Gentamicin Blood Levels: a Guide to Nephrotoxicity

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Gentamicin blood levels were monitored in 86 patients. Twenty-one patients had valley levels over 2 μg/ml and 36% of these patients developed abnormal serum creatinine or a further rise in creatinine. No patient had a rise in creatinine without a valley level over 2. The peak levels in patients with valleys over 2 were above 10 μg/ml in only one case, whereas four patients had peaks over 10 μg/ml without nephrotoxicity. The mean peak blood levels in patients with a normal creatinine were dose related. An initial dose of 2.0, 1.5, and 1.3 or less mpk (mg/kg) yielded mean peak blood levels of 5.2, 4.7, and 3.7, respectively. To assure an initial peak blood level over 4 μg/ml a loading dose of 2 mpk was required. A rise in peak and valley levels during therapy appeared dose related, being observed in all patients treated with 4.5 mpk daily but not in those receiving 3.0 mpk daily. A radioenzymatic assay was used to validate the standard agar diffusion assay method. The results from the two assays were statistically identical. Valley blood levels of gentamicin may be useful for predicting accumulation of gentamicin which in turn may be correlated with early renal impairment before potentially toxic serum levels of gentamicin develop.

Gentamicin is an aminoglycoside antimicrobial agent widely used in the treatment of serious gram-negative bacillary infections. The range between effective and toxic blood levels is narrow. Administration of a given dose of gentamicin results in widely differing blood levels. Monitoring of blood levels has been recommended to assure effective therapy and avoidance of toxicity with this drug (4). This paper reports a prospective study of gentamicin dose-blood level relationships and examines the value of blood levels as a guide to preventing nephrotoxicity.

MATERIALS AND METHODS

All gentamicin serum levels were determined by the agar diffusion method of Winters et al. (8). The radioenzymatic method of Smith et al. (6), utilizing an adenylylating enzyme, was used as an additional assay on 360 specimens. The radioenzymatic assay was modified by soaking the phosphocellulose paper (Whatman PC-81) in 29 mM adenosine (Sigma) for 12 h. This step assured a reproducible background level which was not obtained with unsoaked paper.

Serum samples from 86 patients were obtained at various intervals to determine peak and valley serum concentrations after an intramuscular or intravenous dose. Extreme care was exercised in timing blood samples representing peak determinations 30 to 45 min after intramuscular injections and within 30 min after completion of intravenous infusion. Valley samples were obtained during the hour preceding a dose.

Patients were selected at random from among all patients receiving gentamicin at the University of California at Los Angeles during one 10-month period. No patient was excluded from the monitoring study for any reason. An attempt was made to classify the severity of illness in each patient at the time of entry into the study. On this basis 7% of the patients had mild problems of infection and a similar percentage had critical illness from which they were not expected to survive; 56% of the patients had serious infections with a good prognosis, and 29% had serious infections of uncertain outcome. Doses ranged from 0.8 to 2.0 mg/kg (mpk) at hourly dose intervals determined by multiplying the serum creatinine times eight.

The interval between doses in patients with normal renal function with 8 h. In patients with elevation of the serum creatinine the interval between doses was determined by multiplying the serum creatinine times eight, which gave the number of hours between doses (1).

RESULTS

Peak serum concentrations varied widely even with identical doses. For example, even on days 1 to 3 the peaks after the 1.5 mpk dose varied from 1.1 to 6.8 μg/ml and the overall variation of peaks after this dose was 1.1 to 18.0 μg/ml (Table 1). However, the mean peak serum blood level rose as the dose was increased from 0.8 to 2.0 mpk in patients with normal renal function (Fig. 1). An initial dose of 2.0 mpk yielded serum levels over 4 μg/ml in 91% of the patients. Initial doses of 0.8 to 1.2
patients with valley levels between 3 and 4 
ug/ml and in all of five patients with levels over 
4 \( \mu \)g/ml. All of the patients whose serum creati-
nine rose to abnormal levels had received a 
loading dose of 2 \( \mu \)pk and a maintenance dose 
of 1.5 \( \mu \)pk; no other cause of renal dysfunction 
was apparent. There was no increased use of 
cephalosporins or diuretics in the nephrotoxic 
group. Serum creatinine returned to the normal 
range within a short period in all patients after 
gentamicin was discontinued.

