SIDE-EFFECTS OF PENICILLIN TREATMENT*

BY

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In comparison with the many millions of injections of penicillin given annually all over the world, the incidence of reported reactions to the drug is small. Untoward effects vary from simple discomfort at the site of injection to sudden death (Kern and Wimberley, 1953; Welch, Lewis, Kerlan, and Putnam, 1953). The amount and duration of pain at the injection site may vary with the technical skill of the operator, or with the type of penicillin used, or both. Reports of sudden death suggest that these are anaphylactoid in nature (Siegal, Steinhardt, and Gerber, 1953; Pick and Patterson, 1953). The "terror" reactions described by Batchelor, Horne, and Rogerson (1951) and further similar cases reported by Mayer, Mosko, Schutz, Osterman, Steen, and Baker (1953) and Berger and Eisen (1955) also appear to be anaphylactoid. In addition, delayed reactions, intermediate in severity between the two extremes described, may occur. These delayed reactions are serum sickness-like, with erythema, urticaria, pruritus, joint swellings, and orbital oedema in varying degrees (Winton and Nora, 1955). Exfoliative dermatitis may also occur (Langdon, 1950). Manufacturers warn us that nurses may show skin sensitivity from handling penicillin. Mention has been made of the possibility of precipitating manifestations of lupus erythematosus by penicillin (Gold, 1951). Erythema-vesicular or "ide-like" reactions probably indicate previous sensitivity by dermatomycosis.

Serum sickness-like and anaphylactoid reactions are those which have caused the most trouble. As regards the mechanisms underlying these side-effects, many believe that the penicillin moiety, itself, is the cause. Winton and Nora (1955) have suggested that the penicillin links up with serum albumin (*sic*) to cause the serum sickness type of reactions. The procaine element in the procaine penicillin preparations has been mentioned as a possible cause of anaphylactoid reactions, but this idea does not seem to have received general support (Thomson, 1952). In Thomson's case he believed

the procaine element to be the cause of the anaphylactoid reaction, but when a change was made to crystalline penicillin G, an injection caused an immediate fatality. That the penicillin moiety is culpable is supported, too, by strongly positive skin tests of the immediate type. Anaphylactoid and serum sickness-like reactions may occur when penicillin is given by other routes, particularly orally (Eisenstadter and Hussar, 1954; Lang and Claggett, 1955; Calvert and Smith, 1955). Siegal (1955) states that the strange taste in the mouth accompanying some anaphylactoid reactions may occur even after intracutaneous injections of penicillin. He finds little or no support for the inadvertent intravenous injection theory. With reference to long-acting penicillin, benzathine has been described as causing a prolonged reaction of the serum sickness type (Anderson, 1954), but the fears originally expressed about the long-acting penicillins (Fletcher and Knappet, 1953) as a possible cause of prolonged reactions do not seem to have been justified (Grin and Guthe, 1954). Benzathine penicillin given orally has also been described as causing anaphylactoid reactions (Welsh, Lewis, Kerlan, and Putnam, 1953; Bell, 1956). The other long-acting penicillin, benethamine, has not, so far as I can find from the literature, been described as causing anaphylactoid reactions, although the manufacturers warn us that as with other penicillins such reactions may be expected. There seems no doubt, therefore, that the penicillin itself is a potent cause of reactions, although the "caine" element in procaine penicillin may be culpable on occasion.

Present Study

For some years until April, 1954, it was the practice at my clinics to use a procaine penicillin preparation in the treatment of all stages of syphilis. During the 30 months preceding this date, 5,870 injections of procaine penicillin were given to 256 patients, mostly in courses of 600,000 units per day for 10 days.

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Induration of the buttock after injection occurred fifteen times.

Local urticaria at the site of the injection was seen in six patients (all females).

Serum sickness-like reactions in the form of generalized urticaria with pruritus occurred in six patients, in two of whom there was also generalized oedema.

Anaphylactoid reactions occurred in nine patients (six females and three males); two of these females had already reported with local urticaria at the site of injection in the same or in a previous course of daily treatment. The anaphylactoid-type reactions were similar to those described by Batchelor, Horne, and Rogerson (1951). A description of one case is given below:

Case Report

The patient was referred from an antenatal clinic and latent syphilis was diagnosed. She received a course of daily procaine penicillin in April, 1951, and further courses in October, 1951, and April, 1952. Immediately after the ninth injection of the third course the patient collapsed, complaining of a burning sensation in the throat. She was groaning and looked very apprehensive. She stated that her heart was thumping wildly and she thought her chest was going to burst. On examination her colour appeared fairly good. The pulse was irregular in rhythm and volume. She recovered quickly and, when her blood pressure was taken some 2 minutes after the reaction started, the level was 125/80. No further penicillin was given to this patient.

