CORRESPONDENCE

Serum Levels of Penicillin in Basic Trainees in the U.S. Army Who Received Intramuscular Penicillin G Benzathine

SIR—I read with interest the brief report by Bass et al. in which they described an unexpected reduction in the duration of therapeutic penicillin levels in the sera of adult young male recruits given 1.2 million units of im benzathine penicillin G [1]. The adequacy of serum penicillin levels following injection of benzathine penicillin G has been carefully scrutinized for several years.

The initial study by Stollerman and Rusoff in 1952 demonstrated adequate levels of penicillin for about 4 weeks after the injection [2]. This finding was generally accepted until the report by Ginsburg and colleagues in 1982 raised the possibility of lower-than-expected serum penicillin levels in a relatively small number of individuals [3]. In contrast, in studies of a larger group of rheumatic individuals whose mean body weight was 55 kg, mean serum penicillin levels remained >0.02 μg/mL until after 21 days but fell below that level by 28 days [4]. It is unclear whether the difference between the results in the latter studies and those in the report by Bass et al. is influenced by the fact that the recruits described by Bass and colleagues were heavier or more active or whether the difference may be related to the laboratory techniques used for determining penicillin levels.

If confirmed, the findings in the report by Bass et al. would lead investigators to consider modifying current dose recommendations for im benzathine penicillin G. Therefore, other possible explanations must be considered, and the observation must be confirmed.

In a study published by Zaher and colleagues, impressive differences in serum penicillin levels and in their duration were noted after im administration of 1.2 million units of either of two preparations of benzathine penicillin G from different manufacturers [5]. Could the results reported by Bass and colleagues be attributed to the benzathine penicillin G preparation(s) used? It is entirely possible that benzathine penicillin G was formulated differently in the study published in the early report by Stollerman and Rusoff [2]. The determining factor may be the actual amount of penicillin in the reconstituted benzathine penicillin G as well as the constituents of the vehicle. I am unaware of any published descriptions of changes in the manufacturing process of benzathine penicillin G, but this is a possibility.

If the findings from the study by Bass et al. can be confirmed, the question that must be considered is what should be done for a patient? There is now published evidence that increasing the dose of benzathine penicillin G will result in increased serum penicillin levels. In a recent study by Currie and colleagues, plasma penicillin levels were examined 2, 3, and 4 weeks after im benzathine penicillin G doses of 1.2, 1.8, and 2.4 million units, respectively, were administered [6]. The data strongly suggested a “beneficial” effect of injecting increased amounts of benzathine penicillin G. Larger doses of benzathine penicillin G resulted in higher levels of penicillin for longer periods. Can one extrapolate to suggest that penicillin doses must be increased to provide an optimal prophylactic or therapeutic effect?

With regard to clinical relevance, the data from Bass and colleagues are in contrast to those from an earlier study that also involved military personnel, although the two studies are not exactly similar in design. In that published report, eradication rates of group A streptococci from the upper respiratory tract exceeded 96% after only 600,000 units of im benzathine penicillin G was administered [7]. While serum levels were not reported in the study by Brooks and Moe in 1956 [7], there is evidence that the MICs of penicillin for group A streptococcus are no greater now than they were 40 years ago, certainly ruling out the possibility of penicillin resistance in group A streptococci as an explanation for the findings [8]. Perhaps Bass and colleagues cannot address the implied difference in the results of the two studies, but this difference certainly does appear to raise important clinical questions.

Bass and colleagues have rendered a service by pointing out the possibility of the reduced duration of protective penicillin levels in serum, even in a unique group of individuals like healthy military personnel. However, one might—perhaps prematurely—be left with the impression that this documented effective form of therapy and prophylaxis (im benzathine penicillin G) for group A streptococci is no longer appropriate. We must be cautious until more complete confirmatory data are available to explain these findings.

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Reply

SIR—We agree that Kaplan has reasons to be concerned with our findings about the duration of therapeutic penicillin levels following injection of im benzathine penicillin G (IBPG). If confirmed, they may be of considerable importance in formulating new schedules for the use of im benzathine penicillin G for continued control of epidemic infections due to group A β-hemolytic streptococci (GABHS) in military basic trainees and for continuing prophylaxis for active adults who have had rheumatic fever. As stated in our report, all sera collected from our study subjects were immediately frozen to −80°C and then assayed together at an independent laboratory with rigid controls. The fact that the serum levels of penicillin at 24 hours were consistent with those in previous studies confirm that the integrity of the specimens was maintained throughout processing and that the assay was valid.

