especially against measles, should be pursued vigorously. For all children the management of acute respiratory infection, malnutrition, and enteric disease requires strengthening, as does the appropriate management of malaria and meningitis.

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Single or multiple daily doses of aminoglycosides: a meta-analysis

Michael Barza, John PA Ioannidis, Joseph C Cappelleri, Joseph Lau

Abstract

***Objective*—To assess relative efficacy and toxicity of aminoglycosides given by single daily dose compared with multiple daily doses.**

***Design*—Meta-analysis of 21 randomised trials identified through MEDLARS (1966 to January 1995). Data were overviewed with fixed effects and random effects models and with meta-regression analysis.**

***Subjects*—Total of 3091 patients with bacterial infection, most without pre-existing renal disease.**

***Interventions*—Patients were randomised to receive aminoglycosides once daily or multiple times daily with similar total daily dose.**

***Main outcome measures*—Clinical failure of treatment, nephrotoxicity, ototoxicity, and mortality.**

***Results*—Single daily dose regimen produced a non-significant decrease in risk of antibiotic failures (random effects risk ratio 0·83 (95% confidence interval 0·57 to 1·21)). Benefit of once daily dosing was greater when the percentage of pseudomonas isolates in a trial was larger. Once daily administration reduced risk of nephrotoxicity (fixed effects risk ratio 0·74 (0·54 to 1·00)). Similar trends were noted for patients with febrile neutropenia and for children. There was no significant difference in ototoxicity between the two dosing regimens, but the power of the pooled trials to detect a meaningful difference was low. There was no significant difference in mortality.**

***Conclusions*—Once daily administration of aminoglycosides in patients without pre-existing renal impairment is as effective as multiple daily dosing, has a lower risk of nephrotoxicity, and no greater risk of ototoxicity. Given the additional convenience and reduced cost, once daily dosing should be the preferred mode of administration.**

Division of Geographic Medicine and Infectious Diseases, New England Medical Center Hospitals, Tufts University School of Medicine, Boston, MA 02111, USA
Michael Barza, *professor of medicine*
John PA Ioannidis, *research fellow*

Division of Clinical Care Research, New England Medical Center Hospitals, Tufts University School of Medicine
Joseph C Cappelleri, *assistant professor*
Joseph Lau, *associate professor*

Correspondence to:
Dr Barza.

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Introduction

Aminoglycosides have potent activity against Gram negative bacilli and are often used to treat infections caused by these species, especially when resistance to beta lactam antibiotics is suspected. However, use of aminoglycosides is limited by concerns about toxicity, primarily nephrotoxicity and ototoxicity. The drugs are usually administered intravenously in two to four doses a day in patients with normal renal function. A once daily dose is more convenient and has been proposed to be an equally effective and potentially less toxic mode of administration.[1-4]

Numerous randomised trials have compared a single daily dose with multiple doses of aminoglycosides in hospital inpatients. Although a few studies showed one or the other regimen to be of superior merit,[1,5] most found no significant difference in efficacy or toxicity between the two regimens. Individual trials, however, have been of relatively small size, and their power to detect a significant difference in outcome was low. Thus, although there is evidence from in vitro and animal studies to suggest that administering aminoglycosides once daily is advantageous, the validity of

this hypothesis has not yet been established in clinical trials or in an earlier, small meta-analysis.[6] In order to combine the current clinical evidence about this important issue, we carried out a meta-analysis of all randomised clinical trials comparing a single daily dose of aminoglycosides with multiple daily doses.

Methods

IDENTIFICATION AND ELIGIBILITY OF CLINICAL TRIALS

We identified published randomised controlled trials by means of a MEDLARS literature search (January 1966 to January 1995). The key words for the initial search strategy were aminoglycoside and the names of individual drugs. We then screened potentially relevant abstracts and papers to determine whether they qualified for the meta-analysis. Finally, we reviewed the references of qualifying papers to ensure that we had retrieved all pertinent articles.

The meta-analysis considered all randomised trials in which administration of a single daily dose of an aminoglycoside was compared with the same total daily dose given in multiple treatments each day. We excluded studies of different total daily doses in the treatment arm, trials of aminoglycosides used for surgical prophylaxis, and pharmacokinetic studies with no identifiable outcomes for efficacy and toxicity. Furthermore, we excluded a study from the analysis of clinical efficacy if the randomised comparison was of an aminoglycoside combined with other antibiotics that were systematically different in each treatment arm. We also excluded a study from the nephrotoxicity analysis if use of amphotericin was allowed. In both cases sensitivity analysis assessed the effect of including these studies. Otherwise, concomitant use of other antibiotics was not considered an exclusion criterion. Both unblinded and blinded studies qualified.

