THE SERUM CONCENTRATION OF PENICILLIN G IN MICE, RABBITS, AND MEN AFTER ITS INTRAMUSCULAR INJECTION IN AQUEOUS SOLUTION

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The serum levels of penicillin G in man after its intramuscular injection in aqueous solution or peanut-oil-beeswax suspension have been described in a preceding paper (Tucker and Eagle, 1948). Similar data are here reported with respect to the plasma levels afforded by the intramuscular injection of aqueous penicillin G in mice and rabbits.

METHODS AND MATERIALS

The solutions were injected intramuscularly into the thigh, in a volume of 1 ml per kg in rabbits, and in 0.2-ml volume in mice. In the latter species the injection was partially subcutaneous, because of leakage from the muscle into the surrounding tissues. The courtesy of the manufacturers in supplying the penicillin G used in these studies (Squibb lot numbers V-31, CRA214-20, and 17579, and Commercial Solvents lot number 46042605) is gratefully acknowledged.

The method of assay was a serial dilution technique in which inhibition of hemolysis by the C-203 strain of *Streptococcus pyogenes* was the end point (Rammelkamp, 1942; Kirby and Rantz, 1944). The details of the method have been given elsewhere (Eagle and Newman, 1947). In the assays of human and rabbit serum, the data have been corrected for the inhibitory effect of serum in the assay (Eagle, 1947a,b; Tompsett, Schultz, and McDermott, 1947a,b), using the corrective factors as experimentally determined for human serum (Eagle and Tucker, 1948) and since found to be valid also for rabbit serum. No corrective factors have been applied to the mouse data. The values in which, because of the high concentration of serum in the indicator tube, that correction would probably have been significant are indicated in the tables.

It is a pleasure to acknowledge our indebtedness to Mr. Nathan Mantel, of the Office of Statistical Coordinator, Division of Public Health Methods, for his assistance in the calculation of the probable errors of the median serum levels.

EXPERIMENTAL RESULTS

Figure 1 and the first section of table 1, showing the results obtained in man, are here reproduced in modified form[1] from a previous paper (Tucker and Eagle,

[1] In the previous communication (Tucker and Eagle, 1948) the standard deviation given in the tables was a measure of the variability of the data *about* the median, as calculated by the formula $\left(\sigma = \sqrt{\dfrac{\Sigma d^2 \text{ med}}{n}} \right)$ and the standard error given was calculated by the for-

119

1948) in order to facilitate comparison between the results obtained in the 3 species. Figure 2 and the second section of table 1 show the median serum levels in rabbits after the injection of penicillin G at 60, 10, 3, 1, and 0.6 mg per kg. Figure 3 and the last section of table 1 give the median serum concentrations obtained in mice similarly injected.

In general, the initial blood levels, 15 or 30 minutes after the injection, varied more or less linearly with the amount of penicillin injected. In figure 4, the
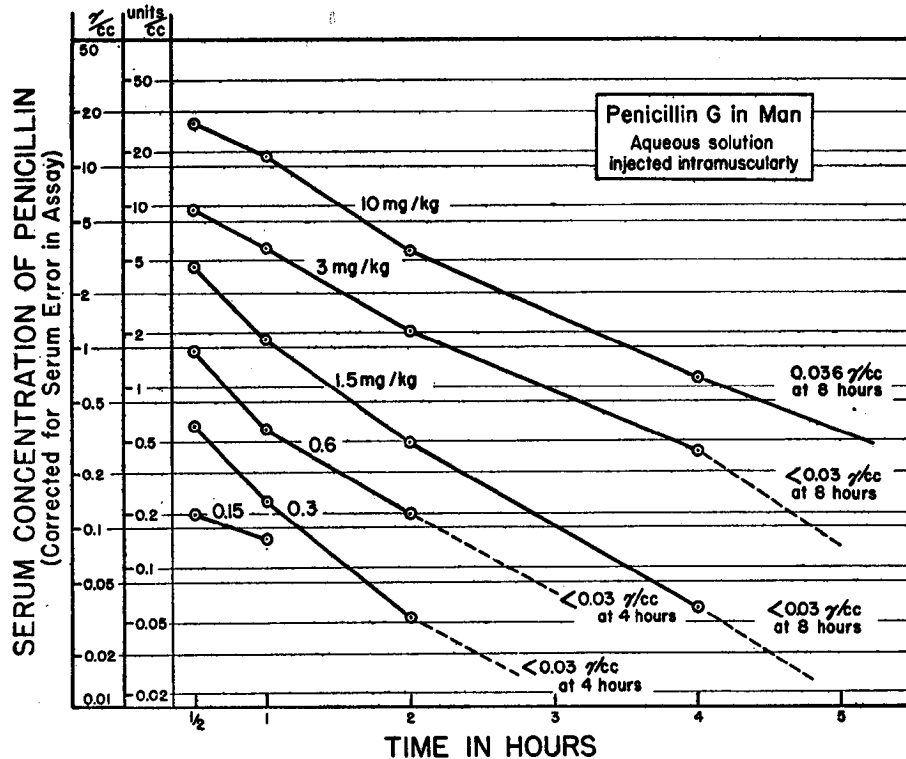

