A NOTE ON THE PHARMACOLOGY OF PHENOXYMETHYL-PENICILLIN (PENICILLIN V)

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ORAL administration, which is a therapeutic advantage, was not always justified with benzylpenicillin owing to its destruction in the acid medium of the stomach[1,2] and by penicillinase in the ileum[3]. Attempts to overcome these difficulties by the use of antacids and penicillinase inhibitors were not wholly successful in practice. The introduction of the long-acting insoluble penicillins, namely procaine and benzathine penicillin, although solving the problem of frequent intramuscular injections did not lead to a great advance in oral penicillin therapy. Oral procaine penicillin combined with sodium benzoate is reported as a satisfactory form of oral penicillin[4]. The results with benzathine penicillin (*NN'*-dibenzylethylenediamine dipenicillin), after oral administration were contradictory; some reported satisfactory serum concentrations after its use by mouth[5–8], while others did not obtain satisfactory results[9–11].

Phenoxymethylpenicillin, or Penicillin V is another form of insoluble penicillin. It was prepared biosynthetically by Behrens and Kingkade[12]. Brandl and Margreiter[2], demonstrated that it is insoluble in acid but soluble in alkaline medium and hence its antibacterial power is not appreciably reduced in the stomach. They showed that after two hours' exposure to hydrochloric acid at pH 2·8, the loss of potency of phenoxymethylpenicillin compared with benzylpenicillin is 9·2 and 44·4 per cent. respectively. A preliminary report[13] shows that it is rapidly absorbed from the duodenum producing adequate serum concentrations for 4 hours after a dose of 100,000 units. In the present study the concentration of penicillin in the serum and in the urine of normal adults was estimated after oral administration of different doses of phenoxymethylpenicillin.

MATERIAL AND METHODS

Phenoxymethylpenicillin was given to normal adult medical students as well as to members of the staff of this department. Each of a group of 10 volunteers was given a single dose of 600,000 units (6 tablets), of phenoxymethylpenicillin, on an empty stomach. The products were swallowed intact, to avoid prolonged contact with the saliva. Samples of blood were taken from one of the cubital veins at intervals of 1, 2, 3, 4, 5 and 6 hours, three samples being taken from each subject alternately. The blood samples were centrifuged to separate the serum which was used for the assay. To each member of a second group of 20 volunteers, a single dose of 100,000 units each (one tablet of 60 mg.) was given on an empty stomach as above. Samples of blood were taken at intervals of ½, 1, 2, 4 and 6 hours. Urine samples were also taken from the latter group who

were made to empty the bladder completely before swallowing the tablets. The urine was collected at ½, 1, 2, 4, 6, 8 and 12 hours intervals. The urine was filtered and sterilised by heating at 60° C. for half an hour, to kill interfering bacteria[14] and then stored in the refrigerator until required.

The technique adopted for penicillin assay was the agar plate diffusion method using *Staph. aureus* (Oxford strain) as a test organism. The standard used for comparison was a stock solution of benzylpenicillin prepared fresh weekly and kept in a refrigerator. From this stock solution, suitable dilutions were prepared at the time of the assay. A duplicate assay was carried out on each sample of urine or blood. After incubation overnight, the diameter of the inhibition zones was read for the two plates and averaged. The concentration of penicillin in the unknown sample was read from a curve drawn for the standard concentrations.

Results

Table I shows the penicillin serum concentration after a single dose of 600,000 units. From the Table it is seen that there is a high penicillin concentration one hour after administration to the fasting stomach. In only one of five was this concentration very low. During the following 3 hours, penicillin concentration declined slowly to an average of 0·15 units/ml. at the end of the fourth hour. It will be noted that individual variations are considerable. At the end of 6 hours the serum of all 4 volunteers tested still showed an inhibitory penicillin concentration, though to a minimum degree. The comparatively high penicillin concentration at the end of 4 hours, together with the suggestion of the preliminary report led us to the use of a smaller oral dose.

TABLE I

PENICILLIN SERUM CONCENTRATION IN NORMAL ADULTS AFTER A SINGLE ORAL DOSE OF PHENOXYMETHYLPENICILLIN

(DOSE: 600,000 UNITS APPROX.)

	Penicillin concentration in units/ml.					
Number	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
1	0·25	—	0·61	—	—	—
2	—	0·46	—	0·35	—	—
3	0·03	—	—	—	0·03	—
4	—	0·03	—	0·14	—	0·03
5	0·71	—	0·10	—	0·06	—
6	—	0·24	—	0·06	—	0·03
7	0·19	—	0·36	—	—	—
8	—	0·44	—	0·04	—	0·04
9	1·19	—	0·45	—	—	—
10	—	0·34	—	0·16	—	0·03
Mean	0·47	0·30	0·38	0·15	0·04	0·03
S.D.	0·47	0·18	0·21	0·12	0·03	0·005

— = No sample taken.

