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Original Article

Clinically Monitoring and Evaluating Tobramycin Concentration at Cho Ray Hospital, Hochiminh City

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Abstract Tobramycin has been primarily used in case of severe infections caused by gram negative bacteria. However, as an aminoglycoside antibiotic, tobramycin can cause nephrotoxicity and otoxicity. In addition, it is also an antibiotic with narrow therapeutic window. A prospective study was conducted on 30 patients to monitor the concentrations of tobramycin at peak and trough levels as well as renal function to evaluate the dosage and possibility of nephrotoxicity during treatment. Only 53.3% and 56.7% patients possessed tobramycin trough and peak concentrations, respectively within normal limits. No significant difference was found in trough and peak concentrations between 3rd and 9th doses. After five days of drug therapy, no significant influence on renal function was recorded. Trough concentrations seemed to exceed normal range (0.5-2 µg/ml) in those with low clearance creatinine before treatment as well as in those using tobramycin concomitantly with other medicines which can influence renal function. However, there must be larger studies to re-examine this judgement.

Keywords: BUN, creatinine, intramuscular injection, tobramycin

INTRODUCTION

Tobramycin has been primarily used in case of severe infections caused by gram negative bacteria,[1] which has been considered less toxicity compared to gentamicin.[2-4] However, as an aminoglycoside antibiotic, tobramycin can cause nephrotoxicity and otoxicity. In addition, it is also an antibiotic with narrow therapeutic window. Therefore, it is warned to be strictly monitored in treatment.

There have been a lot of studies on the correlation between tobramycin plasma concentration and its effect as well as toxicity. However, in Vietnam, monitoring tobramycin concentration has not been taken into guidelines for antibiotic usage. As a result, there is no accurate data for dose adjustment. The aim of this study is to evaluate the plasma concentration of tobramycin at peak and trough levels as a foundation for dose adjustment and detection of nephrotoxicity during treatment.

MATERIALS AND METHODS

Materials

Patients Thirty in-patients administered tobramycin intramuscularly were randomly selected from the Department of Surgical Gastroenterology of Cho Ray Hospital, Hochiminh city, Vietnam from April to June 2007. Only women during pregnancy, children under 15 and patients undergoing hemodialysis were omitted from the study. Basing on duration of treatment, these patients were divided into 2 groups:

Group 1: 30 patients whose plasma tobramycin concentrations were measured at the third dose (before for trough and after for peak concentrations).

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Group 2: 16 patients from group 1 who took tobramycin for at least five days. The plasma tobramycin concentrations were measured at the ninth dose.

Tobramycin Two brand names of tobramycin were used, Tobramicina IBI (vials of 100mg, manufactured by Giovanni Lorenzini S.p.A. Institute, Italy) and Brulamycin (vials of 80 mg, manufactured by TEVA Pharmaceutical Works Co. Ltd., Hungary). Tobramycin was administered at 80-100 mg /12 hours.

Renal function tests Blood urea nitrogen (BUN) and serum creatinine were measured before and after day 5 of treatment. Creatinine clearance (Cl_{cr}) was calculated by Cockcroft and Gault's formula:

$$Cl_{cr}\ male\ (\text{ml/minute}) = \frac{(140 - age) \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dl)}$$

$$Cl_{cr}\ female = 0.85 \times Cl_{cr}\ male$$

Methods

Study design A prospective study was conducted on these 30 patients. Tobramycin blood concentration was monitored through peak and trough levels.

Sampling time Blood samples were drawn within 30 minutes before the dose and 60 minutes after the dose for measuring trough and peak concentrations, respectively.

Normal levels Trough, 0.5-2 µg/ml and peak, 5-10 µg/ml.

Determination assay Fluorescence polarization immunoassay (FPIA) was used.

RESULTS

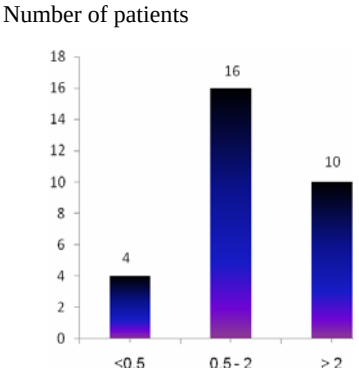
The general information of patients in Group 1 (tobramycin concentrations being measured at 3rd dose) is indicated in Table 1. Patients in this group were also classified into two sub-groups basing on medicines concomitantly used as followed:

- *Group 1a*: 24 patients (80%) administered tobramycin together with medicines which can influence renal function such as cephalosporin antibiotics, diuretics, NSAIDs.
- *Group 1b*: 6 patients (20%) not administered tobramycin together with medicines which can influence renal function.

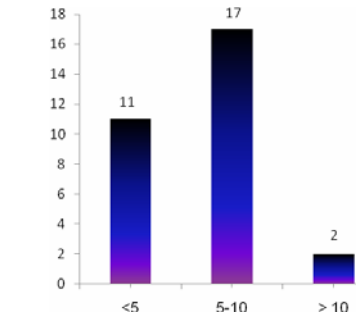
Table 1. Patients' general information in Group 1

	Mean ± S.D.
Sex Male	n = 21 (70%)
Female	n = 9 (30%)
Age (years)	59.9 ± 3.5
BUN (mg/dl)	12.5 ± 2.6
Creatinine (mg/dl)	1.1 ± 0.1
Cl_{cr} (ml/min)	54.6 ± 3.7

The results of tobramycin concentrations of this group are shown in Table 2 and Figure 1. All 10 patients whose tobramycin trough concentration exceeded 2 µg/ml belong to subgroup 1a.



