THE CENTRAL AFRICAN JOURNAL OF MEDICINE

Vol. 43, No. 3 March, 1997

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THE CENTRAL AFRICAN JOURNAL OF MEDICINE

ORIGINAL ARTICLES

Once versus thrice daily intramuscular gentamicin in children with systemic infections

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Objective: To evaluate the clinical efficacy, pharmacokinetic profiles and nephrotoxicity of once daily versus thrice daily doses of intramuscular gentamicin in infants and children.

Design: A randomized trial.

Subjects: Patients between ages of one month and eight years with clinically suspected or proven severe bacterial infection with no prior history of aminoglycoside therapy.

Interventions: Patients were randomized to receive gentamicin once daily or thrice daily with the same total daily dose of 6 mg/kg body weight.

Main Outcome Measures: Clinical efficacy, pharmacokinetic profiles and nephrotoxicity.

Results: A total of 107 children were enrolled in the study, and randomized to the intervention. The baseline characteristics were comparable. Only 74 patients who continued to receive gentamicin therapy beyond 48 hours were evaluated. A favourable clinical response was found in 27/35 (77%)in the OD group and 32/39 (82%)in the TD group (p=0.814). Only 52 patients (26 in each group) had pharmacokinetic profiles determined. A statistically significantly higher mean (SD) serum peak concentration was present in the OD [6.45 (1.95) μg/ml] group compared to the TD group [2.75 (1.3) μg/ml] (p<0.001). Trough concentrations in both groups were within the desired levels of less than 2 μg/ml. Evidence of apparent nephrotoxicity was absent in both groups.

Conclusion: Compared to the recommended thrice daily dosing, once daily administration of intramuscular gentamicin in children achieves better therapeutic drug levels. The once daily intramuscular dose is more convenient for both patients and health workers, is less costly and should therefore be recommended for use in children.

Introduction

Aminoglycosides are commonly used worldwide in the treatment of severe bacterial infections especially aerobic gram-negative infections.[1] Due to its low cost, gentamicin is commonly used in developing countries. In the paediatric medical wards at Harare Central Hospital (HCH), gentamicin was the fifth most commonly used antimicrobial agent in 1992.[2]

It is now generally accepted that peak concentrations of gentamicin greater than 4 μg/ml are necessary for optimum antibacterial efficacy and trough levels above 2 μg/ml are a risk factor for toxicity.[3,4] A review of aminoglycoside toxicity in infants in a small number of well designed studies has not shown a significant difference in rates of ototoxicity or nephrotoxicity between aminoglycoside treated paediatric patients and untreated control subjects.[5] Clinical experience has shown that aminoglycosides have occasionally caused ototoxicity in children and although nephrotoxic effects have also been observed, these are usually transient.[5]

Intravenous administration of a single total daily dose of gentamicin results in transiently higher peak serum levels but reduced trough levels after a 24 hour period as compared to thrice daily dosage.[6,7] Aminoglycosides cause concentration

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Comparisons of the distributions of discrete or continuous variables between the two study groups were done using the Yates' corrected Chi-squared test, the Fishers' exact test or the Students' t test where appropriate. A result with a p value of less than 0.05 was considered statistically significant.

Results

A total of 107 children were enrolled in the study. There were 51 boys and 56 girls giving a male to female ratio of 1 to 1.1. The median age (Q_1, Q_3) was five (three, 15) months. Of the 107 children, 49 (46%) received IM gentamicin OD and 58 (54%) received IM gentamicin thrice daily (Table I). The two groups were comparable with respect to the baseline characteristics of age, weight, nutritional status, sex and mean admission temperature.

Table I: Baseline characteristics of 107 patients.

	OD Total=49	TD Total=58	p-value
Sex (M/F)	26/23	25/33	0.405
Age in months*	4.0(3,9)	5.5(3,17)	0.216
Weight'KG	5.2(4.3,6.6)	5.5(4.7,8.7)	0.108
Nutrition(Weight for age)			
>80%	19	33	
≤80%	30	25	0.094
Temperature"	38.1(0.8)	37.9(0.9)	0.136
Therapy received for <48 hours	11	16	
Therpy changed after 48 hrs	3	3	
Therapy continued for >48 hrs	35	39	

**Median (1st and 3rd quartiles).*
"Mean (SD).
OD once daily.
TD thrice daily.

Twenty seven patients (25%) had therapy discontinued within 48 hrs, 11/49 in the OD (22%) and 16/58 in the TD group (28%). Reasons for discontinuing therapy were discharge within 48 hours (11), transfer to infectious disease hospitals (4), deaths (11), and change of therapy by the attending physician (1). A further six patients were excluded because therapy was changed after completing 48 hours of gentamicin therapy. Therefore a total of 74 (70%) of the original study sample, 35 in the OD and 39 in the TD groups were evaluable.

