

Meta-analysis: A single daily dose of aminoglycosides is as effective as multiple daily dosing in immunocompetent adults

Hatala R, Dimb T, Cook DJ. *Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. Ann Intern Med.* 1996 Apr 15;124:717-25.

Objective

To evaluate the efficacy, nephrotoxicity, and ototoxicity of once-daily aminoglycoside dosing compared with standard (multiple daily) dosing in immunocompetent adults.

Data sources

Studies were identified by searching MEDLINE (1966 to April 1995) using the keywords aminoglycosides (exploded), drug administration schedule, and adult. Additional articles were identified by hand searching of selected infectious disease journals from November 1994 to April 1995 and by scanning bibliographies of review articles, position papers, and identified articles. Primary authors of selected articles were also contacted to obtain a list of potentially relevant articles.

Study selection

Studies were selected if they were randomized controlled trials of an intravenous, once-daily aminoglycoside regimen compared with a multiple

daily dosing regimen in infected, immunocompetent adults and if the outcomes assessed were efficacy, all-cause mortality, or toxicity. Studies were excluded if > 50% of patients had a lower urinary tract infection or if the aminoglycosides were given for surgical prophylaxis.

Data extraction

Data were extracted on bacteriologic cure (using individual study definition), clinical cure (using individual study definition), mortality, nephrotoxicity (defined as a rise in serum creatinine levels of at least 35 to 45 $\mu\text{mol/L}$ during the study period), ototoxicity (defined as a 15-decibel change in hearing at any frequency), and methodologic quality. Additional information about outcome measures not provided in the published report was sought by contacting the primary investigators.

Main results

42 studies were reviewed for study selection, and 13 met the criteria. Their mean methodologic quality score was 0.69 (range 0.50 to 0.91). Pooling data across studies, {84%}* of patients assigned to a once-daily dose attained bacteriologic cure compared

with {77%}* assigned to standard aminoglycoside dosing (risk ratio 1.02, 95% CI 0.99 to 1.05), indicating equivalency between the two types of dosing. {7%}* of patients assigned to once-daily dosing died compared with {8%}* assigned to standard dosing (risk ratio 0.91, CI 0.63 to 1.31). The pooled risk ratio for nephrotoxicity was 0.87 (CI 0.60 to 1.26, {7% vs 8%}*) and for ototoxicity was 0.67 (CI 0.35 to 1.28, {4% vs 6%}*). Data for clinical cure were not pooled because of heterogeneity among studies.

Conclusion

Once-daily aminoglycoside dosing regimens in immunocompetent adults are equivalent to conventional dosing methods in terms of bacteriologic cure, nephrotoxicity, ototoxicity, and mortality.

Source of funding: None.

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*Numbers calculated from data in article.

Abstract and Commentary also published in *ACP Journal Club*. 1996;125:11.

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analysis. The individual studies included in both meta-analyses varied substantially in terms of patient characteristics, clinical setting, type of infection, aminoglycoside used, and outcomes measured.

These meta-analyses show the extent to which estimates of clinical efficacy vary among individual studies, most of which favor once-daily dosing, but a few favor multiple daily dosing (in epidemiologic terms, individual trial results were *heterogeneous*). When results are "all over the board," it is risky to attempt an "overall" estimate, but once-daily dosing appears to be at least as effective as multiple daily dosing. Barza and colleagues included 2

studies among pediatric patients and 4 studies among neutropenic patients, which also suggested that the 2 dosing regimens are equivalent. The individual studies are reasonably consistent in showing that once-daily dosing results in less nephrotoxicity and ototoxicity.

Although these meta-analyses strongly support the use of once-daily dosing, several important problems remain unresolved. We still do not know how particular dosing regimens may benefit different subgroups of patients (e.g., patients with mild renal impairment) or how to calculate doses and monitor patients given once-daily dosing. A lesson that can be learned

from these 2 meta-analyses is that a few large, multicenter trials would be far more helpful than numerous small studies in answering these remaining questions.

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