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Gentamicin Monitoring Practices in Teaching Hospitals – Time to Undertake the Necessary Randomised Controlled Trial

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Abstract

Objective: To compare the clinical appropriateness of the prescribing and monitoring of gentamicin.

Method: A retrospective study was undertaken at two tertiary teaching hospitals in Australia. 161 adult patients administered gentamicin and who had at least one serum concentration taken whilst an inpatient were eligible for analysis.

The main outcome measures were adherence to local and national guidelines for dosing and monitoring of gentamicin, and percentage of the recommended measure of adequate gentamicin exposure (Area-Under the concentration-time Curve (AUC)) using a nomogram and a Bayesian calculation.

Results: Results were similar in both hospitals.

Initial dosing: Adherence to local and national dosing guidelines was poor - approximately 50% of initial doses using less than local and 88% less than national recommendations.

Monitoring: Approximately 20% of all gentamicin concentrations were collected outside the required sampling window. Sampling was particularly problematic after the initial dose. Here up with to half of the samples were taken outside the recommended time frame for sampling, therefore making interpretation of the nomogram difficult.

Dose adjustment: 15% of doses were adjusted without monitoring and approximately half of all dose adjustments were based on inadequate information or inaccurate nomogram interpretation.

Dose evaluation: Approximately half of the AUCs were below the therapeutic range.

Conclusion: A large number of issues around appropriate use and monitoring of gentamicin were seen. This is particularly concerning considering both hospitals are large tertiary hospitals with expert clinical pharmacy support. We believe it is time for a randomised controlled trial to be undertaken, comparing Bayesian modelling techniques with standard nomogram, powered for clinical endpoints.

Keywords: Gentamicin; Therapeutic drug monitoring; TCI works; Adherence

Introduction

Gentamicin is an aminoglycoside antibiotic that has been commonly used for over 50 years due to its low cost, rapid and effective concentration-dependent bactericidal effect, synergism with beta-lactam antibiotics and a low rate of true resistance [1]. Despite the benefits of gentamicin, its use is linked to nephrotoxicity and ototoxicity [2]. In response, there has been a plethora of dosing and monitoring strategies aimed at reducing toxicity while maintaining effectiveness [3]. To ensure a bactericidal effect, a peak plasma concentration above the mean inhibitory concentration is required. Toxicity is related to a sustained elevated trough concentration, usually greater than 0.5 mg/L. To achieve these scenarios a once daily dosing regimen is used and has been demonstrated to improve patient outcomes [4,5].

Wide intra and inter-patient variability exists in the Pharmacokinetics (PK) of aminoglycosides [6], therefore Therapeutic Drug Monitoring (TDM) has been widely used to individualise dosing regimens and ensure optimal concentrations. There have been a number of methodologies and many clinicians choose nomogram methods [1] of which the method described by Begg is most popular [4]. Here concentrations at the 6-14 hour time point are plotted on the nomogram that indicates the minimum and maximum plasma concentrations expected at a given time post dose. If concentrations lie outside the range, a new dose is calculated. However, this method was developed using data from an adult population with normal renal function. As gentamicin is almost 100% renally cleared, the nomogram is therefore not suitable for patient populations where the PK of gentamicin is unpredictable such as patients with impaired or supra-normal renal function. Ignoring this limitation of the nomogram can result in sub-therapeutic concentrations [7] leading to unresolved or resistant infection or supra-therapeutic concentrations, resulting in renal or ototoxicity.

New methods of dose individualisation link population PK models, Bayesian modelling and relevant patient demographics such as renal function, to estimate an individual's specific PK parameters and to predict future doses [8]. With this method, pre-developed population PK models are used for initial parameter estimates (clearance, volume of distribution etc.) and subsequent plasma concentrations are used to further "individualise" the PK model. Measures of drug exposure such as Area Under the concentration time Curve (AUC) can then be calculated and the dose adjusted to a therapeutic range. Traditional AUC based methods [7] rely on two concentrations to predict an AUC (although Seba-Gen can calculate an AUC on one concentration), however recent Bayesian software such as TCI Works® has the ability to predict accurate AUCs using 1 concentration [9]. This has obvious implications for nursing, prescriber, and pharmacist time, as well as benefits to the patient (especially children and neonates) as one less blood sample is required.

