Once-daily dosing of aminoglycosides

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OBJECTIVE: To review the pharmacodynamic rationale for once-daily dosing of aminoglycosides and to summarize the results of comparative trials in animals and humans.
DATA SOURCES: Published articles on the pharmacodynamics of aminoglycosides and those comparing the therapeutic efficacy and toxicity of once-daily administration with more frequent dosing regimens.
DATA SELECTION: Fourteen randomized studies in infected patients that compared the efficacy and toxicity of once-daily aminoglycoside dosing with twice- or thrice-daily dosing regimens were available for review. Ten studies comparing the efficacy and toxicity of different aminoglycoside dosing regimens in animal models were also reviewed.
DATA EXTRACTION: Frequency of clinical response, nephrotoxicity and ototoxicity with each dosing regimen were compared graphically and by χ^2 for statistical significance ($P<0.05$).
DATA SYNTHESIS: Once-daily dosing was consistently less toxic than more frequent dosing in animals. When human pharmacokinetics were simulated in animals, efficacy of once-daily dosing was similar or enhanced over more frequent dosing regimens. Once-daily dosing in patients, compared with twice- or thrice-daily administration, was statistically more effective in two studies, less nephrotoxic in six studies, and less ototoxic in one study. Similar efficacy and toxicity were observed in all the other studies.
CONCLUSIONS: Once-daily dosing of aminoglycosides has the potential to enhance efficacy, reduce toxicity and lower administration costs for this drug class. The once-daily dosing regimen deserves serious consideration for routine use of the aminoglycosides.

Key Words: *Aminoglycosides, Dosing regimen, Pharmacodynamics, Pharmacokinetics*

Posologie uniquotidienne d'aminoglycosides

OBJECTIFS : Passer en revue les bases pharmacodynamiques de l'administration uniquotidienne d'aminoglycosides et résumer les résultats d'essais comparatifs menés chez les animaux et chez les humains.
SOURCE DES DONNÉES : Articles publiés sur la pharmacodynamie des aminoglycosides et articles comparatifs sur l'efficacité thérapeutique et la toxicité liées à une administration uniquotidienne par rapport à des schémas posologiques plus fréquents.
SÉLECTION DES DONNÉES : Quatorze études randomisées, menées auprès de patients infectés, et qui comparaient l'efficacité et la toxicité d'aminoglycosides administrés une fois par jour et avec celles de schémas thérapeutiques b.i.d. ou t.i.d., étaient disponibles aux fins de cette revue d'utilisation. Dix études comparant l'efficacité, la toxicité de différents schémas posologiques d'aminoglycosides dans des modèles animaux ont également été passées en revue.
EXTRACTION DES DONNÉES : La fréquence de la réponse clinique et la néphrotoxicité et l'ototoxicité accompagnant chaque schéma posologique ont été comparées graphiquement et à l'aide du χ^2 pour en évaluer la portée statistique ($P<0,05$).
SYNTHÈSE DES DONNÉES : La posologie uniquotidienne s'est révélée constamment moins toxique que les

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posologies plus fréquentes chez les animaux. Lorsque la pharmacocinétique humaine a été simulée dans un modèle animal, l'efficacité de la posologie uniquotidienne s'est révélée semblable ou meilleure par rapport aux schémas d'administration pluriquotidienne. L'administration uniquotidienne chez les patients, en comparaison avec l'administration b.i.d. ou t.i.d., s'est révélée statistiquement plus efficace dans deux études, moins néphrotoxique dans six études et moins ototoxique dans une étude. Une efficacité et une toxicité semblables ont été observées dans toutes les autres études.

Conclusions : La posologie uniquotidienne des aminoglycosides peut améliorer l'efficacité, réduire la toxicité et diminuer les coûts d'administration de cette classe de médicaments. Les schémas posologiques uniquotidiens méritent qu'on les envisage sérieusement dans l'emploi courant des aminoglycosides.

THE AMINOGLYCOSIDES CONTINUE TO BE WIDELY USED FOR treating severe infections despite their narrow therapeutic index and the availability of other less toxic antimicrobials. Most of this use is due to rapid bactericidal activity against Gram-negative bacilli, synergism with beta-lactam antibiotics and low cost. More recent experimental data suggest that once-daily dosing of the aminoglycosides may improve efficacy and decrease toxicity (1,2). This review discusses the pharmacodynamic rationale for this dosing regimen and summarizes the results of therapeutic trials in both animals and humans.

