Serum concentrations of penicillin after intramuscular administration of procaine, benzyl, and benethamine penicillin in children with pneumonia

Serum concentrations of penicillin were measured in 37 children with pneumonia. The mean serum concentration of penicillin was >1.0 μg/mL for 11 hours after intramuscular administration of 48,000 U/kg penethamine penicillin compound (nine children), for 26 hours after 48,000 U/kg aqueous procaine penicillin (10 children), and for 40 hours after 79,000 U/kg aqueous procaine penicillin (seven children). After intramuscular administration of 35,000 U/kg benzyl penicillin in 11 children, the serum concentration was 13.3 ± 7.4 μg/mL (mean ± SD) 30 minutes after the injection, and 4.9 ± 3.2 μg/mL after 3 hours. Our findings lend support to the World Health Organization recommendation that children with mild pneumonia in developing countries be given daily intramuscular injections of 50,000 U/kg aqueous procaine penicillin. (J Pediatr 1987;110:299-302)

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In developing countries, more than four million children die of acute respiratory tract infections every year; most of these deaths are caused by pneumonia. In an attempt to reduce this high mortality, the World Health Organization has developed standard protocols for the management of acute respiratory tract infections in children in developing countries. The protocols recommend that children with mild pneumonia be given procaine penicillin, ampicillin, or cotrimoxazole and that children with more severe pneumonia be given benzyl penicillin.

If penicillin is to be used to treat pneumonia, as recommended by WHO, it will be important to ensure that the doses used provide adequate concentrations of penicillin. Very little is known about the serum concentrations of penicillin achieved after intramuscular administration of either procaine or benzyl penicillin in children older than 28 days of age; the only studies done in this age group have used very low doses of procaine penicillin. We therefore measured serum concentrations of penicillin after intramuscular administration of aqueous procaine penicillin and benzyl penicillin in children. Because it has been widely used as an alternative to procaine penicillin for the treatment of pneumonia, we also studied penicillin benethamine compound.

| MIC | Minimum inhibitory concentration |

**METHODS**

We examined children admitted to Goroka Hospital, in the highlands of Papua New Guinea, in October and November 1980. The study was approved by the Papua New Guinea National Research Advisory Committee.
Verbal consent was obtained from the parent(s) of each child. The age of the children ranged from 5 months to 10 years: 18 children were 5 to 12 months, 17 were 1 to 5 years, and five children were 5 to 10 years of age. All the children had consolidation on a chest radiograph. Children given procaine or benethamine penicillin had tachypnea but no intercostal recession; no formal method of randomization was used to allocate children to the treatment groups. Children given benzyl penicillin had intercostal recession but no cyanosis or cardiac failure.

Ten children were examined after intramuscular administration of 48,000 U/kg (0.2 mL/kg) aqueous procaine penicillin (Farbwerke Hoechst AG, Frankfurt, West Germany; 10 mL sterile water added to a 3,000,000 U vial, to make 12.5 mL). Blood samples were collected just before the injection and at 3, 6, 12, and 24 hours afterward. Another seven children were examined after intramuscular administration of 79,000 U/kg (0.2 mL/kg) aqueous procaine penicillin (5 mL sterile water added to a 3,000,000 U vial, to make 7.6 mL). Blood samples were collected just before the injection and at 3, 12, 24, and 48 hours afterward. Nine children were examined after a dose of 48,000 U/kg (0.2 mL/kg) penicillin benethamine compound (Triplopen, Glaxo Inc., New Zealand; 2 mL sterile water added to a 1,250,000 U vial, to make 3.1 mL). Each vial of Triplopen contains 500,000 U benethamine penicillin, 250,000 U procaine penicillin, and 500,000 U benzyl penicillin. The benzyl penicillin content of Triplopen was ignored when calculating the dose, so that penicillin concentrations from 12 hours after the injection were comparable to those in children who received aqueous procaine penicillin. Eleven children were examined after intramuscular administration of 35,000 U/kg (0.08 mL/kg) benzyl penicillin (Galenika, Yugoslavia, 2 mL sterile water added to a 1,000,000 U vial, to make 2.3 mL). Blood samples were collected just before the injection, and at ½, 1, 2, and 3 hours afterward.

Blood samples were collected by venipuncture or capillary collection, and stored at -20°C. Most of the children had one or more doses of penicillin before the test dose, but four of 10 children in the 48,000 U/kg procaine penicillin group, four of seven in the 79,000 U/kg procaine penicillin group, five of nine in the benethamine penicillin compound group, and four of 11 in the benzyl penicillin group were examined after the first dose of penicillin.

Penicillin concentrations were measured by bioassay performed on Wellcotest sensitivity test agar (Wellcome Diagnostics, Research Triangle Park, N.C.). All assays were performed in duplicate, and the mean value calculated. A culture of Oxford Staphylococcus aureus NCTC 6571 was grown for 24 hours in brain-heart infusion broth. The agar plates were flooded with a suspension of 10 μL culture in 50 mL sterile distilled water, the surplus was pipetted off, and the plates were dried at 37°C for 30 minutes. Sterile antibiotic assay paper disks (Schleicher and Schuell Inc., Keene, N.H.) were inoculated with either 10 μL serum to be assayed or a standard solution of 0.5, 1, 2.5, 5, 10, 15, 25, or 50 μg/ml sodium benzyl penicillin (CSL, Melbourne, Australia) in horse serum. When the disks were dry, they were pressed firmly onto the agar surface and kept at room temperature for 3 hours before being incubated at 37°C for about 18 hours. Each zone of
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Table. Half-life, volume of distribution, and clearance of procaine penicillin and benzyl penicillin

