ABSORPTION OF FREE ACID, POTASSIUM, AND BENZATHINE PHENOXYMETHYLPENICILLIN AFTER ORAL ADMINISTRATION

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Phenoxymethylpenicillin (penicillin V) was first prepared in 1947 (Behrens *et al.*, 1948), but was not used as a therapeutic agent until 1953 (Brandl *et al.*, 1953). Since then many reports have demonstrated that it is more reliably absorbed after oral administration than other forms of penicillin (Jones and Finland, 1955; Juncher and Raaschou, 1955; Wright *et al.*, 1955; Heatley, 1956; Welch, 1956; Rinsler and Cunliffe, 1956; Bunn, 1956). It is also therapeutically effective (Martin *et al.*, 1955; Hart *et al.*, 1956; Wood *et al.*, 1956). In the majority of these investigations, phenoxymethylpenicillin free acid has been used, but more recently some attention has been given to phenoxymethylpenicillin salts (Andresen, 1955; Björkman and Löfberg, 1956; Brunner and Giovannini, 1956; Kaipainen and Härkönen, 1956). A knowledge of the blood levels and persistence of effect that can be obtained with different preparations and doses is clearly of importance in planning treatment. This report describes the levels achieved with 60-mg. and 240-mg. doses of phenoxymethylpenicillin free acid, and compares the results from the higher dose of this compound with those from corresponding amounts of potassium and benzathine salts of phenoxymethylpenicillin. The absorption of the benzathine salt has also been studied in patients with treated pernicious anaemia in whom there was complete gastric achlorhydria.

Methods

The subjects comprised volunteers from amongst doctors, medical students, nurses, and convalescent patients not suffering from cardiac, renal, or gastro-intestinal disease. In the first series of observations on 24 people a single dose of 60 mg. of phenoxymethylpenicillin free acid was given half an hour before breakfast. Serum concentrations were measured at $\frac{1}{2}$, 1, 2, 3, 4, 5, and 6 hours after swallowing the tablet. Twenty subjects took part in the second series of observations, in which the serum levels obtained with single doses of 240 mg. of phenoxymethylpenicillin free acid, 266 mg. of potassium phenoxymethylpenicillin, and 320 mg. of benzathine phenoxymethylpenicillin were compared. Equivalent weights of penicillin were present in these three different doses, which were administered in two tablets. The 20 subjects all took the three preparations in successive weeks in a random order. The tablets were taken half to one hour before breakfast. The interval and the type of meal were kept constant for each subject, so that the comparisons were made so far as possible under identical conditions. Finally, to investigate the importance of gastric hydrochloric acid in the absorption of benzathine phenoxymethylpenicillin, this compound was given to 11 patients with treated pernicious anaemia who had agreed to take part

in the trial. The diagnosis had been confirmed by examination of the peripheral blood and bone marrow and the demonstration of a histamine-fast achlorhydria.

The concentration of penicillin in the serum was estimated by dilutions in phenol-red-glucose-serum medium (May *et al.*, 1947), which were inoculated with *Streptococcus pyogenes*. Comparisons were made with similarly inoculated dilutions of benzylpenicillin in the same medium. This technique was used in previous studies from these departments (Wayne *et al.*, 1949).

Results

The serum concentrations obtained with the 60-mg. dose of phenoxymethylpenicillin free acid are shown in Table I. With this dose, high concentrations were not obtained in the blood, but appreciable levels persisted for up to three hours.

The results with 240 mg. of phenoxymethylpenicillin free acid are shown in Table II and the comparison with the two salts in Tables III and IV. There was considerable variation between individuals in the concentrations achieved with each preparation. The most rapid absorption and highest concentrations were achieved with the potassium salt. At the half-hour measurement the potassium salt gives a significantly higher mean level than the benzathine salt. The other comparisons do not show a significant difference. With all three forms the mean persisted for up to four hours

TABLE I.—Serum Levels (Units/ml.) After 60 mg. of Phenoxymethylpenicillin Free Acid by Mouth