Table II shows the penicillin serum concentration after a single dose of 100,000 units to a fasting stomach. In this case of 9 samples taken half an hour after administration, 6 showed an inhibitory concentration of penicillin, but in 3 no such concentration could be detected. As before, individual variation is great. It was found that the mean penicillin concentration rises rather rapidly during the first hour to 0·19 units/ml. and then declines during the next 3 hours. At the end of 4 hours 6 out of 15 persons showed an inhibitory penicillin concentration in the serum. At the end of 6 hours there was practically no penicillin in the blood.

Comparison of the results recorded in Tables I and II show that although the one dose is 6 times larger than the other, the penicillin serum concentration is just over twice as much; this is a well-known pharmacological

phenomenon. It will be also seen that a dose of 100,000 units (one tablet) maintains an effective serum concentration adequate for most susceptible infections for a duration of 4 hours. The reduction of penicillin concentration at the end of 4 hours to the mean value of 0·02 units/ml. does not mean that the antibiotic effect has ceased altogether because it is known that penicillin will be found in the tissues for some time after its disappearance from the blood.

Excretion in the urine. Table III shows that penicillin has been detected in the urine in all our cases half an hour after oral administration with an average concentration of 5·6 units/ml. Excretion continued and the antibiotic is present in the urine in a concentration 1000 times or more its blood level. The maximum urinary concentration was obtained 2 hours after administration and at 12 hours, a considerable amount (1·3 units/ml.) was still present.

Side effects. In this series side effects were noticed in two subjects in the first group (6 tablets); one complained of a sensation of heaviness in

TABLE II

PENICILLIN SERUM CONCENTRATION IN NORMAL ADULTS AFTER A SINGLE ORAL DOSE OF PHENOXYMETHYLPENICILLIN

(DOSE: 100,000 UNITS APPROX.)

Number	Penicillin concentration in units/ml.				
	½ hr.	1 hr.	2 hr.	4 hr.	6 hr.
1	0·09	—	0·12	—	—
2	—	0·03	—	0·03	0·39
3	—	—	0·03	N.I.	—
4	0·19	—	0·21	N.I.	—
5	—	0·30	—	N.I.	N.I.
6	0·12	—	0·27	N.I.	N.I.
7	0·29	—	0·11	N.I.	—
8	—	0·69	—	—	N.I.
9	—	0·03	—	—	—
10	—	0·21	—	N.I.	N.I.
11	0·03	—	0·07	0·08	—
12	N.I.	—	0·23	N.I.	—
13	—	0·04	—	—	N.I.
14	N.I.	—	—	0·14	—
15	—	0·13	0·07	—	N.I.
16	—	0·21	—	N.I.	N.I.
17	—	0·20	—	0·03	N.I.
18	0·06	—	0·17	N.I.	—
19	—	0·07	0·08	0·06	—
20	N.I.	—	0·03	0·03	—
Mean	0·09	0·19	0·13	0·02	
S.D.	0·08	0·197	0·08	0·04	

— = No sample taken.
N.I. = Non-inhibitory concentration.

TABLE III

PENICILLIN CONCENTRATION IN URINE OF NORMAL ADULTS AFTER A SINGLE ORAL DOSE OF PHENOXYMETHYLPENICILLIN

(DOSE: 100,000 UNITS)

Number	Penicillin concentration in units/ml.						
	½ hr.	1 hr.	2 hr.	4 hr.	6 hr.	8 hr.	12 hr.
1	1·70	—	85·60	25·00	—	—	—
2	19·00	—	400·00	57·50	—	0·60	N.I.
3	—	44·00	—	—	—	10·00	N.I.
4	5·00	—	1187·50	362·50	58·75	—	—
5	14·00	—	775·00	155·65	—	—	7·50
6	—	830·00	—	—	4·40	—	—
7	3·10	—	850·00	—	147·50	1·36	0·36
8	—	303·00	—	—	—	1·09	0·29
9	1·63	—	8·75	194·00	—	—	—
10	—	0·61	—	—	50·00	—	0·60
11	—	1·00	50·00	1125·00	—	—	0·50
12	—	625·00	1700·00	581·50	44·00	—	4·40
13	7·13	—	212·50	587·50	27·50	—	—
14	0·64	—	156·50	13·75	—	—	0·25
15	—	6·38	—	—	77·50	—	—
16	3·44	—	—	350·00	—	—	0·13
17	—	53·75	58·75	—	31·30	—	—
18	—	118·75	—	75·00	—	—	—
19	0·06	—	53·75	53·75	2·00	—	—
20	—	4·50	52·50	197·00	—	—	0·07
Mean	5·60	198·70	430·10	290·60	49·20	3·30	1·30
S.D.	6·24	297·30	537·60	318·50	44·20	4·50	2·35

— = No sample taken. N.I. = Non-inhibitory concentration.

the stomach and the other of joint pains especially in the wrist and fingers. These symptoms disappeared next morning.

SUMMARY

1. Penicillin serum concentrations were estimated on several occasions after a dose of 600,000 units of Penicillin V given once to each of 10 persons and after a dose of 100,000 units of Penicillin V given once to each of 20 persons. Serum concentrations from ½ to 6 hours are tabulated.

2. Penicillin concentration in the urine was estimated in the latter group and very high levels for 12 hours were obtained. Side effects were slight.

3. It is suggested that this new penicillin may prove effective for oral penicillin therapy.

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