figs 3 and 4, respectively.

## Discussion

Several of the previously mentioned hospitals, other than Tygerberg Academic Hospital, as well as certain private pathology laboratories, provide their own daytime analytical services for serum determination of aminoglycosides. As a result of these daytime services, data obtained from the current study are therefore necessarily somewhat conservative with regard to the true usage and demand for aminoglycoside TDM in the Western Cape.

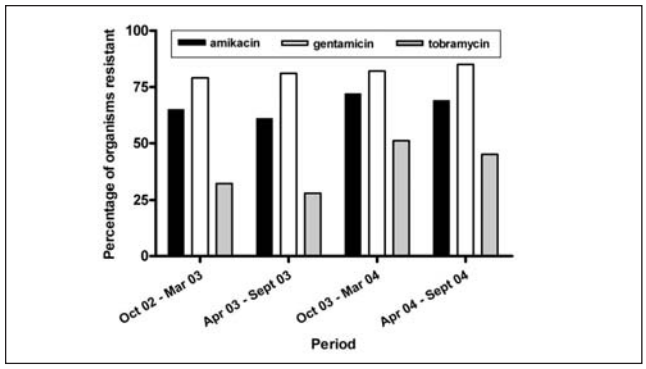


*Fig. 3. Percentage of* Acinetobacter *species resistant to amikacin, gentamicin and tobramycin.*

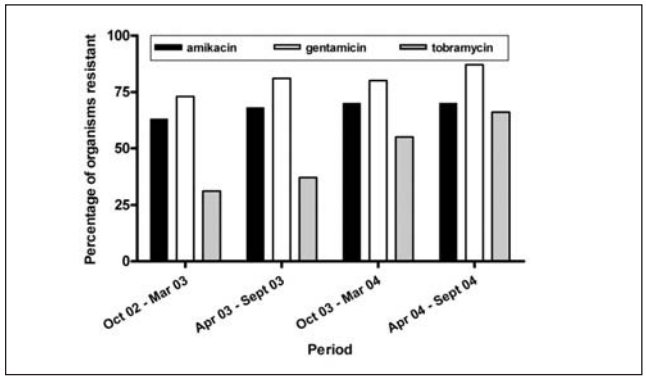


*Fig. 4. Percentage of* Acinetobacter baumannii *resistant to amikacin, gentamicin and tobramycin.*

The data on microbial resistance reflect only the patterns at Tygerberg Academic Hospital, since the Department of Medical Microbiology of Stellenbosch University and Tygerberg Academic Hospital performs these determinations only for this particular institution.

From the number of serum level requests per month (average approximately 3 000) (Fig. 1) it appears that peaks occurred in early winter and spring for amikacin TDM, therefore reflecting a seasonal pattern in the demand for analyses for this aminoglycoside antibiotic. A similar pattern was observed for netilmicin and tobramycin, with monthly totals for these two agents approximating 16 and 50 analyses, respectively. However, in contrast, this did not appear to be the case for gentamicin, for which the monthly demand remained relatively constant at approximately 2 000. While no definite explanation can be given for these observations, one may speculate that the increased number of seasonally related requests is associated with a higher incidence of infections occurring during winter and early spring.

As far as the annual trends are concerned, it is clear from Fig. 2 that the number of requests for analyses of amikacin and gentamicin declined steadily between 1991 and 2001. There was a sharp decline in the usage of amikacin, the number of requests falling below those of gentamicin between 1999 and 2001. It is conceivable that the higher cost of amikacin versus gentamicin (the former being at least twice as expensive as the latter) in the usual daily doses, and the budgetary restraints placed on state hospitals, may have contributed to this observation. However, demands for amikacin blood levels peaked in 2002. Although this antibiotic is expensive, it is generally less toxic than gentamicin and higher doses may be administered owing to its better safety profile, the ensuing relatively higher blood levels making monitoring more accurate. Furthermore, amikacin is less prone to inducing enzymatic resistance (see above) and is therefore a reliable antibiotic. The number of requests for netilmicin also gradually decreased from 35 in 1991 to 1 in 2003, a small peak occurring between 1999 and 2002. After 1991, the demands for tobramycin analyses also decreased in a marked fluctuating manner, requests peaking in 1995, 1997 and between 1999 and 2000. A sudden and significant rise (almost 10-fold) in requests for tobramycin was observed in 2003 compared with requests for this antibiotic in the preceding 12 years. Although the requests for tobramycin in 2004 remained high, the total number was somewhat lower than in the preceding year. This sharp increase in 2003/2004 almost certainly reflects its reasonably successful, albeit intermittent, use for treating patients in intensive care units in Western Cape hospitals who are infected with *Acinetobacter* species resistant to all other antimicrobial agents, including amikacin and gentamicin. Although tobramycin has one of the less favourable toxicity profiles among the aminoglycosides, it is effective when used in combination with other agents, e.g. ampicillin/sulbactam, in infections with antibiotic-resistant *Acinetobacter* organisms.[10] The occurrence of multidrug resistance to these ubiquitous Gram-negative coccobacilli, which are widespread in nature, is an increasing problem worldwide in critically ill patients.[8,9,11]

In general, the gradual chronological decline in the usage of aminoglycosides over the past 13 years may be related to the use of pulse-dosing regimens and the availability of alternative antibiotics, e.g. 3rd and 4th generations of cephalosporins and quinolones.

The percentage of *Acinetobacter* species and *A. baumannii* resistant to gentamicin and amikacin has remained fairly constant during the period October 2002 - September 2004 (Figs

3 and 4). However, the pattern of *Acinetobacter* species resistant to tobramycin has been more dynamic, the number of isolates resistant to this drug ranging between 32% and 51% (Fig. 3). This concurs with the average percentage of resistant isolates to tobramycin (54%) found in 2001 in Latin American countries, which have similar socioeconomic structures to that of South Africa.[9] Although, in the present study, the general trend with regard to *Acinetobacter* species suggests an increase in resistance, this pattern is much more pronounced for *A. baumannii* (Figs 3 and 4). For the latter species the percentage of resistant isolates increased from 31% to 66% over the period October 2002 - September 2004. These observations would concur with the increased frequency of the use of tobramycin during the same period.

## Conclusions

As far as I am aware, this is the first extended trends study with regard to the demand for TDM of aminoglycosides and its correlation with resistance patterns in the Western Cape. Aminoglycosides will continue to be used and monitored in the foreseeable future, and it is important to observe the trends of their use, monitoring and resistance patterns continually. This will be in the best interests of all patients.

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