MONITORING OF SERUM GENTAMICIN LEVEL IN A GENERAL HOSPITAL

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SUMMARY

Gentamicin is an aminoglycoside antibiotic which is commonly used in the treatment of serious Gram-negative infections. However, gentamicin like other aminoglycosides, has a narrow therapeutic index and is potentially ototoxic and nephrotoxic. Blood levels following administration of gentamicin has been shown to be highly unpredictable and monitoring of gentamicin levels is necessary to ensure effective therapeutic levels as well as to avoid toxicity. The Department of Microbiology, Universiti Kebangsaan Malaysia offers such a monitoring service. This paper analyses the results of 135 such estimations performed between August 1979 and May 1981. It is shown that a significant proportion of patients were receiving either too much or too little gentamicin. Empirical determinations of dosages is unsatisfactory and as the microbiological assay method of determining gentamicin levels is both easy to perform and inexpensive, such a service should be offered by all general hospitals in Malaysia.

MATERIALS AND METHODS

Serum samples were obtained from a total of 135 patients in the General Hospital, Kuala Lumpur. All patients were being treated with gentamicin. Wherever possible, two blood specimens related to the time of giving the antibiotic were taken. The first specimen was taken just before giving a dose of gentamicin and is a measure of the lowest (trough) level of gentamicin. The second specimen was taken one hour after an intramuscular injection. In cases where gentamicin was administered intravenously, the blood specimen was obtained either at the end of a continuous infusion or 30 minutes after a bolus injectin. The second specimen gives an estimation of the highest (peak) level of gentamicin.

The serum gentamicin level was assayed using a standard microbiological assay technique. Gentamicin standard solution (2000 mg/L) was obtained from Roussel Lab Ltd, Middlesex. The indicator strain used in all assays was *Klebsiella edwardsii* NCTC 10896. An inoculum of approximately 5 x 10^5 organisms was used to seed a 14 cm assay plate containing 80 ml of Sensitest Agar (Oxoid). Wells were punched in the agar using an 8 mm cork-borer. The wells were filled with (i) gentamicin standard solutions of the following concentrations; 1.25 mg/L, 2.5 mg/L, 5.0 mg/L, 10.0 mg/L and 20.0 mg/L (ii) the patient's serum (iii) a pooled serum sample to serve as an internal control. The assay plate was then incubated at 37°C and the diameters of the zones of inhibition measured the following day using a vernier caliper. A standard curve of gentamicin concentration versus diameter of zone of inhibition was plotted on semi-logarithmic paper (see Fig. 1). The concentration of the gentamicin in the patient's serum is estimated by reading off the standard curve. The microbiological assay method

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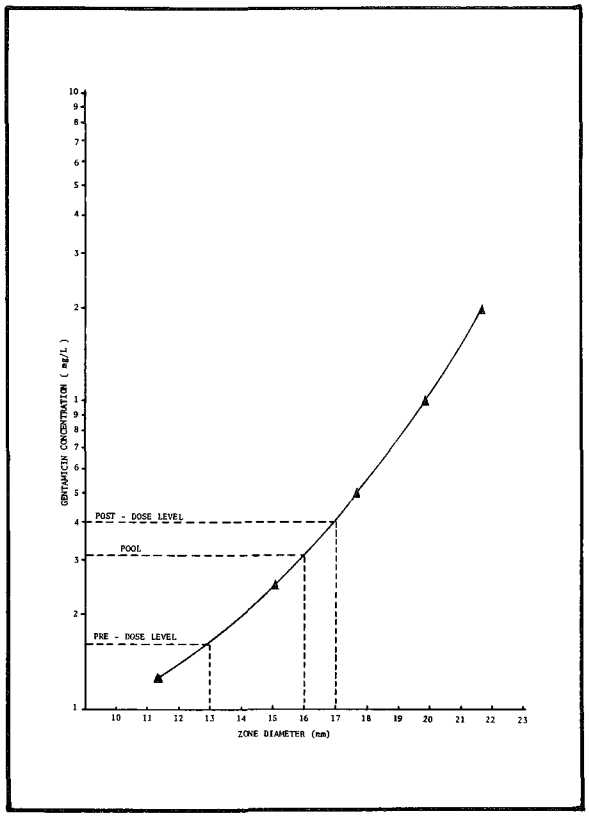

Fig. 1 Standard curve of gentamicin concentration (mg/L) versus diameter of zone of inhibition (mm).

has been described in detail in a standard textbook. [1]

RESULTS

Most of the patients involved in this analysis had serious underlying diseases - septicaemia, renal failure, endocarditis, burns, post-amputations and crush injuries. Table I shows the distribution of the sources of the specimens with respect to units/wards.

