Urinary tract infection and oral penicillin G

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SYNOPSIS The urinary excretion of three oral preparations of penicillin G was measured in six subjects. After a dose of 500 mg of potassium penicillin G the mean urine level was 597 $\mu\text{g/ml}$ in the first of three two-hour periods, 324 $\mu\text{g/ml}$ in the second, and 40 $\mu\text{g/ml}$ between the fourth and sixth hours. Of the dose, 13.4% was excreted in the urine in 24 hours. Differences among the three preparations were not significant therapeutically.

Most Gram-negative urinary pathogens are sensitive to 5-50 μg of penicillin G per ml.

There is a rational basis for the use of oral penicillin G to treat urinary infection due to Gram-negative bacilli.

About 15% of an oral dose of penicillin G is absorbed, and about 80% of this is excreted in the urine. Individual variability in the amount absorbed is considerable, but this can be greatly reduced by taking the drug half an hour before meals. Acid protective agents do not improve absorption (Finland, Meads, and Ory, 1945; McDermott, Bunn, Benoit, DuBois, and Reynolds, 1946; Wright, Kirschbaum, Arret, Putnam, and Welch, 1955).

In a careful search of the literature only one paper could be found in which measured concentrations of penicillin in urine after oral therapy were recorded. Peeney (1947) administered 90,000 Oxford units of penicillin to a subject and found 42 units/ml in the urine after one hour and 22 units/ml after three hours. No information about urine volume or bladder voiding was noted. However, if 10% of an oral dose of 500 mg of penicillin is excreted in the urine in six hours, then a patient passing 1,200 ml of urine per day would have a mean concentration of 160 μg of penicillin per ml of urine.

Most strains of *Escherichia coli* are sensitive to 12.5-50 μg of penicillin G per ml (Rolinson and Stevens, 1961; Sutherland, 1964; Garrod and O'Grady, 1968), and most strains of *Proteus mirabilis* are sensitive to 5-10 $\mu\text{g/ml}$ (Barber and Waterworth, 1964).

The position of nitrofurantoin, nalidixic acid, and cycloserine (none of which achieves bacteriostatic levels in the serum) as established urinary antibiotics (Carroll, 1963; Stamey, Govan, and Palmer, 1965; Murdoch, Speirs, Geddes, Wright, and

Wallace, 1968) suggests that oral penicillin G, which is cheap and not toxic, may be a useful urinary antibiotic if it is confirmed that adequate urine levels are attained.

Materials and Methods

SUBJECTS AND PENICILLINS

Six healthy subjects (aged 17-28 years) took part in the experiment. Each drug was taken about 30 min before breakfast after the bladder had been emptied. There were no restrictions on fluid intake. At least one day elapsed before the experiment was repeated by each subject with another drug.

Potassium penicillin G (Crystapen G)

Two 250 mg sugar-coated tablets were taken.

Sustained action penicillin G (Hyasorb)

This enteric-coated formulation of penicillin G is presented in 150 mg tablets. The dose was 3 tablets.

Penamicillin (Havapen)

This acetoxymethyl ester of penicillin G is hydrolysed to penicillin G in the body. The dose was 2 tablets of 350 mg, each tablet containing an equivalent of 305 mg of penicillin.

The manufacturers of Hyasorb (Berk) and Havapen (Wyeth) claim improved absorption resulting in prolonged effective serum levels for their products compared with those achieved with potassium penicillin. The approximate cost of one dose of each drug is: Crystapen G, 2p. Hyasorb, 6½p, Havapen, 4p.

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BLOOD AND URINE LEVELS OF PENICILLIN

Two and six hours after the drug was given venous blood was withdrawn, separated, and the serum filtered (Millipore filters, with 0.45 μ m pores). The bladder was emptied at two, four, six, eight, 12, and 24 hours and the whole of the specimen was collected. The volume of each specimen was recorded and an aliquot filtered. The tests were carried out by a doubling dilution technique (Cruickshank, 1965), the indicator organism being the Oxford (Heatley) strain of *Staphylococcus aureus*. The range of penicillin concentrations detectable in the serum was 0.02-10.24 μ g/ml and in the urine, which was diluted 100-fold initially, it was 2-2,048 μ g/ml.

Results

Table I records the results of the experiment.

