PROCAINE PENICILLIN; THERAPEUTIC EFFICIENCY AND A COMPARATIVE STUDY OF THE ABSORPTION OF SUSPENSIONS IN OIL AND IN OIL PLUS ALUMINUM MONOSTEARATE AND OF AN AQUEOUS SUSPENSION CONTAINING SODIUM CARBOXYMETHYLCELLULOSE

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ONE of the greatest disadvantages of penicillin is its rapid elimination from the body. In order to decrease the frequency of injections many attempts have been made to delay the absorption or excretion of penicillin and thus prolong the action of an injected dose. Until recently the most successful method of prolonging the concentrations of penicillin in the blood has been the incorporation of penicillin in peanut oil and beeswax.[1] With this preparation a single injection of 1 c.c. containing 300,000 units of penicillin was usually followed by assayable blood concentrations for twenty-four hours in 90 to 92 per cent of patients. The introduction of a fluid preparation obviated some of the difficulties inherent in the administration of this material.[2] Fluid penicillin in peanut oil and beeswax was found to be as effective as the original viscid preparation when 50 per cent of the total relative weight is made up of particles of 50 μ or more in length.[3] Discomfort to the patient in the form of local pain, tenderness, and nodule formation at the site of injection, however, still persisted.

For some time it has been known that a mixture of concentrated solutions of penicillin and procaine resulted in the formation of crystals which were identified as the procaine salt of penicillin. Whereas the commercially available salts (sodium, potassium, and calcium) are highly soluble in aqueous solutions and body fluids, the procaine salt is relatively insoluble. This property forms the basis of a new principle of penicillin administration. As a result of the low solubility of procaine penicillin, a repository injection of a suspension of this salt in oil or water results in delayed absorption and prolonged blood concentrations. This report presents the results of our studies on absorption following the intramuscular injection of procaine penicillin and the treatment of patients with various infections when procaine penicillin in oil was used.

MATERIALS

Crystalline procaine penicillin is usually prepared by the double decomposition of sodium penicillin G and procaine hydrochloride. The original commercial preparations were suspended in refined sesame or peanut oil so that 300,000 units were present in 1 c.c. as a free-flowing fluid material. Such a preparation need not be refrigerated since it will remain stable for at least one year at room temperature. Because the procaine penicillin on standing separates from the oil and because of the necessity for vigorous agitation in

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order to re-establish the suspension, detergents such as Tween 80* and Span 80† have been added to facilitate resuspension. These measures have been only partially successful. Other investigators[4] have added aluminum monostearate to the mixture to maintain the suspension. The addition of aluminum monostearate to procaine penicillin in oil results in a gel formation which maintains the suspension of the penicillin in the oil.

Peanut or sesame oil was originally employed as a vehicle for injecting procaine penicillin since it was impossible to prepare injectable water suspensions of this penicillin salt. Recently it has been demonstrated that the addition of dried sodium carboxymethylcellulose to dry crystalline procaine penicillin results in a stable suspension in diluents containing water.[5] Sodium carboxymethylcellulose in aqueous solution forms a viscous gel which maintains the procaine penicillin in discrete particulate suspension. This has eliminated the necessity for the use of oils, which have been shown to be antigenic and which may cause serious complications if they are injected accidentally into a blood vessel.[6]

All of the procaine penicillin preparations can be withdrawn from the vial and administered through a 19 or 20 gauge needle. For the preparations containing aluminum monostearate or sodium carboxymethylcellulose, dry syringes and needles are not needed. When procaine penicillin in oil is administered, moist needles and syringes may be used if the injection is made immediately after the syringe is filled. Although we have given multiple injections of procaine penicillin in oil from a single syringe without difficulty provided the withdrawal and injections were made within a very few minutes, these precautions are not necessary with the preparations containing aluminum monostearate or sodium carboxymethylcellulose.

STUDIES ON ABSORPTION

The concentrations of penicillin in the blood at various intervals were determined according to the method of Randall and associates[7] following the intramuscular injection of (1) procaine penicillin in oil,‡ (2) procaine penicillin in oil plus aluminum monostearate,§ and (3) procaine penicillin plus sodium carboxymethylcellulose in aqueous suspension.‖ The results are expressed both as percentage of patients having assayable concentrations (.03 units per cubic centimeter or more) and as the median concentrations at the various intervals tested.

