When should gentamicin levels be taken after once daily administration?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

Before using this Q&A, read the disclaimer at www.ukmi.nhs.uk/activities/medicinesQAs/default.asp

Date prepared: 17th June 2013

Background

Gentamicin is the aminoglycoside of choice in the UK. All aminoglycosides are bactericidal and active against some Gram-positive and many Gram-negative organisms (1). These antibiotics should generally only be used for the treatment of serious infections because of their potential toxicity and antimicrobial spectrum (2). Aminoglycosides show concentration-dependent activity (3). Most side effects of the aminoglycosides are dose related. The important side effects are damage to the ear and the kidney (ototoxicity and nephrotoxicity respectively) (1). Ototoxicity is irreversible whereas nephrotoxicity is reversible (4).

The aim of aminoglycoside treatment is to achieve an initial high peak concentration to kill the microorganism but allow the concentration to fall to a low (trough) level between doses to avoid accumulation and side effects (3, 4). Traditionally aminoglycoside antibiotics have been administered as multiple daily dose regimens (2-3 divided doses over 24 hours). To check the peak and trough levels of aminoglycosides were within the target ranges, (for gentamicin: 5-10mg/L and <2mg/L respectively) blood samples were collected shortly after doses were given and just before the next dose was due (1). However, therapeutic drug monitoring showed that multiple daily dosing rarely achieved adequate peaks and often produced high trough levels (3).

Once daily administration has largely superseded multiple daily dose regimens as it is more convenient, cost effective, leads to higher initial antibacterial concentrations at the site of infection and provides adequate serum concentrations (1, 4, 5). Once daily administration has been shown to be at least as effective as multiple daily dosing, and results in less nephrotoxicity (4, 5). It should be noted that once daily administration is not suitable for all patients. Patients with infective endocarditis, extensive burns, or renal impairment (creatinine clearance less than 20mL/minute) should be excluded from this regimen (1, 4). With regards to renal impairment, expert opinion is that patients presenting with a creatinine clearance of less than 60mL/minute should not receive once daily dosing of gentamicin (6).

Monitoring peak and trough plasma concentrations is generally not suitable for once daily gentamicin dosing. This is because the 24-hour trough concentration is unmeasurable in patients with normal renal function using standard aminoglycoside assays. Measurement of the peak concentration is not necessary as giving a larger once daily dose instead of 2-3 smaller doses throughout the day means that the peak concentration will be above 10mg/L (5). If a once daily regimen is used, an alternative method of monitoring gentamicin levels has to be applied.

Answer

The British National Formulary (BNF) recommends a once daily gentamicin dose of 5-7mg/kg per day (1). A variety of methods exist for monitoring gentamicin plasma concentrations after once daily administration. For most patients a predictive nomogram is the method of choice, primarily because of its simplicity. It is not possible to use the nomogram for patients with a very high clearance of aminoglycosides or a high volume of distribution. Examples include those with ascites, burns, cystic fibrosis, or in other conditions such as pregnancy, where the fixed dose assumed in the construction of the nomogram is irrelevant (4). There are some disadvantages to using a nomogram. They are based on average pharmacokinetic parameters and they do not allow the clinician to individualise the dosing regimens according to the type of infection or individual patient needs (7).
**Hartford Nomogram (7mg/kg/day)**

If a once daily dose of 7mg/kg is administered, the ‘Hartford nomogram’ can be used to monitor gentamicin plasma levels (7-9). This nomogram has been tested in a study published in 1995. Over 2,100 patients were treated with aminoglycosides, of which gentamicin accounted for 94%. Patients were excluded from the study if they had renal disease requiring dialysis, enterococcal endocarditis, ascites, burns over more than 20% of the total body surface area or were pregnant. Patients presenting with renal impairment (creatinine clearance less than 60mL/minute) were given the aminoglycoside at a dosing interval of more than 24 hours (9).

