ORIGINAL ARTICLE

Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis

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Objectives: To review the evidence from controlled clinical trials of neonates given equal daily aminoglycoside doses as extended interval dosing (dosage interval typically 24 hours in term and 36–48 hours in immature neonates) compared with traditional dosing (dosage interval typically 8–12 hours in term and 12–24 hours in immature neonates).
Design: Systematic review and meta-analysis of controlled trials found in electronic databases, trial registers, and references in reviews and selected trials.
Settings: The selected trials were blinded and assessed for methodological quality. Each trial's own predefined criteria for treatment failure, nephrotoxicity, ototoxicity, and therapeutic serum drug concentrations were used.
Subjects: Controlled trials of neonatal aminoglycoside treatment in which equal aminoglycoside daily doses were given at traditional and extended dosage intervals.
Main outcome measures: Serum drug concentrations outside the therapeutic range. Treatment failure and toxicity.
Results: Sixteen trials involving 823 neonates met the inclusion criteria for the systematic review. Twelve trials involving 698 neonates were included in the meta-analysis of the pharmacokinetics. Compared with traditional dosing, extended interval dosing was associated with a significantly lower risk of both peak (summary risk ratio 0.50, 95% confidence interval 0.26 to 0.94) and trough (0.36, 0.25 to 0.56) serum drug concentrations outside the therapeutic range. Accurate information on treatment failure was obtained in nine trials involving 555 neonates. One trial reported treatment failure. In this trial two neonates in the traditional dosing group did not respond to treatment within 72 hours. Nephrotoxicity was investigated in 589 neonates in 12 trials and ototoxicity in 210 neonates in four trials, with no significant differences between the two dosing regimens.
Conclusions: Extended interval dosing of aminoglycosides in neonates is safe and effective, with a reduced risk of serum drug concentrations outside the therapeutic range.

Aminoglycosides, usually combined with a betalactam, are widely used for neonatal sepsis. The serum drug concentration (SDC) should be within the therapeutic range to secure effect and avoid toxicity. In adult patients, an early high peak SDC has been associated with an improved clinical outcome in severe infections.[1] In extended interval dosing (EID) a higher dose is given less frequently than in traditional dosing (TD). Meta-analysis of trials in adults and children have shown equal or better performance with EID than with TD.[2–9] Several trials have addressed the pharmacokinetic performance of EID compared with TD in neonates, often without sufficient statistical power. The dose and dosage interval for neonatal aminoglycoside dosing varies widely among guidelines. We have carried out a systematic review of controlled trials in neonates given aminoglycosides as EID or TD. We compared efficacy and toxicity and performed a meta-analysis of the pharmacokinetics based on each trial's own predefined criteria for treatment failure, nephrotoxicity, ototoxicity, and therapeutic SDC.

METHODS

Search strategy

The databases Biosis, Cochrane, Embase, and Medline were searched from their inception to October 2004. Trials in any language were considered. References in reviews and the trials found were searched manually. Electronic trial registers were searched for unpublished and ongoing trials (details shown in box 1). The manufacturers of aminoglycosides were not contacted for unpublished trials.

Selection

Controlled clinical trials were evaluated for inclusion on the basis of the study design, the target population, and the end points reported (box 2). In trials with subgroups fulfilling the criteria, these were included if data extraction was possible.

Data extracted

From each trial, the following data were extracted: inclusion criteria, type of aminoglycoside used, dose and dosage interval, therapeutic range for peak and trough SDC, number of neonates evaluated, prevalence of therapeutic SDC, toxicity, and clinical cure rate.

Data abstraction

EN performed the search and blinded the trials. HJB and KOW independently filled in a form for data extraction and assessed the presence of possible systematic errors[10] in each trial. Disagreements were solved by consensus. Data were extracted from final reports, except for one question concerning clinical cure rate. Some authors did not report clinical cure rate completely and were contacted by mail or email for additional information.

