DAILY PENICILLIN SERUM CONCENTRATIONS AFTER THE INJECTION OF 1·2 MEGA UNITS OF "ALL PURPOSE" PENICILLIN*

BY

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This paper reports the results of daily penicillin serum assays on ambulant adult males during the week following the injection of 1·2 mega units of "All-Purpose" penicillin, *i.e.* a complex containing 0·3 mega units potassium benzyl penicillin, 0·3 mega units procaine penicillin, and 0·6 mega units benzathine penicillin†. One of the two products used had been the subject of a personal communication which claimed that, in the treatment of a small group of patients for syphilis with 1·2 mega units weekly, the daily serum levels were found to be considerably below those to be expected. As "All-Purpose" penicillin is widely used in both prophylaxis and treatment against a variety of sensitive organisms and depends for success on the maintenance of satisfactory levels in the intervals between injection, it seemed important to investigate this observation.

168 assays were completed, 24 each day, twelve for each product. Table I and Fig. 1 show the MEAN daily serum levels for each product.

Fig. 1 shows satisfactory decay curves for each product when plotted from the observed daily means.

Table I shows that the daily means for both products were treponemicidal for 6 days and fell to 0·026 and 0·024 units penicillin per ml. serum on the

Fig. 1.—Mean daily serum concentrations (groups of 12).

seventh day. It is generally accepted that 0·03 units per ml. serum is the level of therapeutic effectiveness against the treponeme, but it has been shown that levels well below this are in fact treponemicidal and there is ample clinical and experimental evidence to support the conclusion that the means found in this trial remained treponemicidal for the whole week after the injection.

The observation of MEAN levels provides no more than a rough guide to the clinician as to the expected daily serum concentrations of a majority of his patients after a given dosage. A much more useful guide is provided by calculating the RANGES of penicillinaemia to be expected after a given dosage. A detailed statistical analysis of the results was therefore undertaken to delineate:

TABLE I
UNITS PENICILLIN/ML. SERUM

Product	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
A	0·16	0·11	0·06	0·06	0·04	0·04	0·026
B	0·20	0·09	0·06	0·05	0·04	0·03	0·024

* Read at the MSSVD meeting in Amsterdam on May 29, 1965. This is a summary of a paper to be published in full in the *Bulletin of the World Health Organization*.

† Two "All-Purpose" products were used in the trial (A) Penidural A.P. (Wyeth, England) and (B) Retarcillin D.F. (Royal Netherlands Fermentation Industries).

(1) The daily RANGES of penicillinaemia within which the serum levels of groups of 24 will lie after this dosage;

(2) The estimated daily ranges within which the serum concentration of any INDIVIDUAL of a large group will lie.

Table II and Fig. 2 show the ranges of penicillinaemia within which the means of groups of 24 should fall.

TABLE II
UNITS PER/ML. SERUM

Day	Range
2	0.084 to 0.113
3	0.052 to 0.066
4—Product A Product B	0.055 to 0.063
5	0.041 to 0.061
6	0.035 to 0.047
7	0.030 to 0.040
	0.022 to 0.028

Fig. 2.—Mean responses and 95 per cent. confidence limits of the means of 24 responses.

Table II shows the calculated ranges in figures; the narrowness of these ranges suggests that the long-acting component of the complex (benzathine penicillin) provides a degree of reliability and predictability of concentration superior to that commonly reported after the use of penicillin preparations which depend for their long-acting properties on the oily gel in which they are suspended.

The calculation of such ranges provides a much better guide to expected serum levels than the observation of means, but even these ranges do not show the extremes of daily levels which any individual of a large group may exhibit.

Table III and Fig. 3 show that, in a large group of patients all receiving the same dose of the same batch

of the same product, the serum concentration in any individual of the group may lie between very wide limits. Fig. 3 shows the extremely wide daily ranges as calculated for individuals, the majority will of course be clustered about the means.

TABLE III
UNITS PER/ML. SERUM

Day	Range
2	0.028 to 0.170
3	0.027 to 0.091
4—Product A Product B	0.039 to 0.079
5	0.06 to 0.096
6	0.015 to 0.067
7	0.009 to 0.061
	0.010 to 0.040

Fig. 3.—Mean responses and 95 per cent. confidence limits for individuals.

Table III shows the calculated ranges in figures within which the concentrations of any individual will fall according to the result of this trial. As all calculations were made to 95 per cent. confidence limits, it follows that one patient in twenty will have serum concentrations outside even these very wide limits and that the levels of one patient in forty will therefore be below the minima on any one day.

This demonstrates that a particular patient's failure to respond to standard treatment or prophylaxis may be due to factors quite unrelated to the quality or specificity of the product used or to the resistance of the organism. Failure to reach satisfactory serum levels in such cases will be due to factors inherent in the patient himself. It is suggested that these provide sufficient risk of failure without the introduction of

any further extrinsic factor which makes for unreliability in absorption and depot release.

Summary

The mean penicillin serum concentrations of groups of 24 patients, assayed daily for 7 days after the intramuscular injection of 1·2 mega units "All-Purpose" penicillin, were found to be treponemicidal on each of the seven post-injection days.

The ranges of penicillinaemia within which the serum concentration of any individual of a large group will fall after receiving this dosage, which were calculated for each of the seven post-injection days, were found to lie between very wide extremes.

Thus a particular patient's failure to respond to standard treatment or prophylaxis against a sensitive organism may well be due to factors quite unrelated to the resistance of the organism or to the quality and specificity of the product used.

Failure to reach satisfactory serum levels in such cases is due to factors inherent in the patient himself, and it is suggested that penicillin preparations which depend for their long-acting property on an oily vehicle introduce an additional factor making for unreliability in absorption and will thus tend to increase the proportion of such failures.

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Étude des taux de pénicilline obtenus dans le sérum après utilisation de la pénicilline à tous usages

RÉSUMÉ

On détermina les taux moyens de concentration de pénicilline obtenus dans le sérum de 24 malades pendant 7 jours après l'injection intramusculaire de 1,2 mega unités de pénicilline à tous usages, et on trouva qu'ils étaient tréponémicides pendant les 7 jours après l'injection.

Les taux de pénicillémie individuels peuvent varier considérablement parmi un large groupe, après l'injection mentionnée.

L'absence de réponse au traitement standard ou prophylactique peut être due à des facteurs autres que la résistance du microbe ou la qualité ou la spécificité du produit utilisé. L'impossibilité d'atteindre des taux de pénicilline satisfaisants dans le sérum est due à des facteurs inhérents au malade lui-même et on pense que les préparations de pénicilline dont l'action retard dépend de la substance huileuse qu'elles contiennent, introduisent un facteur supplémentaire de hasard dans l'absorption de ce produit qui tend à augmenter la proportion des échecs thérapeutiques.