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SERUM PENICILLIN LEVEL AFTER INTRAMUSCULAR INJECTION OF 1,200,000 UNITS OF BENZATHINE PENICILLIN G IN CHILDREN WITH RHEUMATIC FEVER

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ABSTRACT

The most accepted method of secondary prophylaxis in rheumatic fever (RF) has been an injection of 1,200,000 units of benzathine penicillin G (BPG) every 4 weeks, but recurrences have been reported in some patients despite such a prophylaxis program. The WHO recommended BPG injections every 3 weeks in high risk patients and situations due to some published data in favor of inadequacy of once every 4 weeks injection of BPG.

Our study was designed to determine serum penicillin levels (SPL) during the 4 weeks after an intramuscular injection of 1,200,000 units of BPG, in order to find the appropriate interval between BPG injections and also to assess the effects of weight and sex on this level. We included 42 RF patients (mean ±SD=14.8 ±11.9 years) in our study. SPL was determined by disk agar diffusion method. In this study the minimum accepted SPL to be effective against group A β-hemolytic streptococci was 0.02 μg/mL. In 46% of the patients the mean SPL decreased to <0.02 μg/mL at the end of the third week (mean ±SD=2.35 ±1.3 weeks). The mean SPLs were significantly higher in patients who weighed <45 kg (mean ±SD=38.6 ±4.3 kg) in comparison with those who weighed ≥45 kg (mean ±SD=54.25 ±4.87 kg), with a p value <0.0001. There was no significant differences in mean SPL between boys and girls (p =0.145). Although in this study the mean SPL was <0.02 μg/mL in 46% of patients at the end of the third week, we could not recommend every 3 weeks injections of BPG in all patients, except in high risk patients and situations as recommended by the WHO and also in those patients who weighed ≥45 kg.

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INTRODUCTION

Rheumatic fever (RF)–with its cardiac sequelae–is still the most common cause of acquired heart disease in children older than 5 years in developing countries. The recurrence rate without secondary prophylaxis is 66-85%.[1-3] The best and most effective type of secondary prevention of RF recurrence is intramuscular injection of 1,200,000 units of benzathine penicillin G (BPG) and there are no reports of resistance of group A β-hemolytic streptococci to BPG.[4-6,10] However, there are controversies about the time interval between the injections of BPG. The recurrence rate with every 4 weeks BPG injection was reported to be high (0.4-3%).[3,7] We observed 8 recurrences in 123 rheumatic fever patients in a five year period, among which 3 of them occurred despite regular 4-weekly BPG injections (our unpublished data). Ginsburg et al. showed that 18 days after BPG injection, only two-thirds of patients had acceptable SPLs and on the 30th day no patient had an adequate level.[8] Other studies showed that the recurrence rate with every 4 weeks BPG injection is more than every 3 weeks injections.[9-11] Some authors and also the WHO recommend every 3 weeks injections in high-risk patients and situations,[5,12] and some even recommend every 2 weeks injections.[13]

One of the factors which affects the SPL is patient weight. We performed this study in order to assess the effect of weight and sex of RF patients and to determine the SPL in our patients in Shiraz Medical School.

MATERIALS AND METHODS

The study group was selected from RF patients who were followed in the out-patient department of Shiraz Medical School. The inclusion criteria were: age less than or equal to 18 years, documented RF according to modified Jones' criteria, no extra medications during the 5 weeks of follow-up and weekly follow-up for 4 weeks. Forty-two patients met our inclusion criteria and were included in the study. Twenty-seven patients received one injection of 1,200,000 units of BPG, manufactured by Jaber-ebn-Hayan Laboratories (Iran), and 15 patients received 1,200,000 units of BPG manufactured by Wyeth Laboratories (Holland). The BPG was given by deep intragluteal muscle injection. The patients were followed at 7, 14, 21, and 28 day periods after injection. In each visit 5 mL of blood was taken and the serum was frozen in a freezer with a temperature less than -20 degrees Celsius. The serum was then tested for SPL every 3 weeks.