DATA EXTRACTED

We extracted the following data from each study: clinical setting and anatomical sites of infection; number of randomised and evaluable patients in each treatment arm; specific aminoglycoside used and route, dose, and dosing frequency used in each arm; mean (or median) duration of treatment; bacteriological data (specific pathogens isolated, with particular attention to the number of pseudomonas isolates); use of concurrent antibiotics; definitions and numbers of failures of antibiotic treatment in each arm; definitions and number of events of nephrotoxicity and ototoxicity in each arm; and mortality.

For each study, we used its own predefined criteria for clinical failure. When data were available for both bacteriological and clinical responses we used only the clinical data. As a general rule, we counted relapses as failures because they signified failure to eradicate the original infection; we did not count reinfections, superinfections, and indeterminate events as failures. Similarly, for each study, we used its predefined criteria for nephrotoxicity (rise in creatinine concentration) and ototoxicity. When two or more definitions of nephrotoxicity were used in a study we performed sensitivity analyses to address the use of alternative definitions. For the main analysis, the absolute or percentage rise in creatinine concentration from its baseline value was preferred over definitions that used final creatinine concentrations without considering the baseline. One study reported five different definitions with different percentage increases[7]; we used the definition with 50% increase (the one most commonly used in other trials) in the main analysis.

Two readers independently performed the data extraction, and they disagreed on only a few points. From the several hundred items of data extracted, only 12 discrepancies were noted. For eight of these, one of the readers had initially failed to find the pertinent data in the extracted paper. For the other four points, one of the readers had entered data based on definitions slightly different from those specified in our protocol—such as using bacteriological rather than clinical definitions of failure of treatment. All these subtle discrepancies were settled by a third reader acting as arbiter in a collaborative review. Consensus was reached for all data.

DATA ANALYSIS

We performed two different analyses for each outcome. In one we used only the evaluable patients (as judged by the authors of each study) as the denominator for each outcome. The other analysis was done on an intention to treat basis, and we used all randomised patients unless data were given only for evaluable patients. Unevaluable patients were not counted in the number of failures for any outcome. For all outcomes, the results were similar, and we report only the results from the intention to treat analysis. In studies where patients could have been randomised for more than one episode of infection, we used the total number of episodes for the calculations.

STATISTICAL METHODS

We calculated pooled risk ratios (relative risks) with both the Mantel-Haenszel fixed effects model[8] and the DerSimonian and Laird random effects model.[9] The use of random versus fixed effects models has been extensively discussed in the literature.[9–12] In addition to incorporating variability within studies, the random effects model also incorporates the variance of treatment effect among studies, which gives the magnitude of heterogeneity of treatment effect. When heterogeneity is present, the confidence interval becomes wider. When a study had no events in either treatment group, 0·5 was added to each cell of the table. The magnitude and the significance of heterogeneity of risk ratios were considered in the interpretation of the results. The χ^2 statistic for heterogeneity is not very sensitive, and we considered the presence of significant heterogeneity at the 0.10 level of significance as evidence that the random effects model would be more appropriate than the fixed effects model.

We examined the effect of the following variables on nephrotoxicity and clinical failures: frequency of multiple doses (twice or thrice daily; trials with variable dosing were analysed both ways); specific aminoglycoside (amikacin, gentamicin, netilmicin, sisomicin, and tobramycin); whether concurrent antibiotics were used; year of publication (between 1977 and 1993); mean (or median) duration of treatment in a study (days); percentage of pseudomonas species among the total isolates in a study; and frequency of events in the group given multiple doses (that is, the control rate). We conducted simple linear regressions of the natural logarithm of the risk ratio on each of these variables. Studies were weighted by the inverse of the variance of the natural logarithm of the risk ratio. Regression analyses were done with SAS.[13] Subgroup analyses were also performed on trials of children and on trials of patients with febrile neutropenia. All P values are two tailed, and confidence intervals are 95%.

