Amikacin use and Therapeutic Drug Monitoring in adults: Do dose regimens and drug exposures affect either outcome or adverse events?

BSAC Working Party on Therapeutic Drug Monitoring¥.

¥ Members are listed in the acknowledgements section

Abstract

Objectives

To identify the amikacin dosage regimens and drug concentrations consistent with good outcomes and to determine the drug exposures related to nephrotoxicity and ototoxicity.

Methods

A literature review was conducted in Medline, EMBASE and the Cochrane Central Register of Controlled Trials. Full journal articles of randomised controlled trials, controlled clinical trials, interrupted time series trials and controlled before and after studies involving amikacin TDM and dose adjustment were considered for inclusion.

Results

Seventeen included studies were identified, comprising 1677 participants. Amikacin doses ranged from 11-15 mg/kg/day with thirteen studies using 15 mg/kg/day. Studies were generally designed to compare different aminoglycosides rather than to assess concentration-effect relationships. Only eleven papers presented data on target concentrations, rate of clinical cure and toxicity. Target peak concentrations ranged from 15 – 40 mg/L and target troughs were typically <10 mg/L or <5 mg/L. It was not clear whether these targets were achieved. Measured peaks averaged 28 mg/L for twice daily dosing and 40-45 mg/L for once daily dosing; troughs averaged 5 mg/L and 1-2 mg/L, respectively.

Fifteen of the included studies reported rates of nephrotoxicity; auditory and vestibular toxicities were reported in twelve and eight studies.

Conclusions

This systematic review found little published evidence to support an optimal dosage regimen or TDM targets for amikacin therapy.

The use of alternative approaches, such as consensus opinion and a review of current practice, will be required to develop guidelines to maximise therapeutic outcomes and minimise toxicity with amikacin.

Background

Five aminoglycosides are listed in the British National Formulary for clinical use in the UK: amikacin, gentamicin, neomycin (only topical), streptomycin (mainly for tuberculosis) and tobramycin.[1] All systemically administered aminoglycosides have a narrow therapeutic window and there is wide variability in the relationship between the dose and the measured serum level. Not all of this variability can be explained by clinical factors, such as renal function and the physiological changes that occur in sepsis. Consequently, over the last forty years therapeutic drug monitoring (TDM) has been an integral part of the management of patients during treatment with an aminoglycoside. TDM has helped to reduce the incidence of adverse events seen with this class of antibacterial, and in the UK most patients receiving more than a few days of therapy with such agents will have their serum level monitored by TDM.

Although historically there has been a consensus on the general objectives of TDM for aminoglycosides, at present there are almost no evidence-based guidelines, and in a number of areas there is wide international variation and controversy. Since the mid-1990s, there has been a general trend towards the use of once-daily administration (extended dosing interval) for aminoglycosides and much of the usage in the UK is on this basis.

One of the frequently monitored aminoglycosides for which there is a pressing need for clear guidance is amikacin. From an extensive search, there is only one systematic review which compares once-daily dosing with multiple-daily dose administration.[2] Due to a lack of high quality evidence to support dosage recommendations, locally developed guidelines are forced to select management pathways without a clear understanding of the optimal treatment and preferred TDM regimen. This review will cover the scientific basis for both the dosing and TDM of amikacin.

Objectives

To identify amikacin TDM regimens and drug concentrations consistent with good outcomes and to determine drug exposures related to the adverse events of nephrotoxicity and ototoxicity in adults.

Methods

This literature review considered TDM and dose adjustment for amikacin as a single agent. Comparators could be single or combination agents or different treatment durations or regimens. The inclusion criteria comprised adults with infections treated with amikacin and aged 18 and above, randomised control trials (RCT), controlled clinical trials (CCTs), interrupted time series with at least three data points before and after implementation of the guideline (ITS) and controlled before and after studies (CBA). Full details of the protocol are presented in the Supplementary Data.

Searches were conducted in Medline, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library*. Reference lists of included studies were scanned to identify any further studies that had not been identified by electronic searching.

Studies meeting the inclusion criteria were identified by two authors (AJ, PW) independently and any discrepancies were resolved by discussion with other authors. Studies which were excluded after an initial sorting were recorded with a brief description of the reason for exclusion. Studies were restricted to those in the English language. A data extraction form was developed to facilitate the collection of data from each of the included studies.

Two authors independently assessed the risk of bias for each study and the Cochrane Risk of bias tool for randomised controlled trials

was adapted for this review.[3] Each study was assessed for selection, detection and attrition biases and also possible biases confounded by small size and sponsorship. Additional information can be found in the supplementary information to this article.

