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Therapeutic drug monitoring for gentamicin in Hospital Universiti Sains Malaysia

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Summary

We evaluated the usefulness of therapeutic drug monitoring (TDM) for gentamicin and the use of a two-point peak and trough pair concentration method to adjust its dose. Of the 194 patients included, initial concentrations were appropriate in only sixty nine. In the seventy one cases of dosage adjustments using this method, those attaining therapeutic levels increased overall from 38% to 67%. It is concluded that TDM for gentamicin with dosage adjustment using this simple pharmacokinetic approach is useful and adequate in monitoring for gentamicin therapy.

Key Words: TDM; monitoring gentamicin therapy; peak and trough concentration; therapeutic levels; dosage adjustment; two-point method; pharmacokinetic calculation.

Introduction

The chemotherapy of life-threatening gram-negative bacterial infections still poses a challenge. Gentamicin rapidly kills gram-negative aerobic bacilli and is therefore widely used for these infections[1] and at the Hospital Universiti Sains Malaysia (HUSM), about thirty thousand Malaysian ringgit is spent annually for its purchase. Gentamicin however has a narrow therapeutic index. Prolonged subtherapeutic levels resulted in breakthrough bacteraemia[2], low peak with inefficacy and high trough with toxicity[3]. Dosage requirements varied[4] and standard dosing methods were unreliable[5,6] The clinical monitoring of gentamicin toxicity is difficult. The use of serum creatinine as a guide for nephrotoxicity for instance, delayed its diagnosis as elevation in serum creatinine was delayed[7] and accumulation as evidenced by sustained high trough predisposed to toxicity[3,8]. There is therefore a need for TDM for gentamicin.

The objectives of this study were to evaluate the adequacy of 'standard' gentamicin dosage in HUSM patients, as defined by desired concentrations, and the usefulness of a two-point peak and trough pair method adopted to adjust dosages in the TDM for gentamicin at HUSM. We did not however attempt to evaluate the appropriateness of gentamicin therapy itself. The results will hopefully contribute towards optimising TDM for gentamicin in Malaysia.

Materials and methods

Patients received gentamicin for persumptive or laboratory diagnoses of gram-negative bacterial infections and TDM was initiated by their respective clinicians who sent serum samples for gentamicin determination. The trough sample was obtained 30 minutes prior to and the peak 30 minutes after the (usually third) dose of gentamicin.

Fluorescence polarisation immunoassay (TDx^R, Abbott Lab.,USA) was employed to determine gentamicin concentrations. Samples with known LOW (1.0 ug/ml), MEDIUM (4.0 ug/ml) and HIGH (8.0 ug/ml) concentrations of gentamicin were used in quality assurance.

Dosage adjustment was recommended if the trough and/or peak concentration(s) fell out of a predetermined range. Subsequent serum samples for gentamicin concentrations were obtained to ensure attainment of therapuetic levels. Assuming one compartment pharmacokinetics for gentamicin. First order elimination rate constant(k_e) and plasma half life were determined from:

$$k_e = \frac{\ln C_{max} - \ln C_{min}}{T} \quad \text{.....(1)}$$

$$t_{1/2} = \frac{0.693}{k_e} \quad \text{.....(2)}$$

where, C_{max} = peak concentration (ug/ml)

C_{min} = trough concentration (ug/ml)

$\triangle$ -T = Time difference between the peak and trough concentration (hrs)

$t_{1/2}$ = plasma half-life (hrs).

Dosing interval T was calculated from 3 x $t_{1/2}$. The apparent volume of distribution V_d was estimated from the extrapolated C_{max} (maximum concentration) and maintenance dose (D_m) from:[9]

