Once-daily dosing regimen for aminoglycoside plus betalactam combination therapy of serious lower respiratory tract infections

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Once-Daily Dosing Regimen for Aminoglycoside plus Betalactam Combination Therapy of Serious Lower Respiratory Tract Infections

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Summary

Aminoglycosides are important antibacterial agents for treatment of serious gram-negative bacillary infections including lower respiratory tract infection. Once-daily aminoglycosides result in higher peak and lower trough plasma concentrations than conventional multiple daily dosing regimens; once-daily aminoglycoside therapy is equally effective, generally less toxic and much less expensive and therefore this regimen is more and more frequently used for treatment of suspected or confirmed gram-negative bacillary infections and of febrile episodes in neutropenic patients, in particular in combination with an appropriate betalactam antibiotic. Despite the lack of studies on this topic, once-daily aminoglycosides in combination with a betalactam agent can be used in subjects with lower respiratory tract infection, including patients with cystic fibrosis, in which tobramycin appears to be the aminoglycoside antibiotic of choice.

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INTRODUCTION

Aminoglycosides have been available for many years and continue to be widely used for treatment of severe infections because of their favorable microbiological characteristics, such as a broad antimicrobial spectrum including both gram-positive cocci and aerobic gram-negative bacilli (AGNB), high bactericidal activity, mainly directed against AGNB and synergic with betalactam antibiotics, and a relatively rare emergence of resistance [1-3].

However, a negative feature is represented by the nephro- and ototoxicity of these molecules, which makes drug monitoring essential to maintain both therapeutic and non-toxic plasma concentrations [4]. Monitoring is also required to avoid the opposite effect due to the risk of renal and otovestibular toxicity: in fact, approximately one-third of patients treated with standard doses of gentamicin have peak serum levels below the therapeutic range [5]. The increased economic costs deriving from the onset of side effects or from the need of drug monitoring can represent a valid reason to change the therapeutic choice.

AMINOGLYCOSIDE DOSING REGIMENS: ONCE-DAILY DOSE VERSUS DIVIDED DOSES

The administration of aminoglycosides in two or three divided doses was originally

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devised to avoid excessively high peak serum levels - believed as toxic - and to maintain serum concentrations above the MIC against infecting microorganisms throughout the day [6]. However, it was soon noted that the risk of ototoxicity would be minimized with lower trough concentrations [7] and that higher peak levels would allow a greater penetration of the drug into infected tissues and result in an optimal therapeutic effect [8]. As early as 1974 once-daily (OD) dosing regimens of aminoglycosides seemed to be efficacious [9] and subsequently many other studies showed that less frequent administration was associated with less toxicity and with unaffected efficacy [10]. Therefore, the administration of aminoglycosides once-a-day rather than in divided doses, still only rarely put into practice [11], has recently been proposed both to improve efficacy and to reduce toxicity of aminoglycoside antibiotics [12], based on findings summarized in *Table 1*.

TABLE 1 - *Rationale for use of aminoglycosides once-a-day (modified from [11]).*

Microbiological advantages
enhanced antibacterial activity
prolonged post-antibiotic effect
more rapid bacterial killing
reduced risk of adaptive phenotypic bacterial resistance
increased synergism with betalactam antibiotics
Pharmacokinetic advantages
little reduction in the volume of distribution
higher peak serum concentrations
larger area under the concentration-time curve (AUC)
lower trough serum concentrations
Toxicologic advantages (deriving from lower trough serum levels)
lower renal cortical concentrations
lower inner ear concentrations
Clinical advantages (deriving from higher serum concentration and larger AUC)
efficacy similar to that of multiple-daily doses
Economic advantages
lower costs

In particular, it has been noted that a significantly improved clinical response was associated with peak serum concentrations of 5-7 mg/L or more for gentamicin and tobramycin and of 20-28 mg/L or more for amikacin [8,14-16], and that a significantly lower toxicity was caused by trough serum levels of 5 mg/L or less for amikacin and of 2 mg/L or less for other aminoglycosides [17]. These trough concentration limits, established for multiple-daily (MD) dosing regimens, may not apply to OD doses; therefore, trough limits for OD aminoglycosides have been recently considered to be 1 mg/L for gentamicin and tobramycin and 3 mg/L for amikacin and netilmicin [18].

Last but not least, OD dosing regimens might also allow the frequency of measuring the aminoglycoside plasma concentrations to be reduced since high peak and low trough levels are more likely to be reached with these regimens, with important cost savings. Further economy occurs because OD aminoglycoside schedules consume fewer disposables (i.e., syringes, intravenous bags and lines, infusion bottles) [19] and because the incidence of nephrotoxicity - known to carry considerable additional costs [20] - is generally reduced.