Results

The literature search was initially run in 2013 and updated in June 2015 when no new included studies were identified. A PRISMA flow chart is presented in **Figure S1.** Seventeen included studies (22 reports) comprising 1677 participants were identified during the literature search which are summarised in table S1. Four of these studies comprised more than one report:

- Ibrahim et al (Ibrahim et al and two papers published by Tulkens et al).[4,5,6]
- Maller et al (four papers published by Maller between 1988 and 1993).[7,8,9,10]
- Smith et al (three papers published by Smith between 1977 and 1983).[11,12,13]
- Gatell (three papers published by Gatell between 1983 and 1987).[14,15,16]

Two papers were non-evaluable. The study by Kiel *et al*[17], had a short follow-up time (1.3 days), high drop out rate (55%) and unclear study population. DeMaria *et al* [18] combined the results of the tobramycin and amikacin arms. Of the 15 evaluable studies, five compared different amikacin dosage regimens, nine compared

amikacin with another aminoglycoside and one compared amikacin with cefotaxime (**table 1**). Galvez et al[20] provided little data on cure or toxicity and was also excluded. Amikacin doses ranged from 9-15 mg/kg/day; thirteen studies used 15 mg/kg/day.

Effects of interventions

Amikacin concentrations

Eleven studies used TDM with dose modification to achieve concentrations within a pre-defined range but did not confirm if their targets were achieved.[2,7,11,14,19,20,21,22,23,24,25,26] Dillon[19] divided patients into two arms and modified doses in response to serum amikacin concentrations in one arm. In three papers, serum concentrations were measured but no action was taken.[4,27,28]

Clinical Cure

As only one study[8] compared clinical cure rates with different amikacin dosage regimens, there were insufficient data to conduct a meta-analysis. Four papers compared clinical cure rates with amikacin and another aminoglycoside in bacteraemic patients.[11,21,24,25] The meta-analysis included 479 participants and is presented in **figure S2**. There was no difference in clinical cure rate between amikacin and other aminoglycosides (risk ratio 1.00, 95% CI 0.90, 1.12).

Nephrotoxicity

Four of the 5 studies that compared amikacin dosage regimens were included in the meta-analysis; the remaining study[20] reported "no evidence of renal function impairment at day 28". F**igure S3** shows a non-significant risk ratio of 1.42 (95% CI 0.68, 2.93) in favour of once daily administration.

Data on nephrotoxicity rates were available from 9 studies (872 patients) that compared amikacin to another aminoglycoside; one additional study[28] found no evidence of nephrotoxicity. The meta-analysis presented in **figure 1** shows a significant risk ratio of 0.48 (95% CI 0.32, 0.72) in favour of amikacin over other aminoglycosides.

Auditory Toxicity

The results of three papers[2,3,8] that compared auditory toxicity with different amikacin dosage regimens are summarised in **figure S4**. There was a non- significant risk ratio of 0.77 (95% CI 0.28, 2.11) in favour of twice daily amikacin. All nine papers that compared amikacin with another aminoglycoside included rates of auditory toxicity. F**igure 2** shows a non- significant risk ratio of 1.15 (95% CI 0.76, 1.76) in favour of other aminoglycosides over amikacin.

Vestibular Toxicity

Maller et al[7] is the only paper that evaluated vestibular toxicity with different amikacin dosage regimens. The results from 4 studies that compared vestibular toxicity with amikacin and other aminoglycosides are summarised in **figure S5**. There was a non-

significant risk ratio of 1.61 (95% CI 0.39, 6.68) in favour of other aminoglycosides over amikacin.

Secondary Outcomes

Only Maller et al[7,8,9,10] presented data on 28 day mortality and Dillon[18] on length of hospital stay with different amikacin dosage regimens. Two studies reported on duration of therapy.[4,19] Only one paper reported 28-day mortality with amikacin and each of gentamicin[11], tobramycin[14] and netilmicin.[24] One death was reported in the Barza et al[23] study but it was not clear if this occurred with amikacin or netilmicin. None of the papers considered length of hospital stay as an outcome; five papers presented data on duration of therapy. Only Bock et al[24] described a patient who required an alternative antibiotic due to treatment failure with netilmicin. None of these papers presented data that related concentration measurements to cure or nephrotoxicity.

An assessment of bias was completed for all included studies and shown in **figure S6**.

Excluded Studies

Twenty-eight studies were excluded and the reasons can be found in Table S2 in the supplementary information to this paper.

