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Pharmacokinetics of Ampicillin Trihydrate, Sodium Ampicillin, and Sodium Dicloxacillin following Intramuscular Injection

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Abstract □ Serum levels of penicillin activity were determined following intramuscular administration to humans of sodium ampicillin solution, three ampicillin trihydrate suspensions, and sodium dicloxacillin solution. The rates of absorption of the drugs from the intramuscular injection sites were calculated using the method of Wagner and Nelson, with and without intravenously determined elimination constants, and the method of Loo and Riegelman. The ampicillin suspension and dicloxacillin solution data exemplified the interesting pharmacokinetic case in which the absorption process is slower than the elimination process. In this situation, the descending portion of the serum curve reflects the absorption process rather than the elimination process. Calculations confirmed that intravenous data were required to differentiate these processes under these conditions. Ampicillin solution data followed the usual pattern where the descending portion of the serum curve reflects the elimination process. Serum level curves were displayed by an analog computer programmed with a two-compartment open model, and the rate constants were calculated by the Loo–Riegelman method. The computer-generated lines agreed with the experimental data except for the early times following the ampicillin trihydrate suspensions. When the computer was programmed with a kinetic model that depicted absorption as two successive first-order steps, however, the computer lines agreed with the experimental data at all times.

Keyphrases □ Ampicillin, sodium and trihydrate—pharmacokinetics □ Dicloxacillin, sodium—pharmacokinetics □ Absorption rates, half-lives, intramuscular injection—penicillins □ Biological availability—penicillins

The absorption rates of various dosage forms can be quantitated, at least comparatively, without knowledge of the absolute amount of drug absorbed (1); but this amount must be known to estimate availability reliably. If biological availability is defined in terms of the amount of drug that appears in the blood, the only method of drug administration certain to provide 100% of the dose to the blood is intravenous injection. Loo and Riegelman (2) developed a method for calculating the rate and extent of absorption of a drug from an extravascular dosage form when intravenous data are available. Often it is not practical during early stages of drug product development to administer a new drug intravenously to humans, and comparisons must be made between the dosage form candidate and a "readily available" extravascular dosage form. However, the use of extravascular reference dosage forms has important limitations which must be recognized by the investigator. It is not unusual to find that some drugs are not completely absorbed even from oral solutions. On the other hand, it is generally considered safe to assume that an intramuscular injection is completely absorbed. Intramuscular injections of penicillins do not appear to be completely absorbed; this paper deals with the hazards of interpreting penicillin serum data pharmacokinetically, especially with regard to biological availability, on the basis of intramuscular data.

The intramuscular route of administration is traditional for the penicillins, and many methods have been used to prolong their release from intramuscular injection sites. For example, suspensions of relatively insoluble penicillin salts have been used for this purpose. Ampicillin trihydrate is a relatively water-insoluble, chemically stable powder, and its potential use in formulating a sustained-release intramuscular dosage form of ampicillin was investigated. A dosage form that produces slow absorption of a drug which is rapidly eliminated presents an interesting pharmacokinetic case. If the kinetic model is assumed to be:

$$\text{dosage form} \xrightarrow{k_a} \text{blood} \xrightarrow{k_e} \text{eliminated drug}$$

Scheme I

and both processes are first order, it can be shown (3) that the rate constant corresponding to the descending curve of a semilogarithmic plot of blood level *versus* time is not necessarily k_e. In fact, such a procedure yields the smaller of the two rate constants whether it be k_a or k_e. In this paper, penicillin serum level data will be presented which demonstrate this point, and methods for handling such data will be discussed.

The purposes of these studies were: (*a*) to compare the rates of release from intramuscular injection sites

Table I—Intramuscular Ampicillin and Dicloxacillin (20 Subjects)

Dose and Dosage Form	Mean Serum Levels (±*SD*), mcg./ml.							
	0	15 min.	30 min.	1 hr.	2 hr.	3 hr.	4 hr.	6 hr.	8 hr.
Ampicillin trihydrate suspension									
250 mg.	0	0.48 ±0.27	1.09 ±0.49	1.68 ±0.63	1.84 ±0.59	—	1.10 ±0.34	0.54 ±0.24	0.24 ±0.17
500 mg.	0	0.52 ±0.25	1.12 ±0.51	2.03 ±0.95	2.75 ±0.86	—	2.55 ±0.66	1.57 ±0.38	0.95 ±0.43
1000 mg.	0	1.30 ±2.0	2.27 ±2.0	3.67 ±2.1	4.84 ±2.6	—	4.71 ±1.6	3.12 ±1.1	2.28 ±0.78
Ampicillin sodium solution									
500 mg.	0	3.37 ±1.6	5.40 ±2.0	6.79 ±1.6	5.07 ±0.74	—	1.50 ±0.42	0.45 ±0.14	0.14 ±0.06
Dicloxacillin sodium solution with lidocaine									
250 mg.	0	—	4.67 ±1.0	5.07 ±0.79	4.61 ±0.65	3.12 ±0.46	2.18 ±0.39	1.14 ±0.34	—