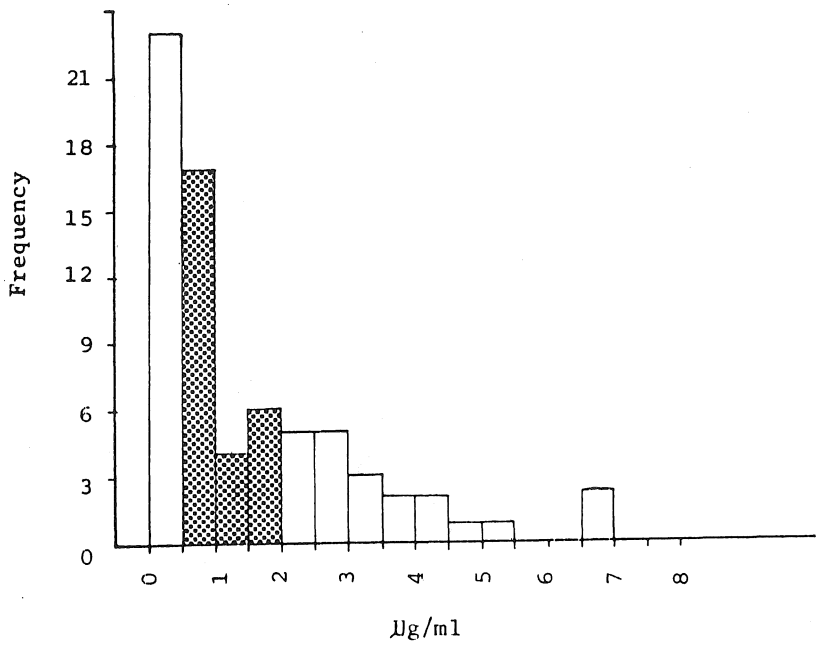
$D_m = C_{max} \times V_d \times (1-e^{-kT})$ 3

Results

194 patients received the TDM services for gentamicin and the results of serum gentamicin concentrations obtained were analysed. They received gentamicin for a mean duration of 5.7 days (range 1 - 38 days) and the indications are listed in Table 1.

Before dosage adjustment concentrations were therapeutic in only sixty nine (35.6%) (Table 2). Of the remaining 125 patients, ninety-four were outside the therapeutic range, seventeen were discontinued from further doses of gentamicin due to excessively high levels and in another fourteen very low concentrations were obtained and were found to be due to drug misadministration. The number of patients who recieved adjusted doses based on three-point and two-point methods were 13 and 81 respectively. However in the group using two-point method, recommendations for ten patients were not complied with, leaving only 71 for further analysis.

The distribution of gentamicin peak and trough concentrations in the seventy one patients prior to dosage changes are shown in Figs 1 and 2. Only twenty-seven patients (38%) had levels in the therapeutic range and twenty one (30%) actually had a trough in excess of 2 ug/ml. Following



1. Histogram showing frequency and distribtion of gentamicin trough levels before dos-adjustments. The shaded area represents the therapeutic range used.

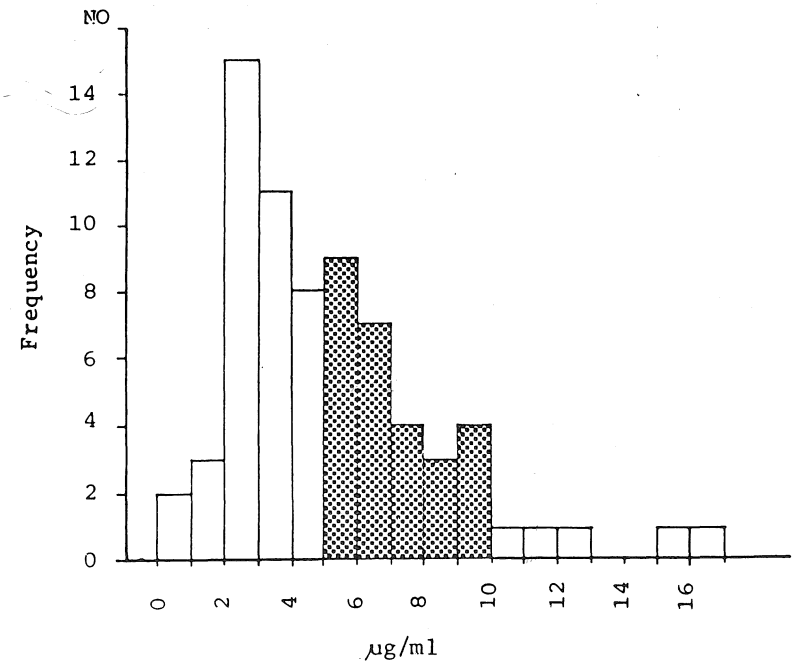


Fig 2. Histogram showing frequency and distribution of gentamicin peak levels before dosage adjustment. The shaded area represents the therapeutic range used.