Abbreviations: CI, confidence interval; EID, extended interval dosing, typically 4–5 mg/kg gentamicin given to neonates at dosage interval 24 hours or longer; SDC, serum drug concentration; TD, traditional dosing, typically 2–3 mg/kg gentamicin given to neonates at dosage interval 8–24 hours

Box 1: search methods

Bibliographic databases (to October 2004)
- Biosis (Winspirs)
- Cochrane controlled trial register (2004 issue 4)
- Embase (Winspirs)
- Medline (PubMed)

Search terms
- (newborn OR newborns OR neonate OR neonates OR infant OR infants) AND (aminoglycoside OR aminoglycosides OR gentamicin OR tobramycin OR netilmicin OR amikacin OR dibekacin OR isepamicin)

Reference lists
- Selected reports and review articles

Other resources (October 2004)
- United Kingdom National Research Register of ongoing health research (www.doh.gov.uk/research/nrr.htm)
- Current Science register of controlled trials (www.controlled-trials.com)

Box 2: inclusion criteria

Design
- Controlled clinical trials of neonates given the same type of aminoglycoside as EID or TD
- Maximum 20% difference in daily dose between the EID and the TD group
- The EID dosage interval at least 24 hours
- The EID dosage interval at least 50% longer than the TD dosage interval

Target population
- Neonates aged less than 30 days at start of treatment

End points
- Clinical cure rate, toxicity, or prevalence of peak and trough SDC inside and outside the therapeutic range reported in both the EID and TD group

Outcome measures
The primary outcome in the meta-analysis was the SDC within and outside the therapeutic range. The occurrence of treatment failure and toxicity was recorded. For each trial, we used its own predefined criteria for treatment failure, toxicity, and therapeutic SDC.

Validity assessment
The presence of systematic errors[11] was assessed in each trial (details given in box 3), and all trials were classified according to design.

Quantitative data synthesis
The main results are presented as estimates of summary risk ratios. A risk ratio less than one reflects a lower risk of SDC outside the therapeutic range in the EID group than in the TD group. Each trial was weighted by the inverse variance of the natural logarithm of risk ratio. We considered the finding of heterogeneity at the 0.1 level of significance as proof of the random effects model being more suitable than the fixed effects model,[12] and we chose the same level of significance for heterogeneity between subgroups. In the case of no events, 0.5 was added to each cell of the table. We performed a subgroup analysis based on the a priori hypothesis that the therapeutic peak SDC range chosen could influence the difference in pharmacokinetic performance between the EID and TD groups. Two sided p values and 95% confidence intervals (CI) were used. We performed tests for the presence of publication bias (funnel plot asymmetry[13]) and sensitivity analyses[14] for design (randomised versus other trials) and internal validity (bias versus no bias). The regression analyses for funnel plot asymmetry were performed using SPSS 11.0.0 for Windows. All other analyses were performed using EasyMA.[15]

Box 3: assessment of internal validity—extent to which systematic error (bias) is minimised in clinical trials[11]
- Selection bias: biased allocation to comparison groups
- Performance bias: unequal provision of care apart from treatment under evaluation
- Detection bias: biased assessment of outcome
- Attrition bias: biased occurrence and handling of deviation from protocol and loss of follow up

RESULTS
We found 16 trials[16–31] from which data for 823 neonates could be used (table 1). In five trials[16–19 31] only a subgroup of neonates fulfilled our inclusion criteria. All trials were found in electronic databases.

Trial characteristics
Eleven of the trials[18–20 22–25 27–30] had a prospective randomised design, four[16 17 21 31] used a historical control group, and one [26] had a cohort design. Asphyxia, risk of deafness, kidney malformations, and concomitant use of potentially nephrotoxic or ototoxic drugs were often used exclusion criteria. Amikacin was studied in two trials.[18 30] In all other trials, gentamicin was used. The daily amikacin dose was 15 mg/kg in both trials. The daily gentamicin dose was 2.5–5 mg/kg. The dosage interval was 12 hours in the TD group and 24 hours in the EID group in all but two trials. Gooding *et al*[16] used a 24 hour TD dosage interval and 36 hour EID dosage interval, and Mercado *et al*[19] compared 24 hours in the TD group with 48 hours in the EID group.

Methodological quality assessment
In general, design and methodology were seldom completely reported. Often the process of randomisation and the blinding towards both the caregivers and those determining outcome was not described. Four trials used a historical control group. In two trials[17 21] the control group consisted of neonates given aminoglycoside treatment within a specified

Box 4: number of hits in the initial search and trials included from each database

Database	Biosis	Cochrane	Embase	PubMed
No of hits	574	197	4788	5408
Trials included	8	11	13	15

Table 1 Design, inclusion criteria, and number of neonates included from the relevant trials (see box 3 for criteria used for evaluation on systematic errors)