(a) Tobramycin concentration (µg/ml)



(b) Tobramycin concentration (µg/ml)

Figure 1. Distribution of tobramycin trough concentrations (a) and peak concentrations (b) in Group 1.

Table 2. Tobramycin concentrations (µg/ml) in Group 1

	Mean ± S.D.	Normal range
Peak	6.4 ± 0.6	5-10
Trough	1.8 ± 0.3	0.5-2

The general information of patients in Group 2 (tobramycin concentrations being measured at 9th dose) is indicated in Table 3. Renal function tests were done before and after five days of treatment and the results are presented in Table 4. The statistic *t*-pair test was used to compare the difference in these tests before and after day 5 of treatment with tobramycin and no significant difference in renal function tests was found.

Table 3. Patients' general information in Group 2

		Mean ± S.D.
Sex	Male	n = 11 (68.8%)
	Female	n = 5 (31.3%)
Age		50.5 ± 2.4
BUN (mg/dl)		15.1 ± 1.5
Creatinine (mg/dl)		0.9 ± 0.06
Cl_{cr} (ml/min)		60.1 ± 5.5

The results of tobramycin concentrations of Group 2 are shown in Table 5. No significant difference was found in both tobramycin peak and trough concentrations when measured at 3rd and 9th doses. The distributions of tobramycin peak and trough concentrations in this group are presented in Figure 2**.**

Table 4. Results of renal function tests in Group 2

Test	BUN (mg/dl)	Creatinine (mg/dl)	Cl_{cr} (ml/min)
Before treatment	13.8 ± 1.2	1.1 ± 0.1	57.1 ± 4.4
After 5 days of treatment	15.1 ± 1.5	0.9 ± 0.06	60.1 ± 5.5

No significant difference in renal function tests was found.

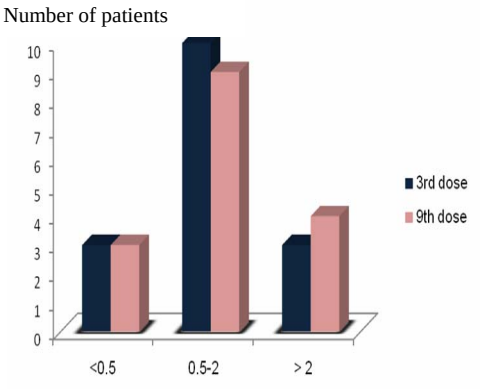
DISCUSSION

Only 53.3% and 56.7% patients possessed tobramycin trough and peak concentration, respectively, within normal limits. However, almost all patients got improvement during treatment. Therefore, it is not absolutely necessary to increase tobramycin dosage.

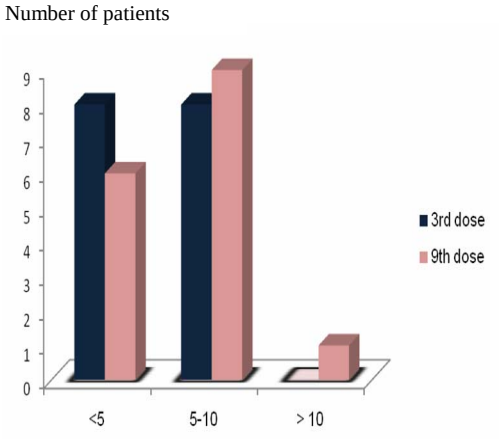
There were ten patients in subgroup 1a with tobramycin trough concentration exceeding 2 µg/ml, which could be the beginning of nephrotoxicity. Among these 10 patients, 2

Table 5. Tobramycin concentrations in (µg/ml) Group 2

	Mean ± S.D.		Normal range
	3rd Dose	9th Dose	
Peak	5.25 ± 0.38	5.83 ± 0.43	5-10
Trough	1.4 ± 0.35	1.8 ± 0.5	0.5-2



(a) Tobramycin concentration (µg/ml)



(b) Tobramycin concentration (µg/ml)

Figure 2. Distribution of tobramycin trough concentrations (a) and peak concentrations (b) in Group 2.

had low creatinine clearance before treatment (< 20 ml/min), the others had normal renal function. Therefore, there must be larger studies to re-examine whether concomitant use of tobramycin with other medicines which can influence renal function can cause the increase in tobramycin trough concentration. However, in the renal function tests, no difference was found. This can lead to a suggestion to decrease tobramycin dosage when concomitantly administered with other antibiotics, *e.g.* cephalosporins, if possible.

CONCLUSION

The results from the study suggested that tobramycin concentrations do not seem to be stable when intramuscularly administered. It would be much more stable if administered through parenterally intravenous injection. In cases with tobramycin trough concentration exceeds normal range; there must be strict follow-up of renal functions. The one-daily dose may also be considered in these cases to decrease tobramycin trough concentration. An adjustment by increasing dose may only be necessary in case there is no or slow improvement in signs and symptoms.

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