Subject No.	Hours after Administration						
	$\frac{1}{2}$	1	2	3	4	5	6
1	0.125	2.0	1.0	0.25	0.125	0.03	0
2	0.25	0.5	0.25	0.125	0.03	—	0
3	0	0.03	0.25	0.125	0.06	0	0
4	1.0	0.5	0.25	0.03	0	0	0
5	0.125	0.5	0	0	0	0	0
6	0.03	0.25	0.125	0.06	0.03	0.03	0
7	—	0.125	0.25	—	0.03	0.03	0
8	0.5	0.25	0.03	0	0	—	0
9	0.125	0.25	0.25	0.06	0	0	0
10	0	0.25	0.25	0.03	0	0	0
11	0.06	0.25	0.125	0.06	0	0	0
12	1.0	1.0	0.125	0.03	0	0	0
13	0.5	0.25	0.125	0.06	0	0	0
14	0	0.03	0.25	0.25	0.03	0	—
15	0.06	0.5	0.125	0	—	0	—
16	0.125	0.25	1.0	0.125	0.06	0	—
17	1.0	0.5	0.5	0.25	0.03	0	—
18	0.03	0.125	0.25	0.125	0.06	0	0
19	0.25	0.5	0.125	0.06	0.03	0	0
20	0.5	1.0	0.06	0.03	0	—	—
21	0.125	0.5	0.125	0.03	0	0	—
22	0.125	0.25	0.25	0.125	0.06	0	—
23	0.25	0.5	1.0	0.5	0.25	0.125	—
24	0	0.125	0.125	0.25	0.125	0.03	0
Mean	0.27	0.43	0.28	0.11	0.04	—	—
Standard error	0.07	0.08	0.06	0.03	0.01	—	—

TABLE II.—Serum Penicillin Levels (Units/ml.) After 240 mg. of Phenoxymethylpenicillin Free Acid by Mouth

Subject No.	Hours after Administration					
	$\frac{1}{2}$	1	2	3	4	6
25	0.25	0.5	0.25	0.125	0.06	0
26	2.0	1.0	0.5	0.25	0.125	0
27	2.0	2.0	0.5	0.06	0	0
28	4.0	2.0	0.5	0.06	0	0
29	4.0	2.0	0.25	0.06	0	0
30	0	2.0	0.5	0.06	0	0
31	1.0	2.0	1.0	0.25	0.03	0
32	4.0	2.0	0.5	0.125	0	0
33	1.0	2.0	2.0	0.25	0.125	0.03
34	8.0	8.0	1.0	0.125	0.06	0.03
35	0.5	0.5	1.0	0.5	0.25	0
36	0.03	0.5	2.0	0.5	0.125	0
37	4.0	4.0	0.25	0.06	0.03	0
38	0.06	1.0	1.0	0.25	0.125	0
39	2.0	4.0	2.0	0.25	0.03	0
40	4.0	2.0	0.25	0.06	0	0
41	2.0	8.0	1.0	0.25	0.125	0
42	0.5	1.0	1.0	2.0	0.1	0.03
43	0.125	2.0	0.25	0.06	0.03	0
44	4.0	4.0	0.25	0.06	0.06	0
Mean	2.17	2.52	0.80	0.27	0.06	0.004
Standard error	0.47	0.48	0.13	0.03	0.002	—

above 0.06 unit per ml., which may be taken as the minimum bacteriostatic level (Wayne *et al.*, 1949).

The benzathine salt was given by mouth to 11 patients with pernicious anaemia (Table V). The mean levels were higher than in the subjects with normal gastric function.

Discussion

The lower (60-mg.) dose of phenoxymethylpenicillin is the amount that might be given in the long-term prevention of infection. The concentrations obtained here with this dose are similar to those reported by Henry and Meynell

(1956). High levels cannot be obtained with this small amount, which will have an effect only on highly sensitive organisms.

The larger dose (240 mg.) of phenoxymethylpenicillin free acid gave much higher serum levels, and effective amounts were present in the blood for up to four hours. The higher concentrations achieved with the potassium salt have also been reported by Kaipainen and Härkönen (1956) and by Björkman and Löfberg (1956). The calcium salt apparently gives levels similar to those afforded by the free acid (Henriksen *et al.*, 1956; Rinsler and Cunliffe, 1956).

Some of the physical and chemical properties of the benzathine salt of phenoxymethylpenicillin have been described by Brunner and Giovannini (1956). The solubility in water of benzathine phenoxymethylpenicillin is 0.08% at 37° C. The pH of the saturated solution is about 5 and the solubility rises with increasing pH values. The minimum solubility is at pH 4.5, but in more acid conditions the solubility of the compound increases sharply. In the group of subjects with normal gastric function, lower levels were attained with the benzathine salt than with the free acid and potassium salt. The results in the patients with pernicious anaemia suggest that in the absence of gastric hydrochloric acid the benzathine salt is more fully absorbed. In tablet form it has no advantages over the other preparations. The lower peak values are not associated with a longer persistence of effective concentrations. However, the low solubility of the salt in water means that oral suspensions are relatively stable and it may be more suitable for administration in syrup form. In adults the potassium salt in tablet form is clearly preferable.

Summary

The serum concentrations achieved after 60-mg. and 240-mg. oral doses of phenoxymethylpenicillin free acid have been investigated.

