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PROCAINE PENICILLIN: EFFECT OF SINGLE DAILY INJECTIONS

BY

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Among the devices for prolonging the presence of penicillin in the body, suspensions of penicillin in oil and beeswax have until recently been those most commonly used. These suspensions are apt to give rise to local reactions, for which the beeswax is blamed. A more recent preparation, also designed to prolong the presence of penicillin but thought to be free from undesirable complications, is procaine penicillin.

This substance, described by Salivar, Hedger, and Brown (1948) and Sullivan, Symmes, Miller, and Rhodehamel (1948), is a true salt formed by the equimolecular combination of procaine and sodium or potassium penicillin G. It has a solubility in water of 0.43%, and is administered as a suspension in oil—sesame, arachis, and cotton-seed oils all having been used. The use of oil as a vehicle enables the compound to be dispensed ready for use in a stable form, and further prolongs absorption. From the reports of Hobby, Brown, and Patelski (1948) it appears that *in vitro* and in laboratory animals it is little if at all inferior to sodium penicillin G, and the persistence of penicillin in the blood of animals following a single injection, which they describe, has been shown to occur in humans by Herrell, Nicols, and Heilman (1947), by Boger, Oritt, Israel, and Flippin (1948), and by Hewitt, Whittlesey, and Keefer (1948). Following a single injection of 300,000 units of procaine penicillin Herrell *et al.* (1947) found detectable amounts of penicillin in the blood of nine out of ten patients after 24 hours. Boger *et al.* (1948) showed that after an injection of 300,000 units of procaine penicillin in ambulatory patients detectable amounts of penicillin remained in the blood from six to thirty hours, while in patients with pneumonia the range varied from seven to seventy hours. Of 11 cases of pneumonia treated with a single injection of procaine penicillin eight required no further treatment. Hewitt *et al.* (1948) showed that after an injection of 300,000 units of procaine penicillin, out of 63 patients 58 had detectable amounts of penicillin in their blood at twenty-four hours and 21 at forty-eight hours.

Tests in a Series of Cases

This paper presents information derived from the treatment of 45 ambulant patients and four ward patients with procaine penicillin G in arachis oil.

All the ambulant patients received five daily injections of 1 ml. of procaine penicillin in arachis oil which contained 300,000 units of penicillin. No difficulty was experienced in administering the compound so long as, after shaking, it was withdrawn from the bottle with a wide-bore needle, not less than a No. 1 serum needle, and it was recognized that it would take 10 to 15 seconds to withdraw 1 ml. For administration a No. 1 hypodermic needle was satisfactory.

The ambulant patients comprised 45 persons of both sexes attending the casualty department of the hospital, their ages ranging from 17 to 83. Although ambulant in that they attended the hospital daily, the majority of them were unfit for work, and were instructed to rest as much as possible at home. In addition 12 children have been treated with procaine penicillin, the youngest aged 14 days, from whom it was not desirable to obtain blood and who are therefore not included in this report. The diseases for which treatment was given were all inflammatory in nature and included carbuncles, furunculosis, breast abscesses, cellulitis, pulp infections, and infected abrasions with lymphangitis and adenitis. The injections were said to be painless, and no local or general reactions were seen.

Penicillin blood levels were determined by the Oxford slide method, using the Oxford H staphylococcus, immediately before the second injection of penicillin in each patient, and in as many cases as possible further levels were determined before the third, fourth, and fifth injections and at approximately 24 hours after the fifth injection. The results are shown in Charts 1 and 2.

It will be seen that it has been possible to find detectable amounts of penicillin in the blood of 37 out of 45 patients at times varying from 18 to 26 hours after their first injection of 300,000 units of procaine penicillin. Determinations made between 18 and 26 hours after the second or subsequent daily injections have shown detectable amounts of penicillin in 93 out of 109 samples. Neither

age nor sex appeared to be a common factor accounting for the varying responses in individuals, but, in general, initial low levels of penicillin were followed by subsequent low ones and vice versa.

In one ward patient and in three ambulant patients a total of 38 penicillin estimations were made at intervals throughout 24-hour periods after injections of 300,000 units of procaine penicillin. In these patients, although the highest levels tended to appear in samples taken in the five hours following each injection, the high peak levels which occur shortly after the injection of most preparations of penicillin in oil and beeswax were not seen. The highest level reached was 1.44 units, and on the whole the amount of penicillin in the blood remained fairly constant throughout the 24 hours.