The current Australian national antibiotic guidelines [10] recommend that computerized methods with dose adjustments should be based on AUCs. However many hospitals still use the nomogram methods due to their ease of use, apparent lack of IT support for Bayesian software, clinical expertise required and assumed health professional workload implications. Target AUCs are usually around 70-100 mg/L/h, with specific targets of 80 mg/L/h proposed by some [11].

To investigate if the current nomogram method of dosing and monitoring is clinically appropriate, the two major aims of this study were to:

1. Evaluate the initial dosing and management of gentamicin in two Australian tertiary hospitals – private (Mater Health Services, Brisbane) and public (Royal Brisbane and Women's Hospital, Brisbane), serving different patient and demographic groups.

2. Evaluate the ability of nomogram based dosing to achieve a therapeutic AUC as determined using TCIWorks® [12], based on a target range of 70-100 mg/L/hr for AUC.

Methods

Ethics approval was granted by the Human Research Ethics Committees of both the Mater Private and Royal Brisbane and Women's Hospitals. Patients were excluded if they had extensive burns, were below the age of 18, or were diagnosed with cystic fibrosis or endocarditis. Patient demographics and dosing data were collected from each patient's medical record and included: date of birth, sex, age, and height, and Total Body Weight (TBW), indication for therapy, length of therapy and reason for cessation of therapy. Monitoring data included the time of blood collection, serum creatinine and gentamicin concentrations that were obtained from the relevant pathology database. TCIWorks® version 1.0-RC1 (November 2008) was used in all data analysis for the evaluation of gentamicin dosing and the embedded adult population PK model for gentamicin chosen [13].

The dosing and management practices were evaluated using the following methods:

(a) Initial doses of gentamicin were compared to local, peer-reviewed dosing guidelines (based on the Begg nomogram) to evaluate adherence to these guidelines.

(b) The appropriateness of the timing of plasma concentrations

and documentation of the gentamicin administration times in the medication chart.

(c) The management of the plasma concentration.

To evaluate the appropriateness of the timing of sample collection, samples taken outside the 6 to 14 hour post dose window, or with non-documented were considered inappropriate. To evaluate the appropriateness of the prescribed doses of gentamicin, TCIWorks® was used to estimate an AUC for each dose (first and subsequent doses). Where dosing was maintained and multiple AUC's available (taken from the single concentration per dose), an average AUC was determined. A "maintained" dose was classified as two consecutive doses of the same amount. The AUC results were divided into three ranges; supra-therapeutic (> 100 mg.h/L), therapeutic (70 to100 mg.h/L) and sub-therapeutic (<70 mg.h/L).

Patient height was required to determine Lean Body Weight (LBW), which is used in both local guidelines for the estimation of Creatinine Clearance (CrCL) using the Cockcroft-Gault equation and the initial dose. It was presumed that many patients would not have a height documented; therefore if TBW was greater than 80 kg the patients were assigned the population average LBW of 70 kg for males and 60 kg for females [14], for the TCIWorks® calculations only. The calculations were conducted using the lesser of either the total or LBW as previously validated [15]. Where the height was not recorded on the patient's chart a population average of 175 cm (male) and 165 cm (female) was used in TCIWorks® only. When gentamicin concentrations were reported as <0.5 mg/L the concentration recorded in TCIWorks® was 0.3 mg/L; the lower limit of quantification of the assay. As the standard infusion is 30 minutes, the length of infusion was assumed to be 30 minutes unless otherwise specified.

