Plasma Penicillin Levels from Oral Penicillins V and G and Intramuscular Penicillin G.* (22137)

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Penicillin V (phenoxymethyl penicillin), because of its stability at low pH ranges, its low solubility in an acid medium and rapid conversion to the water soluble salt at neutral or alkaline pH. has been suggested as possibly superior to penicillin G for oral administration(1-3). The available information concerning penicillin V was reviewed recently by Jones and Finland(4) who, in a controlled study. compared the penicillin activity in the plasma of normal subjects following ingestion of single tablets of 200,000 units of penicillins G and V. They found that penicillin V produced higher and more prolonged blood levels than did penicillin G as judged by the antistreptococcal and antistaphylococcal activity of the plasma. particularly when the doses were taken after a meal. They also showed that the numerical value assigned to the concentration of penicillin in plasma depends on the strain used in the assay and on the type of penicillin (*i.e.*, V or G) in the standard solution employed as the control from which the concentrations are computed. Wright *et al.*(5) also showed that differences found by microbiological assay methods depend mainly on the assay organism but also on the medium used for the dilutions. They too found considerably higher blood concentrations from penicillin V than from the same 200,000 unit dose of penicillin G given orally. and, in addition. they showed that twice as much of penicillin V is excreted as the active form in the urine.

The present paper presents further comparisons of levels of penicillin in plasma resulting from the same amounts of penicillins V and G given orally at various dosage levels, and these, in turn, are compared with levels obtained from intramuscular injection of the same amount of penicillin G.

Materials and methods. The subjects were 8 normal young men and 24 ward patients, 3 of whom were women; their ages ranged from 15 to 86 (avg 50 yr) and their weights ranged from 40 to 95 kg (avg 66 kg). None had recently received any antimicrobial agents. All had grossly normal renal function as judged by routine clinical laboratory tests except one who had renal insufficiency with nonprotein nitrogen levels ranging as high as 145 mg%. All were able to and did ingest normal quantities of food and liquids, but the intakes were not controlled. Three dosage forms of penicillin were used, *viz.* (1) the free acid of penicillin V in 200000 unit tablets, (2) buffered potassium penicillin G ("Pentids," Squibb) in 200000 unit tablets, and (3) aqueous potassium penicillin G intramuscularly. These were given at 3 dosage levels, *viz.* 200000 units, 400000 units and 1000000 units; individual doses were separated by at least 48 hours. Every dose was given ½ hr after breakfast. All subjects received both penicillin V and G orally at least at one and the same dosage level and many also received an i.m. injection of the same number of units of penicillin G. Three of the young men received all 3 dosage forms at all 3 levels, and 5 subjects, including these 3, received all 3 dosage forms at each of the 3 levels. Assays for penicillin in plasma were done by the 2-fold dilution method in broth as in the previous study(4) except that only *Strep. 98* was used as the assay organism and the numerical values assigned were based only on comparisons with a standard of penicillin G. As in the previous study(4), graphic comparisons will be based only on the maxi-

* Aided by grant from the National Institutes of Health. Authors are indebted to Dr. Edward F. Roberts of Wyeth Laboratories for the supply of penicillin V tablets and to E. R. Squibb & Sons for tablets of buffered penicillin G (Pentids).

