BENETHAMINE PENICILLIN: A NEW SALT WITH A PROLONGED ACTION

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During the past ten years a great deal of research has been directed towards finding a method of giving penicillin that would be efficient and reliable and yet cause both patient and doctor the minimum of inconvenience. It has been found possible to increase the interval between injections by giving larger doses, by using less soluble salts, or by means of vehicles that delay absorption. Procaine penicillin, for instance, because of its low solubility, will maintain bacteriostatic penicillin blood levels for as long as twenty-four hours. In practice, however, many infections require treatment for four to six days, and a preparation with an even longer duration of action would have obvious advantages, since many cases could then be treated with only one or two injections. This paper describes the first clinical trials of a new penicillin salt that has been developed with this object in view.

Chemical and Physical Properties

The approved name for the salt is benethamine penicillin ("benapen"). Chemically it is the N-benzyl-β-phenylethylamine salt of penicillin. Its structural formula is as follows:

It is a white crystalline compound, very slightly soluble in water (0.1% w/v at 40° C.). Its potency is approximately 1,100 units per mg. It is prepared as an aqueous suspension ready for injection in a vehicle containing suspending, buffering, wetting, and bacteriostatic agents.

Pharmacology

Investigations that are being prepared for publication elsewhere have shown that benethamine penicillin is slightly less toxic than procaine penicillin when injected intravenously or subcutaneously into mice and rats. In mice the intravenous LD₅₀ is 170 mg. per kg., compared with 130 mg. per kg. for procaine penicillin. In the anaesthetized cat benethamine penicillin caused a greater fall of blood pressure and a smaller increase in respiration rate than the same weight of procaine penicillin. It can be administered orally to mice in doses exceeding 10 g. per kg. without causing any ill effects. No untoward reactions were observed in rabbits given single intramuscular injections of 100 mg., and macroscopic examination of the injected muscle after 72 hours revealed no signs of irritation other than slight hyperaemia.

During subacute toxicity tests on rats no ill effects or evidence of pain were noted when injections of 250 mg. per

kg. were given into the same muscle daily for two weeks. This dose corresponds to nearly 30 times the expected dose in man. Post-mortem examination of these rats, killed after two weeks, revealed no abnormal changes in the viscera. Deposits of unabsorbed particles were found at the site of injection, and histologically these were surrounded by zones of foreign-body reaction.

Serum Penicillin Levels

A co-ordinated trial was carried out at three hospitals to determine the serum levels attained after the intramuscular injection of different doses of the salt.

Selection of Patients.—The subjects chosen for the investigation were adult bed patients of average size with no fluid or electrolyte imbalance and no obvious evidence of renal disease. As indicated in the text, some healthy ambulant medical students were later included in the trial. Care was always taken to see that the individual had not recently been given any antibiotic that might interfere with the results of the assays.

Method of Assay.—Assays were performed on serum obtained by vein or ear puncture. The technique was that recommended by the U.S. Food and Drugs Administration Antibiotics Laboratory, Washington, D.C., with *Sarcina lutea* strain CP1-1001 as the test organism. For convenience, minor modifications were made as follows: (a) Holes (9 mm.) cut with a cork-borer were used instead of steel "penicillinders" on the assay plates. (b) The number of plates for each sample was increased from two to three. (c) Two dilutions of each serum were used—neat and 1/2 in pH 7 phosphate buffer. Standard solutions, usually 0.05 and 0.1 unit of penicillin per ml., were included on each plate. Since two dilutions of standard and unknown sera were used, the penicillin content of the unknown sera could be calculated from the zone of inhibition diameters by a method such as that recently described by Gaddum (1953).

Results

Thirty-three bed patients were given a single intramuscular injection of 300,000 units (1 ml.). Individual and average assay results are given in Table I. Twelve patients

TABLE I.—Penicillin Levels in units/ml. of Serum After a Single Injection of 300,000 units of Benethamine Penicillin Intramuscularly