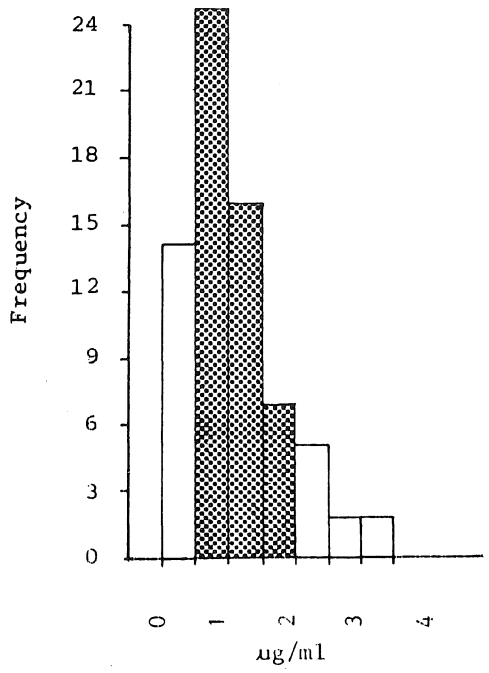


Fig 3. Histogram showing frequency and distribution of gentamicin trough levels after dosage adjustment. The shaded area represents the therapeutic range used.

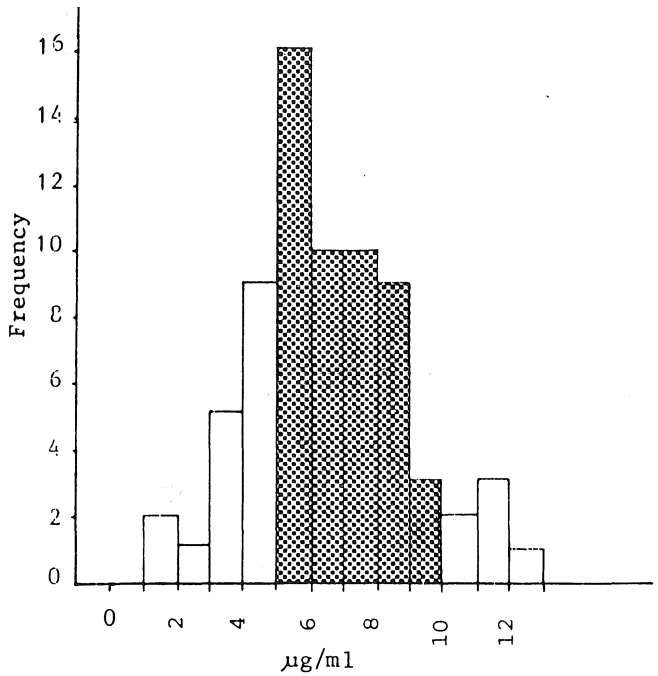


Fig 4. Histogram showing frequency and distribution of gentamicin peak levels after dosage adjustments. The shaded area represents the therapeutic range used.

Table 1: Indications for gentamicin therapy (in descending order of frequencies) in the patients who recieved TDM for gentamicin.

Pneumonia
Gynaecological infections
Intra abdominal infections
Osteomyelitis
Pyrexia of unknown origin
Septicaemia
Soft tissue infections/wounds
Subacute bacterial endocarditis
Urinary tract infection

Table 2. Appropriateness of Gentamicin dose.

Number of patients with appropriate levels	69
Number of patients with inappropriate levels:	
i. Found to be due to drug misadministration	14
ii. Excessively high concentration and gentamicin subsequently discontinued.	17
iii. Concentrations not in therapeutic range, thus dosage adjustment were recommended.	94[a]

[a]included 13 patients with adjustment based on three-point and 81 patients analysed by two-point method.

dosage adjustments, the percentage of patients attaining therapeutic levels increased to 67.6% (Table 3,see also Figs 3 and 4). The trough concentrations of 2 ug/ml and above was reduced to 12.8%. Adjusted doses ranged from 1.3 to 11.0 mg/kg/day (mean: 5.2 +/- 2.1 mg/kg/day). (Fig.5). Compared to the doses recommended in the package inserts for gentamicin, of the seventy one new doses adopted based on the two-point method, 18.3% were less than the minimum recommended of 3mg/kg/day whilst 59.1% were more than the usual recommended maximum of 5 mg/kg/day.