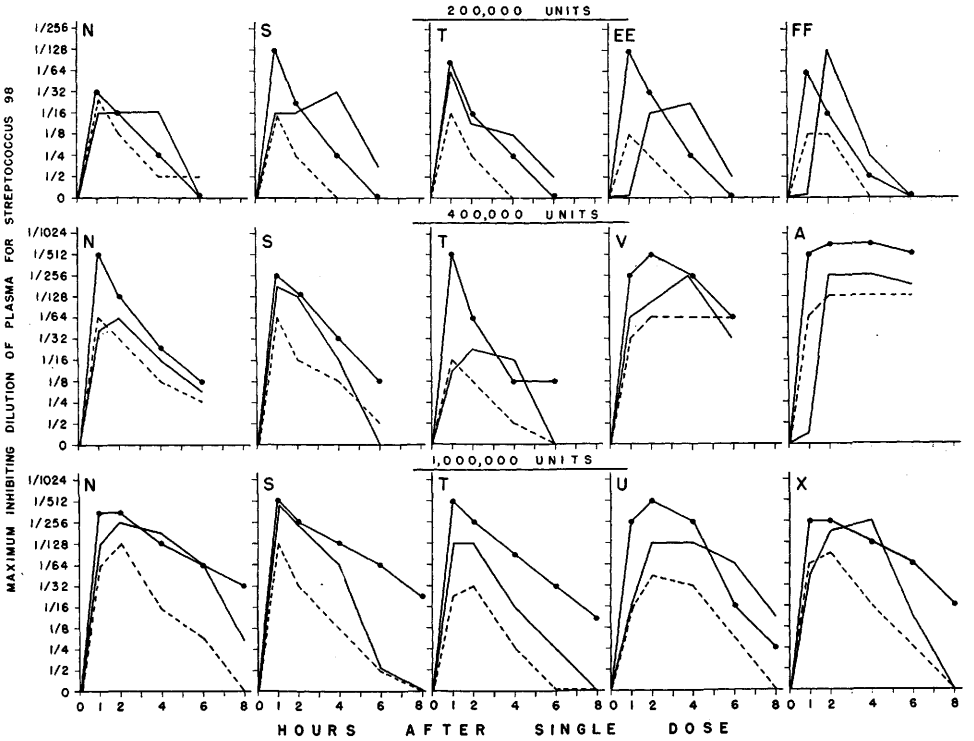

FIG. 1. Plasma penicillin levels in same subjects after same dose of penicillin given as: Penicillin V orally (——), buffered penicillin G orally (– – –), and penicillin G intramuscularly (•——•).

mum dilutions of plasma which inhibit *Strep. 98;* in these studies the standard solution of 1 μg/ml of penicillin G inhibited the test strain at a dilution of 1:128, and 1 μg of the solution of penicillin V inhibited at 1:64. Blood for the assays was obtained before each dose and 1, 2, 4 and 6 hours after the dose in every instance, and also 8 hours after the 1 million unit dose. All specimens of plasma taken immediately prior to a dose showed no detectable penicillin activity.

Results. Comparative Levels in the Same Subject. The levels of antistreptococcal activity obtained in the plasmas of 5 subjects who received all 3 dosage forms at the same dosage level are shown graphically in Fig. 1. The letters in each panel identify the subjects. It is seen from this figure the relative levels of penicillin activity in plasma obtained from the 3 dosage forms varied with the dose. In general, i. m. penicillin G produced higher peak levels more rapidly than the other forms. With the dose of 200000 units these were not as well sustained as from oral penicillin V, whereas with the higher doses they were bet-

TABLE I. Average Concentrations of Penicillin in the Same 5 Subjects after the Same Dose of Penicillin Given in 3 Forms.

Dose units* (×1000)	Hr after dose	Dosage form: Penicillin G, orally	Penicillin V, orally	Penicillin G, intramusc.
		Avg level† in plasma, μg/ml		
200	1	.22	.21	1.63
	2	.12	.35	.39
	4	.018	.19	.06
	6	.005	.046	0
400	1	.99	.47	7.5
	2	.93	1.8	3.97
	4	.40	1.05	1.40
	6	.20	.22	.70
1000	1	1.01	1.16	7.0
	2	1.4	2.69	6.07
	4	.39	1.40	2.53
	6	.11	.29	.82
	8	.05	.08	.26

* 200000 units = approximately 120 mg penicillin, either as G or V.

† Determined by broth-dilution method using Streptococcus 98, and comparing with a penicillin G standard solution.