TABLE 1
Impact of dosing regimen on renal cortical concentrations of aminoglycosides in humans

Drug	Tissue levels (μg/g)			
	Continuous infusion	Every 8 h (x3)	Every 12 h (x2)	Single-dose
Amikacin	168	–	142	115
Gentamicin	158	–	–	103
Netilmicin	179	–	–	137
Tobramycin	106	76	–	69

Based on references 18 and 19

PHARMACODYNAMIC RATIONALE

The pharmacodynamic characteristics of the aminoglycosides, both in terms of efficacy and toxicity, explain why once-daily administration of these agents could be the optimal dosing regimen. Aminoglycosides exhibit concentration-dependent bactericidal activity and produce prolonged postantibiotic effects against susceptible organisms (3-5). High concentrations of these drugs are expected to produce more rapid and extensive bacterial killing than lower levels. Furthermore, the postantibiotic effect would protect against bacterial regrowth when serum and tissue concentrations fall below inhibitory levels. Thus, one would predict that the magnitude of the peak serum concentration or the area under the concentration-versus-time curve (AUC) would be the important determinants of efficacy for these drugs.

Experimental studies in murine pneumonia and thigh infection models have evaluated a large number of different dosing regimens to determine which pharmacokinetic parameter best correlates with therapeutic efficacy. With the aminoglycosides, AUC and/or peak level were the major determinants for efficacy (6-8). Studies by Moore et al (9) in patients with a variety of Gram-negative bacillary infections have demonstrated that clinical response to the aminoglycosides is dependent on the ratio of peak level to the minimum inhibitory concentration (MIC) of the infecting pathogen. Since they could not accurately calculate the AUC for each patient, we do not know if the magnitude of the AUC:MIC ratio also correlated with efficacy. To obtain a clinical response of 90%, a peak level:MIC ratio of 8:1 to 10:1 was required. However, some Gram-negative bacilli, such as *Pseudomonas aeruginosa*, are still considered susceptible despite high MICs in the range of 1 to 4 mg/L. It would be very difficult to obtain peak level:MIC ratios of 8:1 to 10:1 for these organisms with standard thrice-daily dosing of the aminoglycosides. For example, eight-hourly dosing of gentamicin at 1.7 mg/kg would produce serum concentrations of approximately 6.7 mg/L, which is only 1.7-fold higher than a MIC of 4 mg/L. On the other hand, once-daily administration of the entire daily amount of drug would increase peak level:MIC ratios about threefold and increase the likelihood of reaching peak levels that were eight to 10 times the MIC. Levels of this magnitude have also been shown in vitro to eliminate the emergence of drug-resistant populations (10).

Another reason for administrating the aminoglycosides once daily is the first exposure effect (11,12). Initial exposure of bacteria to the aminoglycosides down-regulates subsequent uptake of the drug. During this period of down-regulation, bacteria exhibit decreased killing and shorter postantibiotic effects. Since the first exposure effect lasts for several hours, once-daily dosing of the aminoglycosides allows for this effect to dissipate completely between doses.

Once-daily administration of the aminoglycosides will result in prolonged periods of time during which serum concentrations are below the MIC of the infecting pathogen. Most in vitro and in vivo studies with aminoglycosides have exhibited postantibiotic effects of only 1 to 7 h duration (4,8,13,14). However, in vivo studies in nonneutropenic animals or with simulation of human pharmacokinetics in neutropenic animals have resulted in postantibiotic effects of 9 to 15 h (8,14). These durations are clearly long enough to support a once-daily dosing regimen.

