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A TRIAL OF PROCAINE PENICILLIN PREPARATIONS

BY

E. GRIFFITHS, F.R.C.S.

A. J. WALKER, F.R.C.S.

(From the Surgical Professorial Unit, St. Bartholomew's Hospital)

AND

R. A. SHOOTER, M.D.

(From the Department of Bacteriology, St. Bartholomew's Hospital)

It now seems likely that for some time to come procaine penicillin will play an important part in penicillin therapy. The first paper describing its clinical use (Herrell, Nichols, and Heilman, 1947) advocated a dosage of 300,000 units in oil, this amount being contained in a total volume of 1 ml. Although a satisfactory clinical response was claimed with this dosage at the time, and by other authors subsequently, it has been criticized on the theoretical grounds that it would not provide throughout the whole of any 24-hour period detectable amounts of penicillin in the blood of all patients treated. Various preparations of procaine penicillin designed to overcome this drawback have been described, but as yet the majority of the reports have been mainly concerned with recording the blood levels obtained by their use.

This paper is an account of a trial of three preparations of procaine penicillin to determine whether any of them would satisfy the following criteria: (1) Provide a satisfactory preparation with which to treat acute staphylococcal infections of the skin and subcutaneous tissues, and, by analogy, infections due to more sensitive organisms. (2) Maintain detectable amounts of penicillin in the blood throughout 24 hours after a single injection. (3) Allow the dose to be given without difficulty in a volume of not more than 1 ml.

Preliminary Trials

Thomas, Lyons, Romansky, Rein, and Kitchen (1948) showed that the addition of aluminium stearate to procaine penicillin resulted in a slower release of penicillin from the site of injection and a consequent lengthening of the time during which penicillin could be found in the blood.

The first preparation tried by us consisted of 300,000 units of procaine penicillin in oil with 2% aluminium stearate contained in 1 ml., and this was used in the treatment of 24 patients with acute staphylococcal infections. This dose was given once every 48 hours, and penicillin was found in the blood of 22 of the patients after 24 hours and in the blood of 10 of the 11 patients tested after 48 hours. As reported previously, however (Griffiths,

Jones, Shooter, and Heady, 1949), the clinical response was not as satisfactory as that seen with 300,000 units of procaine penicillin. No attempt was made to use this preparation in daily doses or in larger amounts, as the immediate response in the first 24 hours of treatment was thought to be less satisfactory than with procaine penicillin and it was not desired to increase the volume of the injection above 1 ml.

A similar series of 41 patients was treated with daily injections of a mixture of 200,000 units of procaine penicillin in oil with 2% aluminium stearate and 100,000 units of sodium penicillin, again contained in 1 ml. With this preparation penicillin was found in the blood of only 29 out of the 38 patients tested at the end of 24 hours; and, as the clinical results compared unfavourably with those in patients treated with 300,000 units of procaine penicillin, this preparation also was discarded.

The third preparation tested consisted of a mixture containing 300,000 units of procaine penicillin in oil with 1% of aluminium stearate and 100,000 units of sodium penicillin contained in 1 ml. Initial clinical trials of this preparation were satisfactory. We have attempted to compare its action in the treatment of acute staphylococcal infections of the skin and subcutaneous tissues with that of 300,000 units of sodium penicillin in saline given twice daily, and 300,000 units of procaine penicillin given once daily, and records have been kept of penicillin levels in the blood throughout treatment.

Methods of Treatment

Patients were given an intramuscular injection of 1 ml. of the trial preparation, and this injection was repeated daily for five days. As local treatment, sodium sulphate (12½%) and, in some cases, kaolin poultices were used, and immobilization of the affected part was advised wherever practicable. Only unavoidable and minimal incisions were made. Carbuncles were never incised. Most of the patients were examined at daily intervals, the remainder never less than once in three days. Clinical findings were recorded on a special form. As a rule a swab was taken from a lesion before the start of treatment or as soon as possible after pus had begun to discharge.

Conditions Treated.—Only out-patients with acute septic infections of the skin and subcutaneous tissues, mainly staphylococcal, who required penicillin were treated. The types of infection are given in Table I. Some of the

TABLE I.—Types of Infection Treated (113 Cases)

Boils	..	..	..	..	..	..	..	41
Cellulitis	..	..	..	..	..	..	..	22
Carbuncles (except dorsal finger carbuncles)	..	..	..	..	..	..	..	32
Dorsal finger carbuncles	..	..	..	..	..	..	..	5
Other conditions	..	..	..	..	..	..	..	13

