Editorial Response: Meta-Analyses Are No Longer Required for Determining the Efficacy of Single Daily Dosing of Aminoglycosides

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Investigators conducting clinical trials may have trouble replicating in ill patients results obtained in tightly controlled models of efficacy and toxicity that use healthy animals [1]. Trials of single daily dosing (SDD) of aminoglycosides (also known as once-daily aminoglycoside therapy) vs. multiple daily dosing (MDD) are a good example. The rationale for SDD therapy is clear [1]: SDD of aminoglycosides results in high peak serum concentrations that enhance the concentration-dependent bactericidal activity of these drugs against susceptible aerobic gram-negative bacilli. Aminoglycosides have a postantibiotic effect (PAE) that is longer when the peak drug level is higher. SDD results in the absence of detectable drug in serum for several hours at the end of a dosage interval, whereas the drug remains detectable with MDD. Because of the PAE, this drug-free period does not appear to compromise antibacterial efficacy (although it may be compromised in cases of infective endocarditis).

The clearance of aminoglycosides from serum has two advantages, including a lower risk of nephrotoxicity and ototoxicity and a reduced likelihood that "adaptive resistance" to the drug might occur [2-5]. Hence, the clinical assessment of SDD vs. MDD of aminoglycosides requires documentation that the patients randomized to SDD have high peak levels and low (<1 µg/mL) or undetectable drug levels for several hours at the end of the 24-hour dosage interval.

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Ideally, clinical trials designed to compare the safety and efficacy of SDD vs. MDD of aminoglycosides would include only otherwise healthy patients with normal renal, vestibular, and cochlear function. The same aminoglycoside would be used in all trials, as there is potential variability in antibacterial efficacy and toxicity among the drugs in this group [6]. The patients would receive either no companion antibacterial or the same companion antibacterial, as concomitant administration of β-lactams and vancomycin can influence both antibacterial efficacy and the risk of toxicity [6]. One method of overcoming these and other variables is meta-analysis. Meta-analysis combines quantitative information from individual sources to yield a summary statistic that is more powerful than the statistics generated by smaller, individual trials.

The ultimate value of a meta-analysis depends on the validity of the data in the individual clinical trials and the methods used to perform the meta-analysis.

Three meta-analyses of clinical trials that compared MDD with SDD of aminoglycosides appear in this issue of Clinical Infectious Diseases (CID). Another five meta-analyses have recently been published [7-11]. The number of clinical trials accepted as valid for the individual meta-analysis ranged from four to 26 [12-41]. The published meta-analyses are consistent in that they included only those clinical trials that enrolled patients who received the same dosage (mg/[kg·d]) of an aminoglycoside, given either in MDDs or SDDs, for the treatment of an active infection. The individual clinical trials and, hence, the meta-analyses have lacked uniformity in terms of the enrolled patient populations, the specific aminoglycoside used, the comparison antibacterials administered, and the use of other potentially nephrotoxic or ototoxic drugs.

The investigators conducting the clinical trials have allowed great variability in baseline renal function, which is of particular relevance to the theoretical advantage of SDD of aminoglycosides. As summarized in table 3 of the meta-analysis of Ali and Goetz in this issue of CID, some trials excluded patients with baseline serum concentrations of >1.0 mg/dL, while others allowed baseline values of ≤4.0 mg/dL. Hence, with the exception of children, it is fair to say that a substantial percentage of patients enrolled in these trials had baseline reductions in renal function sufficient to prolong the serum half-life (t1/2) of the administered aminoglycoside.

How were the issues of adjustment of dosage and documentation of low trough serum levels in patients with predictable prolongation of the t1/2 of the aminoglycoside handled in the 26 trials [22-41]? A variety of approaches were used. In at least four of the studies, patients were excluded if the baseline serum creatinine concentration exceeded 1.4-1.8 mg/dL or the estimated creatinine clearance was <60 mL/min [13, 22, 34, 39]. Either low trough serum levels (<1 µg/mL) were documented [34, 39], the single daily dose was reduced [13], or high trough serum levels were documented [25]. In four other studies, the baseline dosage of the aminoglycoside was adjusted...
on the basis of estimated creatinine clearance values [21, 27, 28, 32]. In most cases the 24-hr mg/kg dose was reduced, and the dosing interval was not extended. The majority of the studies did not address the issue.

A few of the published trials do document the desired low or undetectable levels of aminoglycosides at the end of the dosage interval in patients randomized to the SDD regimen [13, 32, 34, 39]. In one trial, the aminoglycoside dosage was reduced on the basis of baseline renal function estimates [32], and in another, the baseline renal function of the enrolled patients was predictably good because they were young [23]. It is of interest that the first trial [32] showed a significant reduction in nephrotoxicity in the patients receiving the SDD regimen \( P = .016 \) and that the second trial showed higher clinical and bacteriologic cure rates for the patients receiving the SDD regimen \( P \leq .005 \), while the incidence of nephrotoxicity was low for patients receiving either regimen [23].