Results

CHARACTERISTICS OF ELIGIBLE TRIALS

We identified 25 trials[1 4 5 7 14–34] and used 21 of them, with a total of 3091 patients, in the meta-analysis (table 1). We excluded four studies, three because the total daily dose of aminoglycosides was different in the two treatment arms[32–34] and the fourth because amino-

Table 1—*Characteristics of the 21 trials included in meta-analysis of daily dosing regimen of aminoglycosides*

Study	Clinical setting	Site of infection	Drug (route)	No of multiple doses per day	No of patients*	Mean length of treatment (days)	Concurrent antibiotics
Klastersky *et al*[5]	Cancer	Urinary	Sisomicin (intramuscular)	2	50	7·3	No
Hansen *et al*[14]	Febrile neutropenia	Diverse	Netilmicin (intravenous)	3	56	7·0	Yes
Muijsken *et al*[15]	NS	Diverse	Netilmicin (intravenous)	2 or 3	90	NR	Yes
Tulkens *et al*[16]	Gynaecological	Pelvic	Netilmicin (intravenous)	3	38	7·2	Yes
Hollender *et al*[17]	Surgical	Intra-abdominal	Netilmicin (intravenous and intramuscular)	3	114	8·8	Yes
Mauracher *et al*[18]	NS	Diverse	Netilmicin (intravenous and intramuscular)	3	194	7·9	Yes
Sturm *et al*[19]	NS	Bacteraemia	Netilmicin (intravenous)	3	72	5·4	No
De Vries *et al*[20]	Surgical	Intra-abdominal	Netilmicin (intravenous)	3	211	6·6	Yes
Nordstrom *et al*[7]	NS	Diverse	Two drugs (intramuscular)†	3	60	10·0	Yes
Ter Braak *et al*[21]	NS	Diverse	Netilmicin (intravenous)	2 or 3	141	8·4	Yes
Giamarellou *et al*[22]	NS	Diverse	Amikacin (intravenous)	2	60	10·0	Yes
Marik *et al*[23]	Intensive care unit	Diverse	Amikacin (intravenous)	2	348	7·5	Yes
Van der Auwera *et al*[24]	Cancer	Urinary	Netilmicin (intravenous)	3	60	7·0	No
Vigano *et al*[25]	Paediatric	Urinary	Netilmicin (intramuscular)	3	150	10·0	No
Calandra *et al*[26]	Febrile neutropenia	Diverse	Amikacin (intravenous)	3	677	8·3	Yes
Gonzaiez *et al*[27]	NR	NR	Gentamicin (intravenous)	3	54	NR	Yes
Maller *et al*[28]	NS	Diverse	Amikacin (intravenous)	2	316	NR	Yes
Prins *et al*[1]	NS	Diverse	Gentamicin (intravenous)	3	123	5·8	Yes
Rozdzinski *et al*[4]	Febrile neutropenia	Diverse	Netilmicin (intravenous)	3	143	8·0	Yes
Vanhaeverbeek *et al*[29]	NS	Diverse	Amikacin (intravenous)	2	39	9·9	Yes
Gibson *et al*[30]	Febrile neutropenia	Diverse	Tobramycin (intravenous)	3	95	NR	Yes

NR=Not reported. NS=Inpatient service, not further specified. *No of patients randomised. †Two arms with netilmicin and two arms with gentamicin.

glycosides were used for prophylaxis for colorectal surgery.[31] We excluded two of the 21 eligible trials from the main clinical efficacy analysis because the beta lactam antibiotics used in each arm were systematically different. One study compared amikacin and ceftriaxone given once daily with amikacin and ceftazidime given thrice daily.[26] This study used amphotericin extensively and so was also excluded from the main analysis of nephrotoxicity. The other study compared tobramycin plus ceftriaxone given once daily with tobramycin plus azlocillin given thrice daily.[30] This study provided no extractable data on toxicity.

Most of the trials were conducted in Europe. The clinical settings were diverse. The infections were usually serious or potentially serious, including bacteraemia, surgical abdominal infections, urinary tract infections, pelvic inflammatory disease, pneumonia, and combinations of these. Most of the studies were done in adults, but a substantial number of children were studied in two trials.[23 25] Patients with abnormal renal function and known auditory or vestibular impairment were typically not eligible for enrolment. The aminoglycosides studied were netilmicin (12 studies), amikacin (5 studies), gentamicin (3 studies), sisomicin (1 study), and tobramycin (1 study). Aminoglycosides were administered intravenously in 16 trials, by intramuscular injection in three, and by both routes in two. A single daily dose was compared with twice daily administration in five trials and with thrice daily administration in 14 trials; two trials used both twice and thrice daily doses. The mean duration of aminoglycoside treatment varied from 5·4 to 10 days, but individual patients were treated for as short a time as two days or for as long as more than three weeks. Other antibiotics, usually beta lactams, were used concomitantly in all but four of the trials.

