Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis

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Authors' objectives
To compare the efficacy, nephrotoxicity and ototoxicity of once-daily aminoglycoside dosing, with those of standard aminoglycoside regimens, in immunocompetent adults.

Searching
MEDLINE was searched from 1966 to April 1995, and selected infectious disease journals were handsearched from November 1994 to April 1995. Bibliographies of review articles were examined for additional material, and experts in the field were contacted for unpublished data.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were included. No information was given on the length of follow-up in individual trials.

Specific interventions included in the review
Aminoglycoside antibiotics. The patients in the included trials received netilmicin, amikacin or gentamicin.

Participants included in the review
Infected immunocompetent adults were included. The mean age of the treatment group in the included trials varied from 27 to 71 years.

Outcomes assessed in the review
The outcomes varied between the trials, but data were extracted on the basis of bacteriological cure, clinical cure, mortality, nephrotoxicity (increase in serum creatinine concentration of at least 35 to 45 micromol/L, i.e. 0.5 mg/dL, during the study period), and ototoxicity (a 15 dB change in hearing at any frequency, as assessed by audiometry).

How were decisions on the relevance of primary studies made?
Two independent reviewers assessed the papers, and any disagreements were resolved by consensus.

Assessment of study quality
The studies were assessed for methodological quality using a grading system to rank the included studies, and to calculate an overall quality score for the trials contributing to the meta-analysis. The following criteria were assessed for each trial: randomisation, follow-up, blinding of outcome assessor, use of intention to treat analysis, inclusion and exclusion criteria specified, existence of co-intervention in both treatment and control groups, compliance, blinding of patients, and defined outcome measures. Two independent reviewers assessed validity.

Data extraction
The outcome data were extracted by two independent reviewers.

Methods of synthesis
How were the studies combined?
The pooled risk ratios were calculated for efficacy and toxicity outcomes using a random-effects model.

How were differences between studies investigated?
Visual inspection of the individual risk ratios indicated heterogeneity in the estimates of clinical cure between trials. The authors also report that statistical heterogeneity existed between trials. Pre-planned sensitivity analyses were also...
carried out to investigate aminoglycoside type, co-intervention type and primary source of infection as sources of heterogeneity.

**Results of the review**
Thirteen studies with a total of 1,625 patients were included.

The mean methodology quality score of the 13 included trials was 0.69 (range: 0.50-0.91) with a maximum possible score of 1.0.

Bacteriologic cure: pooled risk ratio 1.02 (95% confidence interval, CI: 0.99, 1.05).

Clinical cure: no pooling took place due to heterogeneity between trials.

Mortality: pooled risk ratio 0.91 (95% CI: 0.63, 1.31) in favour of once-daily dosing, equivalent to a relative risk reduction of 9% and a numbers-needed-to-treat (NNT) value of 111 to prevent 1 death.

Nephrotoxicity: pooled risk ratio 0.87 (95% CI: 0.60, 1.26), corresponding to a relative risk reduction of 13% with a once-daily regimen, and a NNT with once-daily dosing (instead of standard dosing) of 77 to prevent nephrotoxicity.

Ototoxicity: pooled risk ratio 0.67 (95% CI: 0.35, 1.28), corresponding to a relative risk reduction of 33% and a NNT of 61.

**Authors’ conclusions**
Once-daily dosing is as effective as standard dosing in terms of bacteriological cure, and may be associated with reduced nephrotoxicity, ototoxicity and mortality. The mortality risk is similar with either regimen, and there is some evidence of a trend towards reduced mortality with daily dosing.

**CRD commentary**
There is some variability in methodological quality, so it may have been useful to examine to what extent the findings of the review are sensitive to the quality score, e.g. by analysing higher quality trials separately. Overall, there is adequate investigation of heterogeneity, and the authors’ conclusions and recommendations for further research are warranted.

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