TABLE II

	Mean Redness				Mean Induration			
	Present Series		Previous Series		Present Series		Previous Series	
	in.	cm.	in.	cm.	in.	cm.	in.	cm.
Boils	1.9	4.8	1.4	3.6	1.2	3.0	1.1	2.8
Cellulitis	3.4	8.6	2.7	6.9	1.3	3.3	1.4	3.6
Carbuncles of neck	2.0	5.1	2.1	5.3	1.7	4.3	2.1	5.3
All carbuncles except dorsal finger carbuncles	2.2	5.6	2.1	5.3	1.7	4.3	1.8	4.6
Dorsal finger carbuncles	1.1	2.8	1.7	4.3	0.9	2.3	1.1	2.8
Other conditions	1.9	4.8	2.1	5.3	0.9	2.3	1.5	3.8
All conditions	2.2	5.6	2.0	5.1	1.2	3.0	1.4	3.6

Present series = Treatment with 300,000 units of procaine penicillin + 100,000 units of sodium penicillin and 1% aluminium stearate. Previous series in Tables II and III = Combined procaine penicillin and sodium penicillin series taken from the paper by Griffiths, Jones, Shooter, and Heady (1949).

patients did not complete the full course of treatment; these have been excluded from the series. Among the "other conditions" are included lesions not numerous enough to form separate groups, such as lymphadenitis and abscesses.

Severity of Infections Treated.—To allow adequate comparison between this series and previous ones, the same criteria of severity—the maximum diameters of redness and induration—have been adopted. The average for the various groups of lesions, compared with similar figures from the previous series, is shown in Table II. It will be seen that there is a close similarity between the two series at the start of treatment.

TABLE III

	Mean Time to Relief of Pain (Hours)		Mean Healing Time (Days)	
	Present Series	Previous Series	Present Series	Previous Series
Boils	31 (33)	26 (36)	7.3 (39)	8.0 (50)
Cellulitis .. .	29 (19)	27 (15)	7.0 (21)	7.9 (27)
Carbuncles of neck ..	34 (9)	38 (10)	12.7 (10)	12.8 (17)
All carbuncles except dorsal finger carbuncles ..	34 (26)	29 (31)	12.8 (29)	13.2 (45)
Dorsal finger carbuncles ..	42 (5)	23 (13)	10.0 (5)	12.2 (13)
Other conditions .. .	44 (7)	27 (54)	7.7 (13)	8.1 (83)
All conditions .. .	33 (90)	27 (148)	8.9 (107)	9.4 (218)

The information was not available in every case, and the figures in parentheses indicate the number of cases on which the times were based.

Results of Treatment.—The results, again compared with those of the previous series, are recorded in Table III under the headings of relief of pain and healing time, defined

FIG. 1

as the time from the start of treatment to epithelization. The healing times are also shown diagrammatically in Fig. 1. No complications were seen in any of the patients, nor did any of them require to be admitted to the wards.

Bacteriology.—All the swabs were sown direct on to horse-blood-agar plates in

TABLE IV.—Organisms Isolated from Initial Swabs

	No. of Cases
<i>Staph. pyogenes</i> , penicillin-sensitive	65
penicillin-resistant	3
<i>Coliform bacilli</i>	3
<i>Haemolytic streptococci</i>	2

Penicillin Blood Levels during Treatment.—Blood was taken from 81 patients when they attended on the second day of their treatment and before they received their second daily injection of penicillin. From these samples it was possible to estimate the amount of penicillin in the blood towards the end of the 24-hour period. The results are shown in Fig 2. Penicillin was assayed by the Oxford slide method, using the Oxford H staphylococcus. It will be seen that in 78 out of 81 patients detectable amounts of penicillin were present towards the end of the first 24 hours of treatment.

FIG. 2

Conclusions

From the results obtained and the clinical impressions during the course of the trial it would seem that this compound provides a form of treatment of acute staphylococcal infections which is as satisfactory as daily doses of 300,000 units of procaine penicillin, or twice-daily doses of 300,000 units of sodium penicillin in saline. As the figures agree so closely it has not been considered necessary to submit them to detailed statistical analysis.

This preparation also seems to provide detectable amounts of penicillin in the blood throughout most of the 24 hours in the majority of patients. This apparent advantage over treatment with procaine penicillin, in which a larger number of patients have periods of a few hours at the end of the 24 hours when penicillin can no longer be found, has not been shown to produce any markedly superior result. The explanation of this probably lies in the work of Eagle and Musselman (1949), who have shown that for many organisms penicillin has a bacteriostatic effect which persists for a number of hours after the removal of the drug. The therapeutic significance of this post-penicillin recovery period is enhanced by the fact that the recovering bacteria, damaged but not killed by the previous exposure to penicillin, are abnormally sensitive to the host's defences. In consequence the bactericidal process continues *in vivo* for some hours after the concentration of the drug itself has fallen so low as to be ineffective.

