PENICILLIN BY MOUTH IN INFANCY

A COMPARISON BETWEEN BENZATHINE AND SODIUM PENICILLINS

BY

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With the increasing rate in the production of new preparations of penicillin, it is important to know which preparations are economical yet efficient.

Benzathine (N : N'dibenzylethylenediamine) penicillin has been introduced into this country recently and is already available under a variety of names. Elias *et al.* (1951) thought that benzathine penicillin administered by mouth gave concentrations in the blood comparable to those obtained with similar oral doses of potassium penicillin and procaine penicillins. Cathie and MacFarlane (1953) reported it to be "reliably absorbed" in all of 118 patients, 101 of whom were children, "adequate" blood levels being maintained in some of their patients if it was given six-hourly; a cumulative effect was observed. Foltz and Schimmel (1953) found that benzathine penicillin gave lower peak serum concentrations, did not have a better cumulative effect, and did not remain longer in the serum than oral potassium or intramuscular procaine penicillins. Welch *et al.* (1953), from a study of oral benzathine penicillin suspension and tablets alone, and Bayne *et al.* (1953), from a comparison of oral potassium penicillin and benzathine penicillin, reached similar conclusions. Fairbrother and Daber (1954) estimated the serum penicillin levels after a single oral dose of 300,000 units of benzathine penicillin given to 181 patients, including 29 children and 2 infants; all absorbed the drug satisfactorily and the two infants maintained high serum penicillin levels for four to six hours after the dose. Beasley and Macpherson (1954) found that 300,000 units of benzathine penicillin given by mouth to children under 25 lb. (11.3 kg.) (the lowest weights are not stated) maintained "satisfactory" serum penicillin levels for six hours after the dose.

Before the latest reports were published, the present trial was begun in order to compare the efficiency of oral benzathine penicillin and oral crystalline sodium penicillin when given to infants, and to determine (1) What practical minimum dose of penicillin is required to give adequate blood levels and how long an adequate blood level is maintained after one dose, and (2) What is the optimum interval between doses and what should be the dosage.

Materials and Methods

This study was carried out on babies born at the Bristol Maternity Hospital. In this hospital there are two nurseries, each administered by a sister and nursing staff. A total of 20 babies under 12 days of age were selected at random from both of these nurseries provided their birth weights were over 5½ lb. (2.5 kg.) and they were normal. The average weight of the babies was 7 lb. 7½ oz. (3.4 kg.), ranging from 6 lb. 11 oz. to 9 lb. 12 oz. (3 to 4.4 kg.). In one nursery each baby received a single dose of 150,000 units of benzathine penicillin, while those in the other nursery received a single dose of 150,000 units of sodium penicillin. At the end of a week the type of penicillin used in each nursery was reversed. By this means, differences were avoided which might have arisen due to different feeding times or methods of administering the drug; individual variations in its absorption were also eliminated. The sodium penicillin solution was kept for four days in a domestic refrigerator at a temperature below 4° C., after which it was discarded; the benzathine penicillin suspension was kept at room temperature. Because the latter is marketed in a dose of 300,000 units per American teaspoon (5 ml.) it was only practicable to give 150,000 or 300,000 units; all doses were measured by syringe.

The effect of repeated doses was investigated by estimating the serum penicillin levels after giving four doses of 150,000 units of sodium penicillin and benzathine penicillin to 15 and 12 different babies respectively at eight-hourly intervals. These babies' average weights were 7 lb. 7 oz. (3.4 kg.), ranging from 6 lb. 4 oz. to 9 lb. 6 oz. (2.8 to 4.3 kg.) and 7 lb. 9 oz. (3.4 kg.), ranging from 5 lb. 14 oz. to 9 lb. 9 oz. (2.7 to 4.5 kg.) respectively.

Blood for serum estimations of the penicillin level was collected from a heel prick and assayed by a modification of the *Sarcina lutea* plate technique of the Food and Drugs Administration, Washington (1948). The culture of the test organism was kept at -20° C. and was used in a final dilution of 1 in 2,000. Because of the small size of the samples which could be collected from the newborn, it was only possible to determine accurately serum levels of up to 2 units per ml. In the accompanying figures any level above 0 but below 0.02 unit per ml. (the lowest assayable level) is recorded as <0.02, and levels greater than 2 units per ml. are recorded as >2.