ONCE-DAILY AMINOGLYCOSIDE THERAPY IN SYSTEMIC INFECTIONS

To date, OD aminoglycosides have been used in the treatment of serious gram-negative bacillary infections, intra-abdominal infections, and pelvic inflammatory disease, generally in combination with a betalactam antibiotic (plus metronidazole or tinidazole in the case of intra-abdominal infections). Clinical trials comparing OD and MD aminoglycoside therapies indicated the use of amikacin 15 mg/kg q24h or 7.5 mg/kg q12h [21-24], gentamicin 4 mg/kg q24h or 1.33 mg/kg q8h [25], netilmicin 3.9-6.6 mg/kg q24h or 1.3-2.2 mg/kg q8h [6,26-31], and tobramycin 5 mg/kg q24h or 3.2 mg/kg q8h [32].

The results of these studies can be summarized as follows:

1) Significantly higher peak levels, larger AUC, and lower trough concentrations are obtained with OD aminoglycosides [2].
2) Only two studies showed a statistically better clinical response with OD than with MD regimen; Raz and colleagues found a significantly greater clinical cure rate with OD gentamicin (87.5% vs 69.2%) [33] and Giamarellou et al. with OD amikacin (97% vs 76.6%) [24] in the treatment of various gram-negative infections, whereas the other

studies evidenced no significant differences.

3) The vast majority of authors generally evidenced less toxicity with OD aminoglycosides but not at significant levels except for a few studies:

A) Nephrotoxicity, as measured by an increase in the serum creatinine concentration of at least 45 mmol/L (or 0.5 mg/dl) above the initial value [34], was statistically less frequent with OD gentamicin in the study by Prins et al. (5% versus 24% with MD doses, p=0.016) [25]; moreover, a significantly delayed onset of the increase in the serum creatinine concentration was observed in two trials with OD amikacin and netilmicin [31,35]. Nephrotoxicity, as measured by an increased urinary excretion of phospholipids, was significantly reduced in two further studies using both amikacin and netilmicin [36,37].

B) It is very difficult to assess aminoglycoside-related ototoxicity because audiometry is not always possible and, if so, the range of frequencies is generally limited to 8,000 Hz, whereas aminoglycosides primarily affect high tone frequency [38]; only two trials using high frequency audiometry evidenced a significantly less ototoxicity with OD than with MD dosing regimens [28,37].

In recent years, there has been increasing interest in the use of OD aminoglycosides for treatment of febrile episodes in neutropenic patients in combination with a semi-synthetic penicillin or a third-generation cephalosporin. Some comparative and non-comparative studies were carried out on subjects with a neutrophil count <1,000/mm^3 determined by both the underlying disease (leukemia, lymphoma, aplastic anemia, bone marrow transplant, solid tumor) and the concomitant cytotoxic and immunosuppressive therapies. Two non-comparative trials found the combination of amikacin plus ceftriaxone (at the OD dosing regimen of 22 mg/kg and 2 g, respectively) to be effective in approximately 60% of febrile episodes after producing high peak levels (i.e., 60 mg/L for amikacin and 140 mg/L for ceftriaxone) [39,40]. Better success rates (70-95%) were provided by a study using tobramycin 5 mg/kg OD plus ceftazidime 1-2 g q8h [41]. Finally, two clinical trials compared OD amikacin (20 mg/kg q24h) plus ceftriaxone (2 g q24h) with MD amikacin (6.7 mg/kg q8h) plus ceftazidime (2 g q8h) [35], and netilmicin 6 mg/kg q24h with netilmicin 2 mg/kg q8h (both in combination with piperacillin 4 g q8h, azlocillin 5 g q8h, or cefotaxime or ceftazidime 2 g q8h) [42] showing much higher peak concentrations with the OD aminoglycoside therapy and a similar clinical success rate with each regimen, i.e. approximately 70%.

It can be concluded that OD aminoglycosides result in higher peak and lower trough plasma levels with optimization of pharmacodynamic properties and without increasing toxic reactions. The consequences are that OD aminoglycoside therapy of systemic infections is equally effective as, generally less toxic, and much less expensive than conventional MD schedules.

ONCE-DAILY AMINOGLYCOSIDE THERAPY IN LOWER RESPIRATORY TRACT INFECTIONS

Betalactam antibiotics are generally the drugs of choice for the empiric treatment of both community and nosocomial bacterial lower respiratory tract infections (LRTIs) because of several characteristics such as: a broad antimicrobial spectrum, high bactericidal activity, good penetration into the respiratory tract and low toxicity. In particular, semi-synthetic penicillins such as mezlocillin, piperacillin or ticarcillin, and third-generation cephalosporins such as cefotaxime, ceftazidime, or ceftriaxone, are most used because of their excellent activity against the prevalent agents of LRTI, i.e. pneumococcus, *Haemophilus influenzae*, and AGNB [1]. Among these molecules, ceftriaxone has the advantage of possessing a prolonged half-life of approximately 8 hours which allows a OD dosing regimen [43].

Aminoglycosides alone do not generally play a role in the therapy of pneumonia because of their poor penetration into respiratory tract secretions [44]; however, their high intrinsic antibacterial activity and their synergic effect with betalactams make combinations of these two antibiotic classes appropriate for therapy of severe infection such as LRTI in "difficult" subjects (hospitalized, elderly, or immunocompromised hosts). In this case, it is of the greatest importance that a peak serum level of 7 mg/L

or more for gentamicin and tobramycin and of 28 mg/L or more for amikacin is achieved to obtain a significantly improved therapeutic outcome [45].