Results

Evaluation of the initial dosing and management of gentamicin

A total of 100 patients were identified in hospital 1 and 61 in hospital 2, with a corresponding 288 and 125 gentamicin concentrations respectively (Table 1). In hospital 1, 97 had their TBW documented, however only 25 had their height recorded. In hospital 2, all 61 patients had their TBW recorded and 35 (57%) had their heights recorded. As seen in table 1, the measured variables matched across both hospitals allowing us to analyze both sites concurrently.

Adherence to local dosing guidelines (Initial dose): Due to a lack of documented heights, only 25/100 (25%) initial doses from hospital 1 and 35/61 (57%) initial doses from hospital 2 could be evaluated when

Variable	Hospital 1	Hospital 2
Females%	40	49
Males %	60	51
Age (years)	55 ± 21	49 ± 20
Height (cm)	175 ± 11	168 ±1 1
Total body weight (kg)	76.5 ± 20	79.2 ± 20.4
Duration of therapy (days)	4 ± 2.7	4 ± 2
Initial dose (mg)	310 ± 74	298 ± 65
Initial dose (mg/kg)	4.2 ± 0.9	3.9 ± 0.9
Total plasma concentrations	288	125

Data presented as number (N) or number ± SD. Hospital 1 is Royal Brisbane and Women's Hospital 2 Mater Private Hospital.

Table 1: Patient demographics and dose data per Hospital, p <0.05 for each variable.

calculated using LBW. In this case, 10 (41%) of initial doses in hospital 1 were consistent with local guidelines (10% of all patients), with the majority of patients being under-dosed. In hospital 2 there were similar results with 18 (52%) of the initial doses matching the guidelines and the remaining 48% under-dosed (29% of all patients).

Appropriateness of the timing of the concentration and documentation of the gentamicin infusion time: Of the 288 gentamicin concentrations obtained in hospital 1, 236 (81%) tests were sampled in accordance with the 6-14 hour post dose window. The remainder were collected outside the window or had insufficient documentation of dose administration times meaning the nomogram should not have been used. In hospital 2, 96 of 125 (77%) concentrations were taken within the desired sampling window.

Overall, a total of 81 (20%) drug concentration tests were disqualified from assessment; 82% were taken at the incorrect time and 18% as infusions times were either inadequately or not documented at all on the medication chart by nursing staff.

