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Penicillin Concentrations after Increased Doses of Benzathine Penicillin G for Prevention of Secondary Rheumatic Fever

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Plasma penicillin levels were studied 2, 3, and 4 weeks after intramuscular benzathine penicillin G (BPG) doses of 1,200,000, 1,800,000, and 2,400,000 U. Proportions of patients with penicillin levels above 25 ng/ml at each week increased with increasing BPG dose. Further studies of higher-dose BPG for rheumatic fever prophylaxis are required.

Since the early 1950s, intramuscular benzathine penicillin G (BPG), given as 1,200,000 U (900 mg) monthly, has been the standard secondary prophylaxis for recurrent rheumatic fever (RF) (7). However, more recent data have raised uncertainty over the most effective prophylactic regimen. Studies suggesting that injections given every 3 weeks are superior to those given every 4 weeks (5, 6) led to recommendations of every-3-weeks regimens in high-risk situations (1, 8). This was supported by findings of detectable penicillin levels in only 44% of samples by 28 days after administration of 1,200,000 U of BPG (4). Although early studies of BPG suggested that larger doses resulted in prolongation of the period of detectable penicillin levels (7), the use of a larger dose of BPG for secondary RF prophylaxis has not been assessed.

We assayed plasma penicillin levels in known rheumatic patients 14, 21, and 28 days after intramuscular administration of 1,200,000, 1,800,000, and 2,400,000 U of BPG. The patients were from rural aboriginal communities in Arnhemland, Northern Territory, Australia, and written informed consent was obtained after approval from the Regional Institutional Ethics Committee. The patients were randomly initiated to receive 1,800,000 or 2,400,000 U, followed at 4 weeks for all patients by the standard dosage of 1,200,000 U. Four weeks after each dose, they received 2,400,000 or 1,800,000 U (whichever dose they did not receive for the first injection). The BPG used (Wyeth) was kept at 4°C refrigeration and injected into the buttock with a 21-gauge needle.

Heparinized blood samples were kept on ice and transported to Darwin the same day, plasma was separated, and samples were stored at 70°C until transported on dry ice to the Wyeth-Ayerst Laboratories, Philadelphia, Pa. An agar diffusion bioassay with Micrococcus luteus ATCC 9341 was utilized for the penicillin assay. A slant of this organism was grown overnight at 35°C on yeast-beef agar and harvested in phosphate-glycerol buffer (pH 7). Inoculum for the assay was prepared by diluting this concentrate in phosphate-glycerol buffer to an optical density of 0.02. Assay plates were prepared by adding 0.5% of the M. luteus suspension to 65 ml of yeast-beef agar. This was poured into a bioassay dish (9 by 9 cm) on a heated level surface. The standard curve was made volumetrically with curve points of 0.2, 0.1, 0.05, and 0.025 μg/ml. Standards or samples were placed (42 μl per well) into wells (6.8 mm in diameter) cut into the assay plate. A complete standard curve in triplicate and 26 samples in duplicate may be placed on a single plate. To maximize precision, the corners were not used in the assay. A randomized design for our samples and standard curve points were utilized. The plates were incubated overnight at 35°C, and zones of inhibition were read to the nearest 0.01 mm. A generalized nonlinear regression program with inverse prediction was used to determine concentrations. The within-day average coefficients of variation for the low and high ranges of the assay obtained from seven separate assay plates were 6.1 and 6.7%, respectively. None of the lack-of-fit (linearity) F tests were statistically significant at the 0.05 level. The assay enabled accurate sample readings from the standard curve down to a penicillin level of 25 ng/ml.

We selected 25 ng/ml to represent an adequate protective penicillin level, on the basis of the 20- and 30-ng/ml levels used in two previous studies (4, 6) and the published MICs for Streptococcus pyogenes being generally <20 ng/ml (4).

Twenty-five patients consented to participate. Fifteen (60%) were female. Ages ranged from 16 to 49 years (mean, 29 years), and weights ranged from 40 to 90 kg (mean, 57 kg). Despite community support, logistical problems were encountered in obtaining blood samples from this remote and mobile population. Results were excluded if samples were not collected within 48 h of the due day, if the BPG dose was given on the wrong date, or if additional penicillin therapy was given for unrelated infections.

One hundred ten penicillin results fulfilled the criteria to be included in the final analysis. Table 1 shows the numbers of patients with protective penicillin levels (>25 ng/ml) 2, 3, and 4 weeks after each of the three BPG doses. Analysis of the nine cells of the table showed no significant differences in mean patient weights or ages. The consistent trend of higher proportions of patients with plasma penicillin levels of >25 ng/ml with higher BPG doses is evident at each week, but our figures do not reach statistical significance. In this study of adults, there was no correlation between weight, age, or sex and penicillin levels (data not shown). Mean levels of penicillin in plasma for patients with levels >25 ng/ml were not significantly different between the dosage groups (Table 1).

Treatment of streptococcal pharyngitis to prevent primary...
TABLE 1. Protective penicillin levels* versus penicillin dose and time

<table>
<thead>
<tr>
<th>Time post-injection</th>
<th>BPG injection dose</th>
<th>1.2 × 10^6 U</th>
<th>1.8 × 10^6 U</th>
<th>2.4 × 10^6 U</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) with protective level</td>
<td>Mean level (ng/ml)</td>
<td>Mean wt of patients (kg)</td>
<td>No. (%) with protective level</td>
</tr>
<tr>
<td>2 wk</td>
<td>11/16 (69)</td>
<td>57.9</td>
<td>54.6</td>
<td>14/15 (93)</td>
</tr>
<tr>
<td>3 wk</td>
<td>8/16 (50)</td>
<td>51.8</td>
<td>55.1</td>
<td>8/11 (73)</td>
</tr>
<tr>
<td>4 wk</td>
<td>4/17 (24)</td>
<td>38.2</td>
<td>57.1</td>
<td>7/18 (39)</td>
</tr>
</tbody>
</table>

* Protective penicillin level is defined as plasma penicillin level >25 ng/ml.

REFERENCES