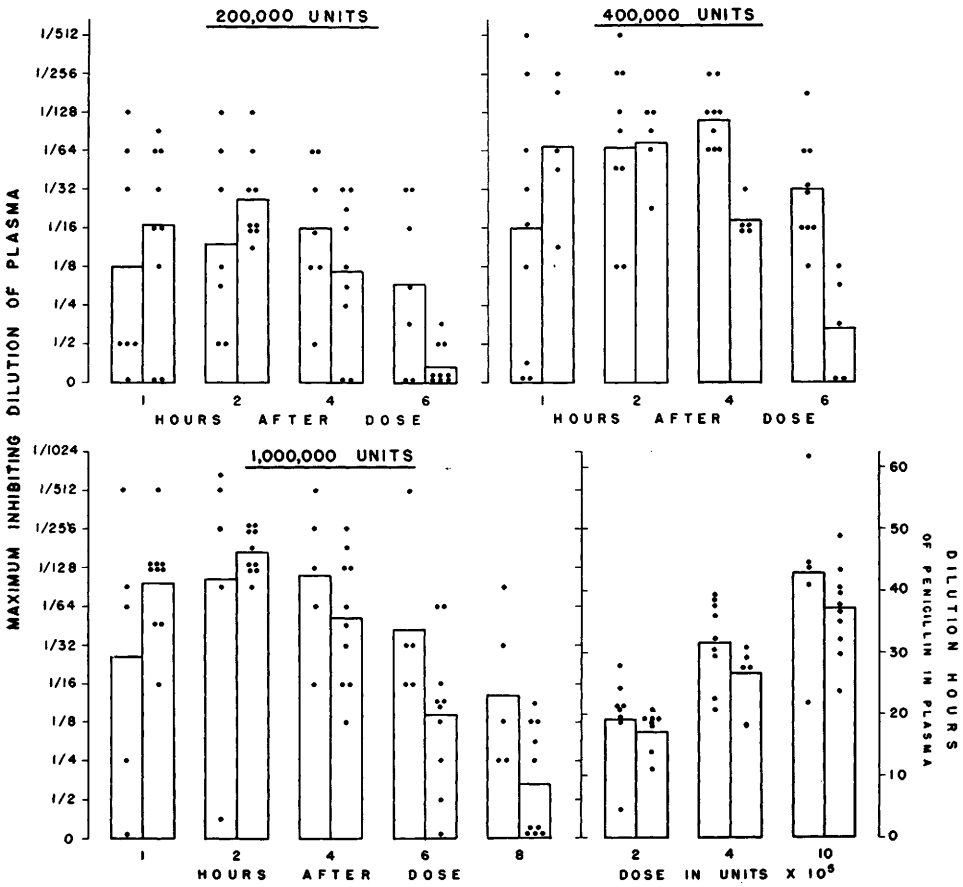

FIG. 2. Effect of age on levels of penicillin in plasma after oral penicillin V. Subjects 60 yr old and over (left) compared with those under 60 (right).

ter sustained and at higher levels. Calculations of the areas ("dilution-hours") under the curves following the 200000 unit doses showed no significant difference between oral penicillin V and i.m. penicillin G ($P = >0.1$), but the differences between both of these and the values for oral penicillin G were significant ($P = <0.02$ in each instance). After the 400000 unit doses, the levels were more or less uniformly higher with i. m. penicillin G than after oral penicillin V, and these in turn were higher than those following oral penicillin G. Calculations of the areas under these curves, however, yield values that are not statistically significant; this is due, in large part, to the fact that plasma-penicillin levels were not obtained after 6 hours and these are not readily extrapolated. On the other hand, 1 million units of i. m. penicillin G gave the highest levels of penicillin activity throughout, and oral penicillin V yielded higher levels than oral penicillin G. In this instance, the differences between the areas under the curves are statistically significant in every instance.

The average plasma penicillin levels, calculated as penicillin G, are shown in Table I; they show the same differences that are reflected in Fig. 1.