Discussion

In contrast to previously published reviews, which assessed the relative benefits of amikacin administered once or multiple times each day[29,30,31,32], the present review used an evidence-based methodology to investigate dosing and TDM regimens associated with best patient outcomes. To this end little published evidence was found to support optimal dosage regimens or TDM targets for amikacin therapy. Studies that met the inclusion criteria were typically designed to compare different aminoglycosides, rather than to examine the impact of dosing regimens and TDM on outcomes and toxicities. Even those studies which compared once and twice daily amikacin dosage regimens provided little information on the value of TDM.

The review aimed to focus on proven Gram-negative bacteraemia, however, most studies included patients with a variety of infections and a mixture of suspected and proven bacteraemias. Clinical cure rates were generally high and amikacin was found to be at least equivalent to that of other aminoglycosides, depending on organism sensitivity. However, since aminoglycosides achieve high concentrations in the urine, caution is required when comparing data on the treatment of urinary tract infections with data on systemic infections, particularly in critically ill patients.

Another clear finding was that amikacin is associated with nephrotoxicity and ototoxicity, particularly auditory toxicity. Interestingly, the reported incidence of auditory and vestibular

toxicities was at least comparable to, if not higher than, the reported incidence of nephrotoxicity in many studies. However, no conclusions can be drawn about the toxicity of amikacin relative to other aminoglycosides since that was outside the scope of this review and relevant data are therefore likely to be missing. Furthermore, there were wide variations in individual study characteristics regarding the definition of nephrotoxicity, assessment of ototoxicity, duration of therapy, concurrent medication, aminoglycoside concentrations and exposure. These variabilities confounded the interpretation of both toxicity incidence rates and potential relationships between nephrotoxicity and amikacin concentrations or exposure.

This review originally planned to examine patients >75 years old or with an estimated creatinine clearance <60 mL/min as a separate group. However, none of the included studies characterised these patients separately and exclusion criteria varied widely, ranging from creatinine concentrations >180 micromol/L to patients receiving dialysis.

Most studies did not include any commentary on dosing in patients with altered pharmacokinetics or body habitus. Only one study specified the use of lean body weight for dosing purposes.[24] One study examined patients with liver cirrhosis, which is likely to have additional effects on drug handling.[26]

As most of the included studies were published before once daily dosing of aminoglycosides became routine clinical practice, most target ranges related to doses of 7.5 mg/kg every 8-12 hours. Peak concentrations ranged from 15 – 40 mg/L one hour after an IM injection or 20 to 30 minutes after a 20 or 30 minute IV infusion and most studies aimed for a trough of either <10 mg/L or <5 mg/L. One study aimed for a trough <30 mg/L.[26] Although concentrations were measured using a range of different assay techniques, measured peak concentrations with twice daily dosing averaged around 28 mg/L and troughs around 5 mg/L. Target serum concentrations for once daily dosing were identified in two studies.[2,7] Both aimed for trough concentrations of <5 mg/L, one also examined the incidence of peaks >40 mg/L.[2] Measured peak and trough concentrations with once daily dosing averaged 40-45 mg/L and 1-2 mg/L, respectively. Although the review found insufficient evidence to compare once and multiple daily dosing, pharmacokinetic and pharmacodynamic principles support the current practice of extended interval dosing to achieve the high peak to MIC ratios that are now considered optimal.

Although mean values reflected the proposed target ranges for once and twice daily dosage regimens, individual measured concentrations were very variable, ranging from 12 to 127 mg/L for peak concentrations and 1 – 74 mg/L for trough concentrations. It is likely that this variability in reported concentrations reflected the use of fixed dose regimens in patients whose renal function covered

a wide range. Only one study reported dose adjustments for renal impairment,[7] In contrast with current practice for gentamicin dosing, they modified the dose amount rather than the dosage interval. In this study, trough concentrations >5 mg/L were observed in seven of the nine patients on once daily dosing and nine of the eleven patients on twice daily dosing who had nephrotoxicity.[7]

The present review has a number of limitations. Only two of the seventeen included papers had more than 200 participants and the potential for bias was high. Studies frequently did not describe how randomisation was achieved and were not double blind. Most of the included studies were published before 1995, do not reflect current practice and offered little opportunity to examine the impact of clinical factors, such as weight, renal function, severity of illness and Cmax/MIC ratio on clinical outcomes. An additional limitation is that aminoglycosides are normally used in combination with other antimicrobial agents, leading to a complex relationship between therapy and outcome. Several recent studies on TDM were excluded from the present analysis because their methodology did not comply with the inclusion criteria. However, such studies may provide useful data to support opinion-based guidelines. For example, Duszynska et al[33] provide data to suggest that higher doses and concentrations of amikacin may be required to manage patients with sepsis.

