Prospective Comparative Study of Variable Dosage and Variable Frequency Regimens for Administration of Gentamicin

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In patients with impaired renal function, careful adjustment of gentamicin dosage is required to achieve therapeutic yet nontoxic concentrations. Two regimens that differ in pharmacodynamic characteristics have been recommended for this purpose: prolonging the intervals between administration of equal doses (variable frequency regimen [VFR]) or administering a loading dose followed at the usual intervals by reduced maintenance doses (variable dosage regimen [VDR]). These regimens were compared in a prospective, randomized study of 20 seriously ill hospitalized patients, 10 on VFR and 10 on VDR. Wide variability in peak serum levels of gentamicin was observed both between patients and in individual patients after separate injections of the same dosage. As predicted by the design of these regimens, the trough serum levels of gentamicin correlated significantly with the serum creatinine concentrations in patients on the VDR but not in patients on the VFR. A gentamicin trough level of ≥4 μg/ml was the only variable among those tested that correlated significantly with development or progression of renal insufficiency during treatment with gentamicin, but such trough levels were observed frequently on both regimens. Whereas this study does not permit a direct comparison of the therapeutic efficacy of VDR and VFR, no difference in the risk of nephrotoxicity with these regimens was observed.

The high degree of variability in peak serum levels of gentamicin (8, 11, 12) and the narrow margin between optimal therapeutic and potentially toxic doses (1, 6) have resulted in recommendations by many investigators to determine serum gentamicin levels frequently during therapy to ensure optimal treatment of infections and to avoid drug toxicity. In patients with impaired renal function, two methods which differ markedly in pharmacodynamic characteristics have been recommended for adjusting the dosage of gentamicin to compensate for the reduced renal clearance: (i) administering a loading dose and then prolonging the intervals between administration of similar maintenance doses of gentamicin (variable frequency regimen [VFR]) (3, 4, 9), or (ii) giving a loading dose of gentamicin followed at the usual time intervals, generally every 8 h, by reduced maintenance doses (variable dosage regimen [VDR]) (2). Dosages with both regimens are calculated to produce similar peak serum levels of gentamicin. With the VDR, the trough serum levels of gentamicin are determined by the severity of renal insufficiency and should be 50% or more of the preceding peak levels when the half-life of gentamicin in serum exceeds the interval between doses. Thus, in patients with severe renal insufficiency treated by the VDR, serum gentamicin levels during therapy should continuously approximate or exceed the minimal inhibitory concentration of gentamicin for many aerobic gram-negative bacilli. In contrast, the intervals between doses with the VFR are calculated to allow the concentration of gentamicin in serum to decline to trough levels that are 25% or less of peak levels. Thus, gentamicin serum levels in patients with severe renal failure on the VFR might be suboptimal for periods of many hours. Few clinical data are available concerning possible differences either in the therapeutic efficacy or in the risk of ototoxicity and nephrotoxicity between VDR and VFR for administration of gentamicin to patients with renal insufficiency (2-4, 9).

In the present prospective study, phar-

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macokinetic responses were compared in 20 seriously ill, hospitalized adult patients treated by intramuscular administration of gentamicin by VFR and VDR. The goals were to extend previous pharmacologic observations on individual variability in dose response during treatment of seriously ill patients, to compare the VDR and VFR in a single study, and to evaluate the possible usefulness of sequential measurements of peak and trough serum levels of gentamicin in prediction of nephrotoxicity. (A preliminary report of these experiments was presented at the 14th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 11–13 September 1974.)

MATERIALS AND METHODS

Subjects included in the study were seriously ill patients on the medical service at Parkland Memorial Hospital, Dallas, Tex., who were being treated with intramuscular gentamicin by their primary physicians either for documented specific infections or for empirical initial therapy of suspected gram-negative bacillary sepsis. VDR and VFR were randomized; patients with even hospital unit numbers were treated by the VFR, and those with odd hospital unit numbers were treated by the VDR. Patients were examined daily by one of us, and therapy with gentamicin was discontinued as soon as permitted by clinical indications.

In the VFR that has been standard at this hospital, an initial dose of 1.5 mg of gentamicin per kg was administered and subsequent doses of 1.5 mg/kg were administered at a frequency in hours equal to eight times the concentration of serum creatinine in mg/100 ml. The intervals were rounded off to the nearest even number of hours. For example, a patient weighing 50 kg with a serum creatinine of 2.9 mg/100 ml received 75 mg of gentamicin every 24 h.

In the VDR a loading dose of 1.7 mg of gentamicin per kg was given, and subsequent doses were administered every 8 h at dosage levels determined from the published nomogram of Chan et al. (2). Use of this nomogram requires knowledge of creatinine clearance (Clcr, ml/min per 1.73 m²). For Clcr greater than 70 ml/min per 1.73 m², each dose of gentamicin was 1.7 mg/kg. When creatinine clearances were not available at the time treatment was begun, estimates of Clcr based on serum creatinine concentrations, age, and sex (7) were used to determine the first maintenance dose.