Although pre-dose and post-dose samples were requested for from all patients, there were specimens where only a pre-dose, post dose or random sample was sent. (Table II).

Figures 2, 3 and 4 summarise the results of the gentamicin level estimations. Levels of less than 3 mg/L for the pre-dose sample and between 3 - 8 mg/L for the post-dose sample were considered to be satisfactory levels. Table III shows the distribution of the specimens into those which were considered low (i.e. not likely to achieve a therapeutic effect), those considered satisfactory and those considered high (i.e. potentially toxic).

TABLE I
SOURCES OF SPECIMENS WITH RESPECT TO UNITS/WARDS

WARDS/UNITS	NUMBER OF SPECIMENS
Orthopaedic	64
Intensive Care Unit/Coronary Care Unit	35
Medical	22
Surgical	6
Urology/Nephrology	7
Paediatric	1
TOTAL	135

TABLE II
SPECIMENS RECEIVED OVER THE PERIOD AUGUST 1979 TO MAY 1981

TYPES OF SPECIMEN	NUMBER
Pre-dose and post-dose	104
Pre-dose only	3
Post-dose only	6
Random only	22
TOTAL	135

DISCUSSION

Antibiotic assays of body fluids are performed for three principal reasons: (i) to ensure the concentration of antibiotic achieved in the patient is adequate for effective therapy (ii) to monitor the presence of unnecessarily high concentrations which may be associated with an increased risk of toxicity (iii) for the pharmacokinetic studies of antibiotics. In the case of gentamicin monitoring of levels is particularly important because of the low therapeutic index of the antibiotic and its serious toxic effects. [2,3] Barza *et al* [4] has shown that the blood levels of gentamicin following administration are unpredictable thus empirical determination of dosage is highly unsatisfactory. There is a noticeable individual variation in the peak serum concentration in response to a fixed dose. Attempts have been made to overcome these difficulties by the production of normograms [5] but these have been shown to be unreliable in life-threatening situations. [6]

Blood levels of gentamicin are fairly

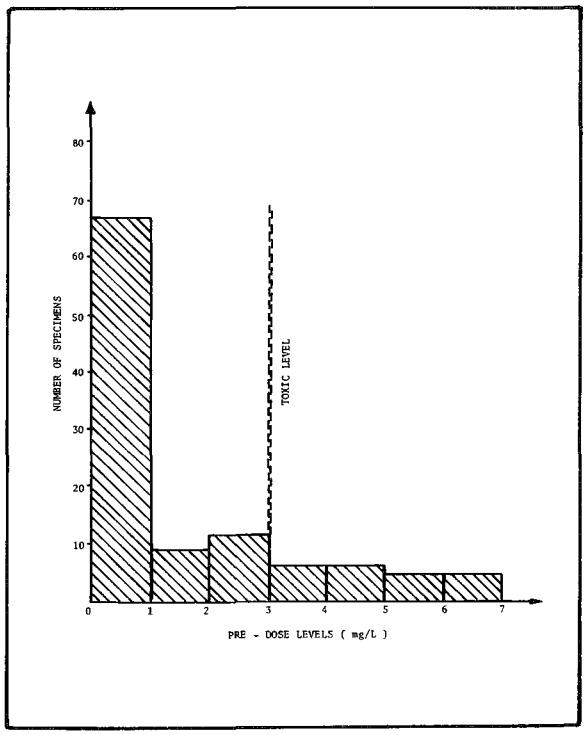

Fig. 2 Pre-dose serum gentamicin levels.