of ampicillin trihydrate suspensions with that of ampicillin sodium solution, and (*b*) to determine the percent of the doses of ampicillin absorbed from the trihydrate suspensions and from the solution of the sodium salt administered intramuscularly. For comparison purposes, the rate of release and percent of the dose of sodium dicloxacillin, a highly protein-bound penicillin derivative absorbed following intramuscular injection, were also studied.

EXPERIMENTAL

Materials—The sodium ampicillin solution used in this study was commercially available[1] and reconstituted according to directions on the package insert. All other drug products were experimental formulations[2].

Clinical Protocol—The subjects were healthy adult volunteers ranging in age from 21 to 63 years and weighing from 125 to 215 lb. The majority were males; no females of childbearing age were included. To assure a relatively steady metabolic state, the subjects were fasted from 8 p.m. on the day preceding the administration of the drugs until after the 4-hr. postdrug blood specimen was drawn. The studies were usually begun at about 8 a.m. Following the 4-hr. postdrug specimen, the subjects were allowed food and water *ad libitum*. Venous blood specimens were collected at appropriate time intervals following drug administration.

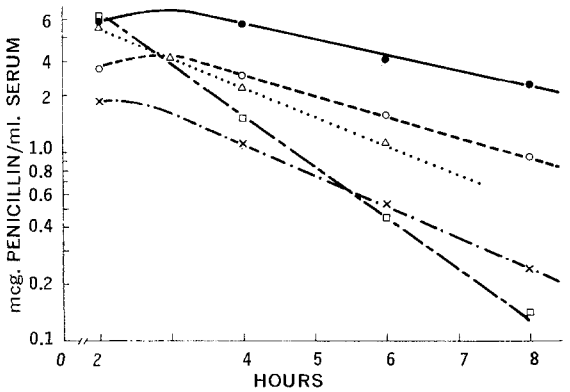


Figure 1—*Semilogarithmic plot of 20-subject average serum levels of penicillin activity following intramuscular administration of 1000 mg. (●), 500 mg. (○), and 250 mg. (×) of ampicillin trihydrate suspension; 500 mg. (□) of ampicillin sodium solution; and 250 mg. (△) of dicloxacillin sodium solution with lidocaine.*

Analytical Procedure—The serum was separated from the blood specimens by centrifugation and was frozen and shipped to be assayed[3] for penicillin activity by the standard cup-plate method (4).

RESULTS AND DISCUSSION

Twenty-subject average serum levels (± standard deviations) of ampicillin and dicloxacillin activity following intramuscular injection of various dosage forms of the two drugs are shown in Table I. Figure 1 shows semilogarithmic plots of the data; half-lives corresponding to the straight-line descending portions of the plots are summarized in Table II. With the exception of the ampicillin sodium solution, these half-lives are all significantly longer than 1 hr.

It is often assumed that the half-life obtained from the descending curve of a plot such as that shown in Fig. 1 corresponds to the half-life for elimination of the drug, *i.e.*, the biological half-life; and the rising portion of the curve is assumed to be associated with the absorption as well as the elimination process. Based upon these assumptions, Wagner and Nelson (1) developed a method for calculating the half-life of the absorption process. Their method involves calculation of the amount of drug unabsorbed; for drugs apparently absorbed by a first-order process, the absorption half-life is determined from a semilogarithmic plot of this quantity against time.

The apparent absorption half-lives for the five intramuscular penicillin dosage forms, as calculated by the method of Wagner and Nelson (1) using the half-lives from the descending curves shown in Fig. 1, are shown in the third column of Table II. These half-lives are all 1 hr. or less; with the exception of the ampicillin sodium solution, they correspond fairly closely with the elimination half-lives of the drugs following intravenous administration shown in the second column of Table II (5). These results suggest that the "absorption" half-lives calculated by the Wagner–Nelson (1) method are, in fact, the biological half-lives for elimination of the drugs, and the half-lives for the descending curves in Fig. 1 may correspond to the absorption half-lives of the dosage forms. The one exception is the ampicillin sodium solution for which the descending curve agrees with the intravenous elimination half-life, and the Wagner–Nelson "absorption" half-life is significantly shorter than those of the other preparations.