Trial	Kind of control group	Year published	Gestational age (weeks)	Birth weight (g)	Drug	Daily dose (EID/TD) (mg/kg/24 h)	Dosage interval (EID/TD) (h)	Therapeutic peak SDC range (mg/l)	Therapeutic trough SDC range (mg/l)	Systematic error (bias in internal validity)	Number of neonates included
Gooding *et al*[16]	Historical	2001	⩽28	*	Gentamicin	2.67/2.5	36/24	5–8	0–1.5	Yes	57
Mercado [19]	Randomised	2004	*	750–1500	Gentamicin	2.5/2.5	48/24	5–12	0–2	No	20
Solomon *et al*[25]	Randomised	1999	⩾32	*	Gentamicin	4/5	24/12	4–10	0–2	Yes	73
Krishnan *et al*[29]	Randomised	1997	32–36	*	Gentamicin	4/5	24/12	>5	0–2	No	18
Kosalaraksa *et al*[20]	Randomised	2004	*	⩽2000	Gentamicin	5/5	24/12	4–12	0–2	Yes	64
Hayani *et al*[22]	Randomised	1997	⩾34	⩾2000	Gentamicin	5/5	24/12	5–18	0–1.5	Yes	24
						4–5/4–5	24/12	5–18 (EID)	0–1.5 (EID)	Yes	54
								4–12 (TD)	0–2 (TD)		
Choligeat *et al*[24]	Randomised	2001	⩾34	⩾2000	Gentamicin						
Thureen *et al*[26]	Cohort	1999	⩾34	*	Gentamicin	5/5	24/12	5–10	0–2	Yes	55
Langhendries *et al*[18]	Randomised	1993	⩾34	*	Amikacin	15/15	24/12	Not stated	Not stated	Yes	22
Andrews *et al*[31]	Historical	2000	⩾36	*	Gentamicin	5/5	24/12	>6	0–2	Yes	49
Katze *et al*[30]	Randomised	1999	37–42	*	Amikacin	15/15	24/12	>20	0–10	No	40
Skopnik *et al*[23]	Randomised	1992	⩾37	⩾2500	Gentamicin	4/4	24/12	4–12	0–2	No	20
Lundergan *et al*[17]	Historical	1999	⩾2500	⩾2500	Gentamicin	4/5	24/12	5–12	0–2	Yes	121
de Alba *et al*[28]	Randomised	1998	⩾37	*	Gentamicin	5/5	24/12	6–12	0–2	No	65
Alsaedi[21]	Historical	2003	⩾1200	⩾2500	Gentamicin	4/5	24/12	5–12	0–2	Yes	100
Agarwal *et al*[27]	Randomised	2002	37–42	⩾2500	Gentamicin	4/5	24/12	5–12	0–2	No	41

*Not an inclusion criterion in the trial.

period. One trial[31] used a group matched for gestational age, whereas the last trial[16] only described a retrospective audit being conducted. In the cohort trial,[26] the cohorts were defined from the time treatment was given. Different daily dose and different point of time for assessing SDCs were the bias in internal validity that occurred most often. Possible systematic errors were found in all but six trials.[19 23 27–30]

Quantitative data synthesis

SDCs inside and outside the therapeutic range were described sufficiently for inclusion in the meta-analysis in 12 of 16 trials[16 17 20–27 30 31] (table 2). We used SDCs assessed at the most equal point of time in the two groups, preferably 48–72 hours after start of treatment. Eleven trials[16 17 20–27 31] used gentamicin and one[30] used amikacin.

When combining all trials, 91 of 355 (25.6%) peak SDCs in neonates given TD and 28 of 343 (8.2%) in neonates given EID were outside the therapeutic range. The summary risk ratio for peak SDC outside the therapeutic range was 0.50 (95% CI 0.26 to 0.94, p = 0.033). A total of 108 of 355 (30.4%) trough SDCs in the TD group and 21 of 343 (6.1%) in the EID group were outside the therapeutic range. The summary risk ratio was 0.36 (95% CI 0.25 to 0.56, p<0.001). No clear evidence of publication bias[13] was found for either peak or trough risk ratio (p>0.10).

The therapeutic peak range

Adequate peak SDC, for gentamicin and tobramycin above 5 mg/l and for amikacin above 20 mg/l, has in adult patients been associated with an improved clinical outcome in severe infections.[1] In the four trials[20 23–25] accepting lower peak SDC in the TD group, the summary peak risk ratio showed no significant difference between the two dosing regimens (fig 1). The summary risk ratio was 1.12 (95% CI 0.56 to 2.24, p = 0.76).