Conclusions

This systematic review has demonstrated that there are insufficient data to produce evidence-based guidelines for amikacin dosing and TDM. Future studies should clearly specify the clinical characteristics of participants, indications, dosage regimens, concentrations, Cmax/MIC ratios and outcomes in terms of clinical cure and relevant adverse effects. Furthermore, traditional systematic review methodology should be expanded to examine outcomes based on PK/PD modelling techniques. At present, guidelines to maximise therapeutic outcomes and minimise toxicity with amikacin must be based on reviews of current practice, published guidelines and expert opinion.

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Contributions of authors

AJ undertook the data extraction, wrote the initial draft of the review, and produced the tables. PW wrote the protocol with NB and this was approved by a clinical guideline group including AM and AL. PW was involved with the data extraction and writing the review. AT wrote the discussion with the support of YS and CS. All authors agreed the final draft.

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Declarations of Conflicts of Interest

AJ, AL, AM, AT, CS, NB, PW and YS have no conflicts related to this literature review.

Transparency

This literature review was circulated to BSAC members for consultation and comment in October 2015. Five comments were returned which were considered by the Working Party and amendments made as appropriate.

Differences between protocol and review

In the protocol a lower age range of 18 years was specified, however three studies included participants of 16 or 17 years old.[6,9,10] We also included all infections rather than simply 'bacteraemia'.

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Table 1: Summary of Included Evaluable Papers

Author	No. Participants	Amikacin Regimen	Comparator		Clinical Cure		Nephrotoxicity		Auditory Toxicity		Vestibular Toxicity		28 Day Mortality		Duration of Therapy (days)		Target or Measured Serum Concentrations (mg/L)	
			Drug	Regimen	Ami	Comp	Ami	Comp	Ami	Comp	Ami	Comp	Ami	Comp	Ami	Comp	Ami	Comp
Dillon[18]	82	7.5 mg/kg bd	Ami	7.5 mg/kg*	No difference between standard dosing and TDM		1/41 (2.4)	3/41 (7.3)	NR	NR	NR	NR	NR	NR	NR	NR	Trough 4-8 Peak 25-30	
**Giamarrelou[2]	60	15 mg/kg/day*	Ami	7.5 mg/kg bd*	29/30 (96.7)	23/30 (76.7)	2/30 (6.7)	2/30 (6.7)	1/30 (6.7)	1/30 (6.7)	NR	NR	NR	NR	NR	NR	Trough <5 Peak >40	
**Ibrahim[4,5,6,]	40	14 mg/kg od	Ami	7 mg/kg bd	20/20 (100)	20/20 (100)	0/20	0/20	3/20 (15.0)	4/20 (10.0)	NR	NR	NR	NR	7	7	Measured Peak od (49-7-53.1) Peak bd (23.5-25.3)	
Maller[7,8,9,10]	316	15 mg/kg/day*	Ami	7.5 mg/kg bd*	92/101 (91.1)	89/99 (89.9)	9/162 (5.6)	11/149 (7.4)	3/164 (1.8)	2/152 (1.3)	1/164 (0.6)	1/152 (0.7)	8/152 (5.3)	7/164 (4.3)	5.4	5.9	Trough od <5 Trough bd <10	
Gilbert[27]	30	9 mg/kg/day	Gent	3-4 mg/kg/day	NR	NR	2/15 (13.3)	2/15 (13.3)	0/15	0/15	0/15	0/15	NR	NR	NR	NR	Measured Peak: 8.2-19.6	Peak 4-8
Holm[20]	135	7.5 mg/kg bd	Gent	1 mg/kg tds	57/71 (80.3)	49/64 (76.6)	3/49 (6.1)	9/46 (20.0)	3/38 (7.9)	5/31 (16.1)	1/38 (2.6)	1/31 (3.2)	NR	NR	NR	NR	Trough <10 Peak <35	Trough < 2 Peak < 10
Lerner[21]	106	6 mg/kg tds*	Gent	1.7 mg/kg tds*	NR	NR	0/52	8/54 (14.8)	7/52 (13.4)	6/54 (11.1)	NR	NR	NR	NR	'No significant difference'		Trough <10 Peak 15-30	Trough < 2.5 Peak 4-8
Smith[11]	71	8 mg/kg loading*	Gent	2 mg/kg loading*	20/39 (51.3)	14/32 (43.8)	5/62 (8.0)	7/62 (11.3)	2/34 (5.9)	3/30 (10.0)	NR	NR	13/39 (33.3)	6/32 (18.8)	'No significant difference'		Peak 20-40	Peak 5-10
Barza[23]	90	5 mg/kg 8 hrly*	Net	2-2.5 mg/kg 8 hrly*	Data combined		0/32	3/37 (8.1)	4/15 (26.7)	3/19 (15.8)	3/16 (18.8)	0/15	NR	NR	NR	NR	Peak 15-25	Peak 6-9
Bock[24]	71	7.5 mg/kg bd*	Net	2-2.5 mg/kg tds*	14/33 (42.4)	17/34 (50.0)	1/29 (3.4)	6/34 (17.6)	6/23 (26.1)	1/29 (3.4)	0/29	1/34 (2.9)	9/35 (25.7)	6/36 (16.7)	11.5	11.7	Trough < 5 Peak <15-25	Trough ≤ 2 Peak 4-8
Maigaard[28]	57	7.5 mg/kg bd	Net	2 mg/kg bd	16/28 (57.1)	20/29 (70.0)	No changes in renal function		0/28	0/29	NR	NR	NR	NR	NR	NR	Measured: Trough 1.4-10.5 Peak 14- 81	Trough 0.1-9.2 Peak 2.6-19.0
Noone[25]	202	7.5mg/kg bd*	Net	3.5 mg/kg bd*	74/82 (90.2)	68/86 (79.0)	4/96 (4.2)	11/91 (12.1)	7/53 (13.2)	8/51 (15.7)	NR	NR	NR	NR	10.4	8.5	Trough < 10 Peak 20-30	Trough < 4 Peak 10-15
Gattell[14,15,16]	113	7.5 mg/kg 12-24 hrs*	Tob	1.7 mg/kg 8-24 hrs*	NR	NR	7/54 (13.0)	4/59 (6.8)	6/17 (35.3)	8/19 (42.1)	NR	NR	4/54 (7.4)	2/59 (3.4)	8.5	8.3	Trough 10 Peak 40	Trough 2 Peak 10
Chen[26]	37	500 mg od*	Cef	1g qds	11/18 (61.1)	15/19 (78.9)	1/18 (5.6)	1/19 (5.3)	NR	NR	NR	NR	4/19 (21.1)	4/18 (22.2)	NR	NR	Trough < 30	

