A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses

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Authors' objectives
To compare the efficacy and toxicity of the same total daily dose of aminoglycosides administered once-daily (OD) with multiple divided daily dosing (MD) for treating human infections.

Searching
MEDLINE was searched from 1966 to November 1994 (the keywords were given). Bibliographies in textbooks, review articles, source articles and reports of symposia were also examined.

Study selection
Study designs of evaluations included in the review
Criteria for inclusion: randomised trials; aminoglycosides used to treat established infection and not for prophylaxis; two or more arms comparing OD with MD administration of aminoglycosides; same total daily dose for OD and MD arms; treatment for at least 72 hours; at least one outcome available for clinical efficacy, bacteriological efficacy, nephrotoxicity, auditory toxicity, or vestibular toxicity.

Specific interventions included in the review
Aminoglycosides administered OD or as MD. The aminoglycosides tested were netilmicin, amikacin and gentamicin.

Participants included in the review
A wide variety of infections was studied: 844 patients with a serious infection as defined in the primary trials, 485 with Gram-negative sepsis, 349 with intra-abdominal sepsis, 70 with pelvic inflammatory disease and 60 with urinary tract infection. Febrile episodes were reported in 1,065 neutropenic patients. Paediatric patients were included in only 2 of the 20 included trials. The mean or median age of the study population is provided, but no other patient characteristics.

Outcomes assessed in the review
Clinical efficacy was defined as cure, improvement or failure.
Bacteriological efficacy was defined by eradication, persistence or relapse.
Nephrotoxicity was defined as an increase in serum creatinine of more than 50% or 35 micromol/L above the baseline.
Clinical auditory toxicity required an increase of more than 15 dB in two or more frequencies in the 0.5 to 8 MHz range, as measured by audiometry.
Vestibular toxicity was defined as any reported dizziness, vertigo or gait disturbance, or as abnormal electronystagmograph.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the relevance of the included studies.

Assessment of study quality
Validity was assessed using the following criteria: randomised trials; aminoglycosides used to treat established infection and not for prophylaxis; two or more arms comparing OD with MD administration of aminoglycosides; same total daily dose for OD and MD arms; treatment for at least 72 hours; at least one outcome available for clinical efficacy, bacteriological efficacy, nephrotoxicity, auditory toxicity, or vestibular toxicity. Validity was assessed by two independent reviewers.
Data extraction
Data from the primary studies were independently extracted by two reviewers and checked by a third.

Methods of synthesis
How were the studies combined?
The overall mean difference in treatment effect was estimated by a random-effects model. A positive difference indicated more events in the OD group than in the MD group.

How were differences between studies investigated?
A chi-squared test of homogeneity was performed.

Results of the review
Twenty trials involving 2,881 patients were included. The overall rate of clinical efficacy was 84.9% in the OD arm and 81.4% in the MD arm; the difference was small but statistically significant (overall rate difference 3.5%, 95% confidence interval, CI: 0.5, 6.5, p=0.027). Significant heterogeneity was found for clinical efficacy results among trials (p=0.018). The overall rate of bacteriological efficacy was not statistically significant between the OD and MD arms (85 versus 81.5%; overall rate difference 3.4%, 95% CI: -0.9, 7.7, p=0.137).

The overall rate of nephrotoxicity was not statistically significant between the OD and MD arms (4.7 versus 5.9%). Overall rate difference 1.3% (95% CI: -3.1, 5, p=0.2).

The overall rate of clinical auditory toxicity was not statistically different between the OD and MD groups (0.4 versus 0.0%). Overall rate difference 0.4% (95% CI: -0.2, 0.9, p=0.489).

Clinical vestibular toxicity was rarely reported and there was no significant difference between the two arms.

Authors' conclusions
Aminoglycosides can be given once-daily without loss of efficacy, or a risk of increased toxicity, thus offering greater simplicity than can be achieved by giving these drugs in divided doses, and potential improvements in cost-effectiveness. More data are required before OD dosing of aminoglycosides can be recommended for children, pregnant women, and patients with endocarditis or renal impairment.

CRD commentary
The authors ignored unpublished studies. It seems that publication bias is not important in this review because most trials showed no significant difference. Authors also mentioned that two trials were published since the review was completed, but the overall conclusion of this review will not be altered if these were included.

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