Effect of Age. Since a number of the subjects were in the older age group, an attempt was made to determine the effect of this factor on the levels of penicillin in the blood. This was done only for oral penicillin V. The data are charted in Fig. 2. For all 3 dosage levels, the penicillin activity in the plasma of the subjects over 60 years old rose more slowly, achieved a peak later, and thereafter

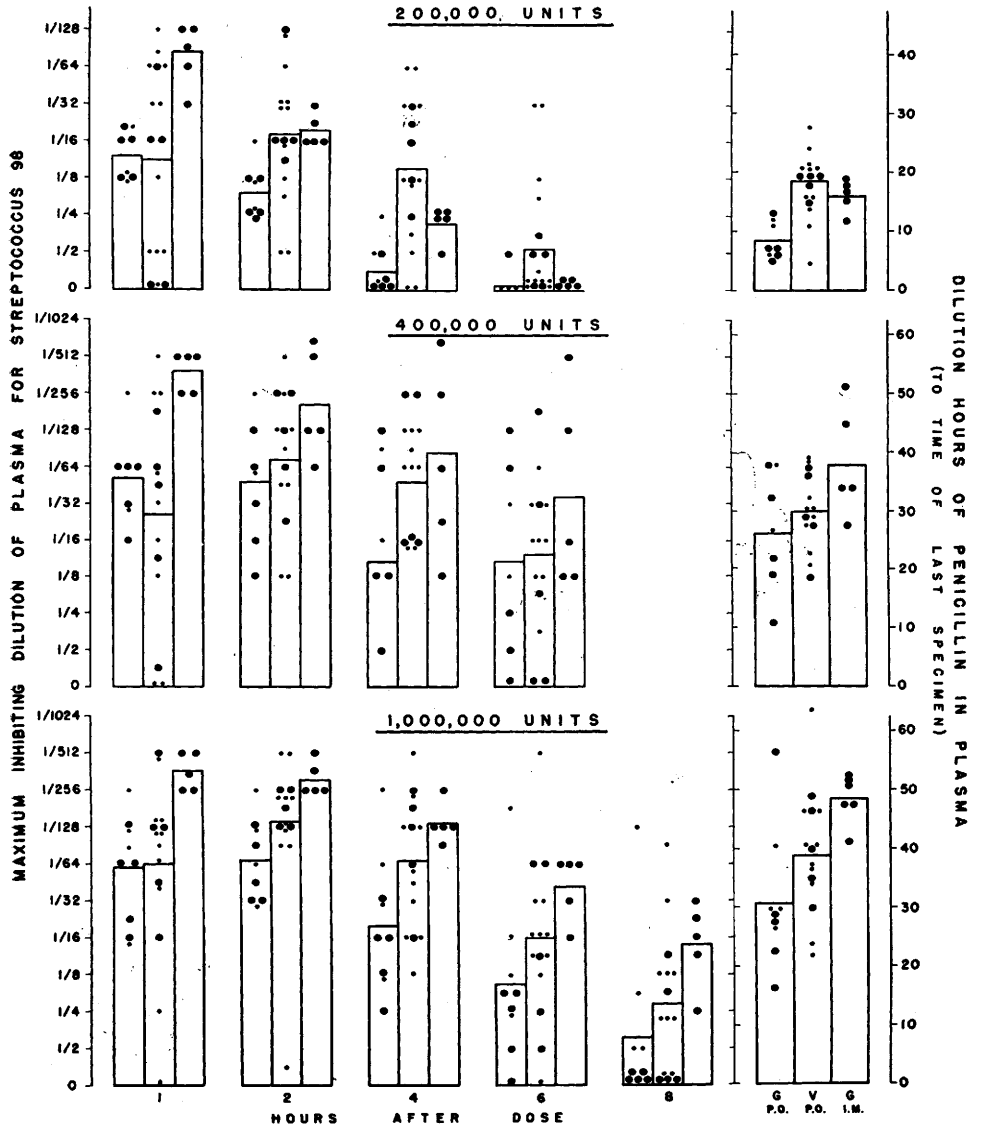

FIG. 3. Penicillin levels in plasma following administration of penicillin V orally (center) compared with penicillin G, orally (left) and intramuscularly (right). The large dots represent subjects who received all 3 dosage forms at the stated intervals.

were sustained better than in the younger ones. This may be a reflection of differences in renal function. This figure also shows the areas (dilution-hours) under the curves of the plasma penicillin levels; these values and their means were higher in the older subjects at each of the 3 dosage levels.