CLINICAL EFFICACY

Table 2 shows the numbers of clinical failures in each study. Reflecting the heterogeneity across patient

Table 2—*Results of 19 trials comparing dosing regimens of aminoglycosides with regard to nephrotoxicity and clinical failures*

		No of nephrotoxic events/patients		No of clinical failures/patients*	
	Main definition of nephrotoxicity (serum creatinine concentration)	Single daily dose	Multiple daily doses	Single daily dose	Multiple daily doses
Gonzalez *et al*[27]	Increase >45 μmol/l	5/27	4/27	6/27	9/27
Prins *et al*[29]	Increase >45 μmol/l	2/59	11/64	3/59	7/64
Giamarellou *et al*[22]	Increase >44·2 μmol/l	3/30	1/30	0/30	5/30
Maller *et al*[28]	Increase >44·2 μmol/l	9/164	11/152	19/164	13/152
Sturm *et al*[19]	Increase >40 μmol/l	1/36	0/36	0/36	2/36
Marik *et al*[23]	Increase >35 μmol/l	1/155	4/145	26/155	49/145
Muijsken *et al*[15]	Increase >30 μmol/l	2/29	5/36	8/32	6/35
Vigano *et al*[25]	Increase >26·5 μmol/l	2/74	2/70	1/74	0/70
Hansen *et al*[14]	Increase >25 μmol/l	0/31	3/33	2/28	11/31
De Vries *et al*[20]	Increase >50% over baseline	9/81	8/90	6/80	3/76
Mauracher *et al*[18]	Increase >50% over baseline	2/92	2/93	0/92	6/93
Nordstrom *et al*[7]	Increase >50% over baseline†	3/29	5/25	3/29	4/27
Rozdzinski *et al*[4]	Increase >50% over baseline	3/71	4/72	16/71	16/72
Ter Braak *et al*[21]	Increase >50% over baseline	14/69	17/72	10/69	8/72
Tulkens *et al*[16]	Increase >20% over baseline	0/19	0/19	0/19	0/19
Van der Auwera *et al*[24]	Increase >20% over baseline†	1/30	3/30	0/30	2/30
Klastersky *et al*[5]	Concentration >132 μmol/l	3/25	3/25	11/25	3/25
Vanhaeverbeek *et al*[29]	Not quantified ("modest increase")	0/19	1/20	0/19	0/20
Hollender *et al*[17]	Not specified	0/58	3/56	0/58	1/56

*When patients were randomised for more than one episode of infection, the number refers to the total number of episodes.
†Alternative definitions of nephrotoxicity were also used.

populations, clinical failure was defined differently in different studies; in some studies (mainly of patients with urinary tract infections or bacteraemia), it coincided with bacteriological failure (that is, failure to eradicate a micro-organism).

As shown in figure 1, there was a trend towards fewer antibiotic failures with a single daily dose. This trend reached significance (P=0·02) only with the fixed effects model. The estimate of the benefit was non-significant when the random effects model was used (risk ratio 0·83 (95% confidence interval 0·57 to 1·21), P=0·32). Inclusion of the two studies that compared combinations of aminoglycoside regimens with different beta lactam antibiotics[26 30] resulted in a pooled estimate of 0·90 (0·67 to 1·21) with the random effects model and 0·91 (0·78 to 1·07) with the fixed effects model.