Patient	Hours							
	1	3	6	24	48	72	96	120
1	0.95	0.23	0.22	0.07	0.03	0.01	0	
2	1.00	0.63	0.24	0.10	0.04	0.01	0	
3	0.44	0.52	0.40	0.19	0.09	0.05	0.01	
4	0.11	0.15	0.09	0.07	0.06	0.04	0	
5	0.14	0.07	0.18	0.03	0.03	0.03	0.01	
6	0.32	0.33	0.30	0.09	0.07	0.04	0.01	
7	0.06	0.05	0.06	0.05	0.03	0.03	0	
8	0.04	0.09	0.06	0.07	0.06	0.08	0.08	
9	0.25	0.11	0.24	0.11	0.03	0.03	—	
10	0.15	0.24	0.19	0.09	0.01	0.01	—	
11	0.10	0.22	0.10	0.08	0.01	0.03	—	
12	—	—	—	0.06	0.02	0.01	0.01	
13	—	—	—	0.05	0.03	0.04	0.01	
14	—	—	—	0.09	0.05	0.01	0	
15	—	—	—	0.11	0.04	0.05	0.03	
16	—	—	—	0.12	0.04	0.02	0	
17	—	—	—	0.13	0.10	0.10	0.06	
18	—	—	—	0.20	0.04	0.02	0	
19	—	—	—	0.09	0.04	0.03	0.01	
20	—	—	—	0.04	0.04	0.03	0.04	
21	0.07	0.08	0.10	0.06	0.05	0.04	0.05	
22	0.08	0.09	0.09	0.02	0	—	—	
23	0.21	—	—	—	0.08	0.07	0.04	0.03
24	0.36	—	—	0.16	0.06	0.05	0.02	
25	0.14	—	—	0.10	0.04	0.01	0.02	0.02
26	0.20	—	—	0.21	0.16	0.14	0.15	0.07
27	0.15	—	—	0.21	0.15	0.09	0.03	0.01
28	—	0.13	0.20	0.08	0.06	0.03	0.01	
29	—	0.15	0.20	0.12	0.10	0.09	0.05	
30	—	0.32	0.38	0.18	0.10	0.06	0.04	
31	—	0.06	0.07	0.04	0.04	0.03	0.04	
32	—	0.23	0.37	0.25	0.09	0.04	0.02	
33	—	0.20	0.27	0.12	0.07	0.06	0.05	
Minimum	0.04	0.05	0.06	0.02	0	0.01	0	0.01
Maximum	1.0	0.63	0.40	0.25	0.16	0.14	0.15	0.07
Average	0.26	0.21	0.20	0.11	0.06	0.04	0.03	0.03

— = Not tested.

received 600,000 units and 10 patients received 900,000 units. The results are given in Tables II and III. In Fig. 1 the average serum concentrations produced by the three doses are compared.

TABLE II.—*Penicillin Levels in units/ml. of Serum After a Single Injection of 600,000 Units of Benethamine Penicillin Intramuscularly*

Patient	Hours							
	1	3	6	24	48	72	96	120
34	0.23	0.18	0.23	0.11	0.04	0.04	0.03	0.04
35	0.17	0.12	0.14	0.08	0.04	0.05	0.04	0.01
36	0.13	0.16	0.13	0.06	0.04	0.05	0.03	0.04
37	0.27	0.24	0.23	0.21	0.10	0.09	0.03	0.01
38	0.34	0.28	0.25	0.20	0.11	0.07	0.03	0.01
39	0.35	0.30	0.25	0.19	0.08	0.08	0.06	0.04
40	0.30	0.38	0.28	0.20	0.10	0.08	0.05	0.04
41	—	—	—	0.14	0.09	0.06	0.05	0.05
42	—	—	—	0.06	0.06	0.05	0.05	0.05
43	—	—	—	0.18	0.12	0.07	0.07	0.08
44	—	—	—	0.31	0.18	0.05	0.05	0.03
45	—	—	—	0.17	0.11	0.10	0.08	0.06
Minimum	0.13	0.12	0.13	0.06	0.04	0.04	0.03	0.01
Maximum	0.35	0.38	0.28	0.31	0.18	0.10	0.08	0.08
Average	0.26	0.24	0.22	0.16	0.09	0.07	0.05	0.04

— = Not tested.

TABLE III.—*Penicillin Levels in units/ml. of Serum After a Single Injection of 900,000 Units of Benethamine Penicillin Intramuscularly*

Patient	Hours							
	1	3	6	24	48	72	96	120
46	0.40	0.53	0.40	0.39	0.32	0.31	0.17	0.09
47	0.21	0.26	0.34	0.22	0.11	0.07	0.03	0
48	0.25	0.25	0.23	0.21	0.10	0.08	0.10	0.07
49	0.17	0.17	0.14	0.14	0.10	0.06	0.05	0.04
50	0.24	0.32	0.18	0.14	0.09	0.08	0.09	0.09
51	0.18	0.18	0.26	0.14	0.08	0.06	0.05	0.03
52	0.20	0.25	0.22	0.11	0.07	0.11	0.08	0.08
53	0.44	0.45	0.31	0.11	0.08	0.07	0.06	0.06
54	0.28	0.33	0.21	0.11	0.07	0.07	0.05	0.04
55	0.11	0.12	0.18	0.05	0.05	0.05	0.05	0.05
Minimum	0.11	0.12	0.14	0.05	0.05	0.05	0.03	0
Maximum	0.44	0.53	0.40	0.39	0.32	0.31	0.17	0.09
Average	0.25	0.29	0.25	0.16	0.11	0.10	0.07	0.06

FIG. 1.—Serum penicillin concentrations after single doses of benethamine penicillin.