The SPL was determined by disk agar diffusion method.[7,10,14] We used the microorganism *Micrococcus luteus*, which is a coagulase negative staphylococcus, for SPL determination. There is no report for any resistance to penicillin by this organism. We added this organism at 30 degrees Celsius to tryptic soy broth (TSB) culture media for one day. In dish plates with 10-cm diameter, we placed 9 mL Muller Hinton agar and then added 2 mL of TSB fluid incubated with the organism on this disk plate and placed it in 50 degrees Celsius and mixed it well. Then we cooled it, and this plate was usable for one week at 4 degrees Celsius. For SPL determination we placed a 6.35-mm paper disk contaminated with 10 microliters of specified concentrations of penicillin over this agar.

For preparation of the paper discs we dissolved the purified penicillin powder in phosphate buffer (pH=7) and gained different solutions with specified concentrations of penicillin and contaminated each paper disk with 10 microliters of these solutions. We placed a maximum of 6 paper discs on each agar plate and incubated it at 30 degrees Celsius for 18 hours. We then measured the zone of inhibition for each paper disc with specified concentrations of penicillin and plotted the diameter of the circle of the zone of inhibition for each penicillin concentration to obtain a standard curve.

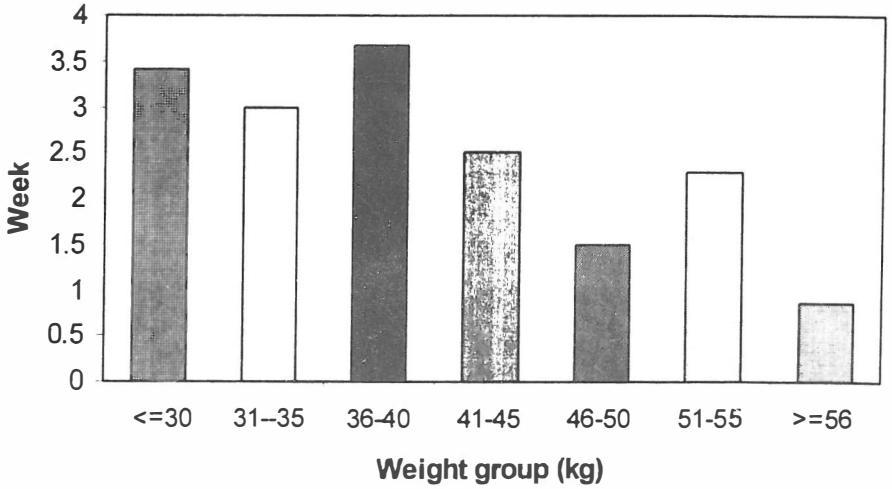

Fig. 1. Comparison of the mean duration of persistence of an acceptable SPL (>0.02 μg/mL) in the study patients according to different weight groups.

Table I. The mean ±SD of SPL (μg/mL) and the percentage of patients who had an acceptable SPL (≥0.02 μg/mL) in the 4 week period after BPG injection.

Weeks after injection	1	2	3	4
SPL (μg/mL)	0.046 ±0.026	0.026 ±0.021	0.015 ±0.014	0.004 ±0.009
Percentage of patients with SPL≥0.02 μg/mL	90.0%	69.1%	54.7%	21.4%

SPL = Serum penicillin level
BPG = Benzathine penicillin G

By using a semi-logarithmic paper we obtained a standard linear relation between the zone of inhibition diameter in the X-axis and penicillin concentration in the Y-axis. We placed a paper disc contaminated by 10 microliters of patient serum on other disc plates with the above mentioned method, and then compared the diameter of the circle of the zone of inhibition with the standard curve and obtained the SPL for each patient's serum specimen. This method can show penicillin concentrations of equal or greater than 0.02 μg/mL of serum which is the accepted SPL by us and others to give an adequate MIC level for group A β-hemolytic streptococci.[6,10,15] So with the above-mentioned method we determined the SPL during the 4-week period for each patient.

Statistical analysis was done by Student's t-test and Fisher exact test and a p value ≤0.05 was considered to be significant.

