REVIEW

ONCE-DAILY AMINOGLYCOSIDE DOSING

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ABSTRACT: The conventional use of aminoglycoside antibiotics has several disadvantages including the need for regular pre- and post-dose assaying and the risks of toxicity. Achieving a therapeutic and non-toxic serum concentration may be difficult in many patients especially those with severe sepsis. Correct timing of doses and assays is essential, but this is often difficult to achieve. Many of these difficulties may be remedied by the use of once daily dosing. This dosing schedule appears to be equally effective as the conventional method and is also less toxic. There are many other advantages including the need for less assays and venepuncture resulting in reduced costs. *(JUMMEC 1996 1(1):17-19)*

KEY WORDS: Aminoglycosides, antibiotic therapy, toxicity, therapeutic monitoring

The Aminoglycoside Antibiotics; Advantages and Disadvantages

The aminoglycosides or more strictly the aminoglycosidic aminocyclitols are a large group of naturally occurring or semisynthetic antimicrobial agents. Streptomycin was the first of these agents to be discovered and was isolated from the soil microorganism *streptomyces griseus* in 1944 (1). Streptomycin revolutionized the treatment of tuberculosis and still remains important in the treatment of this reemerging disease. Kanamycin was the next aminoglycoside to be discovered and was isolated by Japanese workers from another soil organism *Streptomyces kanamyceticus* in 1957 (2). Kanamycin which was used mainly to treat infections caused by Gram-negative organisms has been largely superseded by amikacin, which is a semisynthetic derivative of kanamycin (3). Organisms of the genus *Streptomyces* proved to be a rich source of aminoglycosides and another agent, tobramycin was isolated from *Streptomyces tenebrarius* in 1971(4). Other investigations led to the discovery of aminoglycosides such as gentamicin in 1963 (5), and sisomicin (6), produced by other species of bacteria such as those belonging to the genus *Micromonospora.* Sisomicin has never been widely used and has been replaced by its semisynthetic derivative netilmicin which was first isolated in 1976 (7).

Despite the challenge of alternative antimicrobial agents such as extended-spectrum cepahalosporins and quinolones, gentamicin, netilmicin and amikacin and to a lesser extent tobramycin remain important agents in the treatment of severe sepsis. Unfortunately all drugs have their disadvantages and aminoglycosides can be difficult agents to use effectively and safely. They have a low therapeutic index and may exhibit nephrotoxicity and ototoxicity. Conventionally, they are administered as an initial loading dose, followed by twice or thrice daily maintenance dosing. The aim is to reach a concentration in the patient that is higher than the minimum inhibitory concentration (MIC) of the drug for the infecting organism. A fine balance must be achieved; enough must be given to adequately treat the infection, while at the same time avoiding high and potentially toxic concentrations. It is current practice to measure trough (pre-dose) and peak (post-dose) levels. This practice has evolved for three reasons; to check for a therapeutic concentration, to help avoid toxicity and now increasingly in developed countries for medicolegal reasons. Reappraisal of the conventional assaying of aminoglycosides has led to some interesting observations. Toxicity is more likely in females, the elderly, patients with initially abnormal renal and liver function and bacteraemic patients. However, it is difficult to demonstrate any correlation between resultant toxicity and serum aminoglycoside concentration (8). Despite these findings conventional trough and peak assays should still be performed for patients receiving twice or thrice daily aminoglycosides, if only for medicolegal reasons. Many microbiologist also recognize that toxicity is more likely in patients who receive very long courses of aminoglycosides; this fact is reinforced by the widely referred to British National Formulary which recommends that aminoglycosides should not be given for periods greater than 7 days (9).

Further problems exist with the conventional twice or thrice daily use of aminoglycosides. Studies in Britain and Australia have demonstrated that doses are often not given on time and that assays are often taken at incorrect times and submitted to the laboratory without sufficient information for adequate interpretation (10, 11). Administration of parenteral antibiotics, venepuncture for assays and form-filling are usually the duties of the junior medical staff who seem to face an ever increasing workload. It has been shown that a successful outcome in patients with severe infection is more likely when the peak level is high. Underdosing of patients appears to be a common problem (11), and may occur out of a reluctance to give a sufficiently high dose because of fears of toxicity. In severely ill patients it can be difficult to achieve therapeutic levels with conventional dosing as a result of alterations in the volume of distribution; in one study of critically ill patients attempts to predict the volume of distribution had only a low correlation with actual values when measured in the patients, severely affecting the ability to correctly dose patients (12).

