A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides

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Authors' objectives
To compare the efficacy and toxicity of the same or similar total daily doses of aminoglycosides administered by either conventional (multiple daily dosing) or extended-interval dosing methods.

Searching
MEDLINE was searched from 1 January 1966 to 31 December 1994. Search terms used were: 'aminoglycosides', 'drug administration schedule' and 'clinical trials'). The reference lists of retrieved trials and reviews were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Studies were included if they were randomised trials; published in English; compared extended-interval dosing with conventional multiple daily dosing; with the same aminoglycoside in both arms; reported original data; reported clinical or bacteriological efficacy; counted the number of patients rather than episodes of infection. Studies of the treatment of tuberculosis and the use of aminoglycosides for prophylaxis were excluded.

Specific interventions included in the review
Multiple daily dosing of aminoglycosides: administering the total daily dose in divided doses.

Extended-interval dosing of aminoglycosides: administering a single large dose of drugs (usually 5 mg/kg for gentamicin, tobramycin, or netilmicin and 15 mg/kg for amikacin) at intervals of 24-48 hours.

Aminoglycosides included in the review: gentamicin, sisomicin, netilmicin, amikacin, tobramycin.

Participants included in the review
Patients treated with aminoglycosides for various indications including: urinary tract infection, neutropenia, fever, intraabdominal infection, gram-negative bacteremia, pelvic inflammatory disease or serious mixed infection.

Outcomes assessed in the review
Clinical efficacy, bacteriologic efficacy, nephrotoxicity and ototoxicity. The authors' definitions for each outcome were used in the review, which were often different across studies.

How were decisions on the relevance of primary studies made?
One reviewer determined eligibility for inclusion.

Assessment of study quality
The following quality indications were assessed: well defined duration of follow-up for clinical and bacteriologic outcome; objective definition of nephrotoxicity; use of a high-frequency audiometry for ototoxicity evaluations; method of randomisation; inclusion/exclusion criteria; blinded outcome measures; and statistical methods. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
One reviewer abstracted the data.

Methods of synthesis
How were the studies combined?
The random-effects model of DerSimonian and Laird was used to perform the meta-analysis. The risk difference was defined as the frequency of the event of interest in the extended-dosing-interval group less the frequency of the event in the conventional-dosing group.

How were differences between studies investigated?
Statistical heterogeneity among studies were tested using Q statistic. Subgroup analyses were carried out for subgroups of studies of patients who had serious infections, were neutropenic, were treated with an aminoglycoside as a single agent, were treated with aminoglycosides in combination with other drugs, were treated with netilmicin and were treated with amikacin.

Results of the review
Twenty-two RCTs with a total of 2,500 patients were included.

The results of treatment failure were statistically significantly heterogeneous across studies (p=0.005). Extended-interval dosing was associated with a statistically significant reduction in risk of treatment failure (risk difference -3.4%; 95% CI: -6.7%, -0.2%; p=0.04). Reclassification of intermediate outcomes as failure yielded a smaller risk difference (risk difference -3.1%; 95% CI: -7.4%, 1.1%; p=0.15).

There was a trend toward reduced risk of bacteriologic failure in the extended-interval dosing group (risk difference -1.7%; 95% CI: -5.4%, 2.1%; p=0.38).

There was no significant difference between extended-interval dosing and conventional dosing in nephrotoxicity (risk difference -0.6%; 95% CI: -2.4%, 1.1%; p=0.46) and in ototoxicity (risk difference 0.3%; 95% CI: -1.2%, 1.8%; p=0.71).

Authors’ conclusions
For many indications, extended-interval dosing of aminoglycosides appears to be as effective as conventional dosing, with similar rates of toxicity. The added convenience of extended-interval dosing makes it an attractive alternative to conventional dosing.

CRD commentary
The search strategy, inclusion criteria and quality assessment were satisfactorily reported. The patients' characteristics and results of individual studies were presented in tables and diagrams. The synthesis of evidence was appropriate.

The patients included in the review were heterogeneous, with various indications.

Bibliographic details

PubMedID
9142771

Indexing Status
Subject indexing assigned by NLM

MeSH
Aminoglycosides; Anti-Bacterial Agents /administration & dosage /adverse effects /pharmacokinetics; Bacterial Infections /drug therapy /microbiology; Confidence Intervals; Dose-Response Relationship, Drug; Drug Administration Schedule; Hearing Disorders /chemically induced; Humans; Infusions, Intravenous; Kidney Diseases /chemically
induced; Randomized Controlled Trials as Topic; Risk Factors; Treatment Outcome

AccessionNumber
11997000634

Date bibliographic record published
31/08/1998

Date abstract record published
31/08/1998

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.