Meta-analysis: A single daily dose of aminoglycosides is as effective as multiple daily dosing with less nephrotoxicity

Barza M, Ioannidis JP, Cappelleri JC, Lau J. ***Single or multiple daily doses of aminoglycosides: a meta-analysis.*** *BMJ. 1996 Feb 10;312:338-45.*

Objective

To determine the efficacy and toxicity of aminoglycosides when given as a single daily dose compared with multiple daily doses.

Data sources

Studies were identified by searching MEDLARS databases (January 1966 to January 1995) with the keywords aminoglycoside and the names of individual drugs and by scanning the bibliographies of identified articles.

Study selection

Studies were selected if they were randomized controlled trials comparing a single daily dose of an aminoglycoside with the same total daily dose given multiple times each day. Studies were excluded if the aminoglycosides were used for surgical prophylaxis, there were no identifiable outcomes for efficacy and toxicity, or aminoglycosides were included in combinations differing between treatment groups.

Data extraction

Data were extracted on the clinical setting and anatomic sites of infection; number of randomized and evaluable patients; specific aminoglycoside used; route, dose, and dosing frequency; duration of treatment; bacteriologic data; use of concurrent antibiotics; definitions and number of failures of antibiotic treatment; and definitions and number of events of nephrotoxicity and ototoxicity. Clinical response took priority over bacteriologic results. For the main analysis, a 50% increase in serum creatinine level was used to define nephrotoxicity.

Main results

21 trials, involving 3091 patients with bacterial infection, met the selection criteria. Data pooled from 19 trials showed that a single daily dose produced a nonsignificant increase in clinical successes {90% vs 87%, risk ratio 1.03, 95% CI 0.99 to 1.07, $P = 0.11$}*. Single-dose compared with multiple-dose regimens reduced nephrotoxicity (overall rate weighted by study size 5.5% vs 7.7%, $P = 0.05$). {This absolute risk reduction of 2.2% means that 56 patients (weighted calculation) would need to be treated with a single daily dose (rather than multiple doses) to prevent 1 additional nephrotoxic event, CI 29 to 626; the relative risk reduction was 26%, CI 0% to 46%.}* Ototoxicity did not differ between the 2 dosing regimens, but the statistical power to detect a difference with the pooled results was low. There was also no difference in mortality. The same findings applied to trials with high rates of *Pseudomonas* infections and to trials in febrile neutropenic patients.

Conclusion

A single daily dose of aminoglycosides in patients without pre-existing renal impairment is as effective as multiple daily dosing, has a lower risk for nephrotoxicity, and has no greater risk for ototoxicity or death.

Source of funding: Agency for Health Care Policy and Research.

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*Numbers calculated from data in article.

Abstract and Commentary also published in *ACP Journal Club.* 1996;125:10.

Commentary

Many clinicians have felt perplexed since the first reports that a single daily dose of aminoglycosides may be as effective as multiple daily doses. Although animal studies have provided supporting evidence, clinical trials have been small, the results have been inconsistent, and editorial writers have disagreed about the wisdom of changing clinical practice (1). As a result, adoption of once-daily aminoglycoside dosing has been slow.

These 2 systematic reviews should put an end to clinicians' hesitancy to adopt once-daily dosing. Each team of investigators used a different strategy for identifying and selecting individual studies, and they reached slightly different conclusions. But both meta-analyses strongly support the general conclusion that once-daily dosing is as effective as, and less toxic than, multiple daily dosing.

Meta-analyses are especially helpful in summarizing multiple small studies, none of which if considered on its own has sufficient statistical power to exclude a difference between treatment groups. Meta-analyses are mysterious to many clinicians, but guidelines for critically appraising these overviews have recently been unveiled in the "Users' Guides to the Medical Literature" (2).

Of the 2 meta-analyses, the study by Hatala and colleagues is the more methodologically rigorous, but the study by Barza and colleagues may be more broadly applicable to clinical practice. Hatala and colleagues made a comprehensive search for eligible studies but selected only randomized trials of immunocompentent adults who received intravenous aminoglycosides. After exclusions, their meta-analysis included 13 of the 42 studies identified. On the other hand, Barza and colleagues identified 25 studies by using a MEDLINE search but selected 19 for the review (some of which included children and neutropenic patients). Hatala and colleagues graded studies according to methodologic quality, but did not weight higher-quality studies more heavily in their

(Continued on page 145)