CASE REPORT

Successful Use of Once-Daily Gentamicin

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INTRODUCTION

Aminoglycosides are widely used antibiotics, primarily because of their low level of bacterial resistance, their low cost and their high efficacy. Despite these favourable properties, aminoglycosides are used cautiously. All aminoglycosides share the potential for renal and otovestibular toxicity.[1] A great deal of effort is expended on monitoring aminoglycoside pharmacokinetics in the hope of maintaining therapeutic drug levels but, despite careful attention to dosing regimens, the incidence of nephrotoxicity has not been completely eliminated.[2] There is evidence, however, that pharmacokinetic dosing services may result in cost savings, better therapeutic concentrations, and fewer toxic serum concentrations.[3-6] Once-daily dosing regimens may lower the risk of nephro and ototoxicities while ensuring adequate therapeutic serum concentrations but the acceptable peak and trough levels are still undetermined.[7-12]

The following is a case report of a 46 year-old patient who received her total daily dose of gentamicin once a day and the levels that were achieved. The ability to predict toxicity based on drug levels, as reported in the literature, is also discussed.

CASE

A 46 year-old female, who over the past year had an extended course in hospital, was admitted on April 11, 1993 with cellulitis and necrosis of her left leg stump. In September of 1992, the patient had an aortobifemoral bypass requiring Gortex graft due to a severe claudication of her lower extremity that continued to thrombose. On January 9, 1993 the patient experienced an infected left femoral aneurysm and was admitted for an aneurysm repair and angiography. At this time the graft was clotted off and a left below knee amputation was performed. Two weeks later an above the knee amputation was required due to necrosis of the wound. In February of 1993, the patient was taken to surgery for exploration of the left groin and removal of the Gortex graft. During this admission, the surgical wound grew *Pseudomonas aeruginosa*, sensitive to piperacillin and gentamicin, and the patient was prescribed piperacillin 3g IV q4h and gentamicin 120mg IV q12h. The patient was discharged in March 1993 on ciprofloxacin 750mg po BID x 10 days. One month later the patient was readmitted with cellulitis and necrosis. On examination, the patient was afebrile and in no apparent distress. The patient's stump was warm to palpation with an extended area of cellutitis and a small area of necrotic tissue. The review of systems and serum chemistries were unremarkable. The creatinine clearance, as calculated using the Cockcroft-Gault equation was 73 mL/min and the WBC was 13.5 x 10^9/L. On admission the patient was empirically started on piperacillin 3g IV q4h, gentamicin 120mg IV q12h and cloxacillin 1g IV q4h and the stump was swabbed a day later. The stump grew a heavy growth of *Pseudomonas aeruginosa*, sensitive to piperacillin and gentamicin. Because of the desire to discharge the patient as soon as possible, an attempt was made to change to an oral antibiotic regimen. The patient had been compliant with an oral ciprofloxacin regimen after previous discharge, and thus, it was believed that monotherapy would not be adequate. Ciprofloxacin and gentamicin were chosen. Tobramycin is reserved at our institution for *Pseudomonas* infections known to be resistant to gentamicin, which has not yet been a significant problem with *Pseudomonas aeruginosa*. To facilitate treatment at home, a once

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daily dosing regimen for gentamicin was utilized. The patient was prescribed ciprofloxacin 750mg po BID and gentamicin 360mg IV OD over 30 minutes. The patient was 157 cm (5feet 3 inches) tall and weighed 68kg. Using the equation, 45.5+2.3 (inches over 5 feet)=IBW, the patient's ideal body weight was determined to be about 52.4 kg. Because the patient's actual body weight was more than 30% greater than her ideal body weight, a dosing weight for her was calculated using the equation, DW=0.4 (TBW-IBW)+IBW, and was determined to be 58.6kg. Doses reported in the literature for once-daily aminoglycoside regimens range from 4mg/kg/day to 7mg/kg/day. We chose a starting dose of 6 mg/kg/day.[12-14] Gentamicin levels were drawn and returned at a trough of <0.5 mg/L and a peak of 21.5 mg/L. Pre and post levels were drawn 15 minutes before and 30 minutes after the end of the third infusion to ensure steady state was achieved. From the gentamicin levels received, the following pharmacokinetic parameters were calculated: $k_e=(\ln C_1-\ln C_2)/t=0.165hr^{-1}$; $t_{1/2}=0.693/k_e=4.2hr$; $V_D=(Dose/^{t'})/k_e[(1-e^{-kt'})/(C_{post}-C_{pre}e^{-kt'})]$ =16L. The patient was discharged 12 days after initiating once-daily gentamicin therapy with a nicely healing wound, a WBC of $8.3x10^9$/ L and a creatinine clearance of 60 mL/min. The patient's renal function would appear to have decreased when looking at the change in creatinine clearance from admission to discharge but on admission, the patient's creatinine clearance was unusually high for her. Creatinine clearance calculated from September 1992 and January 1993 were 60ml/min and 56ml/min, respectively. On discharge, and at an outpatient visit on May 13, 1993, no toxicity was detected. The patient did not complain of hearing loss or vestibular problems although no audiograms were performed. The patient's renal function at this time was 62ml/min. The 12 day delay in discharge was due to complications unrelated to her surgery.