The explanation of our failure to achieve equally good results with 300,000 units of procaine penicillin with 2% aluminium stearate given once every 48 hours, or with 200,000 units of procaine penicillin with 2% aluminium stearate and 100,000 units of sodium penicillin given daily, apparently lies in the fact that effective concentrations were not reached for the treatment of such relatively walled-off lesions as the staphylococcal ones treated, though these compounds, in the dose used, might well provide adequate treatment for more amenable infections.

The final requirement, that the dose of penicillin should be given without difficulty in a total volume of 1 ml., was partially fulfilled. A moderately large needle is necessary with all the oily preparations at present available, and a certain amount of pressure has to be used in administration. This preparation compared favourably with any we have tried, but on grounds of convenience alone would be superseded by a preparation having similar properties but able to be injected easily through a hypodermic needle.

Summary

One hundred and thirteen patients with acute staphylococcal infections have been treated with daily doses of a preparation consisting of 300,000 units of procaine penicillin in oil with 1% aluminium stearate and 100,000 units of sodium penicillin. The results have been found to be as satisfactory as those in a similar series of patients treated with 300,000 units of procaine penicillin daily or 300,000 units of sodium penicillin in saline twice daily.

Levels of penicillin in the blood of 81 of these patients during treatment are recorded.

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CANCER OF THE UTERUS IN ADRENOGENITALISM

BY

HUGH C. McLAREN, M.D., F.R.F.P.S., F.R.C.S.Ed., M.R.C.O.G.

Reader, Chair of Obstetrics and Gynaecology,
University of Birmingham

[WITH PHOTOGRAPHIC PLATE]

Tumour formation is not uncommon in the course of adrenogenitalism, but the following case is unusual in that carcinoma of the uterus with the rare features of adenocarcinoma developed in the thirteenth year of illness.

Case Report

The patient, an unmarried woman aged 31, first reported to Professor A. P. Thomson's clinic in 1937. During the previous four years she had doubled her weight to 280 lb. (127 kg.), while menstruation had ceased in 1936. She was grossly obese and hirsute; her blood pressure was 170/110. Within two years a restricted diet with 2 gr. (0.13 g.) of thyroid a day reduced her weight to 145 lb. (66.8 kg.) and her blood pressure to 145/90. Normal menstruation restarted at the outset of treatment.

In 1942 her weight increased by 30 lb. (13.6 kg.) despite her reduced diet and 2 gr. of thyroid a day. She was given 3 gr. (0.2 g.) of thyroid daily, and this, with the work involved in nursing her father in a terminal illness, brought her weight to normal. For the first time, however, her general health then broke down. She was depressed and listless, and became fatigued on slight exertion. She also suffered from vertigo and bouts of left-sided headache.

First Admission

When admitted to hospital on July 21, 1943, the patient was mentally depressed and apathetic. Her face was highly coloured and she had marked generalized hirsuties and acne vulgaris. Visual fields, fundi, x-ray film of pituitary fossa, B.M.R., fractional test meal, and blood Wassermann reaction were all normal. Her weight was 148 lb. (66.7 kg.); serum chlorine ions, 359 mg. per 100 ml.; and serum potassium, 320 mg. per 100 ml.

Her condition was serious enough to cause anxiety, and Mr. H. H. Sampson, honorary surgeon, Queen Elizabeth Hospital, finally agreed to explore her adrenal glands. At a

preliminary laparotomy an enlarged left adrenal gland was felt and a follicular cyst about the size of a hen's egg was removed. Ten days later the enlarged gland was removed without difficulty through a loin incision. Post-operative shock, often described after this operation, was absent.

The gland weighed 13.3 g. and consisted of diffuse cortical hyperplasia with areas of nodular hyperplasia of the zona fasciculata.

Result.—The most striking effect was the great improvement in the generalized acne vulgaris, and this may have contributed to her improved mental state. She became cheerful and regained her usual energy, returning to full work as a clerk. Four weeks before operation her 24-hour urinary androsterone level was 12.4 mg.—that is, within the normal range. Five days after adrenalectomy it fell to 4 mg.

Second Admission

On August 20, 1947, the patient was admitted to the University gynaecological unit on account of continuous uterine bleeding for the previous 12 weeks. She was grossly obese (220 lb.—99.8 kg.); hirsuties was pronounced over the face, areolae of nipples, and legs. There were mild acne vulgaris of her highly coloured face and many healed acne scars over her back and chest. Fat striae were present over the legs and abdomen, while the left tibial region had been swollen and oedematous for the past five months (Figs. A and B). Her voice was hoarse and croaking, but she asserted that this was normal.

FIG. A.—A single woman aged 41 with adrenogenitalism for 13 years. Weight variable, at present 180 lb. (81.6 kg.). Note the fat striae. The deep abdominal scar resulted from a mild infection of the very obese abdominal wall at hysterectomy.

FIG. B.—Same case as Fig. A. Marked hirsuties but without acne vulgaris. The hair is coarse and dry.