TABLE 2
Comparative studies with once-daily dosing of aminoglycosides

Number of studies	Number of patients	Infections	Concomitant drugs
1	52*	Cystic fibrosis	None
3	190	Mixed infections and bacteremia	None
2	78	Pelvic inflammatory disease	Tinidazole
2	152	Abdominal infections	Metronidazole
5	670	Mixed infections and bacteremia	Various beta-lactams
	132*		
1	455	Neutropenic fever, infection and bacteremia	Ceftriaxone, ceftazidime
	239*		

**Pediatric patients. Based on data from references 25,29-40*

In regards to toxicity, one of the first steps in the uptake of aminoglycosides into sites of toxicity is their binding to the brush borders of renal cells and to the cochlear and vestibular membranes. Binding to these membranes demonstrates saturable kinetics. As a result, uptake of aminoglycosides is more efficient with low sustained concentrations than with high intermittent levels (15-17). This has been demonstrated in patients requiring nephrectomy for treatment of malignancy (18,19). The same total amount of aminoglycoside was administered by several different regimens for 24 h before nephrectomy. The mean drug concentrations obtained in kidney cortex of these patients are summarized in Table 1. Levels were significantly lower when the drug was administered as a single dose rather than as a continuous infusion. Twice- or thrice-daily dosing exhibited intermediate concentrations. Thus, the potential to reduce toxicity is a major attraction of the once-daily dosing regimen.

THERAPEUTIC STUDIES IN ANIMALS

Once-daily dosing of aminoglycosides has been evaluated in a variety of animal models. These studies have consistently shown a lower incidence of both nephro- and ototoxicity with once-daily administration than with dosing every 8 h or continuous infusion (20-25). On the other hand, efficacy studies have produced conflicting results. Most studies demonstrating similar or enhanced efficacy with once-daily dosing compared with more frequent dosing have been in medium-sized or nonneutropenic animals (21,25,26). Most studies showing less efficacy with once-daily administration than with more frequent dosing have used small rodents or neutropenic animals (6-8,27,28). Much of this difference could be explained by the more rapid half-life of aminoglycosides in small rodents compared with medium-sized animals. A rapid half-life would require a very long postantibiotic effect to maintain efficacy with once-daily dosing of the drug. Since the presence of neutrophils tends to double the duration of the in vivo postantibiotic effect, this could contribute to the efficacy of once-daily dosing in nonneutropenic animals.

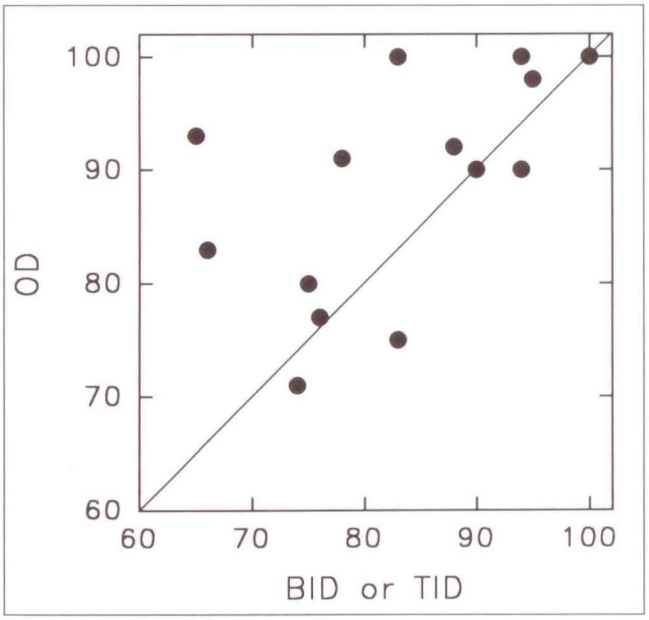

Figure 1) *Percentage clinical efficacy of once-daily (OD) versus twice-daily (BID) or thrice-daily (TID) dosing of aminoglycosides in 14 clinical trials*

Studies in my own laboratory were designed to determine the impact of human pharmacokinetics on the efficacy of once-daily dosing in neutropenic mice (8). Human pharmacokinetics were simulated in mice by inducing renal impairment. These studies clearly demonstrated equal or enhanced efficacy with once-daily dosing of amikacin compared with twice- or thrice-daily administration of the drug. This suggests that the low efficacy with once-daily dosing of aminoglycosides in some animal models is due to the rapid elimination of these drugs in small animals.

