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ANTIMICROBIAL ACTIVITY OF PENICILLIN V AND PHENETHICILLIN WITH SPECIAL REFERENCE TO ORGANISMS ISOLATED FROM 17 PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS

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PREVIOUS STUDIES from this and other laboratories have indicated that phenoxymethyl penicillin (penicillin V) was more efficiently absorbed from the gastraintestinal tract than penicillin G with resultant greater serum concentration and urinary excretion of the former agent.[1-4]

Alpha phenoxyethyl penicillin, (phenethicillin) a semisynthetic penicillin, has been reported to be even more efficiently absorbed from the gastrointestinal tract than penicillin V.[5-7] These reports have been based on the quantitative determination of penicillin present in the serum following a given dose of the agent under test. However, data reported in this manner do not take into consideration possible differences in biologic activity of the various penicillins and thus may be misleading.

The present report concerns a comparative study of penicillin V and phenethicillin that was designed with particular reference to: (1) the serum concentration and urinary excretion of the two agents following oral administration of a large dose similar to that successfully employed in the therapy of subacute bacterial endocarditis;[3] and, (2) the relative potency and serum inhibitory activity of the agents against organisms isolated from 17 patients with subacute bacterial endocarditis.

MATERIALS AND METHODS

Pharmacologic Studies

Crossover studies were performed with potassium penicillin V and potassium phenethicillin in 10 healthy young adults. After an overnight fast half the group received a single 1,250 mg. oral dose of one of the agents and the remainder the alternate agent. Three days later each subject received the alternate medication under similar conditions. Venous bloods were obtained at 0, ¼, ½, 1, 2 and 4 hours and all subjects collected a 24-hour urine specimen following the administration of each agent. Serum and urine

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concentrations of the two penicillins were determined by the cup-plate method utilizing **Sarcina lutea** as the test organism,[8] pooled human plasma or sterile saline as the diluent and standard penicillin V acid (potency 1,672 units per milligram) and potassium phenethicillin (Penicillin-152 Potassium, Lot #A 0188, potency 920 micrograms per milligram) as the reference materials. Penicillin V and phenethicillin serum concentrations were expressed as absolute values and also as penicillin G equivalents.*

The serial two-fold dilution technique[8] in trypticase soy broth pH 7.3 inoculated with an equal volume of a 10^{-3} dilution of an 18 hour broth culture of the test organism (average 7.5 x 10^5 cells) was employed to determine **in vitro** susceptibility of fifteen strains of Viridans streptococci, a single strain of enterococcus and a strain of **Staphylococcus aureus.** These organisms had been isolated from the blood of patients with bacterial endocarditis. Determinations were carried out in parallel, so that inoculum size was constant for both penicillins.

The antibacterial activity of serum following ingestion of the penicillins was determined by the serial two-fold dilution technique employing a representative strain of Viridans streptococcus and the previously mentioned strain of staphylococcus. End points were read as the highest two-fold dilution of serum that completely inhibited growth of the test organism.

Results

Average serum concentrations of the two penicillins observed in the crossover study are presented in Table I. Referring to the absolute values for the two penicillins, it can be seen that both penicillin V and phenethicillin reached peak concentrations rapidly (that is at ½ hour) and that penicillinemia was detectable throughout the four hour test period. It is also apparent that with the exception of the 15 minute interval phenethicillin produced higher serum concentrations than did penicillin V. Differences in concentrations were not significant at ¼ and ½ hour but were significant at the 1, 2 and 4 hour intervals.

The average percentage of the administered dose of penicillin V and phenethicillin excreted in the urine during the 24 hours following administration of the

Table I

Average Serum Concentrations of Potassium Penicillin V and Potassium Phenethicillin.