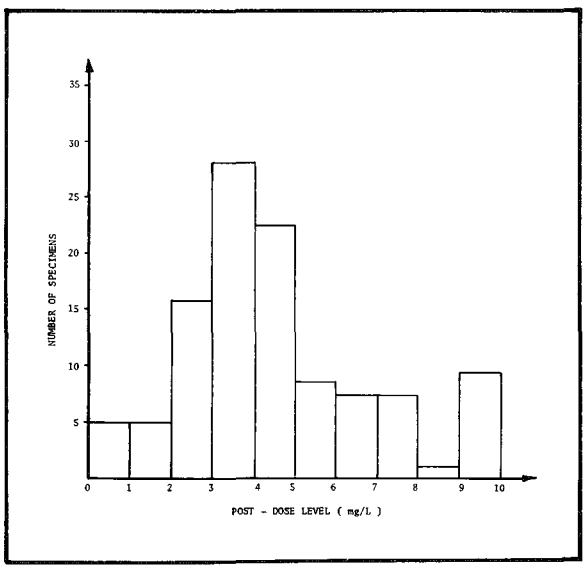

Fig. 3 Post-dose serum gentamicin levels.

representative of the tissue level throughout the body and may be used for therapeutic purposes. Moreover, it has been shown that the peak serum concentration after an intramuscular injection occurs 30 minutes to 120 minutes after the injection and that the concentration in the serum one hour

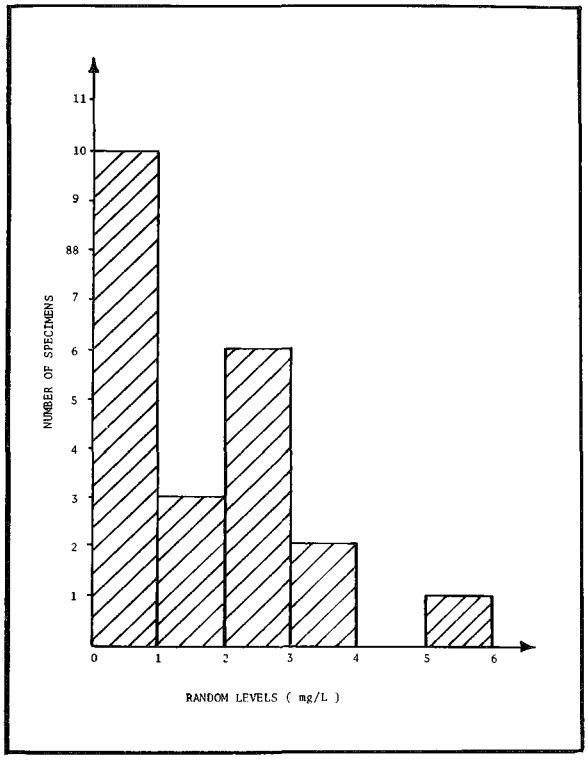

Fig. 4 Random serum gentamicin levels.

after injection is at least 70 percent of the true peak. [7] Keong [8] has shown that the majority of Gram-negative rods isolated in the Kuala Lumpur General Hospital were inhibited by concentrations of gentamicin of between 0.5 to 2.0 mg/L. The peak gentamicin level aimed for should thus be in the region of between 3 - 8 mg/L (approximately 4 times the minimum inhibitory concentration) in order to achieve effective therapeutic effect. It has also been shown that the trough level should be kept below 3 mg/L and the peak should not exceed 10 mg/L in order to avoid toxicity. [9,10]

TABLE III
DISTRIBUTION OF SPECIMENS INTO LOW, SATISFACTORY AND HIGH SERUM GENTAMICIN LEVELS

SERUM GENTAMICIN LEVELS	NUMBER OF SPECIMENS	PERCENTAGE
Low (not achieving therapeutic level)	48	35.6
Satisfactory	64	47.4
High (potentially toxic)	23	17.0
TOTAL	135	100.0

It is shown in this analysis that over a third of patients (35.6 percent) were receiving too little gentamicin and had levels which were unlikely to be therapeutically effective. This is probably a result of excessive anxiety about the toxicity of gentamicin. Seventeen percent of patients were receiving too much gentamicin and had blood levels which were potentially toxic. In all these patients, the results were communicated to the physician in charge and recommendations made for dosage modification. Repeat estimations were requested for to ensure the attainment of satisfactory levels. The fact that more than half of the patients involved in the study (52.6 percent) were found to be receiving sub-optimal dosages of gentamicin stresses the importance of the monitoring service in the General Hospital, Kuala Lumpur.

The microbiological assay technique for the estimation of serum gentamicin level is easy to perform. No expensive reagents or equipment are necessary. We feel, therefore, that this service should be offered by all general hospitals in Malaysia.

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