These apparent anomalies are the result of the mathematics of the kinetic model assumed for the *in vivo* behavior of these drugs and dosage forms.

If the model is:

$$\text{muscle} \xrightarrow{k_a} \text{blood} \xrightarrow{k_e} \text{eliminated drug}$$

Scheme II

[1] Polycillin-N for Injection, Bristol Laboratories, Syracuse, N. Y.
[2] Prepared by Bristol Laboratories, Syracuse, N. Y.
[3] At the Microbiology Control Department of Bristol Laboratories, Syracuse, N. Y.

Table II—Absorption and Elimination Half-Lives for Ampicillin and Dicloxacillin following Intramuscular Injection (20 Subjects)

Dose and Dosage Form	Elimination Half-Lives, hr. From Fig. 1[a]	Elimination Half-Lives, hr. From i.v. Data[b]	Absorption Half-Lives, hr. W–N Calc.[c]	Absorption Half-Lives, hr. W–N Calc.[d]	Absorption Half-Lives, hr. L–R Calc.[e]	Absorption-Rate Constant, hr.$^{-1}$, L–R Calc.
Ampicillin trihydrate suspension						
250 mg.	1.8	1.0	0.7	1.4	1.55	0.45
500 mg.	2.8	1.0	0.9	1.9	2.3	0.30
1000 mg.	3.6	1.0	1.0	2.9	3.3	0.21
Ampicillin sodium solution						
500 mg.	1.1	1.0	0.5	0.6	0.78	0.89
Dicloxacillin sodium solution with lidocaine						
250 mg.	2.0	0.88	0.8	2.0	1.3	0.53

[a] Half-lives determined from the slopes of the descending portions of the plots in Fig. 1. [b] Elimination half-lives from intravenous data (5). [c] Wagner–Nelson calculation (1) using elimination half-lives from Fig. 1. [d] Wagner–Nelson calculation (1) using elimination half-lives from intravenous data (5). [e] Loo–Riegelman calculation (2) using k_{12}, k_{21}, and k_{el} from intravenous data (5).

where k_a and k_e are the rate constants controlling first-order processes, then the blood levels of drug may be described in terms of the following biexponential equation:

$$\text{blood level} = \text{constant}\ (e^{-k_a t} - e^{-k_e t}) \qquad \text{(Eq. 1)}$$

For such a case, the slope of the descending curve of a semilogarithmic plot of blood levels against time yields the half-life of the *slower* of the two processes (3).

With many drugs, elimination is slower than absorption; the slope of the descending curve yields the biological half-life for elimination. The penicillins, however, are rapidly eliminated drugs having biological half-lives of about 1 hr. If the absorption of the penicillins from intramuscular injection sites is relatively slow, *i.e.*, if the half-lives are significantly longer than 1 hr., the slopes of the descending curves will be a function of the absorption half-lives. The results in Table II suggest that this is the case for all the penicillin dosage forms listed except the ampicillin sodium solution which has an apparent absorption half-life of 0.5 hr.

The Wagner–Nelson (1) method of calculation is useful with drugs for which no intravenous data are available to estimate elimination half-lives and for which it can be assumed that absorption is faster than elimination. In these cases, the calculation may be carried out using an elimination half-life estimated from the descending blood level curve following extravascular drug administration. But with drugs such as the penicillins, when elimination is faster than absorption, the half-life estimated from the descending curve will be the absorption half-life, and the half-life estimated from the Wagner–Nelson calculation will be the elimination half-life. On the other hand, if the elimination half-life of such drugs can be estimated from intravenous data, the Wagner–Nelson calculation should yield a reliable estimate of the absorption half-life even if elimination is faster than absorption. A somewhat similar approach was employed by Gibaldi and Schwartz (6) to calculate the rate of oral absorption in dogs of penamecillin, a prodrug of penicillin G. In this case, the biological half-life of penicillin G after oral administration to dogs was utilized in calculating the oral absorption rate of penamecillin by the Wagner–Nelson method.

Since intravenous elimination half-lives for ampicillin and dicloxacillin are available (5), they were employed in a repetition of the Wagner–Nelson calculation. The resulting absorption half-lives, shown in the fourth column of Table II, are in agreement with the half-lives corresponding to the descending curves shown in Fig. 1. The only exception is the ampicillin sodium solution for which the intravenous half-life is essentially the same as the half-life for the descending curve in Fig. 1; the absorption half-lives for the two Wagner–Nelson calculations are, therefore, equivalent. These results show with actual data how the slope of the descending portion of a semilogarithmic plot of drug blood levels following extravascular administration can be misleading with regard to the half-lives of the absorption and elimination processes. Wagner and Metzler (7) discussed the difficulties in estimating elimination half-lives in cases where absorption and elimination are occurring simultaneously. In such cases, the estimated elimination half-life may be significantly higher than the "best" value. In the present case, however, where absorption is slower than elimination, the estimates will be completely erroneous unless intravenous elimination half-lives are used.