Time in Hours	Potassium (a) Penicillin V		Potassium (a) Phenethicillin			Potassium (b) Penicillin V		Potassium (b) Phenethicillin		
	Mean	SD*	Mean	SD	P Value	Mean	SD	Mean	SD	P Value
1/4	2.96 ±	1.56	1.91 ±	1.70	.2	1.60 ±	1.44	0.26 ±	.02	.01
1/2	5.58 ±	2.71	7.96 ±	4.99	.2	2.30 ±	1.12	1.08 ±	.10	.02
1	4.88 ±	1.36	7.15 ±	1.27	.05	2.02 ±	.56	0.97 ±	.48	<.001
2	2.15 ±	0.60	3.50 ±	2.18	.001	0.89 ±	.24	0.48 ±	.29	.001
4	0.60 ±	0.33	1.46 ±	0.71	<.001	0.25 ±	.14	0.20 ±	.22	0.5

* SD Standard Deviation

(a) In mcg./ml. of serum

(b) In mcg./ml. of serum, expressed as Penicillin G equivalents (S. lutea)

* The average ratio of the antibiotic activity of penicillin G to penicillin V and potassium phenethicillin by the *S. lutea* cup-plate method was found to be 1:2.41:7.33 respectively when the standard penicillin reference materials were compared by simultaneous assay on seven occasions. Penicillin V and phenethicillin serum concentrations multiplied by the reciprocals, 0.415 and 0.136 respectively, thus expresses these values as penicillin G activity equivalents with specific reference to the activity of the different penicillins against *S. lutea.* Since the various penicillins exhibit differing degrees of antibiotic activity against other test organisms, e.g. the activity ratio of penicillin G, V and phenethicillin when determined against staphylococcus 209P is 1:0.72:1.64, it is apparent that data expressed as penicillin G equivalents are meaningful only for the particular organism under test.

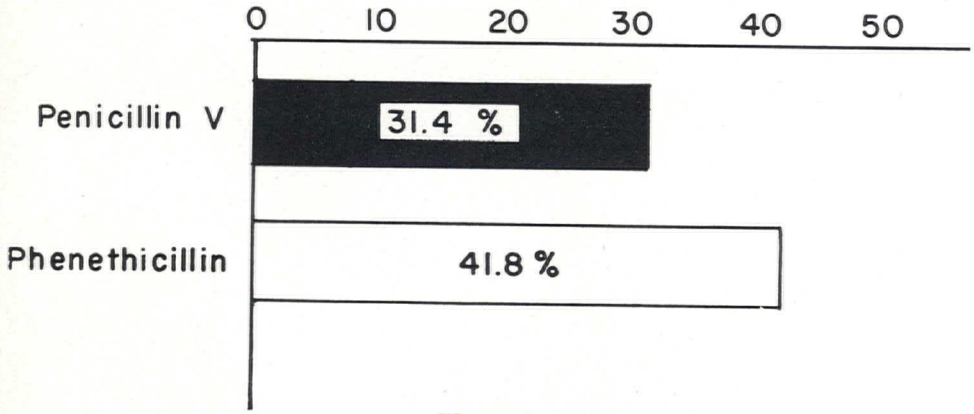

Figure 1

The average percentage of the administered dose of penicillin V and phenethicillin excreted in the urine in 24 hours after ingestion of a single 1,250 mg. dose of each agent.

two agents is presented in Figure 1. It can be seen that approximately 10 per cent more phenethicillin was recovered during the test period.

These studies then of serum concentration and urinary excretion of the two penicillins confirm earlier reports[5-7] that phenethicillin was more efficiently absorbed from the gastrointestinal tract than penicillin V. However, such studies represent only quantitative determinations of penicillin present in the serum and urine and do not take into account possible differences in biologic activity of the two agents. That such differences do exist and may be important is illustrated by the following data.

It is evident from data presented in Table I that when the serum content of the two penicillins was expressed as equivalents in biologic activity using penicillin G as a reference standard and *S. lutea* as the test organism, sera containing phenethicillin were significantly less active than the penicillin V sera at all but the four hour interval.

Table II depicts comparative *in vitro* susceptibility of the various pathogenic test organisms to the two penicillins. Data presented for the Viridans streptococci represent the average inhibitory concentrations observed for fifteen strains of this organism. Data concerning the enterococcus and staphylococcus represent single strain tests.