The management of the plasma concentration following a dose change
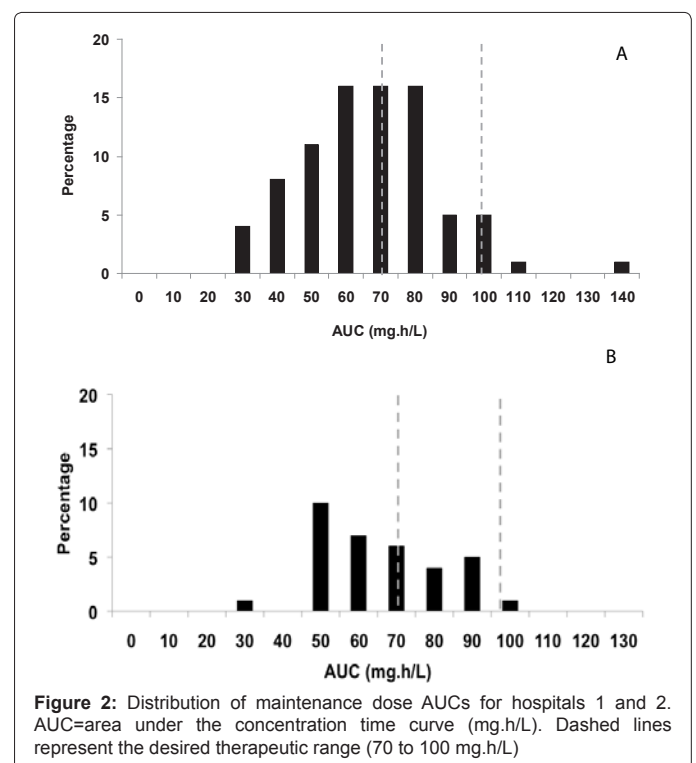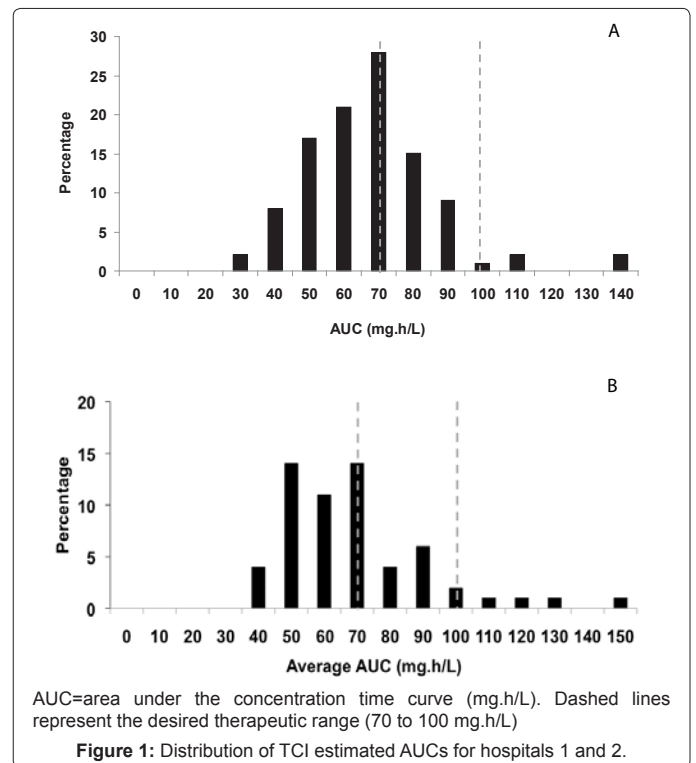
Requests after dosing change: There were a total of 117 dose adjustments made in hospital 1 and 66 in hospital 2. In hospital 1, 105 (90%) and hospital 2, 37 (56%) of dose-adjustments had subsequent gentamicin monitoring appropriately requested in accordance with local guidelines. In hospital 1, 98 of the 117 (84%) dose adjustments, after the initial dose, were based on the reported concentrations, leaving 16% of dose adjustments made without the use of monitoring. Further, 13 (15%) dose adjustments were prescribed despite a 'therapeutic' concentration being attained. This indicated that the treating clinician was probably not aware the concentration was therapeutic or no formal interpretation of the concentration took place. In addition, 15 (18%) of the gentamicin concentrations were sampled outside the 6-14 hour post-dose window, making interpretation difficult. Similar results were seen in hospital 2. Therefore, in total, 34% of doses were prescribed based on inadequate information or inaccurate interpretation of the nomogram, in hospital 1 (23% in Hospital 2).

Evaluation of the accuracy of nomogram based dosing to reach appropriate AUC, as determined using TCIWorks®

A total of 164 concentrations were suitable (because they had all the required documentation for evaluation) to evaluate dose change recommendations: 105 in hospital 1 and 59 in hospital 2. Approximately half (49.5% in hospital 1, 44% in Hospital 2) of the calculated AUCs were within the therapeutic range (70 to 100 mg.h/L). In both hospitals, the majority of the AUCs were sub-therapeutic, indicating under-dosing (Table 2). Similar figures were seen for maintenance dosing (Table 2). Imputed weights and heights were used for TCIWorks® calculations where these were missing.

AUC (mg.h/L)	Hospital 1		Hospital 2	
	Dose adjustment (n=105)	Maintained dose (n=83)	Dose adjustment (n=59)	Maintained Dose (n=34)
>100	4.8%	7.2%	3%	8.5%
70-100	49.5%	45.8%	44%	42.4%
<70	45.7%	47%	53%	49.1%

Table 2: Percentage of AUCs below, within and above the therapeutic range after a dose-adjustment (initial and maintenance).