Figure 1. The serum concentrations of penicillin G in man after its intramuscular injection in aqueous solution at varying dosage. (After Tucker and Eagle, 1948; cf. footnote 1.)

15-minute concentrations in man are approximations only, obtained by the extrapolation of the curves of figure 1. These initial values were of the same order of magnitude in rabbits and mice, but in man were 3 to 5 times higher. This is indicative of a significant species difference, either in the amount of body

mula S.E. $= \frac{\sigma}{\sqrt{2n}}$, and is a measure of the reliability of the variability measure σ. Of greater significance as a measure of the reliability of the median itself is its standard error, given by the formula S.E. med. $= 1.25 \sqrt{\frac{\Sigma d^2 \text{ mean}}{n(n-1)}}$. It is the latter value that is indicated in all the figures and tables of this paper, including the human data of figure 1 and table 1.

TABLE 1

The serum concentrations of penicillin G in man, mouse, and rabbit after its intramuscular injection in aqueous solution

SPECIES	DOSAGE mg/kg	DOSAGE units/kg	NO. OF DETERMINATIONS IN EACH GROUP	MEDIAN SERUM CONCENTRATION (micrograms per ml) ± STANDARD ERROR							
				¼ hr	½ hr	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr
Man	10	16,667	10		17 ± 1.3	11 ± 1.4	3.4 ± 0.77		0.67 ± 0.18		0.036 ± 0.018
	3	5,000	10		5.8 ± 0.88	3.5 ± 0.55	1.22 ± 0.43		0.26 ± 0.089		∨
	1.5	1,667	10		2.8 ± 0.72	1.1 ± 0.25	0.3 ± 0.05		0.036 ± 0.015		∨
	0.6	1,000	10		0.95 ± 0.13	0.35 ± 0.005	0.12 ± 0.017		< *		∨
	0.3	500	10		0.37 ± 0.023	0.14 ± 0.029	0.032 ±		∨		∨
	0.15	250	10		0.12 ± 0.029	0.088 ± 0.012	∨		∨		∨
Rabbit	60	100,000	4–6	42 ± 12.8	38 ± 7.8	20 ± 3.7	5.9 ± 3.1		0.58 ± 1.9		0.033 ± 0.29
	10	16,667	4–7	7.1 ± 0.53	6.1 ± 1.5	4.4 ± 0.88	0.78 ± 0.47		0.087 ± 0.3		∨
	3	5,000	4–7	2.8 ± 0.54	1.63 ± 0.17	1.0 ± 0.27	0.1 ± 0.11		0.031 ± 0.039	∨	
	1	1,667	4–6	0.95 ± 0.31	0.34 ± 0.12	0.22 ± 0.08	0.09 ± 0.05		0.022 ± 0.009	∨	
	0.6	1,000	8–10	0.81 ± 0.33	0.29 ± 0.04	0.14 ± 0.045	0.056 ± 0.014		∨	∨	
Mouse†	200	333,000	5–10	200 ± 20	150 ± 37	39 ± 19	2.5 ± 1.7	0.3 ± 0.17	0.13 ± 0.074		∨
	60	100,000	5–9	44 ± 4.4	23 ± 7.3	3.3 ± 0.95	0.25 ± 0.06	0.04 ± 0.016‡	∨		
	10	16,667	5–8	10 ± 2	2.8 ± 0.92	0.28 ± 0.08	0.025 ± 0.011‡	∨			
	3	5,000	5–	1.5 ± 0.3	0.5 ± 0.052	0.083 ± 0.026‡		∨			
	1	1,667	5–7	0.65 ± 0.082	0.16 ± 0.068	0.05 ± 0.0125‡		∨			
	0.6	1,000	7	0.45 ± 0.12	0.11 ± 0.014	0.011 ± 0.003‡		∨			

