Therapeutic monitoring of amikacin regimen-associated toxicity in febrile neutropenic pediatric cancer patients

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Background
Amikacin is used in the treatment of fever neutropenia (FN) in pediatric cancer patients. However it may be used once or twice daily, so the explanation of which regimen of amikacin (once or twice) is more effective and less toxic and how to detect renal toxicity early may help in a proper treatment of febrile neutropenia.

Aim
This study aimed to compare between once-daily versus twice-daily regimens of amikacin to know which regimen is most effective and less toxic.

Patients and methods
Venous blood from 40 pediatric patients with FN receiving 15 mg/kg amikacin intravenously either once a day (group I) or divided into two equal doses (group II) every 12 h by 30 min infusion. Amikacin was measured by means of homogeneous enzyme immunoassay for all patients. Renal function was assessed by measuring serum creatinine before and after the treatment.

Results
There were higher significant differences between once-daily versus twice-daily regimens of amikacin in the treatment of FN. The peak levels of amikacin were significantly higher in group I than those in group II ($P = 0.001$) and the duration of fever in group I was less than that in group II.

Conclusion
Therapeutic drug monitoring of amikacin should be done to detect its renal toxicity early and the administration of amikacin as a single daily dose may be associated with greater efficacy and less nephrotoxicity compared with that of amikacin administered as twice-daily dose.

Keywords:
amikacin, fever neutropenia, pediatric cancer

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Introduction

Therapeutic drug monitoring (TDM) is a branch of clinical chemistry and clinical pharmacology that specializes in the measurement of concentrations in the blood. Its main focus is on drugs with a narrow therapeutic window. TDM aims at improving patient care by adjusting the dose of drugs for which clinical experience or clinical trials have shown to have improved outcome in the general or special populations [1].

There are numerous variables that influence the interpretation of drug concentration data: time, route, and dose of drug given, time of blood sampling, handling and storage conditions, precision and accuracy of the analytical method, validity of pharmacokinetic models and assumptions, comedications, and clinical status of the patient [2].

Cancer is the second most common cause of death in children. Incidence rates have shown an increase over time since the middle of the last century. The continuous improvement in diagnostic and treatment strategies for cancer has led to significant improvements in survival for a wide range of childhood cancers [3]. The recent advances in the treatment of childhood cancer observed result not only from more effective chemotherapy, but also from improved supportive therapy and treatment of life-threatening infectious complications [4]. The cancer and its treatment by chemotherapy lead to series infection as fever neutropenia and increase morbidity and mortality in cancer patients [5].

With hematological malignancies and chemotherapy, infections in neutropenic patients can rapidly progress leading to life-threatening complications. A prompt initiation of empirical antibiotic therapy is favorable for patients with FN in order to avoid progression to sepsis and regardless of the detection of bacteremia [6].

Amikacin is one of the aminoglycosides which are bactericidal. Their primary site of action is the 30 S subunit of the prokaryotic ribosome, interrupting bacterial protein synthesis. To reach this site they bind to the bacterial cell wall and undergo active transport into the cell cytosol [7].

The significant clinical toxicities of aminoglycosides are ototoxicity, nephrotoxicity, and less often neuromuscular toxicity [8]. Combination of an antipseudomonal β-lactam with an aminoglycoside has been considered the standard empiric treatment of febrile neutropenia patients [9].

Therefore, the explanation of which regimen of amikacin (once or twice) is more effective and less toxic and how to detect renal toxicity early may help in a proper treatment of febrile neutropenia.

Patients and methods

Patients

This is a case–control study that included 40 pediatric patients with hematological malignancies and fever neutropenia (FN) admitted to the South Egypt Cancer Institute, Assiut University from November 2016 to November 2017 to be treated empirically with intravenous amikacin assigned to receive 15 mg/kg amikacin intravenously either once a day (group I) or divided in two equal doses (group II) every 12 h by 30 min infusion. Written informed consent was obtained from parents of the children. The children were subjected to complete diagnostic workup that is always done before starting amikacin. This data include history, physical examination, and routine hematologic and biochemical investigations.

Methods

Two milliliter of blood was collected after the third dose of amikacin for each amikacin level and the blood samples were allowed to coagulate and the serum was separated by centrifugation at 3000 rpm for about 10 min. Amikacin serum concentrations were analyzed in Therapeutic Drug Monitoring Laboratory, Cancer Biology Department, South Egypt Cancer Institute. Amikacin was measured by means of homogeneous enzyme immunoassay using Viva Emit assay (Siemens Healthcare Diagnostics, San Francisco, California, USA).

Peak levels of amikacin concentrations were obtained after 1 h from starting intravenous infusion and trough concentrations were obtained 8–12 h after the last dose for all patients. Renal function was assessed by measuring serum creatinine before and after the treatment. Comparison between once-daily versus twice-daily regimens of amikacin was done to know which regimen is most effective and less toxic. These patients were studied for their demographic data as well as their therapeutic response and renal toxicity of amikacin in the treatment of FN.

Statistical analysis

Data management and analysis were performed using statistical package for the social sciences (SPSS, IBM, Armonk, New York, USA) version 17. Numerical data were summarized using mean and SD or median and range, as appropriate. Categorical data were summarized as number and percentage. Numerical data were explored for normality using the Kolmogorov–Smirnov test and Shapiro–Wilk test.