The patients with normal serum creatinine 
who received gentamicin at a dosage of 1.5 \( \mu \)pk 
every 8 h, with or without a loading dose of 2.0 
\( \mu \)pk, had a progressive rise in both peak and 
valley serum levels (Fig. 3). The mean peak 
level increased at a rate of 0.040 \( \mu \)g/ml per day. 
This rise in blood levels occurred in all patients 
receiving 1.5 \( \mu \)pk. These rises were not apparent 
in patients receiving doses of 0.8 to 1.2 \( \mu \)pk 
every 8 h or in azotemic patients for whom 
dosage was individualized based upon serum

![Fig. 1. Mean peak levels and dose level. The 
values in parenthesis indicate the percentages over 
4 \( \mu \)g/ml.](image)

![Fig. 2. Gentamicin disappearance curve in pa-
tients with normal and abnormal renal function.](image)
Table 2. Relation of selected therapeutic features to renal function during treatment with gentamicin

<table>
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<th>Determinants</th>
<th>Pt. No.</th>
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<th>Loading</th>
<th>Day of Rx</th>
<th>Elevated valley</th>
<th>Serum creatinine</th>
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Normal creatinine equals 0.7 to 1.3 mg%. Loading indicates that the patient received an initial dose of 2 mgk and was then maintained on the dose indicated. The after Rx creatinine is a determination 2 to 5 days after gentamicin was stopped. Cephalosporin refers to concurrent therapy from the time of initiation of gentamicin.

creatinine concentration or gentamicin serum levels.

The agar diffusion and radioenzymatic assay for serum gentamicin concentrations gave statistically similar results (360 serum samples were analyzed by both methods) (matched P = 0.18, t = 1.35 on 360 degrees of freedom). The high degree of statistical correlation between the methods is shown by a correlation coefficient of 0.82, P value <0.001 (r = 0.82, P = <0.001) (Fig. 4). The results from the two methods were analyzed separately at low, middle, and high concentrations and no significant differences in correlation were noted.

DISCUSSION

The outcome of gram-negative bacillary sepsis often seems to be decided in the first 24 h of therapy and patients frequently expire before antimicrobial therapy has had sufficient time to exert any beneficial effect. It has accordingly been thought desirable to ensure adequate blood levels of antimicrobials when the need is greatest and gentamicin serum levels have been proposed as a means to achieve this goal. Peak blood levels of 4 µg/ml or greater have been advocated for treatment of Pseudomonas bacte-
remia (3). In this study a peak serum concentration over 4 µg/ml was obtained in 90% of patients after a loading dose of 2 mgk. Thus, unless higher peak levels were desired, serum assays seem unnecessary to monitor this aspect of therapy. Although in this study the two patients with Pseudomonas sepsis had peak blood levels over 4 µg/ml during the early phase of their therapy and survived, it should be
emphasized that the use of this serum concentration as a guideline for adequate therapy needs further substantiation, and that for infections other than Pseudomonas no evidence exists to support the need for such blood levels.

In this study, as treatment was continued, the peak and valley gentamicin blood levels rose slowly in all patients treated with 4.5 mg/kg per day. In the usual 7- to 10-day course of therapy this rise would probably not be important. When long-term therapy is undertaken in diseases such as endocarditis or osteomyelitis, such accumulation could be important. Although the basis for this accumulation is not established, it is of interest that 7 of 21 patients in the present study who received a loading dose of 2 mg/kg and a maintenance dose of 1.5 mg/kg every 8 h developed an elevated creatinine within the first week of therapy. The elevation of serum creatinine in these patients was not related to either the total dose of gentamicin or the duration of therapy. Contrariwise, none of the patients who received less than 4 mg/kg per day demonstrated gentamicin accumulation and none of them experienced a rise in creatinine. A dose of 1.5 mg/kg every 8 h may exceed the usual excretory capacity. A safer maintenance dose may be 1.3 mg/kg or less every 8 h, especially after 72 to 96 h of therapy in patients who have shown a favorable response.

Seven out of 86 patients had a rise in serum creatinine during gentamicin therapy which promptly returned to normal upon discontinuance of treatment. This is consistent with previous reports of changes in renal function in approximately 8% of patients receiving this drug (5, 7). All of the patients who manifested a rise in serum creatinine had a valley gentamicin level over 2 μg/ml and contrariwise, no patient experienced deterioration in renal function who had valley levels below 2 μg/ml. Although the numbers were small, a clear trend was observed for high valley levels to be associated with a rise in serum creatinine. Inasmuch as a patient with a valley level over 2 μg/ml has one chance in three of experiencing nephrotoxicity, it seems reasonable that monitoring such blood levels can define the high risk subgroup that will experience such an adverse effect and identify the patients who particularly need a reduction in gentamicin dosage. These observations do not imply a cause and effect relationship between a high, persistent level of gentamicin and nephrotoxicity despite the absence of any other obvious cause for renal impairment in these patients. In fact, the serum creatinine promptly returned to pretreatment concentrations upon discontinuance of gentamicin. Similarly, the collection of these data did not permit a judgement as to whether serum gentamicin levels were a more sensitive or an earlier index of
nephrotoxicity than serum creatinine, although this question is now under study.

ACKNOWLEDGMENTS

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LITERATURE CITED