Clinical Diagnosis and Micro-organisms.

The 74 patients who continued to receive gentamicin therapy beyond 48 hours were evaluated. Sixty four (86%) had pneumonia with 32 patients in each group. Three patients had impetigo, two epticaemia and two suspected urinary tract infection in the TD group. In the OD group, two patients had septicaemia and one septic arthritis.

Blood cultures yielded organisms in 23 (31%); 12 (34%) in the OD and 11 (25%)in the TD group (Table II). The majority (78%) were gram-positive organisms. Eight out of 12 (67%) organisms in the OD and six out of 11 (55%) in the TD groups were sensitive to gentamicin at minimum inhibitory concentration (MIC) of less than 2 µg/ml.

Table II: Micro-organism isolated in 74 who received Gentamicin therapy for more than 48 hours.

	OD (Total=35	TD (Total=39)	Total
Staphylococcus aureus	5	2	7
Staphylococcus coagulase negative	4	2	6
Diphtheroids	1	1	2
Viridans group *Streptococcus* spp.	0	1	1
Streptococcus pneumoniae	0	1	1
Lactobacillus spp.	0	1	1
Salmonella/Arizona	0	1	1
Escherichia coli	1	1	2
NLF coliforms	1	0	1
No growth	23	29	52

NLF — Non-lactose fermenting.

Clinical Efficacy.

A favourable clinical response was found in 27 of the patients in the OD (77%) and 32 (82%) in the TD group (p =0.814; Table III). All these patients also received parenteral beta-lactam antibiotics throughout the duration of their hospital stay because of severe illness.

Table III: Clinical efficacy.

	OD Total=35	TD Total=39	p-value
WBC on admission	15.1(8.0)*	15.9(10.0)	0.891
WBC on Discharge (10^3)	10.7(4.3)	10.1(4.4)	0.668
Days to normal temp.	3.6(2.7)	3.4(2.4)	0.779
Discharged	27"	32	
Died	8	7	0.814

** Mean (SD).*
" Absolute numbers.

Bacteriological Response.

In patients with initial bacteraemia, blood cultures repeated after treatment yielded growth in only one patient each in the OD and TD groups, therefore achieving 80% bacteriological cure in both groups.

Pharmacokinetic Profiles.

Only 52 of the 74 (70%) had both serum peak and trough gentamicin levels determined, 26/35 (74%)in the OD and 26/39 (67%)in the TD groups. The baseline characteristics of these two groups were similar.

The mean (SD) peak serum concentration of gentamicin was higher in the OD [6.45(1.95) µg/ml] than in the TD [2.75(1.32) µg/ml] group (p<0.001). Peak serum levels were greater than 4 µg/ml in 24 (92%) of the OD group but only three (12%) of the TD group (p<0.001). Two patients in the OD and nine in the TD group had undetectable peak gentamicin concentrations. All patients had serum peak gentamicin concentrations of less than 12 µg/ml except one patient in the OD group who had a level of 12.7 µg/ml.

The median (Q_1, Q_3) trough serum gentamicin concentrations were comparable in the two groups: 0.40 (0.18,0.72) µg/ml in the OD and 0.71 (0.55,0.96) µg/ml in the TD group (p=0.065). All trough levels were less than 2 µg/ml

with the exception of one patient in the TD group with a level of 2.81 µg/ml because the sample was accidently collected immediately after the gentamicin injection (Table IV).

Table IV: Gentamicin serum levels.

Serum Levels µg/ml	OD Total=26	TD Total=26	p-value
Peak levels			
>4 µg/ml	24	3	
≤4 ug/ml	0	14	
Undetectable	2	9	<0.001
Trough levels			
≥2 ug/ml	0	1	
<2 µg/ml	26	25	
Undetectable	14	16	0.885

The cumulative gentamicin doses in the OD and TD groups were 224 and 196 mgs respectively (p=0.505). The mean (SD) duration of therapy was just over five (2.8) days [5.2 (2.9) days in the OD group and 5.3 (2.7) days in the TD group].

Nephrotoxicity.

Seventy two (90%) had baseline creatinine results available. Only 46 (64%) had repeat creatinine levels determined. Of the 46 patients evaluated for nephrotoxicity, 20/35 were in the OD group (57%) and 26/39 in the TD group (67%). Mean (SD) baseline serum creatinine was marginally significantly lower in the TD; 48.8 (17.5) µmol/l than in the OD group; 58 (14.2) µmol/l, p=0.051. The maximum mean (SD) serum creatinine during treatment was comparable in both groups; OD 56.4(18.2) µmol/l and TD 47.7(21.5) µmol/l. None of the patients had a creatinine rise of over 45 µmol/l or reached a level of 100 µmol/l.