Although the series is a small one, the clinical response to this treatment has seemed to be at least equal to that seen in patients treated with injections of 250,000 units of penicillin in saline twice daily, and the clinical impression is that a number of lesions which probably would have gone on to suppuration with twice-daily injections of penicillin in saline have been aborted. It has proved possible, with one daily out-patient attendance and rest at home, to manage some patients who would otherwise have required admission.

Discussion

In the majority of 49 patients it has been possible with procaine penicillin to maintain detectable amounts of penicillin in the blood throughout treatment. There has been a certain amount of individual variation in the levels maintained. The variation noted has not been so great as that observed by Boger *et al.* (1948), and agrees more closely with that found by Herrell *et al.* (1947) and by Hewitt *et al.* (1948). Whether these variations are due to the use of the compound in different classes of patients or to variations in different batches of procaine penicillin is uncertain.

In the four cases followed more closely the release of penicillin was a gradual process, and, as pointed out by Hewitt *et al.* (1948), the high peak levels usually obtained after injections of most preparations of penicillin in oil and beeswax did not occur.

In the circumstances described here it appeared that, if it is desirable to maintain a low but constant amount of penicillin in the blood throughout treatment, this might be accomplished in the majority of ambulant patients with more certainty by means of procaine penicillin than by the use of penicillin in oil and beeswax, and with an absence of local reactions. Whether the failure of procaine penicillin to produce intermittent high blood concentrations of penicillin will constitute a drawback to its use as a therapeutic agent remains to be seen.

The number of cases treated is too small to draw any conclusions from the clinical results, but if a more extensive trial proved them to be satisfactory the use of a method of treatment with penicillin necessitating only one daily injection would allow the patient considerably more rest, and would have considerable advantages in general practice and in hospital out-patient departments. If procaine penicillin were also shown to be satisfactory for the treatment of in-patients a considerable amount of time in wards would be saved by the substitution of single daily injections for spaced three-, four-, or five-hourly injections of penicillin in saline.

As each dose of 300,000 units of procaine penicillin contains 124.5 mg. of procaine base, it is possible that those sensitive to procaine may show reactions from its use. No such reactions have yet been reported, and it is likely that, owing to the very slow rate of absorption into the circulation, toxic blood concentrations will not be reached.

Summary

Estimations of penicillin in the blood following the use of procaine penicillin G in oil in 45 ambulant patients and 4 ward patients are recorded.

In the majority of the patients penicillin could be detected in the blood between eighteen and twenty-six hours after daily injections of 300,000 units of procaine penicillin G in oil.

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CRYSTALLINE ANTI-PERNICIOUS- ANAEMIA FACTOR IN TREATMENT OF TWO CASES OF TROPICAL MACROCYTIC ANAEMIA

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Recently, crystalline material found to be effective in the treatment of pernicious anaemia has been isolated from liver independently in two laboratories. In America, Rickes, Brink, Koniuszy, Wood, and Folkers (1948) isolated a red crystalline material which they named vitamin B₁₂, and which was shown by West (1948) to be clinically active in microgram quantities. A red crystalline substance which has been shown by Ungley (1948a) to possess in pernicious anaemia similar clinical activity to that described by the American workers has also been isolated in England (Lester Smith, 1948; Lester Smith and Parker, 1948).

Spies, Stone, and Aramburu (1948) treated five patients—two with pernicious anaemia, two with nutritional macrocytic anaemia, and one with non-tropical sprue—with doses of 6 to 15 µg. of vitamin B₁₂, and in all instances haemopoietic responses were observed. Spies, Lopez, Milanes, Toca, and Culver (1948) successfully treated two cases of tropical sprue with 8 µg. of vitamin B₁₂. Ungley (1948a, 1948b) found that in pernicious anaemia single doses of 10 µg. of Lester Smith's red crystalline material induced maximal reticulocyte responses and a rapid increase in red blood cells. Preliminary observations suggested that the material was as effective as liver extract in subacute combined degeneration. However, he recorded that a patient with megaloblastic anaemia of pregnancy did not respond to 65 µg. although she subsequently responded to 2.5 mg. of folic acid daily (Ungley, 1948a).

This paper reports the effect of treatment of two cases of tropical macrocytic anaemia, as occurring in Bombay, with Lester Smith's crystalline anti-pernicious-anaemia factor. The patients were admitted to the Singhanee Hindu Hospital. Detailed medical and dietary histories were obtained and thorough medical examinations carried out. The investigational procedure employed was that described