CLINICAL TRIALS IN HUMANS

Once-daily dosing of aminoglycosides has now been evaluated in 14 comparative trials involving almost 2000 patients (25,29-40). A summary of the number of patients, the infections treated and concomitant drugs is shown in Table 2. Most of the patients were adults, with about 21% in the pediatric age group. Approxi-

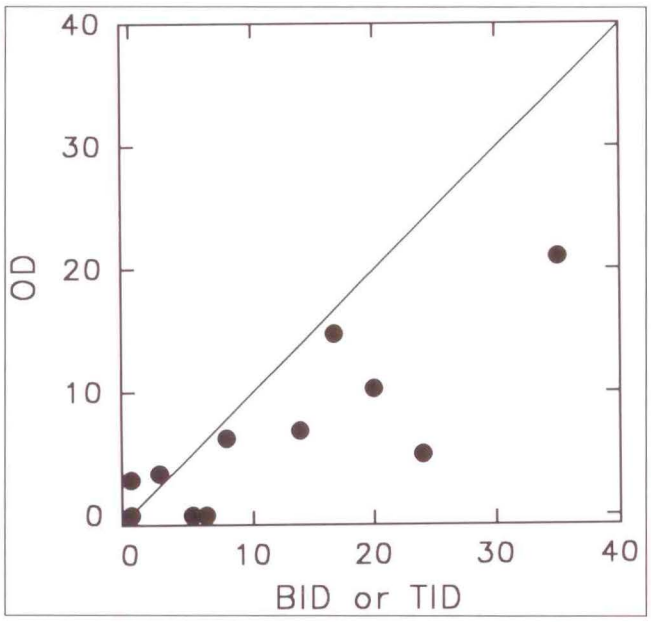

Figure 2) *Percentage nephrotoxicity of once-daily (OD) versus twice-daily (BID) or thrice-daily (TID) dosing of aminoglycosides in 14 clinical trials*

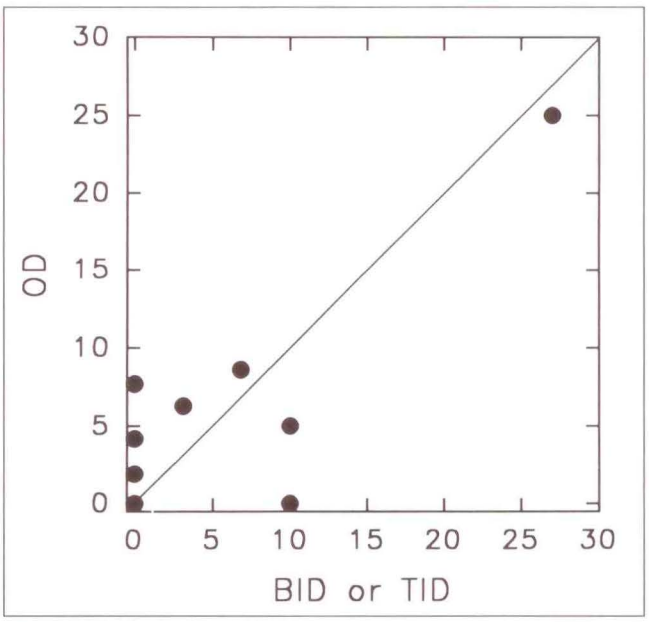

Figure 3) *Percentage ototoxicity of once-daily (OD) versus twice-daily (BID) or thrice-daily (TID) dosing of aminoglycosides in nine clinical trials*

TABLE 3
Incidence and onset of nephrotoxicity with once-daily and multiple daily doses of aminoglycosides

Parameter	Netilmicin		Amikacin	
	Single dose	Multiple dose	Single dose	Multiple dose
Patients	61	66	351	345
Nephrotoxicity	9 (15%)	11 (17%	12 (3%)	8 (2%)
Median days to onset	12 (7-17)	9 (6-15)	10 (7-14)	7 (4-11)

Based on data from references 33 and 40

mately a third of the patients was neutropenic. The severity of the infections varied from pelvic inflammatory disease to severe Gram-negative bacteremia. Eight of the studies used an aminoglycoside alone for activity against aerobic Gram-negative bacteria, while six used aminoglycoside-beta-lactam combinations.