AUC=area under the concentration time curve (mg.h/L). Dashed lines represent the desired therapeutic range (70 to 100 mg.h/L)

Figure 1: Distribution of TCI estimated AUCs for hospitals 1 and 2.

Figure 2: Distribution of maintenance dose AUCs for hospitals 1 and 2. AUC=area under the concentration time curve (mg.h/L). Dashed lines represent the desired therapeutic range (70 to 100 mg.h/L)

The distribution of the calculated AUCs after dose change is shown in figure 1a (Hospital 1) and figure 1b (Hospital 2) and for maintenance doses in figure 2a and figure 2b.

Discussion

We evaluated the current dosing and management of gentamicin

in patients who were monitored using the 6-14 hour nomogram-based method. We chose two major tertiary hospitals to enable a broader evaluation that was applicable across sites and reflective of current practice. Firstly, the dosing and management practices were compared to local aminoglycoside guidelines which have been based on nomogram methods. The evaluation included the assessment of initial doses, monitoring (concentration) requests and whether the appropriate course of action was applied by the treating clinician. Second, any dose adjustments were evaluated using the Bayesian modelling software, TCIWorks®.

Initial dosing

We found poor adherence to local guidelines with approximately 50% of initial doses less than locally agreed methods. Furthermore, 88% of these were found to be under the calculated doses recommended in the Australian therapeutic guidelines [10]. This indicates that clinicians have little confidence in current dosing strategies for gentamicin, perhaps concerned about potential toxicity, and perhaps considering that 'one dose fits all'. This can affect patient outcomes whereby under-dosing can result in drug resistance and overdosing in nephro- and ototoxicity, which can be irreversible. There is also evidence indicating that therapeutic, bactericidal dosing is essential early in therapy as patient outcomes are better if effective treatment is initiated as early as possible [16].

This study is not the first to find that initial dosing of aminoglycosides is inadequate. Avent et al, recently showed that 60% of neutropenia patients received sub-therapeutic dosing [7]. To ensure an adequate peak concentration a weight based 'loading' dose is recommended. However, the weight-based dose, generally used in current aminoglycoside dose guidelines, may not be suitable. A simulation study has demonstrated that the commonly used dosing based on total body weight (mg/kg based dosing) will only achieve therapeutic concentrations in 60% of subjects [17]. The authors advocate for dosing using Target Concentration Intervention (TCI) principles, as used in TCIWorks® which is estimated to increase the number of patients within the therapeutic range to 90%.

Monitoring

Appropriate monitoring is essential to guide effective ongoing dosing. In this study, approximately 20% of gentamicin concentrations were collected at inappropriate times or had insufficient documentation of dose administration times. Both render clinical interpretation of the concentration difficult and inevitably lead to ineffective dosing. Although the majority of patients in both hospitals had requests made for monitoring post the initial dose, only 36% (Hospital 1) and 48% (Hospital 2) of concentrations were taken in the time frame recommended in local guidelines.

Inefficient monitoring practices equate to a large waste of resources in pathology collection time, analytical costs, interpretation time, and the unknown costs associated with inappropriate dosing, such as length of stay or use of other antimicrobials. Most guidelines recommend a concentration the following day if a patient is not stable or dose adjustment has occurred, to ensure that the dose adjustment has achieved the desired concentration. One advantage of TCIWorks® is that a concentration can be sampled at any time post dose, once a patient specific PK model has been achieved. Barras et al recently demonstrated that only one concentration is required when estimating an AUC using TCIWorks® [18]. In addition, Bayesian methods are much more palatable for pathology and clinical staff who often have to sample and interpret concentrations outside normal working hours.