Specimens for determinations of peak serum levels were collected 1 h after intramuscular injection of gentamicin, and those for trough levels were collected 30 min or less before a dose. Peak and trough serum gentamicin levels and serum creatinine concentrations were performed once daily, and timed 4-h creatinine clearances were measured three times each week if possible. Serum specimens were stored at –20 C until assays for gentamicin were performed by an enzymatic method described previously (5). Concentrations of creatinine in serum and urine were performed in the clinical laboratory at Parkland Memorial Hospital by standard automated methods. Linear regression analysis was performed by the least squares method, and other statistical analyses were performed by the two-tailed Student's t test or by the chi-square test.

RESULTS AND DISCUSSION

Twenty patients were studied, ten treated by the VFR and ten by the VDR. There were no statistically significant differences between the two treatment groups as to age, sex, racial distribution, duration of gentamicin therapy, cumulative dosage of gentamicin, or serum creatinine concentration or creatinine clearance at the start of treatment (P > 0.10 for each characteristic). The mean initial serum creatinine concentration was 1.6 ± 1.2 mg/100 ml for patients treated by the VFR and 2.5 ± 1.5 mg/100 ml for patients treated by the VDR. Six of ten patients in the VFR and seven of ten in the VDR had impaired renal function with serum creatinine concentrations exceeding 1.0 mg/100 ml and with creatinine clearances less than 70 ml/min per 1.73 m² at the start of therapy with gentamicin.

An estimate of the pharmacokinetic response resulting from individual doses of gentamicin that is essentially independent of renal function can be obtained by calculating the difference, ΔG, between the peak serum level of gentamicin achieved after a dose and the trough level immediately preceding that dose. The dose-response curve presented in Fig. 1 was constructed by plotting 47 measurements of ΔG against the corresponding dosages of gentamicin. From this dose-response curve, the predicted average increment in serum gentamicin concentration after an intramuscular dose of 1.5 mg/kg is 3.9 μg/ml. At any given dosage of gentamicin the observed values of ΔG varied widely, and this variability is reflected by the low value (0.60) for the linear correlation coefficient (Fig. 1). Three or more measurements of ΔG were performed with serum specimens collected at different times from each of seven patients, and wide variations in the values of ΔG at any given dosage of gentamicin were observed both in individual patients at different times and in different patients.

As predicted by the design of the VDR, trough gentamicin levels were highest in patients with the most severe renal insufficiency (Fig. 2A). This correlation between gentamicin trough levels and serum creatinine concentrations in patients on the VDR was statistically significant (r = 0.65, P < 0.01). Although high trough
levels were also observed in patients treated by the VFR (Fig. 2B), there was no significant correlation between gentamicin trough levels and serum creatinine concentrations on this regimen ($r = 0.28$, $P > 0.10$). In fact, most of the trough levels exceeding 2 μg/ml with the VFR occurred in four patients whose initial serum creatinine concentrations of 1.1, 1.2, 1.4 and 2.0 mg/100 ml did not adequately reflect their low creatinine clearances of 59, 32, 29, and 17 ml/min per 1.73 m². Under these circumstances, accumulation of gentamicin occurred during therapy because the calculated dosage interval based on serum creatinine concentration was too short in comparison with the severity of renal insufficiency.

The development or progression of renal insufficiency as indicated by an increase in serum creatinine concentration to a value at least 1.0 mg/100 ml above the value at the start of gentamicin therapy was common and occurred in five of ten patients treated by the VDR and in two of six patients treated by the VFR (Table 1). Four additional patients treated by the VFR were excluded from analysis because the duration of gentamicin therapy was 2 days or less and repeated measurements of gentamicin and creatinine concentrations were not performed.

Patients in whom a rise in serum creatinine concentration of 1.0 mg/100 ml or greater occurred and those in whom it did not occur (Table 1) did not differ significantly with respect to: (i) initial creatinine concentration, (ii) initial creatinine clearance, (iii) treatment by the VDR or the VFR, (iv) duration of therapy with gentamicin, (v) cumulative dose of gentamicin administered during therapy, (vi) occurrence of a gentamicin peak level exceeding 10 μg/ml at any time during therapy, or (vii) occurrence of a gentamicin trough level exceeding either of the arbitrary values of 2 μg/ml or 3 μg/ml at any time during therapy ($P > 0.10$ for each variable). In contrast, a statistically significant correlation was observed between a trough gentamicin level $\geq 4$ μg/ml on one or more occasions during treatment and an increase in serum creatinine concentration of $\geq 1.0$ mg/100 ml (chi square = 4.89, $P = 0.027$). An elevated trough level of this magnitude was observed in all seven patients with a rising serum creatinine concentration but in only three of nine patients without such a rise in creatinine concentration during treatment by both regimens (Table 1). Although the averages of the initial creatinine clearances were quite different for patients on the VDR with and without a rising serum creatinine concentration during therapy with gentamicin (Table 1), this difference was not statistically significant ($0.05 < P < 0.1$). Thus, a gentamicin trough level of $\geq 4$ μg/ml was the only variable among those tested that correlated significantly with development or progression of renal insufficiency.