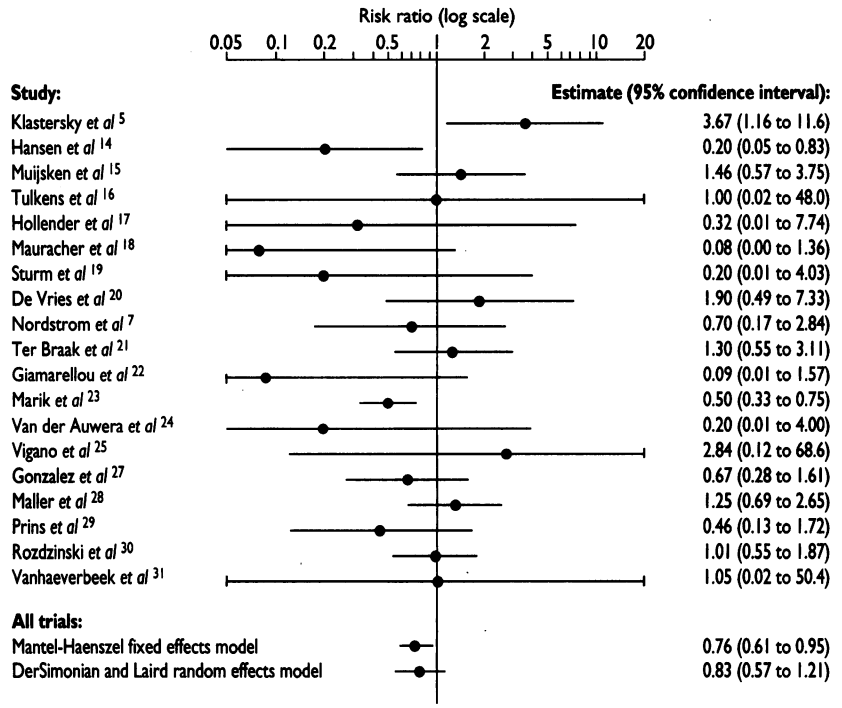

Fig 1—*Relative risk of clinical failure of treatment with single daily doses of aminoglycosides compared with multiple daily doses*

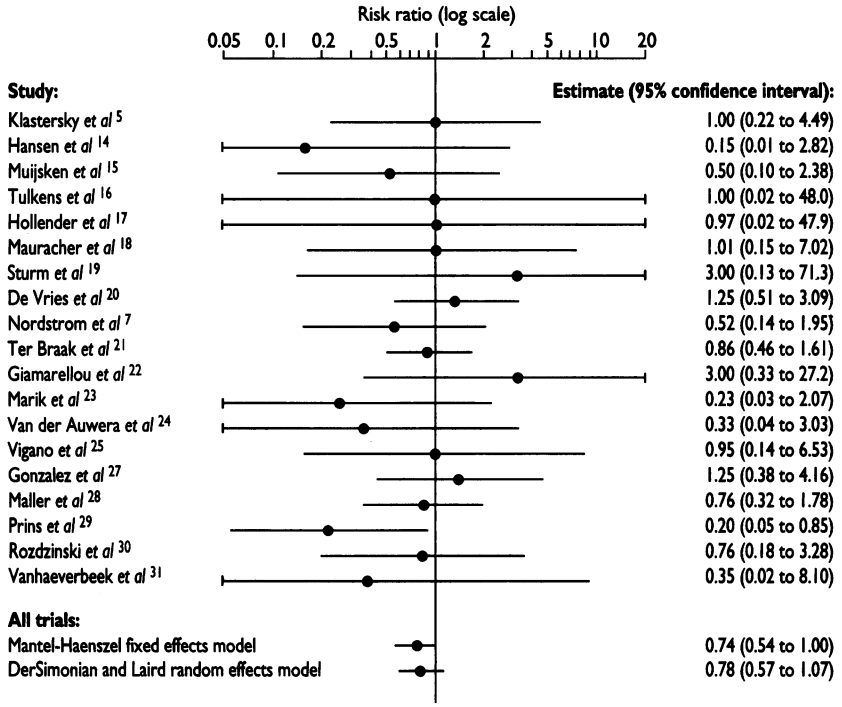

Fig 2—*Relative risk of nephrotoxicity with single daily doses of aminoglycosides compared with multiple daily doses*

Heterogeneity of trials

The risk ratios across the different trials showed substantial and significant heterogeneity (variance among studies=0·22, P=0·03). This heterogeneity throws into question the meaningfulness of the pooled estimate derived from the fixed effects model. To explore this heterogeneity, we examined the effect of several variables on clinical failures. The nature of the studies did not allow for a useful standardisation of the clinical severity of the infections. Thirteen studies offered data on the percentage of pseudomonas species among the total number of isolates in the study. Most of these isolates were *Pseudomonas aeruginosa*. Compared with other gram negative rods such as *Escherichia coli*, *Proteus*, and *Klebsiella*, *Pseudomonas* is less susceptible to commonly used antibiotics. Therefore, infections caused by this species were likely to provide better discrimination of the efficacy of one aminoglycoside regimen compared with another.

Linear regression analysis showed that for every 1% increase in the percentage of pseudomonas isolates, the risk of failures with multiple daily doses relative to that with single doses increased significantly by about 4·1% (95% confidence interval 1·6 to 6·6). This does not necessarily mean that patients with pseudomonas infection did better with a single daily dose, but only that studies with high relative prevalence of pseudomonas isolates were more likely to have reduced failures with a single daily dose.