Most patients developing a skin reaction were given anti-histamine drugs which usually controlled reactions very readily. Six of the nine patients showing anaphylactoid reactions continued with further treatment without ill-effect. In the other three further therapy seemed unwise, as two had urticaria at the site of injection, and in one the anaphylactoid reaction was very severe.

Skin tests, using the components of the procaine penicillin preparation, and control tests were performed on five patients who suffered anaphylactoid reactions. In all five the tests gave negative results.

The possibility of these anaphylactoid reactions caused anxiety, particularly as two of my clinics are of the *ad hoc* type and, with daily treatment in vogue, a death in circumstances where no doctor was readily available would have caused embarrassment to say the least. At this time, general opinion blamed the procaine element in the procaine penicillin and it was decided in April, 1954, to change to a long-acting penicillin preparation. Two preparations were available: benzathine penicillin, which is dibenzylethylenediamine dipenicillin, and

benethamine penicillin, which is the N-benzyl-B-phenylethylamine salt of penicillin G. The manufacturers of this latter preparation claimed that more significant blood levels were obtainable than with the former preparation. The experience gained in the use of benethamine penicillin during the 30 months after April, 1954, is described below.

3,512 injections were given to 147 patients. Most of the injections were given in 10-day courses, but some patients received weekly treatment. This form of penicillin was given daily, although this was not biologically necessary. It is well known that patients attend most regularly for daily treatment, whereas default occurs more frequently during weekly therapy. It seemed an over-riding principle, therefore, to give penicillin therapy daily, whichever form of the drug was used. Benethamine penicillin was given in doses of 300,000 units, whereas the procaine penicillin was given in doses of 600,000 units.

Induration of the buttocks occurred after 63 (1.8 per cent.) injections of benethamine penicillin. In many of these cases the patient complained of severe local irritation as well as pain. In three patients severe bilateral induration necessitated the stopping of the treatment. In six cases of localized urticaria there was also a complaint of induration. Two patients developed generalized urticaria. One patient had an anaphylactoid reaction, a condition so far unreported after benethamine penicillin.

Case Report

A female, aged 35, was referred in July, 1954, the antenatal Wassermann reaction having proved positive. During the next year she completed three courses of daily injections and treatment was being rounded off with a course of weekly injections of benethamine penicillin. Immediately after an injection of 600,000 units on November 28, 1955, she felt faint and giddy, with a burning sensation in the throat and a strange taste in the mouth. Her legs felt very weak and she was very apprehensive. Also she was slightly pale, with a rapid pulse. She recovered fairly quickly and was able to walk home after an hour and a half.

Discussion

All injections were given with a 2½-in. British Wire Gauge needle in the upper and outer quadrant of the buttock.

The same nurses gave all of the injections throughout the whole 5-year period of this review, but no nurse showed any skin sensitivity from handling penicillin. Children included among the patients were treated exclusively with procaine penicillin and showed no reactions at any time. Furthermore, females predominated amongst those

showing all types of side-effects. This also applied to reactions after benethamine penicillin, and it seemed that the fatter the female the more liable she was to develop local induration.

As pointed out in the editorial of this *Journal* in June, 1954, a sharp look-out for minor signs of hypersensitivity and prompt therapeutic measures pay dividends. This was found to be especially true in patients with early signs of delayed reaction. Antihistamines gave adequate control and allowed the completion of daily courses of therapy, irrespective of the type of penicillin prescribed.

From the literature reviewed and from the experience here described, it would appear that while the procaine in procaine penicillin may be responsible for the general reactions, the penicillin must take its full share of blame.

Summary

Experience during 30 months with two types of penicillin, procaine and benethamine, in the treatment of syphilis is described.

The incidence of local reactions after procaine penicillin is much smaller than that after benethamine penicillin; it occurred after nearly 2 per cent. of the latter. Serum sickness-like reactions occurred

infrequently with both types of penicillin, and in about the same numbers.

One case of anaphylactoid reaction occurred after benethamine penicillin, a form of the drug not previously reported as causing this side-effect. The incidence of this type of reaction is much less than after procaine penicillin. It would appear, therefore, that there is a place for this form of penicillin in the ambulant treatment of syphilis.

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