Comparisons between the two groups for normally distributed numeric variables were done using the Student's *t*-test while for nonnormally distributed numeric variables were done by the Mann–Whitney test. χ^2 or Fisher's exact tests were used to compare between the groups with respect to categorical data. *P* values up to 0.05 were considered significant.

Results

Demographic data of the studied groups are shown in Table 1. The peak levels of amikacin were significantly higher in group I than those in group II ($P = 0.001$), while there was no significant difference between the trough levels of amikacin in group I and those in group II ($P = 0.150$) as shown in Table 2. There was a significant difference in the peak amikacin levels between groups I and II as they were effective in 15 (75%) patients and noneffective in five (25%) patients in group I and effective in five (25%) patients and noneffective in 15 (75%) patients in group II ($P = 0.004$). There was no significant difference ($P = 0.548$) in the trough amikacin levels

Table 1 Demographic data of the studied groups

	Groups		*P*
	Once	Twice	
Age (mean±SD) (years)	6.75±4.3	7.97±4.57	0.392
Sex [*n* (%)]			
Male	12 (60)	11 (55)	0.749
Female	8 (40)	9 (45)	

Table 2 Serum amikacin levels (peak and trough) in the studied groups

	Groups (mean±SD)		*P*
	Once	Twice	
Peak amikacin level	39.86±11.08	20.13±6.53	<0.001**
Trough amikacin level	3.01±1.77	3.88±1.97	0.150

**Mean highly significance

between groups I and II as they were toxic in one (5%) patient and nontoxic in 19 (95%) patients in group I and toxic in two (10%) patients and nontoxic in 18 (90%) patients in group II as shown in Table 3. The duration of fever was in group I lower than in group II but with no significant difference between two groups as shown in Table 4. According to renal function there was no patient in group I and two patients in group II had developed nephrotoxicity during the course of therapy with a *P* value 0.147 as shown in Table 5.

Discussion

TDM of aminoglycoside antibacterial with the goal of minimizing toxicity and maximizing effectiveness has become routine. Successful management of serious infections requires the ability to achieve therapeutic peak concentrations, while maintaining low trough concentrations will assist in avoiding nephrotoxicity. TDM services have been shown to reduce amikacin nephrotoxicity [10].

TDM program can markedly reduce the total dose of amikacin, which can potentially reduce tissue accumulation and toxicity. Pharmaceutical care involves the process through which a pharmacist cooperates with a patient and other professionals in designing, implementing, and monitoring a therapeutic plan that will produce specific therapeutic outcomes for the patient. He must identify the potential and actual drug-related problems, resolve actual drug-related problems, and prevent potential drug-related problems. He should always keep a check over the dose and the drugs prescribed to provide the quality care to the patients [11].

Table 3 Interpretation of amikacin levels in the studied groups

	Groups [*n* (%)]		*P*
	Once	Twice	
Peak amikacin level			
Effective	15 (75)	5 (25)	0.004**
Not effective	5 (25)	15 (75)	
Trough amikacin			
Toxic	1 (5)	2 (10)	0.548
Nontoxic	19 (95)	18 (90)	

**Mean highly significance

Table 4 Duration of fever after starting amikacin in the treatment of fever neutropenia in the studied groups

	Groups (mean±SD)		*P*
	Once	Twice	
Temperature	38.63±0.39	38.65±0.37	0.836
Duration of fever	5.85±5.36	6.7±6.25	0.647

Table 5 Nephrotoxicity outcome of amikacin on the studied groups

	Groups [*n* (%)]		*P*
	Once	Twice	
Safe	20 (100)	18 (90)	0.147
Nephrotoxic	0	2 (10)	

Our results showed that once-daily dosing of amikacin may reduce the risk of nephrotoxicity compared with twice-daily dosing because the renal function impairment was higher in group I than in group II, in agreement with what was reported by Barclay and Begg [12] who stated that once-daily administration has resulted in a small reduction in nephrotoxicity but continuous TDM is required.

On the other hand, our results have shown that the peak levels of amikacin were significantly higher in group I than those in group II which resulted in clinically difference between the two groups. These appear in the duration of fever which were in group I lower than in group II and this was provided by Kashuba *et al.* [13] who report a data that made the once-daily regimen more preferred than the twice-daily one, because the concentration-dependent bactericidal activity and the post-antibiotic effect increase with higher peak concentrations and in the once-daily regimen.

There was no statistically significant difference between the two groups in the trough concentration of amikacin and this was in contrast with Hammett-Stabler and Johns [14] who found significant difference between the trough levels of amikacin in once-daily regimen and twice-daily regimen. Trough serum levels generally correspond to toxicity. Amikacin trough levels of more than 10 mcg/ml have been associated with significant ototoxicity and nephrotoxicity [14]. The desired trough levels for conventional dosing are less than 8 mcg/ml [15].

In our study, one patient in group I had a trough amikacin serum level of 8 mcg/ml and no one had nephrotoxicity according to the serum creatinine level. Two patients in group II had a trough serum amikacin level of more than 8 mcg/ml and the same two patients had nephrotoxicity according to their serum creatinine level. Therefore, the low serum trough amikacin serum level reduces the incidence of nephrotoxicity with amikacin [15].

Conclusion

Administration of a therapeutic dose of amikacin as a single daily dose is associated with greater efficacy and less nephrotoxicity compared with the administration of a therapeutic dose of amikacin as twice-daily dose.

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Conflicts of interest

There are no conflicts of interest.

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