The Post Antibiotic Effect and Once Daily Dosing

Can any changes be made to improve the use of aminoglycosides? The simple answer is yes. Laboratory studies looking at the way that antibiotics kill bacteria have led to a reappraisal in the use of aminoglycosides. It appears that antibiotic concentrations continually maintained above the MIC are not necessary. It is the initial concentration of the antibiotic that is important; the higher the better. After the bacteria are initially exposed to the high concentration of the antibiotic they will continue to die even when the antibiotic concentration falls well below the initial MIC. This phenomenon called the post antibiotic effect (PAE) was first described in 1944 by Bigger who was studying the action of penicillin on staphylococci (13). The PAE has been demonstrated for may different classes of antibiotic and bacteria, but the exact mechanism involved has yet to be explained. Although early workers were able to demonstrate successful treatment of infection using only intermittent doses of antibiotics (14), it is only in recent years that the PAE evolved from just a laboratory curiosity into a well proven clinical application; once-daily aminoglycoside dosing. Instead of dividing the total daily dose of the aminoglycoside into three or two doses, the whole daily total is given as one single dose (e.g. instead of 80 mg tds of gentamicin, 240 mg is given as a single daily dose). This results in a very high peak concentration of the drug, which rapidly falls to a concentration well below the MIC. The bactericidal activity is related to this high peak level and there is no need to attempt to reach a steady state concentration above MIC. There are now several published clinical trials showing that the efficacy is either just as good or better than conventional usage. Fears of toxicity resulting from high peak levels appear to be unfounded with all the trials demonstration reduced nephrotoxicity and reduced or equal ototoxicity when compared with conventional dosing schedules (15, 16, 17, 18, 19, 20, 21). Once-daily dosing has also successfully been used in full term neonates (22), though this practice is still controversial.

The observation of reduced toxicity has been complemented by the experimental data of Verpooten *et al* (23), who studied the renal cortical cell uptake of aminoglycosides. Initial high concentrations of aminoglycosides saturate the uptake mechanism; the overall uptake of the drug is thus much reduced compared to that seen when there is a continual low-level of uptake which occurs during steady-state concentrations achieved using conventional dosing schedules.

The Advantages of Once Daily Dosing

There are many other advantages gained by once-daily dosing, especially to the hard pressed doctors on the wards and the budget of the hospital. It is more convenient for the doctors, nurses and laboratory workers; doses are easier to calculate and there is a guaranteed therapeutic level since the dose is so high. Monitoring of antibiotic concentrations in the blood is still required but the number of assays can be reduced. Peak levels do not need to be measured but trough level specimens should be taken so that dosage intervals may be calculated in patients with poor renal function. Such patients may only require doses every other day or even longer time intervals. An alternative method for estimating the frequency of dosing is by the use of the Hartford nomogram (17); which utilizes a post-dose level taken anytime between six and 14 hours after drug administration. This nomogram was developed in North America and it may be necessary to make some modifications when dealing with an Asian population of patients. Less assaying is also more convenient for doctors, nurses and laboratories; less syringes and needles are required and the use of expensive assay reagents is reduced.

Once daily dosing is now used widely in Europe and North America for the treatment of severe sepsis but there still remain a few groups of patients in whom this dosing schedule in not indicated. These exceptions include patients with endocarditis where high serum aminoglycoside levels are not necessary for effective therapy and treatment may also be lengthy. Other groups where once daily dosing is not indicated include patients with ascites, severe burns, cystic fibrosis and also in pregnancy. The use of once daily dosing in children requires further study before firm recommendations can be made.

With the advent of corporatization, cost-saving alterations to medical practice are bound to meet approval from all levels of hospital management. In conclusion, once daily dosing with aminoglycosides appears to be a good choice for the patients; their infections are treated more effectively with less chance of toxicity and less need for venepuncture for assays.

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