In the trials aiming at a higher peak SDC, the summary peak risk ratio was significantly in favour of EID (0.38; 95% CI 0.24 to 0.61; p<0.001). The difference in summary risk ratio between these subgroups was significant (p<0.1).

Design

There were significant differences in peak risk ratio between randomised and non-randomised trials (p<0.1) (fig 2). The summary peak risk ratio in the randomised trials was 0.84 (95% CI 0.45 to 1.58, p = 0.60). When the trials with low therapeutic peak range[20 23–25] were excluded, the summary risk ratio was 0.28 (95% CI 0.07 to 1.12, p = 0.072). The non-randomised trials all had high therapeutic peak range, and the summary risk ratio for these trials was 0.40 (95% CI 0.24 to 0.66, p<0.001). There was no significant difference in summary peak risk ratio between randomised and non-randomised trials when trials with low therapeutic peak range were excluded (p>0.1).

There were no significant differences in summary trough risk ratios between randomised and non-randomised trials (p>0.1) (fig 3). The summary trough risk ratio was significantly in favour of EID for the six randomised trials (0.42; 95% CI 0.26 to 0.66; p<0.001).

Bias in internal validity

There were no significant differences in summary peak or trough risk ratio between trials with and without systematic errors (p>0.1). In trials without systematic errors the summary peak risk ratio was 0.35 (95% CI 0.08 to 1.51, p = 0.16). The summary trough risk ratio was 0.24 (95% CI 0.04 to 1.69, p = 0.15).

Table 2 Pharmacokinetics in trials included in the meta-analysis

Trial	No of neonates included in the meta-analysis	Prevalence of peak SDC outside therapeutic range (outside/total (%))		Prevalence of trough SDC outside therapeutic range (outside/total (%))	
		TD group	EID group	TD group	EID group
Skopnik *et al*[23]	20	0/10 (0.0%)	0/10 (0.0%)	0/10 (0.0%)	0/10 (0.0%)
Hayani *et al*[22]	24	2/13 (15.4%)	0/11 (0.0%)	6/13 (46.2%)	1/11 (9.1%)
Kotze *et al*[30]	40	8/20 (40.0%)	0/20 (0.0%)	0/20 (0.0%)	0/20 (0.0%)
Agarwal *et al*[27]	41	2/21 (9.5%)	1/20 (5.0%)	9/21 (33.3%)	0/20 (0.0%)
Andrews *et al*[31]	49	21/26 (80.8%)	0/23 (0.0%)	13/26 (50.0%)	0/23 (0.0%)
Chotigeat *et al*[24]	54	1/27 (3.7%)	0/27 (0.0%)	2/27 (7.4%)	1/27 (3.7%)
Thureen *et al*[26]	55	2/28 (7.1%)	2/27 (7.4%)	14/28 (50.0%)	0/27 (0.0%)
Gooding *et al*[16]	57	29/36 (80.6%)	7/21 (3.3%)	3/36 (8.3%)	2/21 (9.5%)
Kosalaraksa *et al*[20]	64	1/31 (3.2%)	7/33 (21.2%)	21/31 (67.7)	8/33 (24.2%)
Solomon *et al*[25]	73	9/36 (25.0%)	8/37 (21.6%)	10/36 (27.8%)	6/37 (16.2%)
Alsaedi *et al*[21]	100	7/50 (14.0%)	3/50 (6.0%)	13/50 (26.0%)	3/50 (6.0%)
Lundergan *et al*[17]	121	9/57 (15.8%)	0/64 (0.0%)	17/57 (29.8%)	0/64 (0.0%)
Total	698	91/355 (25.6%)	28/343 (8.2%)	108/355 (30.4%)	21/343 (6.1%)

Efficacy and toxicity

In only three trials were complete data on clinical efficacy reported. After the authors for the other trials had been contacted to ascertain if there were bacterial infections that the aminoglycoside had failed to cure, the complete clinical course was obtained for 555 neonates in nine trials. No deaths were reported. One trial[20] reported two treatment failures, both in the TD group. This trial defined clinical response as improvement within 72 hours of treatment, but clinical improvement was not evaluated in neonates with metabolic disturbances, congenital heart disease, or Gram positive bacterial infections. Of the two neonates, one was diagnosed with bacterial meningitis and the treatment was changed to cefotaxime. The other neonate, who was treated with cloxacillin and gentamicin, had a nosocomial infection after five days of treatment. Both patients had negative blood and cerebrospinal cultures.