If the Hartford nomogram is used a single random blood sample should be taken 6-14 hours after the start of the infusion. If the gentamicin level lies below the 24-hour-line the same daily dose should be given at 24-hour intervals. If the level falls on or above the line the dosing interval should be increased to 36 hours or 48 hours depending on the gentamicin level measured. If the point is near the line the authors suggest selecting the longer dosing interval. If the gentamicin concentration is off (i.e. above) the nomogram between the 6- and 14-hour time points, the scheduled therapy should be stopped and the drug concentration should be monitored to determine the appropriate time for administration of the next dose (i.e. when the concentration is <1mg/L). The authors state that the measurement of gentamicin serum samples is generally not required if the duration of gentamicin treatment is short term unless the patient presents with varying renal function. If the duration of treatment exceeds five days they suggest taking serum levels weekly to monitor therapy (9). In practice however serum levels in different UK hospitals are often taken after the first infusion and then two to three times per week (8).

**Urban-Craig Nomogram (5mg/kg/day)**

If a once daily dose of 5mg/kg is used, the ‘Urban-Craig nomogram’ can be applied to monitor and interpret gentamicin levels (8, 10). This nomogram was published by two American researchers in 1997. Exclusion criteria for its use include patients presenting with a creatinine clearance of less than 20mL/minute, pregnant women, neonates, severe burns, anasarca, cystic fibrosis, meningitis and endocarditis. The authors suggest that the frequency of drug administration should be extended to more than every 24 hours in patients with renal impairment (creatinine clearance less than 60mL/minute).
Using this nomogram, levels should be taken 8-12 hours after the dose. Depending on where the level lies, the dosing interval should be maintained or modified. In contrast to the Hartford nomogram, there is the option to decrease the dosing interval to every 12 hours for patients with unusually low drug levels after dosage. The authors recommend that monitoring of drug concentration is not needed in patients presenting with adequate renal function in whom the expected duration of therapy is under 5 days. It is however recommended to obtain levels in patients at greater risk of drug toxicity or potential for clinical failure. For patients with normal renal function checking the drug level after the first dose can confirm the appropriate dosing interval. If therapy is required for more than 5 days the authors suggest monitoring drug levels weekly and serum creatinine at least every 3 days (10).

Using both nomograms it is essential that the time the gentamicin infusion was started and the time the serum level was taken are documented accurately on the drug chart and on the microbiology request form.

**Summary**
- Once daily dosing of gentamicin has been shown to be at least as effective as and not more toxic than a multiple daily dosing regimen.
- Monitoring peak and trough levels with once daily dosing is generally not suitable.
- For most patients a nomogram is the method of choice in order to confirm or modify dosing intervals.
- For a daily dose of 7mg/kg/day the Hartford nomogram can be used. Gentamicin levels should be taken 6-14 hours after the start of the infusion.
- For a daily dose of 5mg/kg/day the Urban-Craig nomogram can be used. Gentamicin levels should be taken 8-12 hours after the dose.
- It is essential that the time the gentamicin infusion was started and the time the sample was taken are documented accurately.

**Limitations**
This Q&A only looks at adult patients with normal renal function (creatinine clearance above 60mL/minute). Only once daily gentamicin administration is considered. The maximum daily dose and the maximum duration of treatment have not been included. The dose determining weight has not been included. The appropriateness for individual infections and patients has not been investigated. The method of administration has not been included. No critical evaluation of the nomograms has been performed.
References
8. UKMi Discussion Group. Accessed 17/06/2013 via http://list.ecompass.nl/listserv/cgi-bin/wa?A0=MI-UK

Quality Assurance
Prepared by
Mark Cheeseman, East Anglia Medicines Information Service (based on earlier work by Kerstin Weber)

Date this version prepared
17th June 2013

Checked by
Katie Smith, East Anglia Medicines Information Service

Date of check
1st August 2013

Search strategy
Medline: "exp GENTAMICINS" + "DRUG MONITORING" [Limit to: Latest Update and Publication Year 2009-Current]  
Embase: "exp GENTAMICIN" + "exp DRUG MONITORING" [Limit to: Latest Update and Publication Year 2009-Current];  
Cochrane: “gentamicin” + “monitoring”; “aminoglycoside” + “monitoring”; 
NHS Evidence: “gentamicin drug monitoring” [limited to last 3 years]  
In-house database/ resources 
UKMi Discussion Group 
Clinical experts/ professional bodies (Mark Tomlin, Consultant Pharmacist: Critical Care)