The efficacy in these studies of once-daily dosing versus twice- or thrice-daily administration of the aminoglycoside is illustrated in Figure 1. The diagonal line reflects equal efficacy with both dosing regimens. Points to the left of the diagonal line denote studies in which the percentage of clinical response was higher with once-daily dosing than with the more frequent dosing regimens. The opposite applies to those points to the right of the diagonal line. In general, the efficacy of aminoglycosides administered by different dosing regimens was similar. Only three studies had lower efficacy results with once-daily dosing than with twice- or thrice-daily dosing. However, these differences were small, and none of them were statistically significant. On the other hand, two of the eight studies showing a higher percentage of clinical efficacy with once-daily dosing over more frequent dosing regimens were statistically significant (30,38).

A comparison of the incidence of nephrotoxicity with the different dosing regimens is illustrated in a similar manner in Figure 2. Several studies did not observe any nephrotoxicity and are represented by a single point in Figure 2. Although the general trend is for a lower incidence of nephrotoxicity with once-daily administration than with more frequent dosing regimens, only two of the studies showed differences that were statistically significant (38,39). However, two additional studies showed a statistically smaller increase in urinary phospholipid excretion, a sensitive indicator of aminoglycoside-induced nephrotoxicity, with once-daily dosing than with twice- or thrice-daily administration (35). As shown in Table 3, two additional studies demonstrated that once-daily dosing required a longer duration of therapy before onset of nephrotoxicity compared with thrice-daily dosing (33,40). The median number of days to the onset of nephrotoxicity was three days longer with once-daily dosing than with the more frequent dosing regimen, and this difference was statistically significant in both studies. Thus, almost half of the reported clinical trials have observed a significantly lower parameter of nephrotoxicity with the once-daily dosing regimen.

The frequencies of auditory and vestibular ototoxic-

TABLE 4
Pharmacokinetics and nephrotoxicity with once-daily dosing of netilmicin based on 8 h serum level

Parameter	8 h netilmicin serum level (mg/L)		
	<1.5	1.5-6	>6
Patients	7	33	11
Mean peak level	21.5	21.3	21.7
Mean trough level	0.2	0.4	1.5
Patients with nephrotoxicity	0	3 9%	4 36%

Based on data from reference 41

ity with different dosing regimens are compared in Figure 3. These results are based on standard audiometric testing, which was not performed in all of the 14 studies. The incidence was low in all but one study, and none of the differences were statistically significant. However, Tulkens (35) used high-frequency audiometry to compare different aminoglycoside dosing regimens. He observed ototoxicity in nine of 19 patients receiving thrice-daily netilmicin compared with three of 19 patients receiving once-daily drug administration. This difference was statistically significant. Additional studies using high-frequency audiometry are needed to analyze fully the frequency of abnormalities with different aminoglycoside dosing regimens.

MONITORING THERAPY

One potential advantage of once-daily dosing is that the need for drug level monitoring may be eliminated. Administration of large single doses would ensure high peak concentrations and trough levels before the next dose would be almost undetectable. Blaser et al (41) evaluated the value of peak, 8 h and trough levels of netilmicin in patients with a normal serum creatinine. As shown in Table 4, they found that 8 h serum levels were useful in identifying patients at increased risk for nephrotoxicity. If the value was 6 mg/L or less, only three of 40 patients developed nephrotoxicity. On the other hand, four of 11 patients with 8 h levels greater than 6 mg/L developed nephrotoxicity. Peak and trough levels were not as helpful in identifying these patients at risk for nephrotoxicity. Additional studies are needed with other aminoglycosides to determine whether similar or other monitoring schedules are useful in preventing toxicity with these drugs.

CONCLUSIONS

There is an excellent pharmacodynamic rationale, in regards to efficacy and toxicity, for considering administration of aminoglycosides as a single daily dose. Studies in animal models have demonstrated lower toxicity and similar or enhanced efficacy with once-daily dosing compared with more frequent dosing regimens. Most clinical trials have observed similar efficacy and toxicity with different aminoglycoside dosing regimens. However, a few trials have reported greater efficacy, lower toxicity or a delay in the onset of nephrotoxicity with once-daily administration than with twice- or thrice-daily dosing. More importantly, none of the studies has demonstrated any significant adverse effects of once-daily administration of the aminoglycosides. Once-daily dosing is convenient for out-patient therapy, requires fewer materials and less pharmacy preparation time, and may allow for less drug level monitoring. The once-daily dosing regimen deserves serious consideration for routine administration of the aminoglycoside antibiotics.