Nephrotoxicity was investigated in 589 neonates in 12 trials.[17–24 27–30] Skopnik *et al*[23] found alanine aminopeptidase in the urine of all 20 neonates, and Kotze *et al*[30] found at least one raised creatinine concentration in 30 of 40 neonates. Of these, 13 of 20 were given TD and 17 of 20 were given EID.

Information on ototoxicity was obtainable in four trials[17 18 27 30] and 210 neonates. Lundergan *et al*[17] found one event in the EID group.

DISCUSSION

The aim of this meta-analysis was to compare the effect of EID and TD of aminoglycosides. To exclude other possible causes for differences found in pharmacokinetics, efficacy or toxicity, only trials with similar daily dose in the two groups were included. Many trials were excluded on the basis of this criterion (fig 4). Although this meta-analysis was also based on non-randomised trials, we used the QUOROM statement check list. Our findings suggest that EID of aminoglycoside in neonates is safe and effective and decreases the risk of SDCs outside the therapeutic range.

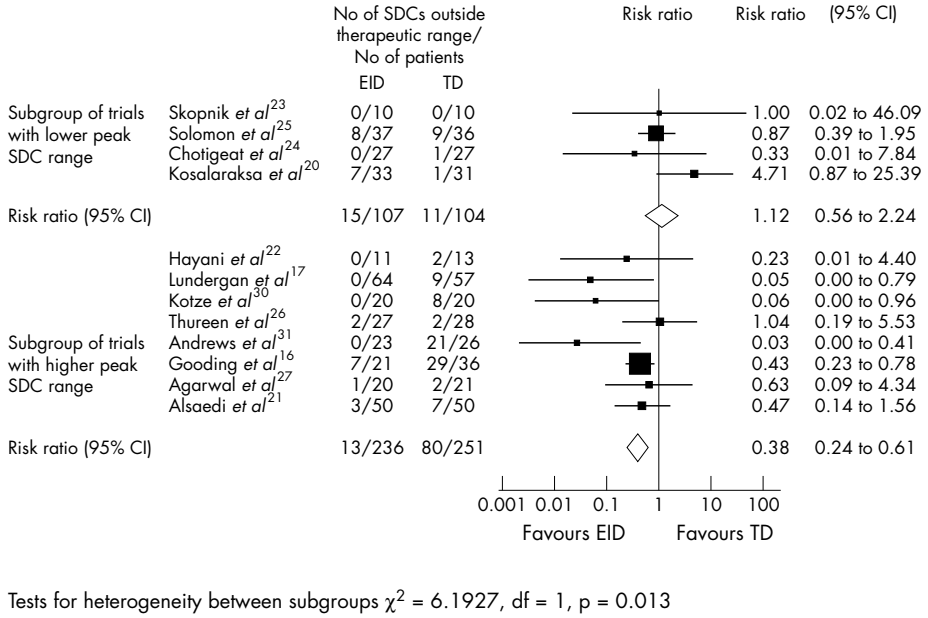
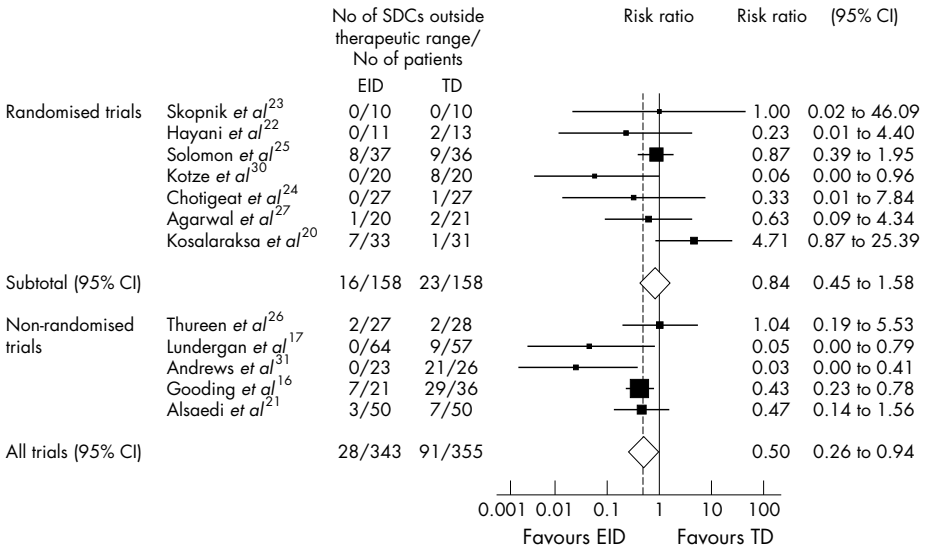