The cause of the decrease in serum penicillin levels in our study subjects after the first week after injection is unknown. We speculate that this decrease may be due to the subjects’ activities and large size and a concomitant increase in daily fluid intake and output secondary to strenuous exercise. No previous study has involved subjects who did such strenuous physical activity or who were as large as our subjects. Their increased muscular activity may promote massage and enhanced circulation about the depot of benzathine penicillin, thus promoting absorption. The subjects’ increased size would allow for a larger volume of distribution, leading to relatively lower serum levels during this period. The increased size of our subjects and their increased physical activity would promote earlier absorption and elimination of the drug without elevation of serum levels, which appears to have occurred in our subjects.

The point raised by Kaplan as to whether serum levels of penicillin may vary with production methods and manufacturer is important. He cites a study from Egypt in which serum levels of penicillin were significantly lower in children who received 1.2 million units of a local brand of IBPG than in those who received an imported brand [1]. In both groups there was a dramatic decrease in penicillin levels after 14 days; <10% of children who received the local product had “protective blood levels” at 14 days, and <10% of those who received the imported product had these levels at 21 days. None had detectable levels at 28 days.

Kaplan referenced an earlier publication by Stollerman and Rusoff [2] in which serum levels of penicillin in subjects who had received 1.2 million units of IBPG were significantly higher and more sustained than were those observed in our military basic trainees. In the report by Stollerman and Rusoff [2], children aged 6 to 14 years of age received monthly IBPG as prophylaxis for recurrent rheumatic fever more than 45 years ago.

To our knowledge, an assay of serum levels of penicillin in healthy active-duty military basic trainees who have received 1.2 million units of IBPG has never been performed except as reported in our study [3]. The only report in which adults were studied was by Wright et al. [4]. The subjects in this study were prisoners who volunteered for the study and whose weight and activities were not stated. “Protective blood levels” were found in 19 (95%) of 20 prisoners after 14 days, 13 (65%) of 20 at 21 days, and 2 (10%) of 20 at 28 days; this study was reported more than 35 years ago.

More recently, Kaplan et al. [5] reported the results of similar studies of children and adults who were receiving IBPG prophylaxis for recurrent rheumatic fever. Their mean weight ranged from 55 to 62 kg; the mean weight (± SD) of our study subjects was 76 kg ± 10.8. “Protective levels” were seen in 25 (81%) of 31 patients described in the study by Kaplan et al. [6] after 21 days and in 19 (36%) of 53 patients after 28 days.

Nathan et al. [6] reported that serum levels of penicillin in adult pregnant females at term who received 2.4 million units of IBPG were ≥0.018 mg/L in 9 (90%) of 10 subjects after 1 day and in 4 (40%) of 10 after 7 days.

Finally, Currie et al. [7] studied Aborigine adults (mean weight, 57 kg) who received 1.2 million units of IBPG. Serum levels of penicillin were ≥0.025 mg/L in 11 (69%) of 16 subjects after 14 days, in 8 (50%) of 16 after 21 days, and in 4 (24%) of 17 after 28 days. None of the studies in this review addressed the problem of what serum levels of penicillin are achieved in highly active adults who are given 1.2 million units of IBPG.

It is of utmost importance that the findings of our study be confirmed. The results of surveillance throat cultures should be obtained before and after administration of IBPG and correlated with serum levels of penicillin. All strains of GABHS isolated during the 8-week period of basic training should be serotyped, and initial and final serum samples from all subjects should be obtained for determination of the development of antibodies to GABHS. The possible role of specific serotypes, the development of subclinical infection, and the host factors affecting the evolution of virulent strains as well as the pharmacokinetics of IBPG could then be reassessed. This study might not only confirm our findings, but it might also show that subclinical infection with GABHS may be anticipated should more-severe infections due to GABHS be avoided. It might also show that subclinical infection with GABHS may be anticipated should more virulent strains of this organism evolve.

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References