The effect of giving repeated doses was then investigated. Groups of six and seven individuals were respectively given 300,000 and 600,000 units intramuscularly on three alternate days. Assays were performed daily, starting 24 hours after the first injection. On the second and fourth days blood was taken before the injection was given, so that only the penicillin given 48 hours previously was assayed. The group receiving the three 300,000 units injections were bed patients as before, but the group given the three 600,000

units course were ambulant medical students. The results of these assays are given in Tables IV and V. Fig. 2 shows the average levels recorded.

TABLE IV.—*Effect of 300,000 units of Benethamine Penicillin Injected on Alternate Days.* Serum Levels in units/ml.*

Patient	Days					
	1	2	3	4	5	6
56	0.09	0.02	0.15	0.02	0.08	0.04
57	0.08	0.02	0.12	0.02	0.08	0.02
58	0.12	0.06	0.17	0.08	0.29	0.08
59	0.09	0.02	0.11	0.03	0.07	0.02
60	0.11	0.11	0.20	0.20	0.24	0.19
61	0.18	0.08	0.16	0.07	0.14	0.03
Average	0.11	0.05	0.15	0.07	0.15	0.06

* The injections were given on days 0, 2, and 4. On days 2 and 4 blood was taken for assay before the injection was given. The patients were in bed.

TABLE V.—*Effect of 600,000 units of Benethamine Penicillin Injected on Alternate Days.* Serum Levels in units/ml.*

Patient	Days					
	1	2	3	4	5	6
62	0.09	0.07	0.25	0.07	—	—
63	0.14	0.06	0.23	0.09	—	—
64	0.20	0.17	0.10	0.05	0.12	—
65	0.26	0.27	0.36	0.16	0.40	—
66	0.23	0.24	0.30	0.22	0.36	0.27
67	0.18	0.11	0.54	0.13	0.35	0.04
68	0.36	0.10	0.15	0.02	0.09	—
Average	0.21	0.15	0.28	0.16	0.26	—

— = Not tested.

* The injections were given on days 0, 2, and 4. On days 2 and 4 blood was taken for assay before the injection was given. The subjects were ambulant volunteers.

FIG. 2.—Serum penicillin concentrations after injection of benethamine penicillin on alternate days.

It will be seen from the tables and figures that the average penicillin serum concentration is maintained above 0.03 unit per ml. for four days after 300,000 units, for five days after 600,000 units, and presumably for six days after 900,000 units, but the level achieved during the first few hours is very similar whichever dose is given. Doses of 300,000 or 600,000 units given on alternate days did not appear to have a cumulative effect. They did, however, serve to confirm the impression that, notwithstanding considerable individual variations, doses of 300,000 units every two days or 600,000 units every three days could be relied on to maintain the penicillin in the blood at over 0.03 unit per ml. Other doses and longer intervals have not yet been investigated.

Handling Properties.—Although as a rule the suspension seemed easy to handle, syringe or needle blockage occasionally occurred in the earlier stages of the trial. This was found more likely to occur in syringes lubricated with paraffin or silicone lubricants. It very rarely happened with wet or even with dry unlubricated syringes. In consistency the preparation is very similar to aqueous suspensions of

procaine penicillin, and it can easily be withdrawn from the bottle and injected into the patient with a 20 or 22 B.W.G. needle.

Side-effects.—During these trials some 120 intramuscular injections of benethamine penicillin were given without any immediate untoward effects beyond the complaint in a few instances of a slight stinging pain or of some mild stiffness or aching at the site of injection. In five instances a more pronounced local reaction occurred later. One volunteer developed a "T.A.B.-like" reaction 72 hours after the injection of 300,000 units into the deltoid. This persisted for about 24 hours and then subsided. Four other ambulant subjects developed a hard tender lump in the buttock or thigh after the injection of 600,000 units; from one of these a small quantity of sterile necrotic material was evacuated. No general reactions occurred.

We have not yet had enough experience to be able to give an accurate assessment of the incidence of reactions, but it would seem a wise precaution to inject benethamine penicillin deeply into the largest muscle available, and preferably into the buttock.

Discussion

Although no direct comparison was made, it is evident that in terms of blood levels benethamine penicillin falls between procaine penicillin (cf. Cohen, 1950) and benzathine penicillin (cf. Elias *et al.*, 1951; Fletcher and Knappett, 1953); that is to say, the levels are lower and more prolonged than those obtained with procaine penicillin but higher and of shorter duration than those that follow the injection of benzathine penicillin.