The levels given by the potassium and benzathine salts in amounts equivalent to the 240-mg. dose of free acid have been compared. The potassium salt was most rapidly absorbed and gave the highest peak values. The benzathine salt gave the lowest values. The persistence of effect was similar in all three substances.

In patients with treated pernicious anaemia the benzathine salt gave higher levels than in the normal subjects.

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TABLE III.—Serum Penicillin Levels (Units/ml.) After 266 mg. of Potassium Phenoxymethylpenicillin by Mouth

Subject No.	Hours after Administration					
	$\frac{1}{2}$	1	2	3	4	6
25	2.0	1.0	1.0	0.5	0.25	0.03
26	0.25	0.5	0.5	0.25	0.125	0
27	4.0	2.0	0.25	0.125	0	0
28	8.0	2.0	0.5	0.125	0	0
29	2.0	2.0	1.0	0.25	0.125	0
30	1.0	4.0	1.0	0.125	0.03	0
31	4.0	4.0	1.0	0.125	0.03	0
32	8.0	2.0	0.5	0.25	0.125	0
33	4.0	4.0	0.5	0.06	0	0
34	—	8.0	2.0	0.5	0.06	0
35	8.0	2.0	0.25	0.03	0	0
36	0	0.25	0.125	0.03	0	—
37	4.0	4.0	0.25	0.03	0	0
38	8.0	8.0	1.0	0.125	0.06	0
39	2.0	2.0	1.0	0.5	0.25	0
40	2.0	1.0	0.5	0.25	0.125	0.06
41	2.0	2.0	1.0	0.25	0.25	0.125
42	1.0	4.0	0.5	0.25	0	0
43	16.0	4.0	0.5	0.125	0.03	0.03
44	4.0	2.0	0.5	0.125	0.03	0
Mean	4.22	2.94	0.69	0.20	0.07	0.013
Standard error	0.90	0.47	0.10	0.03	0.02	—

TABLE IV.—Serum Penicillin Levels (Units/ml.) After 320 mg. of Benzathine Phenoxymethylpenicillin by Mouth

Subject No.	Hours after Administration					
	$\frac{1}{2}$	1	2	3	4	6
25	0.03	0.5	0.5	0.25	0.03	0.03
26	0.5	0.5	0.125	0.125	0.125	0.03
27	2.0	1.0	0.125	0.03	0.03	0
28	2.0	1.0	0.25	0.06	0.03	0
29	2.0	1.0	0.5	0.25	0.125	0.06
30	2.0	2.0	0.25	0.06	0	0
31	0.5	1.0	1.0	0.5	0.03	—
32	2.0	1.0	0.5	0.125	0.06	—
33	0.5	0.5	4.0	2.0	0.25	0
34	1.0	4.0	2.0	1.0	0.5	0
35	1.0	2.0	0.5	0.03	0	0
36	0.25	1.0	2.0	0.25	0	0
37	0.125	0.25	0.5	0.03	0	—
38	2.0	1.0	0.125	0.06	0	0
39	4.0	2.0	1.0	0.5	0.125	0
40	1.0	2.0	0.125	0.06	0	0
41	0.06	2.0	0.25	0.125	0.06	0
42	0.5	1.0	0.125	0.06	0.06	—
43	4.0	8.0	0.25	0.06	0	0
44	4.0	2.0	0.25	0.06	0	0
Mean	1.47	1.69	0.72	0.29	0.07	0.0075
Standard error	0.29	0.38	0.21	0.11	0.05	—

TABLE V.—Serum Penicillin Levels (Units/ml.) After 320 mg. of Benzathine Phenoxymethylpenicillin to Patients with Treated Pernicious Anaemia

Subject No.	Hours after Administration					
	$\frac{1}{2}$	1	2	3	4	6
45	8.0	4.0	4.0	1.0	0.125	—
46	—	4.0	4.0	1.0	0.25	0.03
47	8.0	8.0	2.0	0.5	0.125	0.03
48	2.0	4.0	4.0	1.0	0.25	—
49	0.03	1.0	4.0	0.5	0.03	0
50	—	0.25	1.0	2.0	2.0	0.25
51	0.125	1.0	1.0	0.5	0.06	0.03
52	0.06	0.5	2.0	0.5	0.125	0.03
53	4.0	8.0	1.0	0.25	0.06	—
54	—	4.0	0.5	0.125	0.06	0
55	4.0	4.0	2.0	1.0	0.5	0
Mean	3.28	3.52	2.32	0.76	0.33	0.05
Standard error	1.20	0.82	0.13	0.16	0.17	0.05