Aside from the issue of end-of-dosage-interval clearance of aminoglycosides with SDD, what do the eight meta-analyses tell us? In six of these meta-analyses, a decreased risk of clinical or microbiological failure and a relative decrease in the risk of mortality were observed for the SDD group [7, 9, 11]. A decrease in the relative risk of nephrotoxicity [7, 9, 11] was observed in three of the eight analyses, and in one, a 33% decrease in the risk of otoxicity was observed [9].

The difficulty in accruing otoxicity data is reflected by low numbers of evaluable patients in the published clinical trials. For example, it is not possible to obtain valid bedside audiograms for critically ill patients with metabolic encephalopathy. Furthermore, the earliest evidence of aminoglycoside-induced cochlear injury is high-frequency hearing loss. In addition, age-induced decrements in high-frequency hearing loss are common and thus result in the exclusion of many patients from evaluation.

There are no comparative data on the vestibular toxicity of aminoglycosides. Anecdotal reports indicate that this toxicity occurs with SDD; however, to date there are no data indicating either an increased or reduced incidence of vestibular injury [42].

There are additional relevant data from nonrandomized trials that were not included in the published meta-analyses. For example, Nicolau et al. [42] reported their experience with 2,184 patients who received aminoglycosides in single daily doses. These results were compared with those obtained with MDD regimens for which careful monitoring of peak and trough serum levels was performed.

Two points are of interest: (1) The single daily dose of gentamicin or tobramycin used by Nicolau et al. was larger than that used in most studies. Most investigators have multiplied the standard multiple-dose regimen by two or three to establish the single daily dose (e.g., for gentamicin, \( 1.7 \) mg/kg \( \times 3 = 5.1 \) mg/(kg \( \cdot \) d)). However, on the basis of preliminary drug kinetic studies, Nicolau et al. selected a dose of 7 mg/kg. (2) The single daily dose was adjusted for decrements in estimated renal function by extending the dosage interval to 36 or 48 hours. Nicolau et al. did not report any evidence of microbiologic failures. It is of interest that the incidence of nephrotoxicity fell from a historical rate of 3–5% to 1.2%.

The safety and efficacy of isepamicin are also relevant. Iepamicin is an aminoglycoside that has been licensed recently in Europe, but it has not been marketed in the United States. The clinical trials with isepamicin evaluated only single daily doses of either 8 mg/kg or 15 mg/(kg \( \cdot \) d), depending on the severity of the infection. Amikacin, the comparator drug, was dosed at 7.5 mg/kg b.i.d. Overall, rates of clinical cure or improvement were comparable [43]. Increases in serum creatinine levels occurred in 4.6% of patients receiving isepamicin and 5.1 of patients receiving amikacin. The incidence of otoxicity was low, with no difference between the two drugs [44].

Thus, if the current evidence indicates that SDD of aminoglycosides is at least as safe and effective as MDD, do we need another meta-analysis? I do not believe so. Could we use additional prospective randomized trials? Of course, such trials would be instructive, but the same multiple obstacles in design and implementation would be present. Additional trials of SDD in children, pregnant women, and patients with endocarditis would be of particular interest. In animal models of endocarditis, the results appear dependent on the etiologic bacteria. The best results for experimental enterococcal endocarditis required MDD of an aminoglycoside in combination with a \( \beta \)-lactam [45], while the best results for an infection due to a viridans group streptococcus was achieved with a single daily dose of an aminoglycoside [46].

How high should single daily doses of aminoglycosides be? For patients with normal renal function (e.g., estimated creatinine clearance, \( \geq 80 \) mL/min) at baseline, the choice is between the U.S. Food and Drug Administration–approved maximum daily dose (e.g., \( 5.1 \) mg/[kg \( \cdot \) d] for gentamicin) or the somewhat higher dose (7 mg/[kg \( \cdot \) d]) reported by Nicolau et al. [42]. For patients with a baseline estimated creatinine clearance of \( <80 \) mL/min, should the daily dose be lower, with a constant 24-hour dosage interval, as Bennett and I have proposed [6, 47], or should the dose remain constant and the dosage interval be extended to 36 or 48 hours, as outlined by Nicolau et al. [42]? Space constraints preclude a discussion of the pros and cons of each approach. There are no clinical data that address this issue, and there is no animal model of stable, chronic impaired renal function that could be used to compare the two methods.

In summary, SDD of aminoglycosides has been studied in enough adult nonpregnant patients without endocarditis. SDD appears to be a safe and efficacious approach that does not prevent drug toxicity but may reduce the risk. SDD of aminoglycosides is simpler, less time-consuming, and intuitively more cost-effective than traditional MDD regimens [48].
References


