Single or multiple daily doses of aminoglycosides: a meta-analysis
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Authors' objectives
To assess the relative efficacy and toxicity of aminoglycosides given by a single daily dose, compared with multiple daily doses.

Searching
MEDLARS was searched from 1966 to 1995 using the keywords 'aminoglycosides' and individual drug names. The reference sections of qualifying titles were also examined.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) in which a single dose of an aminoglycoside was compared with the same total daily dose dispensed in multiple treatments each day.

Specific interventions included in the review
Single and multiple daily doses of aminoglycosides with a similar total daily dose. The aminoglycosides studied were netilmicin, gentamicin, sisomicin, amikacin and tobramycin. They were administered either by intramuscular or intravenous injection.

Participants included in the review
People with serious or potentially serious infections. Most studies were performed using adults but 2 trials studied a substantial number of children. Patients with abnormal renal function, and known auditory or vestibular impairment, were typically not eligible for inclusion. Most of the trials were performed in diverse, European clinical settings.

Outcomes assessed in the review
The outcomes were clinical failure of treatment, nephrotoxicity, ototoxicity and mortality.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection. [A: A rejection log and the reason for the rejection is recorded.]

Assessment of study quality
The authors do not report a method for assessing validity. [A: There was not a formal quality scoring but only studies which were randomised, used the same total dose of aminoglycoside in each arm and had no systematic differences in companion drugs were included.]

Data extraction
Two researchers independently extracted the data, and any discrepancies were resolved by a third reader. Each study's own predefined criteria for clinical failure, nephrotoxicity and ototoxicity, were used. Clinical data were used in preference to bacteriological responses.

Methods of synthesis
How were the studies combined?
Two different analyses were performed, one using only the data on evaluable patients, the other on an intention to treat basis. Pooled risk ratios were calculated using both the Mantel-Haenszel fixed-effect model and the Der Simonian and Laird random-effects model (see Other Publications of Related Interest).
How were differences between studies investigated?
The chi-squared statistic for heterogeneity demonstrated substantial heterogeneity in the risk ratios across the different trials. Factors investigated were: the effects of different prevalences of Pseudomonas isolates, the frequency of events in the group given multiple daily doses (i.e. control rate), year of publication, frequency of daily doses, mean duration of aminoglycoside treatment, the specific drug used, and the concurrent use of antibiotics. Subgroup analyses of patients with febrile neutropenia, and paediatric patients, were performed. Sensitivity analyses using alternative definitions of nephrotoxicity were also carried out. [AC: There was not substantial heterogeneity except in regard to clinical features]

Results of the review
Twenty-one RCTs were included in the main meta-analysis (3,091 participants). The clinical efficacy and nephrotoxicity analyses involved 19 trials (2,319 patients), and ototoxicity data were given in 14 trials.

The random-effects risk ratio for a single daily dose of aminoglycosides, compared with multiple doses, was 0.83 (95% confidence interval, CI: 0.57, 1.21, p=0.32) for clinical antibiotic failures, and 0.78 (95% CI: 0.57, 1.07, non significant) for nephrotoxicity. The two treatments showed no difference in ototoxicity: fixed-effect risk ratio was 1.09 (95% CI: 0.68, 1.75, non significant).

Cost information
No formal cost analysis was performed, but the authors note that once-daily dosing regimens have the potential for cost savings in terms of drug administration, monitoring of serum concentrations, and management of side-effects.

Authors’ conclusions
Once-daily administration of aminoglycosides in patients without pre-existing renal failure is as effective as multiple daily dosing, has a lower risk of nephrotoxicity, and no greater risk of ototoxicity. Given the additional convenience and reduced cost, once-daily dosing should be the preferred mode of administration.

CRD commentary
The search strategy depends on a single database for published trials, and it is not stated whether language restrictions were applied. There is no information about the quality of the included studies.

Both fixed-effect and random-effects models have been used; fixed-effect results have sometimes been presented despite the heterogeneity of studies. [A: There was no language restriction applied. See authors’ comments regarding quality.]

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