Footnote:

Galvez et al[20] reported 'no evidence of renal function impairment at day 28" on 120 participants given amikacin doses of 15, 20 or 30 mg/kg/day. Dillon et al[19] reported no difference in length of hospital stay; Chen.[28] reported 13 days stay for amikacin and 12 for cefotaxime

Key: data are presented as number/total number (percentage), Ami = amikacin, Gent = gentamicin, Net= netilmicin, Tob= tobramycin, Cef = cefotaxime, comp= comparator, od= once daily, bd= twice daily, tds= three times a day, qds four times daily, hrly= hourly, NR = not reported *Applied therapeutic drug monitoring and dose modification, **includes non-bacteraemic patients

Figure 1

Forest Plot: Nephrotoxicity with Amikacin Versus other Aminoglycosides[4,11,14,20,21,23,24,25]

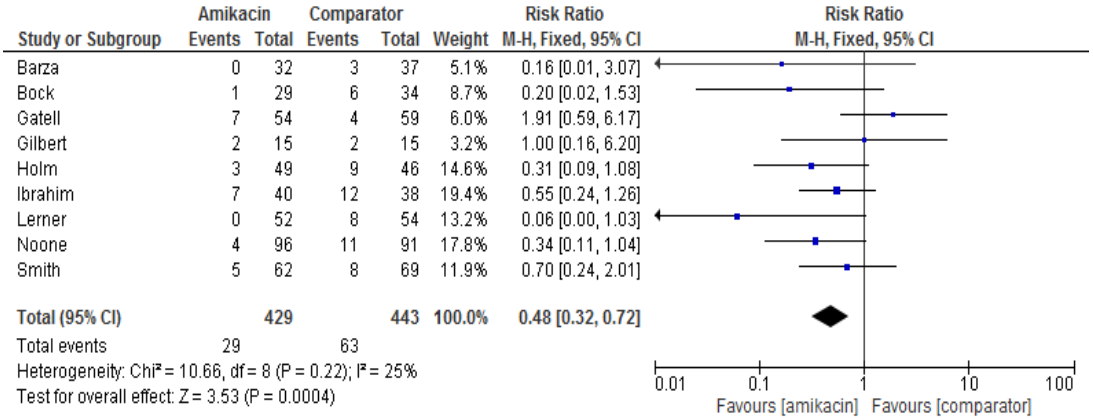

Figure 2

Forest Plot: Auditory toxicity of Amikacin Versus other Aminoglycosides[11,14,20,21,23,24,25,27,28]