REFERENCES

1. Gilbert DN. Once-daily aminoglycoside therapy. Antimicrob Agents Chemother 1991;35:399-405.
2. Pechere J-C, Craig WA, Meunier F. Once daily dosing of aminoglycoside: one step forward. J Antimicrob Chemother 1991;27(Suppl C):149-52.
3. Vogelman B, Craig WA. Kinetics of antimicrobial activity. J Pediatr 1986;108:835-40.
4. Vogelman B, Gudmundsson S, Turnidge, Leggett J, Craig WA. In vivo postantibiotic effect in a thigh infection in neutropenic mice. J Infect Dis 1988;157:287-98.
5. Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: a review. Scand J Infect Dis 1991;Suppl 74:63-70.
6. Vogelman B, Gudmundsson S, Leggett J, Turnidge, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis 1988;158:831-47.
7. Leggett JE, Fantin B, Ebert S, et al. Comparative antibiotic dose-effect relations at several dosing intervals in murine pneumonitis and thigh-infection models. J Infect Dis 1989;159:281-92.
8. Craig WA, Redington J, Ebert SC. Pharmacodynamics of amikacin in vitro and in mouse thigh and lung infections. J Antimicrob Chemother 1991;27(Suppl C):29-40.
9. Moore RD, Lietman P, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 1987;155:93-9.
10. Blaser J, Stone BB, Groner MC, Zinner SH. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. Antimicrob Agents Chemother 1987;31:1054-60.
11. Daikos GL, Jackson GG, Lolans VT, Livermore DM. Adaptive resistance to aminoglycoside antibiotics from first-exposure down-regulation. J Infect Dis 1990;162:414-20.
12. Jackson GG, Daikos GL, Lolans VT. First-exposure effect of netilmicin on bacterial susceptibility as a basis for modifying the dosage regimen of aminoglycoside antibiotics. J Drug Dev 1988;1(Suppl 3):49-54.
13. Fantin B, Ebert S, Leggett J, Vogelman B, Craig WA. Factors affecting duration of in-vivo postantibiotic effect for aminoglycosides against Gram-negative bacilli. J Antimicrob Chemother 1991;27:829-36.
14. Craig WA. Post-antibiotic effects in experimental infection models: relationship to in-vitro phenomena and to treatment of infections in man. J Antimicrob Chemother 1993;31(Suppl D):149-58.
15. Guiliano RA, Verpooten GA, Verbist L, Wedeen RP, De Broe ME. In vivo uptake kinetics of aminoglycosides in