Our observations support the previous suggestion (J. Dahlgren and W. Hewitt, Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 13th, Washington, D.C., Abstr. 57, 1973) that elevated trough levels of gentamicin are statistically associated with nephrotoxicity, but they do not provide evidence for a cause and effect relationship. Although differences in nephrotoxicity between the VDR and VFR were not observed in the present study, such a correlation could have been obscured by the unexpectedly high incidence of elevated gentamicin trough levels in our small population of patients treated by the VFR. Because the severity of renal insufficiency cannot be accurately determined by measurements of serum creatinine concentration in many seriously ill or elderly patients, we recommend that modifications in the dosage of gentamicin be based on creatinine clearances or other appropriate assessments of the glomerular filtration rate in patients treated by the VFR as well as in patients treated by the VDR. This precaution should reduce the incidence of elevated trough levels of gentamicin in patients treated by the VFR and should make it possible to compare the potential toxicity of the VDR and VFR with greater precision in future prospective studies.

Whereas this study did not permit conclu-
Fig. 2. Relationship between trough gentamicin concentrations and serum creatinine concentrations in patients treated by the VDR (A) and the VFR (B). The correlation between trough gentamicin levels and serum creatinine concentrations was statistically significant for patients on the VDR \((r = 0.65, P < 0.01)\) but not for patients on the VFR \((r = 0.28, P > 0.1)\).

Table 1. Summary of pharmacologic data from patients with and without deterioration of renal function during therapy with gentamicin

<table>
<thead>
<tr>
<th>Therapeutic regimen</th>
<th>Rise in Cr during therapy</th>
<th>No. of patients</th>
<th>Cr(^d) (mg/100 ml)</th>
<th>Cl(\text{cr})(^d) (ml/min/1.73 m(^2))</th>
<th>Duration of therapy(^d) (days)</th>
<th>Cumulative dosage(^d) (mg)</th>
<th>No. of patients with any trough level of Cr &gt; 2 (\mu g/ml)</th>
<th>2 (\mu g/ml)</th>
<th>3 (\mu g/ml)</th>
<th>4 (\mu g/ml)</th>
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<td>VDR</td>
<td>Yes</td>
<td>5</td>
<td>2.4</td>
<td>19</td>
<td>5.4</td>
<td>807</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<tr>
<td>VDR</td>
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<td>2.5</td>
<td>68</td>
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<td>770</td>
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<tr>
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<td>1.2</td>
<td>46</td>
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</tr>
<tr>
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<td>38</td>
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<td>1,440</td>
<td>3</td>
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</tbody>
</table>

\(^a\) See text for summary of statistical analyses of these data.

\(^b\) Rise \(\geq 1.0\) mg/ml above initial value. Cr, Creatinine.

\(^c\) Excluding four patients treated by viable frequency regimen for less than 2 days in whom repeated measurements were not obtained.

\(^d\) Average values.

sions to be reached as to the relative therapeutic efficacies of the VFR and VDR, it does support the recommendation that measurements of the concentration of gentamicin in serum are desirable in the evaluation of individual patients. Such measurements may be particularly helpful in seriously ill, elderly, or cachectic patients, in patients with changing renal function, and in patients on prolonged courses of therapy. Measurements of peak levels are useful in documenting that "therapeutic" serum levels of gentamicin are achieved during treatment \((10-12)\), and retrospective studies suggest that gentamicin ototoxicity is correlated with peak serum levels exceeding 10 \(\mu g/ml\) \((6)\). In contrast, an elevated trough level of gentamicin is the only variable tested that was correlated with nephrotoxicity in our patients. Thus, until the determinants of gentamicin ototoxicity and nephrotoxicity can be more completely defined by prospective studies with larger groups of patients, we recommend that measurements of trough serum levels of gentamicin be performed in addition to peak levels, especially in patients treated by the VDR. Elevated trough levels provide a sensitive means for detecting exces-
sive accumulation of gentamicin during therapy and indicate that the dosage of gentamicin should be reduced. These observations on gentamicin may also be applicable to the newer and closely related deoxystreptamine containing aminoglycoside antibiotics, tobramycin and sisomicin.

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LITERATURE CITED