Drug and Dose	Subject	Level of Penicillin in Urine (μ g/ml) Collected at Time (hr) after Drug Given by Mouth						Volume (ml) of Urine Excreted between 0 and 6 Hours	Level of Penicillin in Blood Serum (μ g/ml) at Time (hr) after Drug Given by Mouth	
		2	4	6	8	12	24		2	6
Potassium penicillin G 500 mg	JH	512	512	64	16	0	0	400	1.28	<0.02
	BH	512	256	32	16	8	0	190	0.16	0.02
	AB	512	128	64	32	8	0	215	0.64	0.04
	DG	1,024	256	32	8	2	0	255	0.32	0.02
	JE	512	64	32	8	2	0	410	0.64	0.04
	SH	512	128	16	4	0	0	180	0.32	0.04
Penicillin G 700 mg equivalent to 610 mg penicillin G	JH	128	512	64	16	2	0	560	0.64	0.08
	BH	1,024	256	32	16	8	2	165	0.64	0.04
	AB	1,024	512	64	32	8	4	165	0.64	0.04
	DG	256	128	16	16	8	0	460	0.64	0.04
	JE	256	128	64	32	8	4	440	0.64	0.08
	SH	512	512	128	32	8	2	335	0.64	0.04
Penicillin G sustained action tablets 450 mg	JH	256	128	32	8	2	0	495	1.28	0.08
	BH	512	128	64	8	2	0	200	(contaminated)	
	AB	512	256	64	32	0	0	190	0.16	<0.02
	DG	64	128	32	8	2	0	385	0.32	0.04
	JE	64	32	8	2	0	0	580	0.16	<0.02
	SH	512	128	64	8	0	0	230	0.16	0.02

Table I Levels of penicillin in urine and blood at different times after oral administration of a single dose of one of three preparations of penicillin G

Drug	Adjusted Mean Level of Penicillin in Urine (μ g/ml) at Time (hr) after Drug Given						Adjusted Mean Level of Penicillin in Blood Serum (μ g/ml) at Time (hr) after Drug Given	
	2	4	6	8	12	24	2	6
Potassium penicillin G	597	324	40	14	4	0	0.56	0.03
Penicillin	437	280	52	21	8	2	0.52	0.04
Sustained action penicillin G	350	150	49	13	1	0	0.47	0.03

Table II Mean penicillin levels calculated from the results in Table I and adjusted to a 500 mg dose of penicillin given by mouth

cillin G, 14.1% of penamcillin, and 11.1% of the sustained action penicillin.

Discussion

The concentration of penicillin attainable in the urine following the oral administration of penicillin is clearly in excess of the mean inhibitory concentration of most urinary pathogens. After a dose of 500 mg of penicillin by mouth it is probable that the concentration of penicillin in the ureteric urine exceeds 50 µg/ml for at least four hours with peak concentrations of over 1,000 µg/ml, and if bladder voiding and administration of the antibiotic were synchronized a concentration of penicillin in excess of 150 µg/ml in the bladder could be maintained for six hours or more. The differences between the three preparations of penicillin tested were not significant therapeutically, but Crystapen G was the most cost-effective.

The relative importance of serum and urine levels of antibiotic in the treatment of pyelonephritis is the subject of debate (Stamey *et al.*, 1965; Cockett, Roberts, and Moore, 1966). In an effort to resolve this Stamey has presented data on 15 patients who were investigated in detail and were treated with oral penicillin or nitrofurantoin. Seven patients had radiological abnormalities, and all had over 10⁵ bacteria per ml of urine that had been collected either by suprapubic bladder puncture (seven cases) or from the ureter at cystoscopy (eight cases). Four patients were given penicillin G 250 mg six hourly, eight had penicillin V 250 mg six hourly, and three were treated with nitrofurantoin 100 mg six hourly. While none could have had serum levels in excess of the mean inhibitory concentration of the infecting organism, all but two were cured. Of these two, one who was treated with nitrofurantoin had a renal

stone, and the other (treated with penicillin G) was later shown to have a large residual volume and recurrent infections associated with sexual intercourse.

The results of these experiments establish the urinary concentrations of penicillin which can be achieved with oral therapy, and form a base upon which the use of penicillin for urinary infection may be founded.

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