* No demonstrable penicillin by the particular method of assay used; sensitive to a (corrected) concentration of 0.03 micrograms per ml.

† The penicillin levels in mice have not been corrected for the inhibitory effect of serum in the assay (cf. Eagle and Tucker, 1948).

‡ The values in which corrections for inhibitory effects of serum would probably have been significant.

fluid over which the penicillin is initially distributed, or in the rate of that distribution.

After the initial period of rapid absorption, the blood levels fell off rapidly. In rabbits this rate of decrease averaged 65 per cent each hour, so that the residual serum concentration at time t was $k \times 0.35^t$, in which t is the time in hours over the period of experimental observation, and k is a constant determined by the amount of penicillin injected. In man, the rate of fall was less consistent, the percentage drop per hour over the first 2 hours varying from 65 at the larger
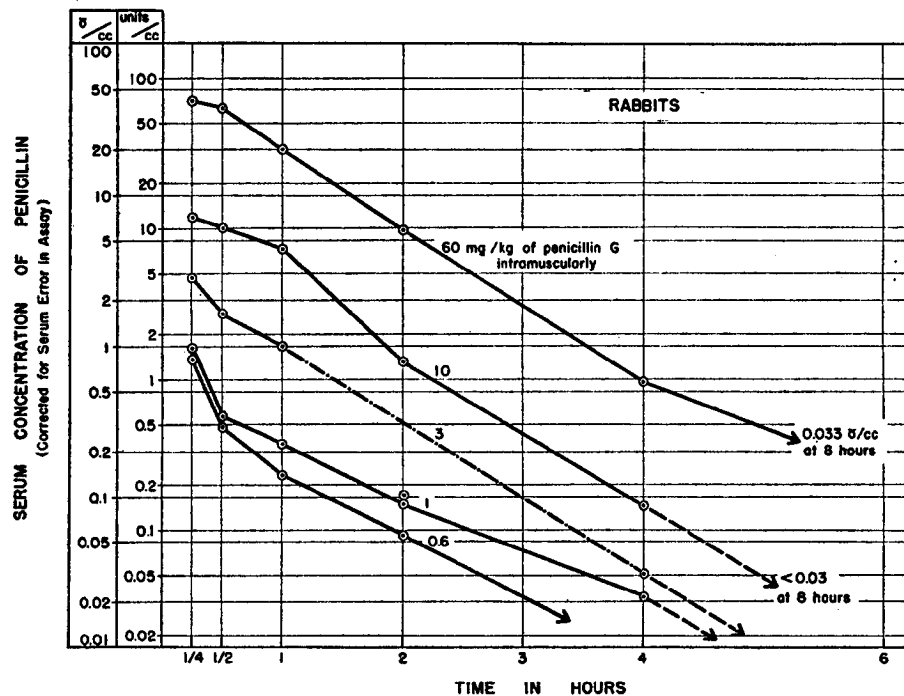

Figure 2. The serum concentrations of penicillin G in rabbits after its intramuscular injection in aqueous solution at varying dosage. The dashed portion of the curve at 3 mg per kg by-passes the low value at 2 hours.

doses to approximately 80 per cent at the smaller (figure 1). In mice, however, the blood levels during the first 2 hours fell off at the extraordinary rate of 91 to 99 per cent per hour (figure 3). At the largest dosage of 200 mg per kg, a slower rate of fall developed after several hours. This probably reflects a reversal in the direction of flow of penicillin out of the tissue reservoir established by its initial distribution and back into the blood.