There was good agreement between the results at the three hospitals, but, as seems to occur with all repository preparations, there was considerable variation from patient to patient in the height and duration of the levels. The difference in the results of the three doses—300,000, 600,000, and 900,000 units—was surprisingly small, but on the whole the levels of the patients who received the larger doses were somewhat higher and more prolonged, and hence probably more efficient therapeutically. For instance, at 72 hours, 9 (27%) of 33 patients who received only 300,000 units had serum concentrations below 0.03 unit per ml., but none of the 22 patients who were given 600,000 or 900,000 units had levels below this figure at either 72 or 96 hours.

These results suggest that for the usual infections seen in everyday practice one injection, or possibly two, of 600,000 units for an adult or 300,000 units for a child should be adequate treatment. Although this investigation was not designed to test the therapeutic response to benethamine penicillin, our experience to date seems to indicate that this is the case. The salt has also obvious possibilities in the treatment of venereal diseases and yaws, for use before and after surgery, and in other forms of prophylaxis. It is clearly unsuitable for the treatment of infections that require a high concentration of penicillin, for which sodium penicillin remains the preparation of choice.

Summary

Benethamine penicillin is a new relatively insoluble penicillin salt. After a single injection a bacteriostatic level of penicillin is maintained in the blood for three to six days, depending on the dose and the individual response. It is best administered by deep intramuscular injection into the buttock or thigh, where it is less likely to provoke any reaction than in the arm.

From a consideration of the blood levels it is suggested that one injection, possibly two, of 600,000 units for an adult or 300,000 units for a child should be adequate to treat the more sensitive and accessible infections seen in everyday practice, and our experience so far suggests that this is in fact the case.

We are grateful to Dr. A. F. Mohun for allowing us to include the results of his assays, and to him and to Dr. A. C. Cunliffe

for their valuable criticism and advice. We also wish to thank Mr. Todd and Mr. Fleming for their technical assistance. Glaxo Laboratories Ltd. kindly supplied the benethamine penicillin. Finally, we should like to record our gratitude to the patients and volunteers who co-operated so willingly during this investigation.

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ASSESSMENT OF 1,011 PATIENTS IN A MENTAL DEFICIENCY HOSPITAL

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Research into various aspects of mental deficiency is in process at Prudhoe and Monkton Hospital. Our work is far from complete, but certain data are already available, and these may be compared with the results obtained by O'Connor and Tizard (1954) in their survey of patients in 12 mental deficiency institutions. Our classification of 1,011 mentally defective patients on clinical and psychometric grounds is at such variance with their figures that we think it may be of some interest.

In order to make it easy to follow and compare both sets of results at a glance we have arranged them exactly according to the pattern given by O'Connor and Tizard in Table II of their survey. We also attempted to follow their line of thought and took a group of 60 males and 24 females whose ages were between 16 and 30 years and who had been previously classified as feeble-minded, and we found their respective mean I.Q.s. Again the discrepancy between results is too wide to be ignored.

Findings

The figures in Table I are based on clinical and psychometric findings. For clinical assessment the medical superintendent was responsible, and for psychometric assessment the clinical psychologist. In most cases clinical and psychological findings have been complementary; in a very few cases when discrepancy occurred, after full discussion of our findings, past history, social aspect, and behaviour of the case, the final classification was agreed upon.

TABLE I.—Distribution of Patients by Sex, Grade, and Age

Age	Male				Female				Totals			
	Idiot	Imbecile	F.-M.	Totals	Idiot	Imbecile	F.-M.	Totals	Idiot	Imbecile	F.-M.	Totals
0-4 ..	3	0	0	3	1	0	0	1	4	0	0	4
5-9 ..	25	14	4	43	9	7	6	22	34	21	10	65
10-14 ..	29	29	10	68	23	17	3	43	52	46	13	111
15 ..	3	10	2	15	5	2	2	9	8	12	4	24
Total (children)	60	53	16	129	38	26	11	75	98	79	27	204
16-19 ..	16	23	10	49	18	7	5	30	34	30	15	79
20-29 ..	30	49	50	129	31	28	19	78	61	77	69	207
30-39 ..	16	73	38	127	15	46	17	78	31	119	55	205
40-49 ..	6	70	38	114	6	45	18	69	12	115	56	183
50+ ..	6	46	14	66	4	43	20	67	10	89	34	133
Total (adults)	74	261	150	485	74	169	79	322	148	430	229	807
Total ..	134	314	166	614	112	195	90	397	246	509	256	1,011