The relative risk of failure was not associated with the failure rate of the treatment arm with multiple daily doses, year of publication of the study, frequency of multiple daily doses, mean duration of aminoglycoside treatment, or use of concurrent antibiotics. For the subgroups of patients with febrile neutropenia and paediatric patients, there was a non-significant reduction in favour of a single daily dose (risk ratios 0·52 (0·11 to 2·46) and 0·95 (0·17 to 5·37) respectively). Finally, the specific drug used bore no significant relation to the relative risk of failure in the two treatment arms of the study. An exception was the one study of sisomicin, which is not commercially available.[5] Only this trial showed a significantly better efficacy with multiple daily doses (fig 1). Its exclusion reduced the heterogeneity among the other studies (variance among studies=0·12, P=0·13).

NEPHROTOXICITY

Table 2 shows that the definition of nephrotoxicity varied among the trials, although most trials used fairly similar criteria (an increase in creatinine concentration of 50% or 25-45 μmol/l over the pretreatment value). With these criteria, the incidence of nephrotoxicity varied from zero to 23·6% among the trials. The overall rate of nephrotoxicity (weighted by study size) was 5·5% for the single daily dose regimen and 7·7% in the multiple dose regimens.

The pooled estimate (fig 2) suggests that, compared with multiple doses, single dose regimens reduced nephrotoxicity. The risk ratio estimate was 0·74 (0·54 to 1·00) with the fixed effects model and 0·78 (0·57 to 1·07) with random effects calculations. While the random effects model estimate was not significant at the 0·05 level of significance, the fixed effects estimate was marginally significant (P=0·05). Risk ratios across studies seemed homogeneous (variance among studies=0, P=0·90), and the confidence intervals from the fixed and random effects models were very similar. Thus, there is statistical evidence that single daily dosing is less nephrotoxic than multiple daily dosing.

Sensitivity analyses with alternative definitions of nephrotoxicity showed that the risk ratio estimate did not change (fixed effects estimate varying from 0·71 to 0·76, P=0·04 to 0·07). Inclusion of the study that

allowed use of amphotericin[26] resulted in a pooled risk ratio estimate of 0·84 (0·62 to 1·14) from the random effects model and 0·80 (0·60 to 1·07) from the fixed effects model. However, if the cases of nephrotoxicity occurring after use of amphotericin were excluded from this study, the pooled risk ratio estimate was 0·76 (0·55 to 1·03) by the random effects model and 0·71 (0·52 to 0·96) by the fixed effects model.

Further analyses showed that the control rate of nephrotoxicity, the frequency of multiple dosing, the use of concurrent antibiotics, the specific aminoglycoside used, the year of publication of the study, the mean duration of treatment, and the percentage of pseudomonas isolates were not associated with the relative risk of nephrotoxicity between the two regimens. There was a trend in favour of single daily doses for both febrile neutropenic patients (risk ratio 0·45 (0·16 to 1·23)) and paediatric patients (risk ratio 0·55 (0·11 to 2·78)).

Trials that reported the mean or median time to development of nephrotoxicity in each arm[1 4 20 21 26] showed that toxicity usually occurred later in patients who received single daily doses rather than multiple doses.[1 4 21 26]

OTOTOXICITY

The two treatment regimens showed no difference in ototoxicity. The pooled risk ratio for the 14 studies that gave data on ototoxicity was 1·09 (0·68 to 1·75) by the fixed effects model. In the 11 studies that assessed cochlear toxicity by audiometry the pooled risk ratio was 1·03 (0·60 to 1·75). Similarly, for the eight studies that reported on vestibular toxicity, the relative risk was 1·11 (0·48 to 2·61). The results of the fixed and random effects models were identical. While the two regimens seemed equivalent with regard to ototoxicity, a clinically important difference could have been missed. A total of 3330 patients would have been required to detect a 50% reduction in risk, assuming 80% statistical power, a 5% level of significance, and control rate of ototoxicity equal to 3·3% (the control rate weighted by size in the 14 studies). This analysis primarily reflects the incomplete data on ototoxic outcomes, rather than showing whether one regimen is less ototoxic than the other. Audiometry was performed in only 855 patients, and vestibular toxicity was recorded only when clinically obvious.