Figure 1 Trials grouped by the peak therapeutic range. Trials accepting lower peak serum drug concentration (SDC; gentamicin/tobramycin <5 mg/l, amikacin <20 mg/l) *v* trials with higher therapeutic peak range. CI, Confidence interval; EID, extended interval dosing, typically 4–5 mg/kg gentamicin given to neonates at dosage interval 24 hours or longer; TD, traditional dosing, typically 2–3 mg/kg gentamicin given to neonates at dosage interval 8–24 hours.



Tests for heterogeneity between trials $\chi^2 = 19.39$, df = 11, p = 0.054

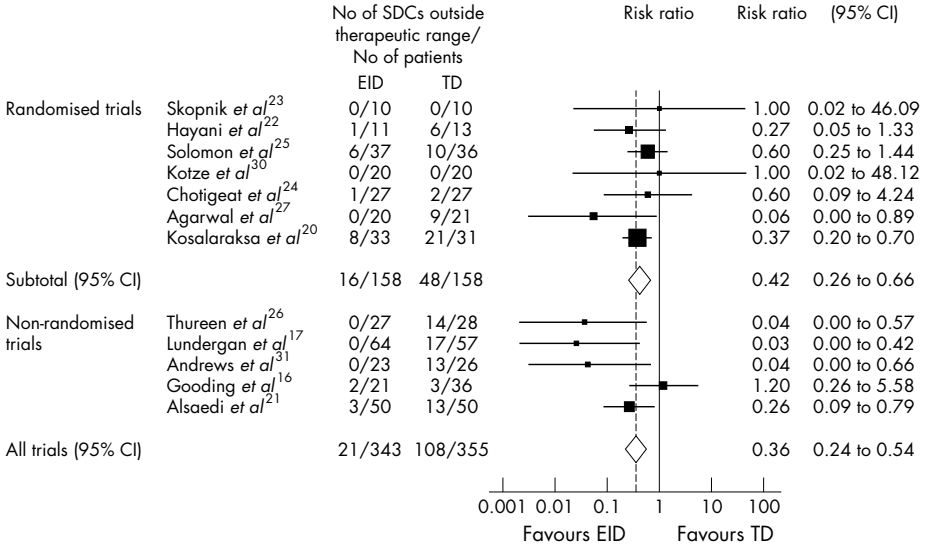
Figure 2 Randomised trials and results when non-randomised trials added: peak serum drug concentration (SDC). CI, Confidence interval; EID, extended interval dosing, typically 4–5 mg/kg gentamicin given to neonates at dosage interval 24 hours or longer; TD, traditional dosing, typically 2–3 mg/kg gentamicin given to neonates at dosage interval 8–24 hours.

Pharmacokinetics

The summary risk ratios for therapeutic SDCs were significantly in favour of the EID for both peak and trough SDCs. The summary peak risk ratio was more in favour of the EID in trials aiming at peak SDCs associated with an improved clinical outcome in severe infections[1] than in trials with lower therapeutic peak range (fig 1). This supports the use of EID. When peak SDCs in trials with lower therapeutic peak range were discarded, the summary peak and trough risk ratio were within the same range in randomised trials and in trials without systematic errors as in all trials. The SDC should be assessed in EID, as 8% of the peak and 6% of the trough SDCs were outside the therapeutic range.

Efficacy and toxicity

In EID the risk of breakthrough infections has been of great concern. However, meta-analyses of trials in adults and children have shown equal or better performance in EID than in TD.[2–9] This could be explained by several in vitro findings. Aminoglycosides show post-antibiotic effects and post-antibiotic leucocyte enhancement.[32] The bacterial killing is concentration dependent and is largest at first exposure.[33] Higher and more infrequent peak SDCs may prevent the



Tests for heterogeneity between trials $\chi^2 = 15.2150$, df = 11, p = 0.17

Figure 3 Randomised trials and results when non-randomised trials added: trough serum drug concentration (SDC). CI, Confidence interval; EID, extended interval dosing, typically 4–5 mg/kg gentamicin given to neonates at dosage interval 24 hours or longer; TD, traditional dosing, typically 2–3 mg/kg gentamicin given to neonates at dosage interval 8–24 hours.