Further Comparisons of the 3 Dosage Forms. The levels of penicillin in plasma obtained in all the subjects studied and the mean values for each dosage form at each dose level are charted in Fig. 3. In this figure the large dots represent the values in the subjects for whom data are available for all 3 forms at the stated dose levels. At the right are also shown the areas or "dilution-hours" under the curves of the plasma penicillin levels and the means of these values. Here again it is seen that penicillin V is superior to penicillin G at each dose level. The dose of

200000 units of i. m. penicillin G gave higher and earlier peak levels but these were less sustained than from oral penicillin V; the average number of dilution-hours, however, was quite similar for these 2 forms at this level, and these were both greater than from oral penicillin G. After doses of 400000 units and 1000000 units, on the other hand, i. m. penicillin G gave the highest and best sustained levels and oral penicillin V gave higher and better sustained levels than oral penicillin G; these differences are reflected in the number of dilution hours of penicillin in the plasma.

Summary. Oral penicillin V gave higher and better sustained levels of penicillin activity in the plasma than oral buffered potassium penicillin G at each of 3 dosage levels, *viz.* 200000, 400000 and 1 million units. Intramuscular penicillin G yielded higher and better sustained levels than oral penicillin V in equivalent doses given at levels of 400000 or 1 million units. An i. m. dose of 200000 units of penicillin G produced higher peak levels and these occurred earlier but they were less well sustained than with this amount of oral penicillin V; the total amount of penicillin absorbed from this amount of penicillin was not significantly different for these 2 dosage forms. Persons over 60 years of age attained peak levels later; in general they had higher and better sustained levels of penicillin in the plasma from any given dose than did younger individuals.

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Received October 31, 1955. P.S.E.B.M., 1955, v90.

Effect of Dietary Protein and Energy on Chick Liver Fat Accumulation.*† (22138)

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Best and Huntsman(1) discovered that a dietary deficiency of choline resulted in an excessive accumulation of fat in rat livers. Later work, Harper *et al.*(2) indicated that such compounds as glycine, serine, methionine and betaine, which may function as choline precursors, are able to reduce the level of liver fat in rats on choline-free diets. Channon and Wilkinson(3) and Best and Huntsman(4) suggested that the deposition of liver fat might

TABLE I. Basal Diet for Preliminary Period.

Ingredient	%
Glucose	54.4
Soy protein*	31.6
Soybean oil	4.0
Cellulose	3.0
Methionine	.5
Mineral mix†	5.5
Vit.-antibiotic mix‡	1.0
Total	100.0

* Drackett Assay Protein C-1.

† Provides per lb diet: NaCl 0.5%, Ca 1.6%, P 0.88%, K 1.3 g, Zn 1.08 mg, Mn 33.3 mg, Fe 30.6 mg, Co 0.6 mg, Cu 1.2 mg, Mg 300 mg, and I 5.0 mg.

‡ Provides per lb diet: Vit. A 4000 I.U., Vit. D_3 500 I.C.U., alpha-tocopherol 7.0 mg, menadione 0.6 mg, choline Cl 868 mg, inositol 455 mg, niacin 45 mg, calcium pantothenate 10 mg, riboflavin 3.6 mg, pyridoxine-HCl 2.7 mg, thianine-HCl 1.8 mg, folic acid 1.4 mg, p-amino benzoic acid 0.9 mg, biotin 90 μg, vit. B_{12} 6 μg, penicillin 4 mg.

* Part of thesis by senior author in partial fulfillment of requirements for degree Doctor of Philosophy, Iowa State College.

† Journal Paper No. J-2839 of the Iowa Agri. Exp. Station, Ames. Project No. 1062.

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