Table II

In Vitro Susceptibility of Various Pathogens* to Potassium Penicillin V and Potassium Phenethicillin.

Organism	Penicillin V (mcg./ml.)	Phenethicillin (mcg./ml.)
Viridans streptococci**	0.027	0.043
Enterococcus	3.68	6.25
Staphylococcus aureus (ID 117A)	0.014	0.073

* Average of 4 determinations for each strain

** Average of 15 strains

Table III

Averge Serum Antistreptococcal Activity.

Time in Hours	Potassium Phenethicillin Mean Titer		Standard Deviation	Potassium Penicillin V Mean Titer		Standard Deviation	P Value
1/4	80.2	±	94.69	177.6	±	140.66	0.1
1/2	304.0	±	217.51	471.0	±	322.84	>0.5
1	281.6	±	259.5	281.6	±	125.42	>0.5
2	92.8	±	67.01	147.2	±	134.40	0.3
4	17.4	±	10.74	19.4	±	16.64	0.4

It can be seen that, on a weight basis, more than one and one-half times as much phenethicillin was required to inhibit the Viridans streptococci and the enterococcus while approximately a five fold greater concentration of this agent was required to inhibit the staphylococcal strain. These data indicate that, within these experimental limits, microgram for microgram penicillin V is biologically more active than phenethicillin.

Table III compares the average titers of serum antistreptococcal activity observed in the sera of the ten subjects following ingestion of the two penicillins employed in the crossover study. It is to be recalled that these are the same sera which were previously assayed for absolute penicillin content. It can be seen that with the exception of the one and four hour intervals when values were essentially the same, potassium penicillin V induced slightly greater (not statistically significant) antistreptococcal activity in the serum than did potassium phenethicillin despite the previously observed higher serum concentrations of the latter agent.

Table IV illustrates the average antistaphylococcal activity of the same sera. It is apparent that during the first one-half hour penicillin V exhibited approximately a four fold greater antistaphylococcal activity than did phenethicillin (P=.01 and .02 at ¼ and ½ hour respectively). No significant differences in activity were noted at 1, 2 or 4 hours (P=0.3, >0.5, >0.5 respectively) although the mean titer at 1 hour was considerably higher after penicillin V administration. Recalling the *in vitro* susceptibility study in which it was observed that approximately five times as much phenethicillin as penicillin V was required to inhibit the test strain of staphylococcus, these results are not surprising.

Table IV

Average Serum Antistaphylococcal Activity.

Time in Hours	Potassium Phenethicillin Mean Titer		Standard Deviation	Potassium Penicillin V Mean Titer		Standard Deviation	P. Value
1/4	15.8	±	7.2	53.6	±	40.8	.01
1/2	59.2	±	39.87	227.2	±	189.02	.02
1	97.6	±	84.19	204.8	±	278.68	0.3
2	67.0	±	71.44	52.8	±	39.22	>0.5
4	4.6	±	2.90	13.4	±	55.91	>0.5

ANTIMICROBIAL ACTIVITY

Neither penicillin V or phenethicillin administered orally in a single 1,250 mg. dose induced serum antienterococcal activity that was detectable by the methods used in this study (lowest detectable titer 1:2).

SUMMARY

1. Phenethicillin has been shown to be more efficiently absorbed from the gastrointestinal tract than penicillin V as evidenced by higher serum concentrations and greater total urinary excretion observed in crossover experiments.

2. *In vitro* susceptibility studies have shown that on a weight basis, penicillin V was one and one-half to five times as active as phenethicillin against a number of microorganisms isolated from patients with endocarditis.

3. Comparison of biologic activity of sera after oral administration of the two penicillins has indicated that the advantage of increased absorption of phenethicillin is nullified by its lesser antimicrobial activity, and, by inference, would imply no advantage of phenethicillin as a therapeutic agent for bacterial endocarditis.

4. Finally, these data illustrate that measuring antibacterial activity in the serum utilizing a pathogen as an indicator organism is more informative concerning antibacterial effectiveness than quantitative determinations of the amount of an antibacterial agent present in the serum.

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