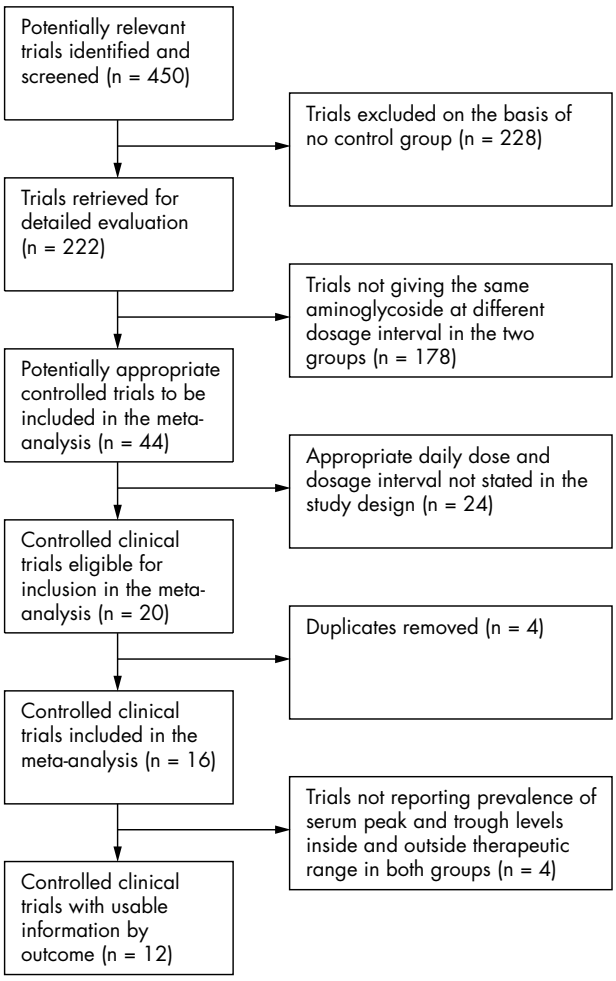


Figure 4 Flow diagram showing the selection of trials for meta-analysis.

development of adaptive resistance after exposure.[34] As shown here, EID will decrease the subtherapeutic peak SDCs, which is a predictor of poor clinical outcome.[1] As only two out of 555 neonates did not respond to the aminoglycoside treatment, both methods of dosing might be regarded as effective. These results should, however, be interpreted with care, as complete data on morbidity and mortality were often not reported, and the presence of persisting positive blood cultures was seldom extractable from the trial reports.

Given the heterogeneity in the definitions and prevalence of nephrotoxicity, it was not possible to compare the different trials. The finding of only one instance of ototoxicity in the 210 neonates tested is consistent with other trials, often failing to identify neonatal aminoglycoside treatment as a major cause of deafness.[35 36]

What is already known on this topic

- In extended interval dosing, peak serum aminoglycoside concentration is higher and trough serum aminoglycoside concentration lower than in traditional dosing.
- The neonatal daily dose and dosage interval varies widely among guidelines, and the need to assess serum drug concentrations is debated.

What this study adds

- In extended interval dosing, therapeutic serum aminoglycoside concentrations are achieved more often than in traditional dosing.
- For the peak serum drug concentration, the difference is more pronounced in trials with therapeutic peak range associated with improved clinical outcome.
- The results of this systematic review indicate that the serum drug concentration should be assessed in extended interval dosing, as 8% of the peak and 6% of the trough serum drug concentrations were outside the therapeutic range.
- No significant differences in clinical cure rate or toxicity were found.

Future trials

Could these findings apply to neonates in all clinical situations? Some of the prospective randomised trials excluded many of the patients often found in neonatal intensive care units, and studies comparing EID with TD in a control group more often had wide inclusion criteria. As treatment failure is rare, large scale studies would be needed to study differences in clinical cure rate between EID and TD.

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CONTRIBUTORS

EN initiated the initial design of this study and undertook the literature search. HJB and KOW extracted the data. LS advised on the statistical analyses. All authors contributed to the writing of the final draft of the manuscript. EN is guarantor.

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