Discussion

There is now substantial evidence that less frequent dosing of aminoglycosides such as once daily gentamicin might enhance or preserve the antibacterial efficacy while lowering the risk of nephro- and ototoxicity.[1,16] This is because aminoglycosides have concentration-dependant antibacterial activity and prolongation of PAE with increase an in peak concentration.[9,17]

This the first study in children and infants over one month of age to compare clinical efficacy, pharmacokinetics and safety of OD versus TD intramuscular gentamicin. Pneumonia accounted for more than 80% of all infections. This is not surprising since up to a third of admissions in the paediatric wards at Harare Central Hospital are usually due to pneumonia.[18] Young infants with severe pneumonia were treated with penicillin and gentamicin as recommended by the World Health Organisation.[19]

No difference in clinical efficacy was observed between the once and thrice daily intramuscular groups. This is comparable to other studies in which the intravenous route was used.[20] In our study, gentamicin antibacterial efficacy could not be specifically evaluated because beta-lactam antibiotics were administered concurrently in all patients. However, in clinical practice, these are commonly used in combination due to the theoretical synergistic effect.[1]

Higher peak serum concentrations have been associated with a higher bacterial kill.[17] This study showed statistically significantly higher mean serum peak concentrations in the OD than the TD group. This finding was comparable to other studies where more than 50% of patients on multiple daily doses were found to have sub-therapeutic levels.[21,22] Hence, once daily gentamicin dosing strategy might maximize its therapeutic potential.

Trough concentrations in the OD and TD groups were within the desired levels of less than 2 µg/ml. In other studies lower trough levels were found in the once daily regime.[11,16] The lower levels in the TD group in this study could be attributed to the fact that most patients in the TD group had sub-therapeutic or undetectable peak serum levels.

There was no difference observed in nephrotoxicity between the two regimes in this study as has also been shown in the few other studies.[16,23] This could be partly explained by the exclusion of high risk patients from the study and also by the fact that a serum creatinine rise of more than 45 µmol/l might be a late marker of nephrotoxicity. Studies that have reported increased renal toxicity with the TD compared to OD regime used early markers of toxicity like phospholipiduria and urinary alanine aminopeptidase excretion.[4]

Risk factors found to be associated with renal toxicity in other studies were prolonged therapy (usually longer than seven days), initial higher creatinine levels, prolonged half-life and high gentamicin trough levels.[24] Recent data suggest that persistently high trough levels rather than transiently high peak levels are responsible for aminoglycoside related toxicity.[23,25]

We did not evaluate ototoxicity because the majority (74%) of the patients were infants and brain evoked response audiometry was not available. A recent meta-analysis of 21 randomized trials using intravenous gentamicin found no difference in the incidence of ototoxicity between single and multiple dosing regimes, but the power of the pooled trials to detect a meaningful difference was low. Audiometry testing and the reporting of vestibular toxicity need to be addressed in future studies.[26]

The power of the current study is 61% based on the clinical efficacy criteria used for the sample size calculation at the start of the study. The reduced power of the study can partly be explained by the high attrition rate within the first 72 hours of the study. All children in this study received parenteral beta-lactam antibiotic in addition to gentamicin and therefore clinical efficacy is likely to assess the effect of the combination of antibiotics. Also of note is the preponderance of gram-positive bacterial isolates in our study which makes the assessment of gentamicin efficacy difficult since the usual indication for using aminoglycosides is proven or suspected gram-negative infections.[5]

It is obvious that once daily gentamicin dosing is more economical in terms of the nursing workload and the number of disposable syringes and needles required. A once daily injection also makes it convenient for patients to be managed in the outpatient setting, therefore potentially reducing the duration of hospitalization in certain patients. From the-

patients' perspective, one injection causes less pain and discomfort than three injections a day.

Most important is that this study has shown that once daily administration of IM gentamicin in children achieves the desired therapeutic drug levels in a significantly higher proportion of patients compared to the conventional thrice daily dosing and with no apparent increased risk of nephrotoxicity. The once daily intramuscular dose is more convenient for both patients and health workers, is less costly and should therefore be recommended for use in children.

Acknowledgements

The authors are grateful to the following: Medical Superintendent, Harare Hospital for allowing access to patients; parents and children who participated in the study; medical and nursing colleagues for their cooperation and help and Professor PR Mason of the Department of Microbiology, Medical School.

We extend our thanks to the German Technical Agency (GTZ) Harare office for the financial support. WM Were was sponsored by MISEREOR.

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