The serum concentrations provided by a given dose of penicillin were usually 3 to 5 times higher in man than they were in rabbits similarly injected. Although the concentrations in rabbits and mice began at the same level, they rapidly diverged because of the faster disappearance of penicillin in mice. These species differences are illustrated for a single dosage of penicillin in figure 5.

In the therapeutic use of penicillin, one of the most important single factors is the length of time for which the tissue levels of penicillin remain at effectively bactericidal levels. When the three species were compared on this basis (figure 6), a given serum level was sustained approximately 50 per cent longer in man than it was in rabbits similarly injected. In large part this reflects the initially higher concentrations provided in man. In turn, the levels were sustained
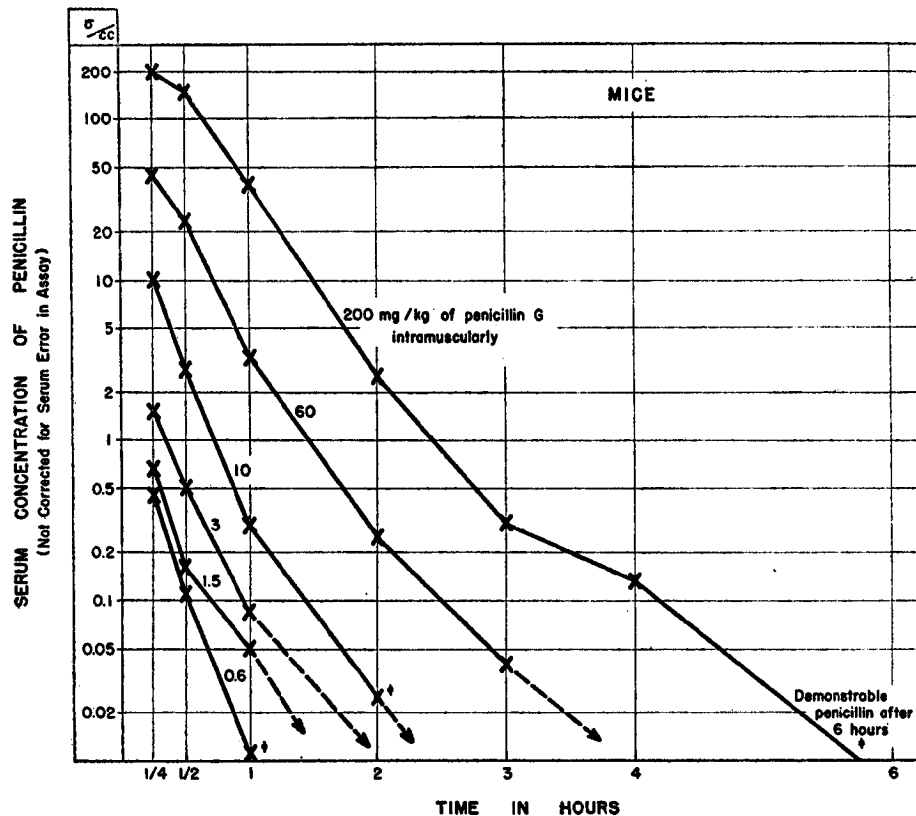

Figure 3. The serum concentrations of penicillin G in mice after its intramuscular injection in aqueous solution at varying dosage. Unlike the man and rabbit data of figures 1 and 2, the data in this figure have not been corrected for the inhibitory effect of serum in the assay. That would probably have been significant only for the two values indicated by the symbol ∓ in the figure.

approximately 3 times longer in rabbits than they were in mice because of the faster rate of fall in the latter species. Thus, as is indicated in figure 6, a dose of 0.6 mg per kg provided serum levels in excess of, e.g., 0.1 microgram per ml for 0.5, 1.4, and 2.3 hours in mice, rabbits, and men, respectively; and after a dose of 10 mg per kg the corresponding time periods were 1.4, 3.9, and 6.6 hours. In order to prolong by 1 hour the time for which this level of 0.1 microgram per ml would be maintained in the serum, the dosage of penicillin would have to be approximately doubled in man, and multiplied approximately 3-fold in rabbits,

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