<table>
<thead>
<tr>
<th></th>
<th>Procaine penicillin (n = 16)</th>
<th>Benzyl penicillin (n = 41)</th>
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<tbody>
<tr>
<td>Half life (hr)</td>
<td>11.0 ± 4.6</td>
<td>2.1 ± 0.9</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>10.9 ± 9.9</td>
<td>0.63 ± 0.41</td>
</tr>
<tr>
<td>Clearance (ml/kg/hr)</td>
<td>0.63 ± 0.41</td>
<td>0.63 ± 0.32</td>
</tr>
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Values represent mean ± SD.

inhibition was the mean of six readings, a standard curve was prepared for each assay, and the unknown was read from the curve.

The elimination half-life of penicillin was calculated for each child individually from the terminal log-linear portion of the concentration-time curve by calculating the regression of the logarithm of the serum concentration of penicillin against time by the least-squares method. To calculate the volume of distribution of penicillin, the serum levels for each child were plotted on graph paper, and the plot extended using the calculated half-life for that child. The area under the curve was determined by weighing. The volume of distribution was calculated from the formula

\[ V_d = \frac{(\text{Dose} \times \text{Half-life})}{(\text{AUC} \times 0.693)} \]

where the dose of penicillin was expressed in milligrams per kilogram and the half-life in hours, and AUC was the area under the serum concentration–time curve in hours per microgram per milliliter.

RESULTS

All but two of the patients had an uneventful recovery (one had persistent diarrhea, and one child who received benzyl penicillin had persistent cough). There were much higher concentrations of penicillin in the serum for 24 hours after intramuscular administration of procaine penicillin than after benethamine penicillin compound (Fig. 1). Benzyl penicillin gave even higher serum concentrations of penicillin, but for a shorter time (Fig. 2). The Table shows the half-life, volume of distribution, and clearance of penicillin. Procaine and benzyl penicillin had a similar clearance, about 0.6 mL/kg/hr. The half-life of 11 hours for procaine penicillin was similar to the half-life in adults, but the half-life of 2.1 hours for benzyl penicillin was longer than the usual half-life of 0.5 hours in adults.

DISCUSSION

Bacterial pneumonia in children in developing countries is usually caused by Haemophilus influenzae or Streptococcus pneumoniae. Providing it does not produce β-lactamase, H. influenzae is usually susceptible to 0.1 to 1.0 µg/mL penicillin. In the past, S. pneumoniae was always susceptible to ≤0.05 µg/mL penicillin, but less sensitive strains with MICs in the range of 0.1 to 1.0 µg/mL are now found in some countries. Peak tissue levels of an antibiotic should be four to eight times the MIC, and the concentration should be higher than the MIC for most of the time between doses. Penicillin penetrates very well into the lung, and in pneumonia the concentration of penicillin in the lung is equal to the concentration in the serum. Thus, when treating these organisms, peak levels of penicillin should be several times the MIC of 0.1 to 1.0 µg/mL, and the concentration should be >1.0 µg/mL for most of the time between doses.

WHO has recommended that children with mild pneumonia be given daily intramuscular injections of 50,000 U/kg aqueous procaine penicillin; in our study, nine of the 10 children in the 48,000 U/kg procaine penicillin group had serum penicillin concentrations of ≥1 µg/mL for at least 18 hours after the injection. Administration of doses of procaine penicillin >50,000 U/kg is likely to increase the incidence of acute psychotic reactions or collapse; although these reactions are self-limiting, they are frightening to parents and staff and could jeopardize acceptance of a program if they occur too frequently. In practice, procaine penicillin can be given only once a day to outpatients; it is unrealistic to expect children in rural
areas in developing countries to be brought twice a day for injections of penicillin, because travel to health facilities is often difficult and expensive. Cotrimoxazole could be used to treat mild pneumonia in areas where a high proportion of respiratory tract pathogens are resistant to penicillin.

Several studies have suggested that procaine penicillin is effective treatment for mild pneumonia in children. Eigner gave 50,000 U/kg procaine penicillin intramuscularly twice a day to every second child with cough and fever admitted to a hospital in Cameroon; in 52% of the 50 children in the control group pneumonia developed, compared with only 6% of the 50 children given penicillin. McCord and Kielman found that mortality from pneumonia fell by 45% when children in India were given a single dose of benzyl penicillin followed by daily injections of procaine penicillin. In four papers reporting retrospective studies of H. influenzae pneumonia in children in the United States, the authors have remarked on the rapid clinical response to treatment with either procaine or benzyl penicillin. This clinical response to penicillin supports the laboratory finding that H. influenzae is almost as susceptible to benzyl penicillin as it is to ampicillin.

In our study, all but one of the children who received 48,000 U/kg procaine penicillin intramuscularly had a serum penicillin concentration of ≥1 µg/mL for at least 18 hours after the injection. This finding provides support for the WHO recommendation that children with pneumonia in developing countries should be given daily intramuscular injections of 50,000 U/kg aqueous procaine penicillin; however, despite the strong theoretical basis for the WHO protocols, carefully designed prospective studies are needed to assess their impact on mortality from pneumonia.

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REFERENCES

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