The OD dosing regimen could be a new, cost-effective mode of aminoglycoside administration even in the treatment of LRTI. The poor results obtained with this regimen in animal models of pneumonia could be abolished with the combination of an appropriate betalactam agent [46] such as a broad-spectrum cephalosporin (cefotaxime, ceftriaxone) or an antipseudomonal molecule (ceftazidime, acylureido-penicillins).

To date, only one specific trial on OD aminoglycosides in the treatment of LRTI has been published where netilmicin alone intramuscularly at 300 mg OD was compared with the same drug at 150 mg bid for 5-7 days in 106 evaluable patients with either pneumonia or acute exacerbation of chronic obstructive pulmonary disease (COPD). The results concerning efficacy and safety were comparable between the two treatment groups and are summarized in *Table 2* [47].

TABLE 2 - *Clinical, bacteriological, and toxicological results of treatment with netilmicin either as 150 mg twice-daily (TD) or 300 mg once-daily (OD) in LRTI (from [47], modified).*

	OD (%)	TD (%)	p value
Clinical response	92.2	89.2	>0.5
Bacteriological eradication	87.8	75.0	>0.1
Toxicity	0	0	-

The vast majority of studies on OD aminoglycosides in systemic infections included some hundreds of patients with pneumonia or COPD treated with the aminoglycoside antibiotic alone [24,25] or in combination with a betalactam agent [6,21,22,31,35]; however, the results of the treatment per site of infection were not taken into account.

One trial evidenced a poor response rate to both OD (38%) and MD (46%) netilmicin plus an antipseudomonal betalactam agent (azlocillin, piperacillin, or ceftazidime) in neutropenic subjects with LRTI [42]. This was not surprising because the type of infection and the severity of neutropenia are shown to have a fundamental prognostic significance for the response to antibiotic therapy in these types of patient: in particular, the presence of either bacteremia or pneumonia and a small or slow granulocyte recovery is associated with a poorer prognosis [48]. Moreover, *Pseudomonas aeruginosa*, against which netilmicin is not the most active aminoglycoside agent, causes important morbidity and mortality in these patients [49].

The combination of an aminoglycoside antibiotic plus an antipseudomonal betalactam agent is the treatment of choice for pulmonary infection in patients with cystic fibrosis (CF) [50]. However, some problems could modify or limit the use of aminoglycosides in this field: for example, subjects with CF have been shown to have altered pharmacokinetics of aminoglycosides (i.e., an increased volume of distribution and an enhanced elimination) [51], so that the efficacy of the antibiotic therapy may be diminished.

Among aminoglycosides, tobramycin has the greatest penetration capacity into bronchial secretions [44] and a high activity against *P.aeruginosa* [52] - a major pathogen in CF patients. For the above mentioned reasons, tobramycin is the antibiotic of choice in these subjects.

Two studies have been carried out using OD tobramycin in young patients with CF and acute pulmonary exacerbations; the dosing regimens were 11 mg/kg/day by constant iv infusion and 9 or 15 mg/kg OD by iv injection over 20 minutes in the former [53], 3.2 mg/kg q8h and 5 mg/kg q24h (plus an anti-pseudomonal betalactam antibiotic with both regimens) in the latter [32]. The results were: a) a significantly higher peak serum level with the OD tobramycin regimen; b) no significant differences on both clinical and toxicological grounds. Given that the best responses to tobramycin therapy occur in CF patients with the highest sputum concentrations of the drug correlating with peak plasma values [54], it appears that OD tobramycin in combination with an appropriate betalactam agent may represent a valid therapeutic option even in CF subjects.

CONCLUSION

Aminoglycosides are important antibacterial agents for treatment of serious infections caused by AGNB; evidence suggests that high

peak plasma levels must be achieved early in the course of therapy if these drugs are to be effective, but prolonged high trough concentrations may be nephro- and ototoxic. An OD aminoglycoside dosing regimen results in higher peak and lower trough plasma levels with optimization of pharmacodynamic properties and without increasing toxic reactions; the consequences are that OD aminoglycoside therapy is equally effective as, generally less toxic, and much less expensive than conventional MD regimens. These are the reasons for which OD aminoglycosides are more and more frequently used for treatment of suspected or confirmed gram-negative bacillary infections and of febrile episodes in neutropenic patients, in particular in combination with an appropriate betalactam antibiotic such as a semi-synthetic penicillin or a third-generation cephalosporin. Very few data are available on the administration of OD aminoglycosides in patients with LRTI, but it may be presumed that in combination with a betalactam agent they are effective even in this field. Tobramycin, which possesses a good penetration capacity into bronchial secretions and high activity against *P.aeruginosa*, may be used once-a-day in combination with an antipseudomonal betalactam agent in CF patients. It can be concluded that OD aminoglycoside therapy is recommended to ensure a savings, both in terms of economic costs and of morbidity, the latter resulting directly from infection and, more frequently, indirectly from drug toxicity.

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