OVERALL MORTALITY

The two treatment regimens showed no significant difference in the overall mortality of patients. The pooled relative risk from the 14 studies that provided mortality data showed a non-significant reduction with the once daily regimen (risk ratio 0·87 (0·58 to 1·28) by fixed effects model, 0·87 (0·58 to 1·30) by random effects model). Because mortality is affected by several other factors pertaining to the underlying disease of each patient, it is unlikely that the superiority of a regimen would have been clearly reflected in a survival benefit.

Discussion

There has been much interest in once daily dosing regimens of aminoglycosides. Studies in animals have shown that once daily regimens are as effective as and less toxic than multiple daily dosing regimens. The results of this meta-analysis of 21 randomised trials comparing single daily doses of aminoglycosides with multiple daily doses support the superiority of once daily regimens.

CLINICAL EFFICACY

Several in vitro observations mitigate concerns that there might be breakthrough of infection during the interval between single daily doses. These observations include the fact that aminoglycosides have a long "post-antibiotic effect,"[35–39] exhibit "concentration-dependent" bactericidal effects,[37–39] and exert their greatest killing effect after the first exposure.[40 41] Finally, once daily dosing avoids the problem of suboptimal peak serum concentrations, which has been a predictor of poor outcome in clinical studies.[42–45] Our meta-analysis showed a trend favouring single daily doses in terms of efficacy. This trend did not reach statistical significance because of the substantial heterogeneity among the different trials. The heterogeneity is not surprising given the diversity in the patient populations studied and in the way that antibiotic failure was defined in each study.

Other concerns relate to the activity of once daily dosing regimens in patients with neutropenia and those with infections caused by *Pseudomonas aeruginosa*, a relatively antibiotic resistant species. However, studies in neutropenic animals have shown a once daily regimen to be of equivalent or superior efficacy,[46–48] and our meta-analysis showed no loss of efficacy with a single daily dose in neutropenic patients. Our analysis actually suggested that a single dose was superior to multiple doses when the percentage of pseudomonas isolates in a study was higher. This finding should be interpreted with caution, as it does not necessarily mean that individual patients with pseudomonas infections did better than other patients with once daily doses. Such a conclusion would require a correlation between the infecting species and the outcome in individual patients, but such data were not available to us.

TOXICITY OF DOSING REGIMENS

Animal studies have shown that once daily regimens are less nephrotoxic[49–53] and possibly less ototoxic[54–57] than multiple dose regimens. Reductions in toxicity by once daily dosing may be related to saturable uptake of the drugs by the renal cortex[58 59] and the inner ear hair cells.[60 61] Indeed, reduced renal cortical accumulation with less frequent dosing has been shown in humans.[59 62] Correspondingly, continuous infusion of aminoglycosides in humans has resulted in a high rate of nephrotoxicity.[63]

Our meta-analysis concurs with these experimental data. It showed that the risk of nephrotoxicity was reduced by 26% in patients given single daily doses, and this estimate seemed to be uniform for different aminoglycosides. Of course, the studies mainly examined patients with no renal impairment. The situation may be different in patients with pre-existing renal dysfunction. However, wide dosing intervals are typically used in such patients.

Although our meta-analysis found no difference in the incidence of ototoxicity, the confidence intervals were wide and the power to detect a clinically meaningful difference was low. Audiometric testing was rarely performed, and vestibular toxicity was reported only incidentally. Future studies might attempt to address these issues more rigidly.

CONCLUSIONS

Can these results favouring single doses of aminoglycosides be generalised to all drugs in this class and to all clinical settings? There was extensive diversity in the underlying diseases of patients, in the infections being treated, and in the drugs used in the trials that we overviewed in this meta-analysis. Subgroup analyses showed trends towards a reduction in antibiotic failures and nephrotoxicity with single doses of aminoglycosides for major patient subgroups, including children and patients with febrile neutropenia. These trends were not significant, perhaps because of the relatively small number of patients in