DISCUSSION

The concept of a single daily dose as a means of reducing aminoglycoside toxicity while ensuring adequate therapeutic serum concentrations has been studied for the past decade.[15] Once-daily dosing appears to be no more toxic than the conventional regimen.[12] The pathogenesis of aminoglycosides nephrotoxicity is closely related to the renal handling, which includes an intracellular accumulation of the drug in the renal cortex. A lower tissue accumulation was found with less frequent dosing.[16] Ototoxic side effects from aminoglycosides may result in permanent hearing loss or vestibular dysfunction. The penetration of these drugs into the inner ear is postulated to be the source of ototoxicity. In guinea pigs, discontinuous administration significantly lowers the drug concentration in the inner ear as compared with continuous administration and thus single daily doses of aminoglycosides may decrease the inner ear drug concentration further by allowing a wash out period.[12,17] While lower renal cortex and inner ear accumulation of aminoglycosides may decrease the nephrotoxicity and ototoxicity respectively, once-daily dosing was; nevertheless, equally effective as other dosing regimens. Aminoglycosides kill bacteria in a dose-dependent or concentration-dependent manner and exhibit a post antibiotic effect that correlates with the extent of peak concentration above the minimal inhibitory concentration of the infecting organism.[12,18] Aminoglycosides eradicate bacteria most effectively when their concentration is 10-12 times the MIC.[19,20]

Clinical studies are needed to determine new therapeutic ranges to follow with these regimens. Using once-daily dosing, peak and trough levels will always be outside of the traditionally accepted range. When monitoring once-daily gentamicin levels, trough levels in most cases need only be monitored. In certain patient subpopulations with severe infections and high aminoglycoside clearances, monitoring of peaks may still be warranted to ensure adequate levels. As trough levels approach 2mg/L one could assume that accumulation is occurring. Peak levels in the range of 16-24 mg/L can be expected but they appear to cause no problems.[21]

In most studies to date, neutropenic patients have been excluded. Additional evidence of the influence of the host immune system on *in-vivo* post antibiotic effect and dosing interval is needed. Patients who are immune compromised rely heavily on the presence of antibiotics to combat infections and repeated exposure to serum concentrations below the MIC may be detrimental.[22] Caution should be exercised in using once-daily aminoglycosides in patients with impaired renal function. In patients with an endogenous creatinine clearance of 20mL/min or less, an every 48 hour regimen could result, especially with *Pseudomonas aeruginosa*, in a protracted period when the concentration in serum is below the MIC and the post antibiotic effect is no longer operative.[21]

Although no comparative pharmaceoconomic evaluations

have been published to date, it stands to reason that once-daily regimens would result in decreased administration costs and decreased cost associated with drug levels.

Retrospectively, assessing this patient's baseline hearing via audiometry and intermittently during therapy would have been useful; however, subjective assessment revealed no hearing loss. Only one set of levels were performed on this patient after three days of therapy. Although she was most certainly at steady state and her pharmacokinetic indices did not change, it would have been prudent to obtain at least one more set for confirmation of therapeutic, non-toxic levels. Despite the apparent benefits of once-daily aminoglycoside dosing, this strategy has not been widely accepted in North America.

In summary, once-daily dosing of aminoglycosides appears to decrease or have no influence on the risk of toxicity while still maintaining antibacterial efficacy and thus deserves further study.

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