Results

After one dose of 150,000 units of penicillin.—Serum penicillin levels were estimated at two, four, six, eight, and ten hours after a single dose of 150,000 units of both the penicillin preparations in 10 of the babies. In the other ten babies, levels were estimated at four and eight hours only. Sodium penicillin reached its peak concentration in the serum within two hours of the oral administration of 150,000 units

FIG. 1.—Serum penicillin levels after a single oral dose of 150,000 units to 20 babies.

and, on the whole, maintained levels which were higher than those obtained with 150,000 units of benzathine penicillin and which fell slowly. Benzathine penicillin reached its peak serum concentration about six hours after the oral administration of 150,000 units, and after eight hours the serum concentration was about the same as, and in some cases lower than, that of sodium penicillin. At ten hours there was a greater range of variation in the serum penicillin levels with both preparations (see Fig. 1).

After four doses of 150,000 units of penicillin given at eight-hourly intervals.—Fifteen babies received four doses of 150,000 units of sodium penicillin at eight-hourly intervals and 12 babies received four similar doses of benzathine penicillin at the same time intervals. The serum levels were assayed, in the majority, seven hours after the first dose of sodium penicillin and eight hours after the first dose of benzathine penicillin and again eight hours after the last dose of the two preparations—that is, thirty-two hours after the first dose. The serum penicillin levels eight and ten hours after the last dose had been given were approximately the same (see Figs. 2 and 3). In all cases, blood levels obtained with both preparations were not lower than 0.06 unit per ml., well above the minimal effective level of 0.03 unit per ml. often stated to be "adequate." There was no evidence of a cumulative effect with benzathine penicillin such as was found by Cathie and MacFarlane (1953) in older children.

Sodium penicillin gave serum penicillin levels at least as high as, or possibly higher than, benzathine penicillin. As, however, levels over 2 units per ml. could not be determined, an exact comparison of the results by statistical analysis was not possible, since values over 2 units per ml. were found on several occasions with both drugs. However, by taking all values higher than 2 units per ml. as 2 units per ml. exactly, there did not appear to be any statistical difference in the serum penicillin levels obtained with the two preparations.

Discussion

A trial of the two penicillin preparations had been made before the one reported here, but, unfortunately, an English teaspoon (3.55 ml.) measure instead of an American teaspoon (5 ml.) was used for the dose of benzathine penicillin, so that the results were not valid. However, valuable information was obtained about the initial dose of oral penicillin required to give adequate blood levels and the time intervals at which the doses should be given, and this information was used in planning the small trial reported here. At the same time it was obvious how easily the administration of doses measured in teaspoons of different nationality may lead to serious error. Whilst an internationally recognized drachm measure would obviously be ideal, until such time

as this is adopted the use of anything but English drachm doses in this country is to be deplored.

In considering the blood levels obtained with the penicillin preparations used in this trial, it must be emphasized that the results in the newborn may well differ from those found in older children and adults. It is known that gastric acidity is high at birth, and thereafter falls to a variable level (Smith, 1951), and so may be related to the variation in the absorption of the penicillin preparations. In addition, relatively high doses were given to the babies, for a dose of 150,000 units to a 7–10-lb. (3.2–4.5-kg.) baby corresponds approximately to 3,000,000–4,000,000 units in an adult of average weight.

The greater number of high levels obtained with sodium penicillin confirms the findings of Foltz and Schimmel (1953). These high levels are obtained more quickly with sodium penicillin than with benzathine penicillin, though by eight hours the serum penicillin levels are approximately the same with the two preparations. This delayed maximum concentration with benzathine penicillin was also found by Lepper *et al.* (1952). Benzathine penicillin proved to be more palatable than sodium penicillin and so more readily taken by babies; in addition, it is said to maintain its activity when stored at room temperature for approximately two years, though we did not attempt to verify this. Freshly made sodium penicillin solution will retain its potency for four days if kept in the coldest compartment of an ordinary domestic refrigerator at a temperature not above 4° C. (National Formulary, 1952). There is no reason, however, why a tablet or powder of penicillin should not be dissolved for each dose, thereby dispensing with the need of a refrigerator.

Buckwalter and Holleran (1953a, 1953b) have shown that both potassium penicillin G soluble and buffered penicillin tablets, when correctly packed, can be stored for long periods of time at normal temperatures. Buckwalter and Walsh (1953) showed that buffered potassium penicillin G powder was similarly stable. The City Analyst of Birmingham (1953), however, has reported upon the doubtful potency of some oral penicillin tablets now on the market and their deterioration once they have been unsealed. If tablets or powder were made available it would be advisable that they should be packed in numbers suitable for a five-day course. It would be desirable that a sodium or potassium penicillin tablet should be produced that was palatable on solution.

The difference in the cost of the two preparations is considerable. For a five-day course of 150,000 units of sodium penicillin given eight-hourly, prescribed by a medical practitioner and dispensed by a chemist, the total cost to the National Health Service is 7s. 8d., while the corresponding

FIG. 2.—Serum levels after oral administration of 150,000 units of benzathine penicillin eight-hourly for four doses to 12 babies. The sera for penicillin estimation at eight hours were taken immediately before the oral dose was given.