As shown in Table I, all of the patients who received a single or initial injection of 300,000 units of procaine penicillin in oil (1 c.c.) had detectable levels at one, four, twelve, sixteen, and twenty hours. Only an occasional patient failed to have an assayable level at the twenty-fourth hour. About one-half of the patients had measurable levels at the thirty-sixth hour, and about one-third at the forty-eighth hour. The median levels at various hours are also shown in Table I.

While this study was in progress, several of the commercially available lots of procaine penicillin in oil were found to be inferior in that only about one-half to one-third of the patients had detectable levels in the blood at the twenty-fourth hour following the injection of 300,000 units of procaine penicillin in oil (1 c.c.).[8] It was found that in conversion to mass production, crystallization was not carefully controlled, so that large particles of procaine penicillin were

*Tween 80, Sorbitan mono-oleate, polypoxyalkylene derivative.
†Span 80, Sorbitan mono-oleate.
‡Supplied by Chas. Pfizer & Company, Inc., Brooklyn, N. Y., and Eli Lilly & Company, Indianapolis, Ind.
§Supplied by Bristol Laboratories, Inc., Syracuse, N. Y.
‖Supplied by Wyeth Incorporated, Philadelphia, Pa.

TABLE I. RESULTS FOLLOWING INTRAMUSCULAR ADMINISTRATION OF VARIOUS PREPARATIONS OF PROCAINE PENICILLIN (300,000 UNITS)

PREPARATION		HOUR									
		12	16	20	24	36	48	60	72	96	120	144
Procaine penicillin in oil	Median levels (U./c.c.)	0.375	0.375	0.25	0.125	0.031	0.031					
	Percentage of patients with assayable levels*	100	100	100	96	57	36					
Procaine penicillin (particles less than 5 μ) in oil plus aluminum monostearate	Median levels (U./c.c.)				0.25		0.125		0.062	0.062	0.031	0
	Percentage of patients with assayable levels*				100		100		100	100	100	42
Procaine penicillin plus sodium carboxymethylcellulose	Median levels (U./c.c.)	0.5	0.25	0.25	0.125	0.125	.062	0.062	0			
	Percentage of patients with assayable levels*	100	100	100	100	100	100	100	25			

At least twenty-five patients were studied at each time interval indicated for the various preparations.
*Method of Randall and associates; detecting 0.03 unit per cubic centimeter and higher.

produced. In grinding these particles to sizes capable of passage through 19 or 20 gauge needles, relatively large amounts of procaine penicillin dust or flour were produced. The fine particles comprising this dust or flour are dissolved and absorbed relatively rapidly, so that prolonged blood concentrations are not maintained. (The manufacturers have taken steps to eliminate the fine particles from their preparations.) Therefore, the blood concentrations obtained after the injection of preparations of this kind are not included in Table I.

The percentage of patients and the median blood concentrations following the injection of 300,000 units of procaine penicillin in oil plus 2 per cent W/V aluminum monostearate are also shown in Table I. It is apparent that the addition of aluminum monostearate not only stabilizes the suspension of procaine penicillin in oil but also results in prolongation of the concentrations of penicillin in the blood. Preparations containing particles of penicillin less than 5 μ in size resulted in measurable blood concentrations in all patients at twenty-four, forty-eight, seventy-two, ninety-six, and one hundred twenty hours after injection. When large particle procaine penicillin crystals are employed in this mixture, the concentrations of penicillin in the blood are not so prolonged.[4, 9]