Table 3: Distribution of trough and peak Gentamicin concentrations before and after dosage adjustment (Numbers in bracket represent the percentage of patients)

	Before Dosage adjustment		After Dosage adjustment	
	Trough	Peak	Trough	Peak
Subtherapeutic	23 (32.4)	39 (55.0)	14 (19.6)	17 (24.0)
Therapeutic	27 (38.0)	27 (38.0)	48 (67.6)	48 (67.6)
Toxic	21 (29.6)	5 (7.0)	9 (12.8)	6 (8.4)

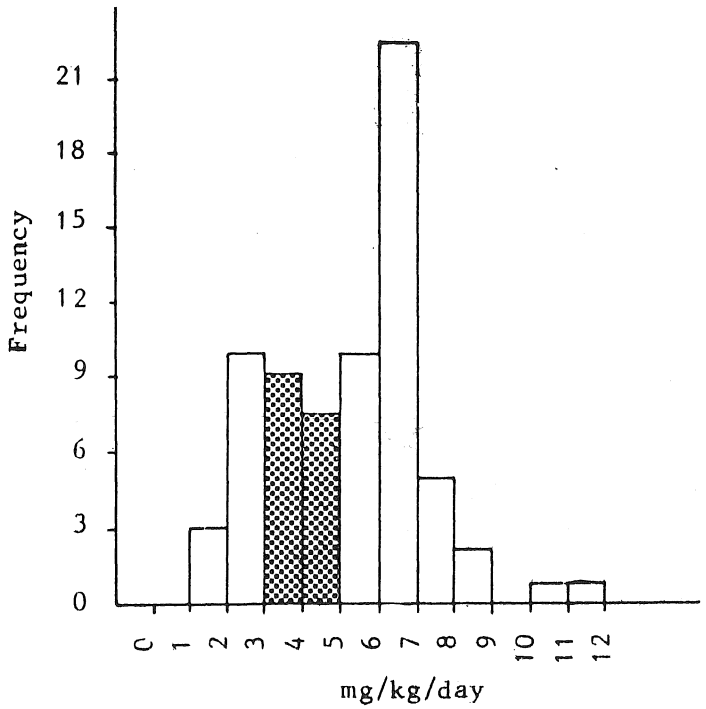


Fig.5 Frequency and distribution of 'adjusted' daily dosage of gentamicin (mg/kg/day) in 71 patients. The shaded area represents the recommended 3 to 5 mg/kg/day.

Discussion

TDM for gentamicin is aimed at achieving therapeutic concentrations early to eradicate the organisms in the potentially life-threatening gram-negative bacterial infection and to avoid prolonged high trough to minimise toxicity. High survival rates have been observed with peak serum concentration of 5 ug/ml or more achieved within the first 24-48hrs of therapy[10.11]

In our study, only sixty nine (35.6%) of the 194 patients given gentamicin received appropriate doses at the first instance as defined by therapeutic levels. In 125 (64.4%) doses were deemed inappropriate and further doses were discontinued in seventeen (8.8%) due to excessively high levels. These patients could potentially develop serious gentamicin toxicity had the levels not been monitored.

Adjusted doses varied greatly (1.3 to 11.10 mg/kg/day)[4,12,13], probably due to altered pharmacokinetics[4]. The volume of distrubution in critically ill patents and in children under five years for instance, has been found to be larger than population averages[12,14].

Therapeutic concentrations in the seventy one patients who had their doses changed based on two-point method increased dramatically from 38% to 67.6%. Clinical correlation was not attempted but it has been shown that survival increased from 33% to 64% for patients receiving individualised doses[13]. There was also a decrease from 30% to 12% of patients who experienced trough in excess of 2 ug/ml, the level usually associated with increased toxicity.

Pharmacokinetic parameters calculated using a two-point curve may lead to some inaccuracy[15]. To use three points however, would require a regression equation for best-fit line which cannot be achieved with an ordinary calculator. We found the two-point method adequate and convenient and reserved the three-point method to problem cases such as those with impaired renal dysfunction.

Recently Zantvoort ref. et. al. [16] reviewed the use of a computer programme (OPT) which considered such errors and employed population data. They increased therapeutic concentrations from 51% (before OPT) to 85% (after OPT). This method may be marginally superior but requires a computer.

Our results support previous findings [17] that TDM for gentamicin helps to optimise gentamicin therapy. With the automated assays costing about MR 7.00 per sample and this simple pharmacokinetic calculation, a suitable dosage regimen for each patient can be rapidly determined and thus TDM for gentamicin can be broadly adopted even in developing countries with limited resources. The cost of assay can be easily offsetted by the reduced morbidity and mortality associated with inappropriate gentamicin dosing.

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