FIG. 3.—Serum levels after oral administration of 150,000 units of sodium penicillin eight-hourly for four doses to 15 babies. The sera for penicillin estimation at eight hours (in 9 of the 15 babies only) were taken immediately before the oral dose was given.

cost of the brand of benzathine penicillin used is 12s. 7d. (personal communication from Joint Pricing Committee for England).

Treatment of a penicillin-sensitive infection in the newborn may be carried out with oral sodium (or potassium) penicillin, 150,000 units, given eight-hourly for five days. As suggested by Cathie and MacFarlane (1953), an initial loading dose of say 100,000 units of an intramuscular crystalline preparation of penicillin ensures an adequate initial blood level. It must be emphasized that these doses are recommended for the newborn only.

Summary

Oral benzathine penicillin has been compared with oral sodium penicillin. For the newborn, sodium penicillin is as effective as benzathine penicillin. The reliability of absorption is about the same for each. Benzathine penicillin is more palatable than sodium penicillin and keeps well at room temperature; it does not, however, give peak levels in the blood quite as quickly or possibly as high as sodium penicillin. There is no evidence that it maintains an adequate serum level for an appreciably longer time than sodium penicillin. The cost of benzathine penicillin is greater than that of sodium penicillin.

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This week has been dubbed "Safety in the Home Week" by the London County Council, which is running a campaign to reduce accidents at home. More people are killed in their own homes, almost always through carelessness, says the L.C.C., than in road accidents. In England and Wales alone about 5,000 people a year die as the result of accidents in their homes, half of them being old people and about a quarter children. Accidents in the home are the commonest cause of death in children between 1 and 5 years of age. The council's health committee regards the teaching of safety in the home as a very important part of its health education duties.

TENDO ACHILLIS BURSITIS ("WINTER HEEL")

BY

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This minor complaint usually occurs in females, often in adolescence, and is caused by the upper rim of the shoe rubbing on the back of the heel. The posterior aspect of the heel is most prominent at its supero-lateral angle, and consequently the shoe does not fit this accurately until it is worn in.

The lesion is an aseptic inflammation of the tendo Achillis bursa. This bursa lies between the tendon and the calcaneum, and encroaches on the upper surface of the bone. A secondary bursitis may appear in a small superficial bursa where the tendon is subcutaneous, this sharply localized area being devoid of underlying fat. The inflammation may also spread to involve the paratenon. Primarily, however, this is a disease of the tendo Achillis bursa.

The condition tends to recur each winter. Why this should be is not clear, unless it is that cold weather and variations of temperature cause a vascular disturbance of the feet comparable to chilblains. The region of the insertion of the tendo Achillis—described in detail below—becomes swollen, and a vicious circle sets in which may not be broken until the shoe is discarded. Walking, especially uphill, aggravates it. It is often bilateral.

Most cases respond to conservative treatment. Care with the fitting of the shoes, and insertion of a thin layer of sorbo rubber moulded to the back of them, will usually prevent a rub. The patient is also advised not to vary the height of the heel. The few cases which do not respond to conservative treatment can be cured by a simple operation. Since an accurate description of the anatomy of this part of the heel is not to be found in textbooks, and as it has a bearing on the cause and operative treatment of the condition, I made several dissections, which are described below.

Anatomy

With the foot on the ground it will often be found that the most prominent part of the heel is a knob on its superior and lateral aspects. This prominence does not coincide with that caused by the insertion of the tendo Achillis in the dried calcaneum; it is due to a thickening of the expanded portion of the tendon itself where it fits snugly, like a cap, on the prominent postero-superior angle of the bone. On the deep aspect of this tendinous prominence there is an oval facet, obliquely placed, which articulates with a corresponding facet on the back of the calcaneum, and the bursa gives this tendo-osseous articulation a kind of synovial lining. It is pressure on this thickened and prominent portion of the tendon, transmitted to the bursa, which causes the inflammation and effusion.

If the tendo Achillis is examined further, it will be found that it does not lie parallel to the tibia; on the contrary, it sweeps backwards in a graceful curve, and opens out like a fan as it reaches the calcaneum (Fig. 1). Since the calcaneum is not parallel with the ground, but meets it obliquely, the bone and tendon form an acute angle, and that is why the bursa encroaches on its superior aspect. A nodding-like action takes place between them at this point, which makes the facets and this arrangement of the bursa necessary. The bursa is concealed on each side by expansions from the paratenon, which also blends with the periosteum, and all other interstices are filled with fat.