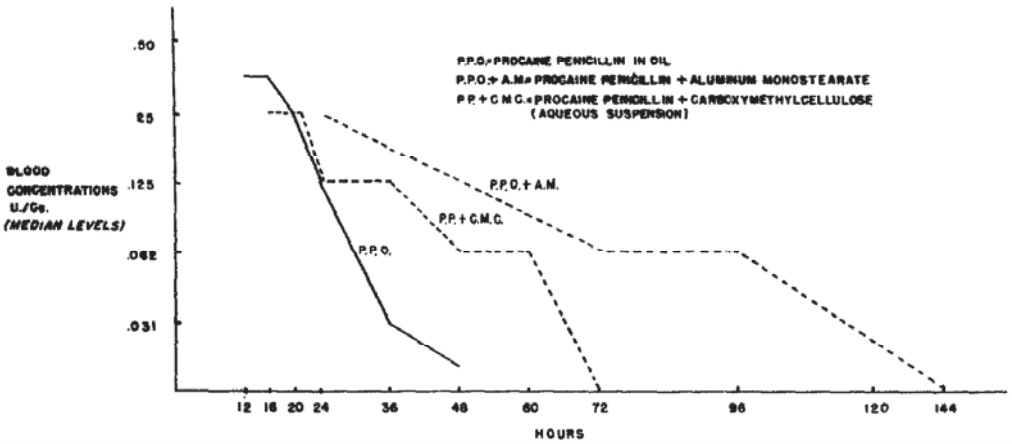

Fig. 1.—Curves of the concentration of penicillin in the blood following intramuscular injection of 300,000 units of procaine penicillin G suspended in various vehicles.

Included in Table I are the data obtained following the injection of 300,000 units of procaine penicillin plus 3.5 Gm. of sodium carboxymethylcellulose contained in 1 c.c. of aqueous solution. All of the patients studied had measurable levels at sixteen, twenty, twenty-four, thirty-six, forty-eight, and sixty hours. Twenty-five per cent had assayable levels at seventy-two hours.

The median concentrations at the various intervals for all three preparations have been plotted in Fig. 1.

Blood concentrations were determined in seventeen patients who were receiving 300,000 units of the procaine penicillin in oil preparations every twelve hours and in fourteen subjects who received 600,000 units (2 c.c.) every twelve hours. Upon such regimens the blood concentrations at the twelfth hour were at least 0.125 unit per cubic centimeter and usually 0.25 and 0.5 unit per cubic centimeter. There were no significant differences between the two doses.

CLINICAL STUDY

We have treated 251 patients with various infections with procaine penicillin in oil. All the patients received plain procaine penicillin in oil except the patients with gonorrhea who were treated with the material containing aluminum monostearate. The results and plans of therapy are summarized in Table II.

Eighty-nine patients with pneumococcic pneumonia of known type or with findings and a course characteristic of pneumococcic pneumonia were treated with 600,000 units of procaine penicillin in oil (2 c.c.) every twelve hours until they were essentially afebrile for forty-eight to seventy-two hours. The course was similar to that seen with the use of other penicillin preparations, and recovery was uneventful in all patients. These large doses were employed as a part of a study to evaluate the effect of massive doses in pneumonia. Other investigators[10] have found that 300,000 units a day for similar periods give satisfactory results.

TABLE II. DOSAGE SCHEDULES AND RESULTS OF TREATMENT OF VARIOUS INFECTIONS WITH PROCAINE PENICILLIN IN OIL

DISEASE	NUMBER OF PATIENTS	DOSAGE SCHEDULE	COMMENT
Pneumonia Typed 41 Untyped 48	89	600,000 units b.i.d. until essentially afebrile for 48 to 72 hours	Recovered
Acute bronchitis	2	300,000 to 600,000 units b.i.d. for 5 days	Recovered
Acute sinusitis	3	300,000 to 600,000 units b.i.d. for 5 days	Recovered
Tonsillitis	3	300,000 units per day for 5 days	Recovered
Scarlet fever	17	300,000 units per day for 5 days	Recovered
Vincent's infection	1	300,000 units per day for 2 days	Recovered
Infectious arthritis Gonococcal 2 Unknown 1	3	300,000 to 600,000 units b.i.d. for 7 to 10 days	Recovered
Gonorrhea*	57	300,000 units	Only 1 patient had return of symptoms—possible reinfection
Syphilis	75	600,000 units per day for 5 days	All patients showed complete healing of lesions and decrease in serologic titers during 2- to 5-month follow-up period
Cellulitis	1	600,000 units per day for 4 days	Recovered
Typhoid fever	1	300,000 units every 6 hours, with sulfathiazole—6 Gm. initial dose and 1 Gm. every 4 hours	No improvement

*Patients treated with procaine penicillin in oil plus aluminum monostearate.

In previous publications[11, 12, 13] the efficacy of penicillin in the treatment of scarlet fever has been reported. Procaine penicillin in oil in doses of 300,000 units per day for five days has resulted in prompt recovery from this streptococcal infection without pyogenic complications in all seventeen patients treated.

Three patients with bacterial arthritis were treated. Two were considered to have had gonococcal arthritis, since gonococci were isolated from a coexistent

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