Key messages

- Many randomised trials have compared relative efficacy and toxicity of single daily doses of aminoglycosides with multiple daily doses, but most have been too small to show any significant difference
- This meta-analysis shows that single daily doses of aminoglycosides were about 25% less nephrotoxic than and at least as effective clinically as multiple daily doses
- The dosing schedule did not significantly affect the incidence of ototoxicity, but the power to detect a difference was small
- Once daily dosing was non-significantly more effective in patients with febrile neutropenia and in children, and the apparent benefit of once daily dosing increased with increasing proportion of pseudomonas isolates in a trial
- Besides the convenience of once daily dosing, reduced costs of drug administration and omission of measurements of peak antibiotic concentrations should result in substantial cost savings

the subgroups. No subgroup of patients seemed to have an increased rate of nephrotoxicity from single doses. Moreover, our findings were consistent for several different aminoglycosides. The one exception was the increased rate of failures with single doses in a small, early trial of sisomicin, an aminoglycoside that is no longer in use. We believe that the results obtained in this meta-analysis are probably broadly applicable, but further clinical trials in specific clinical settings should validate this hypothesis. In this regard, future trials may also address the nephrotoxicity of single daily doses in patients at high baseline risk of nephrotoxicity —such as when other nephrotoxic drugs are given concomitantly or when there is pre-existing mild renal impairment.

Although we have not carried out a formal cost-analysis, it is obvious that the once daily regimens have the potential for cost savings. Several aminoglycosides are available in inexpensive, generic formulations. The major costs of treatment are the costs of administering the drugs, monitoring serum concentrations, and managing side effects. The costs of drug administration should be reduced in proportion as the number of daily doses is reduced. The utility of measuring serum concentrations of aminoglycosides has been debated, and the data are inconclusive.[64] However, with once daily dosing there should be no indication for measuring the peak serum values. A reduction in the incidence of nephrotoxicity by once daily dosing should result in further savings. Another merit of once daily dosing is its convenience, which makes it potentially useful for outpatient treatments. Overall, once daily dosing of aminoglycosides should become the routine way these drugs are administered in clinical practice.

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Commentary: single daily dose of aminoglycoside is the preferred mode of administration

Fiona Smaill

Favourable pharmacokinetics, the results of individual trials, and the recommendations of experts all support once daily administration of aminoglycosides, but the change from a multiple daily dosing regimen has been slow. If better evidence was needed to convince clinicians, this meta-analysis of the results from 21 randomised studies comparing single and multiple daily doses now provides it.

Design of the review

Overall this review is methodologically sound, although there was no specific search for unpublished data or of the literature in other languages. Search strategies were adequately described, data were abstracted in an explicit and unbiased manner, and relevant and clinically useful outcomes were analysed.[1] A meta-analysis is only as good as the trials included. Differences in methodological quality may explain variation in the results, with more rigorous trials generally yielding results that were closer to the "truth." Although experts cannot agree as to how best to assess and report the quality of trials, this meta-analysis should have included some measure of quality; results are more compelling if they are known to come from strong studies.

The studies included in this review had important differences in patient characteristics, clinical setting, type of aminoglycoside used, and outcome measured. Readers need to decide if these variables were so different that it was not sensible to combine the studies. To test how likely it is that any differences among individual studies' results represented real differences due to factors other than chance, a test of heterogeneity should be performed. If the test of heterogeneity is significant, differences among the studies probably exist and, if these differences cannot be satisfactorily explained, an argument can be made not to aggregate the trials.

The authors of this meta-analysis admit that there was substantial heterogeneity of the risk ratios across studies, which they hypothesise was in part due to the diverse patient populations studied. Their explanations make sense, and to combine the studies seems quite reasonable.

Conclusions

The minor criticisms of the methods used in this meta-analysis should not be allowed to detract from the authors' conclusions. A single daily dose of aminoglycoside makes sense microbiologically and is less nephrotoxic, at least as effective, and costs less than multiple daily dosing.

Clinicians who still doubt the benefits of once daily dosing may argue that, until there is better information as to how to determine the appropriate dose and how to monitor treatment, the status quo should be maintained. Although routine monitoring of serum aminoglycoside concentrations is an accepted standard of practice, there is only weak evidence to support it.[2] With once daily dosing, we may at last be able to establish guidelines for monitoring aminoglycosides that are based on well controlled studies. Evaluating different monitoring strategies should be a research priority. Until there is evidence that using a measure of the clearance of the aminoglycoside to adjust the dose is associated with improved outcome or reduced toxicity, I do not recommend routine monitoring of concentrations.

Several questions remain. Can once daily dosing safely be used during pregnancy or to treat endocarditis? How should we determine doses of aminoglycosides for patients with renal impairment or for elderly or obese patients? There is some confusion as to how precise the dosing algorithms should be, whether a complex formula to calculate lean body weight is necessary, and how to adjust the dose for

Pathology and Medicine, McMaster University Medical Centre, Hamilton, Ontario L8N 3Z5, Canada
Fiona Smaill, *associate professor*