the kidney cortex of rats. J Pharmacol Exp Ther 1986;236:470-5.
16. Tran Ba Huy P, Bernard P, Schacht J. Kinetics of gentamicin uptake and release in the rat. Comparison of inner ear tissues and fluids with other organs. J Clin Invest 1986;77:1492-500.
17. Mattie H, Craig WA, Pechere JC. Determinants of efficacy and toxicity of aminoglycosides. J Antimicrob Chemother 1989;24:281-93.
18. Verpooten GA, Guiliano RA, Verbist L, Eestermans G, De Broe ME. Once-daily dosing decreases renal accumulation of gentamicin and netilmicin. Clin Pharmacol Ther 1989;45:22-7.
19. De Broe ME, Verbist L, Verpooten GA. Influence of dosage schedule on renal cortical accumulation of amikacin and tobramycin in man. J Antimicrob Chemother 1991;27(Suppl C):41-7.
20. Frame PT, Phair JP, Watanakunakorn C, Bannister TWP. Pharmacologic factors associated with gentamicin nephrotoxicity in rabbits. J Infect Dis 1977;135:925-6.
21. Wood CA, Norton DR, Kohlhepp SJ, et al. The influence of tobramycin dosage regimen on nephrotoxicity, ototoxicity and antibacterial efficacy in a rat model of subcutaneous abscess. J Infect Dis 1988;158:13-22.
22. Reiner NE, Bloxham DD, Thompson WL. Nephrotoxicity of gentamicin and tobramycin given once daily or continuously in dogs. J Antimicrob Chemother 1978;4(Suppl A):85-101.
23. Bennett WM, Plamp CE, Gilbert DN, Parker RA, Porter GA. The influence of dosage regimen on experimental gentamicin nephrotoxicity: dissociation of peak serum levels from renal failure. J Infect Dis 1979;140:476-580.
24. Pechere JC, Bernard PA. Gentamicin ototoxicity can be avoided if a new therapeutic regimen is used. An experimental animal model. In: Program and Abstracts of the Twenty-Fourth Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington: American Society for Microbiology, 1984:178. (Abst)
25. Powell SLH, Thompson WL, Luthe MA, et al. Once-daily vs continuous aminoglycoside dosing: efficacy and toxicity in animal and clinical studies of gentamicin, netilmicin and tobramycin. J Infect Dis 1983;147:918-32.
26. Kapusnik J, Hackbarth CJ, Chambers HF, Carpenter T, Sande MA. Single, large, daily dosing versus intermittent dosing of tobramycin for treating experimental *Pseudomonas pneumonia*. J Infect Dis 1988;158:7-12.
27. Pechere M, Letarte R, Pechere J-C. Efficacy of different dosing schedules of tobramycin for treating a murine *Klebsiella pneumoniae* bronchopneumonia. J Antimicrob Chemother 1987;19:487-91.
28. Querioz MLS, Bathirunathan N, Mawer GE. Influence of dosage interval on the therapeutic response to gentamicin in mice infected with *Klebsiella pneumoniae*. Chemotherapy 1987;33:68-76.
29. Fan ST, Lan WY, Teoh-Chan CH, Lan KF, Maueracher EM. Once daily administration of netilmicin compared with thrice daily, both in combination with metronidazole, in gangrenous and perforated appendicitis. J Antimicrob Chemother 1988;22:69-74.
30. Hansen M, Achen F, Carstensen C, et al. Once-versus thrice-daily dosing of netilmicin in febrile immunocompromised patients: a randomized, controlled study of efficacy and safety. J Drug Dev 1988;1(Suppl 3):119-24.
31. Sturm AW. Netilmicin in the treatment of Gram-negative bacteremia: single daily versus multiple daily dosage. J Infect Dis 189;159:931-7.
32. Hollener LF, Bahnini J, De Manzini N, et al. A multicentric study of netilmicin once daily versus twice daily in patients with appendicitis and other intra-abdominal infections. J Antimicrob Chemother 1989;23:773-83.
33. Ter Braak EW, De Vries PJ, Bouter KP, et al. Once-daily dosing regimen for aminoglycoside plus β-lactam combination therapy of serious bacterial infections: comparative trial with netilmicin plus ceftriaxone. Am J Med 1990;89:58-66.
34. Nordstrom L, Ringberg H, Cronberg S, Tjernstrom O, Walder M. Does administration of an aminoglycoside in a single daily dose affect its efficacy and toxicity? J Antimicrob Chemother 1990;25:159-73.
35. Tulkens PM. Pharmacokinetic and toxicological evaluation of a once-daily regimen versus conventional schedules of netilmicin and amikacin. J Antimicrob Chemother 1991;27(Suppl C):63-71.
36. Giamarellou H, Yiallouros K, Petrikkos G, et al. Comparative kinetics and efficacy of amikacin administered once or twice daily in the treatment of systemic Gram-negative infections. J Antimicrob Chemother 1991;27(Suppl C):73-9.
37. Maller R, Ahrne H, Eilard T, Erikkson I, Lausen I, and the Scandinavian Amikacin Once Daily Study Group. Efficacy and safety of amikacin in systemic infections when given as a single daily dose or in two divided doses. J Antimicrob Chemother 1991;27(Suppl C):121-8.
38. Marik PE, Lipman J, Sobilski S, Scibante J. A prospective randomized study comparing once- versus twice-daily amikacin dosing in critically ill adult and paediatric patients. J Antimicrob Chemother 1991;28:753-64.
39. Prinz JM, Buller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. Lancet 1993;341:335-9.
40. Int Antimicrob Therap Coop Group of EORTC. Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. Ann Intern Med 1993;119:584-93.
41. Blaser J, Konig C, Simmen HP, Thurnheer U. Serum level monitoring during once daily dosing of aminoglycosides. In: Programme and Abstracts of the 18th International Congress of Chemotherapy. Stockholm: 18th International Congress of Chemotherapy, 1993:128. (Abst)