RESULTS

Seventeen patients were female (mean weight ±SD=50.0 ±9.78 kg) and 25 were male (mean weight ±SD=41.0 ±11.02 kg). The mean ±SD of age of the patients was 14.8 ±2.1 years (range 10-18 years) and mean ±SD from the time of the attack of ARF was 4.2 ±1.8 years (range 2-10 years). Twenty-seven patients received BPG manufactured by Jaber-ebn-Hayan Laboratories (Iran) with a mean weight ±SD of 47.8 ±9.2 kg, and 15 patients received BPG manufactured by Wyeth-Laboratories (Holland) with a mean weight ±SD of 39.2 ±8.31 kg. The SPL was determined every week for 4 weeks after BPG injection. Table I shows the mean ±SD of SPL (all patients) and the percentage of patients who had an acceptable SPL (≥0.02 μg/mL), in different weeks after BPG injections. Although the mean duration in which SPL was ≥0.02 μg/mL was more for the Wyeth-Laboratory BPG (mean ±SD duration=2.8 ±1.2 weeks) than the other type (mean ±SD duration=2.1 ±1.3 weeks), the p-value was not significant (p=0.101).

For evaluation of the effect of the patient's weight on SPL after BPG injection, we divided the patients to 7 weight groups and Figure 1 shows the comparison of the mean duration of persistence of acceptable SPL (≥0.02 μg/mL) in our patients' serum. The mean SPL was significantly higher in patients who weighed <45 kg (mean ±SD=38.6 ±4.3 kg) in comparison with those who weighed ≥45 kg (mean ±SD=54.25 ±4.87 kg), with a p value <0.0001.

The mean ±SD of the duration of persistence of an acceptable SPL (≥0.02 μg/mL) was 2.42 ±1.44 weeks in male patients and 2.05 ±1.16 weeks in female patients. Although the mean ±SD of the duration of persistence of an acceptable SPL was more in boys, the p value was not significant (p=0.145).

DISCUSSION

In this study we used a microbiologic method (disc agar diffusion) to check the SPL in our RF patients. The accepted SPL was ≥0.02 μg/mL as was reported in other studies.[6,10,15] The mean ±SD of the SPL concentration decreased to <0.02 μg/mL in the 3rd week in 46% of patients. In Kaplan's study the SPL decreased to <0.02 μg/mL in the 4th week specimen and in Saran's study in 15-18 day specimens.[6,15] In Kaplan's study, 80% of patients had an SPL ≥0.02 μg/mL at the end of the 3rd week and 36% at the end of the 4th week. Despite the differences between the results of our study and those of Kaplan's, it may be due to effects of lab techniques, race, geographical effect, and weight of the patients studied.

As we have shown the mean ±SD of persistence of an acceptable SPL was more in patients who weighed <45 kg (mean ±SD=3.0 ±0.8 weeks) than those who weighed ≥45 kg (mean ±SD=1.6 ±1.3 weeks), and the p value was significant (p<0.0001). This was also shown in Kaplan's study. We compared the effect of weight for those patients who received the BPG which was manufactured by two different laboratories and the persistence of an acceptable SPL was comparable for those patients who weighed <45 kg (3.0 ±0.4 weeks versus 2.8 ±1.2 weeks).

There were no significant differences between male and female patients in persistence of an acceptable SPL as was shown in the other study.

Despite these results and due to the fact that ARF could be prevented if BPG injection is given within 7-9 days after group A β-hemolytic streptococcal pharyngitis,[16] we recommend to give BPG injections every 3 weeks in specific patients and situations such as: 1) those living in crowded areas, 2) patients who weigh ≥45 kg, 3) recurrence of ARF despite regular 4 week BPG injections, and 4) heart failure or severe valvular regurgitation in the first ARF attack. This suggestion may be helpful, especially in the first 5 years after the initial attack of rheumatic fever, when the chance of recurrence is higher, and for a longer duration in those patients with rheumatic heart disease due to the higher rate and possibility of a more severe attack of carditis with recurrence.[3,7,17] In other patients, due to cost and pain of injection and for the better compliance of patients and their parents, we recommend an injection of BPG every 4 weeks.

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