Dose adjustment

We found that 15% of doses were adjusted without monitoring and many more were adjusted despite the concentration being 'therapeutic'. Overall, approximately half of all dose adjustments were based on inadequate information or inaccurate interpretation of the nomogram. Pharmacy services have traditionally been involved in the interpretation of concentrations in hospitals, although dedicated TDM services are rare. A formal interpretive service, when compared to standard delivery of care has previously been shown to significantly lower mortality for patients with an infection on admission (p=0.023), reduce length of hospital stay and incidence of nephrotoxicity. Further the formal service was cost-effective [19].

Dose evaluation

We observed that when TCIWorks® was used to evaluate the prescribed dose, approximately half of the AUCs were below the therapeutic range in both hospitals. The finding that nomogram based recommendations result in sub-therapeutic concentrations is not new. Studies dating as far back as 1982 have demonstrated that the nomogram method was inadequate, even for patients with normal renal function [1,8, 17, 20]. As a result there is a high probability of sub-therapeutic treatment of infection when using the nomogram monitoring approach. Such studies have led to a recent change in the Australian therapeutic guidelines (Antibiotic) for the dosing and monitoring of aminoglycosides [10]. This latest edition recommends that a nomogram-based method should not be used and that "computerised" Bayesian techniques are preferred. Links are provided to the TCIWorks® and Aladdin® software. Unfortunately, little is provided on the IT and pharmacology strategies hospitals should employ to ensure that the software applications are used appropriately.

Nomogram methods are popular due to their ease of use as they do not require expert knowledge for interpretation and dose-adjustment is usually on a linear basis. However, this 'simple' approach can result in clinically relevant errors such as graphical approximation, with subsequent dosage calculation becoming unreliable the smaller the gentamicin concentration and the more abnormal the renal function. Another major problem is that concentrations are difficult to evaluate when sampled outside the 6-14 hour range, in particular in renally impaired patients or patients with varying PK. The nomogram was proposed from data taken from a cohort of young, healthy adults with normal renal function and therefore provides little relevance to patients with varying PK; typical patients seen in today's hospital environments. The original authors state that the nomogram is not recommended in patients with a CrCL < 0.35 ml/second (21ml/minute)

Limitations

First, only adult patients undergoing once daily treatment were included in this audit. As such, conclusions cannot be extrapolated to patients such as the elderly, young or patients in critical care settings. Second, the therapeutic range used in this study (70 to 100 mg/L/hr) may differ to other hospitals, although it should be noted that this range is wide and a narrower range (as often used in patients with cystic fibrosis) would equate to a greater proportion of patients outside the range. There were also a significant number of patients who had height and weight imputed for TCI calculations. It was of concern for patients having gentamicin therapy that only a very small number of patients had their height recorded. The fact that the height was not measured at any time during the admission is of concern and has quality and safety implications for medical, nursing and pharmacy training and practice.

The additional benefit of obtaining a height is that ideal body weight or LBW can be calculated. We also believe that patients' weight is per se an important prognostic indicator [21-23]. Aminoglycosides are hydrophilic molecules and as such do not distribute into adipose tissue. It is now well known that the distribution and clearance of hydrophilic drugs are best described by LBW rather than TBW, in particular in the obese population [24]. Dosing regimens adjusted by TBW rather than LBW are more likely to result in toxic exposures in obese patients as adipose tissue is included in the dose calculation.

Conclusion

The dosing and monitoring of gentamicin is sub-optimal. The nomogram is an inappropriate dosing tool with a lack of prescribing support for prescribers to adjust dose appropriately. This has the potential to impact on health-costs, patient safety, and the effectiveness of antimicrobial therapy. To improve the practice of TDM we recommend a formal education to pharmacists, nurses and prescribers outlining the medical importance of measuring weight and height need to be implemented to ensure the correct dosing and monitoring of aminoglycosides. Further we recommend a Bayesian approach to the dosing and monitoring of aminoglycosides combined with a proactive interpretative support for prescribers. However this needs to be studied in an appropriately powered RCT.

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