The Wagner–Nelson calculations of absorption and elimination half-lives for the penicillin intramuscular dosage forms are based on the assumption that the body behaves as a one-compartment open model with respect to penicillin. But, a two-compartment body model was shown to be more consistent with intravenous penicillin data; the parameters of the two-compartment models for ampicillin and dicloxacillin were established (5). Furthermore, Loo and Riegelman (2) developed a method for calculating absorption half-lives for such drugs when the parameters of the two-compartment model are known. The fifth column of Table II shows the results of the Loo–Riegelman calculation of absorption half-lives for the intramuscular penicillin dosage forms. These results are probably the best estimates of the absorption half-lives, and they are in good agreement with the half-lives corresponding to the descending curves of Fig. 1, the only exception being the ampicillin sodium solution. Although there are some discrepancies among the absorption half-lives calculated by the two methods, both the Loo–Riegelman and the Wagner–Nelson calculations rank the dosage forms in the same order. Thus, either calculation could be used in ranking intramuscular dosage forms of the penicillins with regard to their absorption rates so long as the correct elimination-rate constants are used in the Wagner–Nelson calculation.

The results in Table II are of interest from a formulation point of view. The absorption half-life for the 500-mg. dose of ampicillin trihydrate suspension is about three times longer than that for a 500-mg. dose of ampicillin sodium solution, suggesting that slow dissolution of the particles in the trihydrate suspension can significantly prolong release of ampicillin from the intramuscular site. The differences in the absorption half-lives for the various doses of ampicillin trihydrate suspension are more difficult to rationalize, but the fact that absorption rate decreases as dose increases suggests that the surface area in contact with the injected dose may be a limiting factor when dose is varied.

The slow absorption rate of dicloxacillin solution compared with that of ampicillin solution suggests that some factor other than solubility or dissolution rate reduces the rate of diffusion of dicloxacillin from the intramuscular injection site. Similarities in the molecular weights and structures of ampicillin and dicloxacillin suggest that their diffusion coefficients in water would probably be similar. However, dicloxacillin is reported to be about 95% bound, whereas ampicillin is reported to be only about 20% bound, to plasma proteins (8); it is conceivable that binding to proteinaceous muscle tissue or to the proteins in interstitial fluids significantly slows the diffusion of dicloxacillin from the injection site. The absorption of dicloxacillin solutions was about as slow as that of ampicillin trihydrate suspensions.

In addition to absorption rates, which often are governed by rate of drug release, dosage forms are also evaluated in terms of the total amount of drug they release in the body, *i.e.*, their biological availabilities. Biological availability may be expressed in terms of the area under the plasma level–time curve following administration of the test dosage form compared with the area following administration of a "standard" dosage form (assuming the plasma clearance is constant). Usually, the standard dosage form is a solu-

Table III—Absorption Efficiencies and Biological Availabilities of Ampicillin and Dicloxacillin Intramuscular Dosage Forms (20 Subjects)

Dose and Dosage Form	Area under Serum Curve, hr. × mcg./ml.	Absorption Efficiency[a]		Biological Availability[c], $Area_{i.m.}/Area_{i.m.soln.}$
		$Area_{i.m.}/Area_{i.v.}$	L–R Calc.[b]	
Ampicillin sodium solution				
250 mg. i.v.	13[d]	100%	100%	—
500 mg. i.m.	20	77%[e]	78%	100%
Ampicillin trihydrate suspension				
250 mg. i.m.	8.2	63%	64%	82%
500 mg. i.m.	17	65%[e]	66%	85%
1000 mg. i.m.	37	71%[f]	71%	92%
Dicloxacillin sodium solution				
250 mg. i.v.	28[d]	100%	100%	—
Dicloxacillin sodium solution with lidocaine				
250 mg. i.m.	21	75%	76%	100%

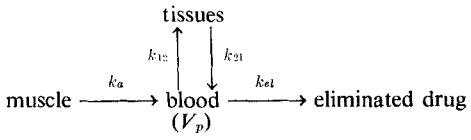
[a] Based on the intravenous dosage form as a reference standard representing 100% absorption. [b] $A_{max.}/dose \times 100$ (2). [c] Based on the intramuscular solution dosage form as a reference standard representing 100% bioavailability; *i.e.*, maximum absorption from the intramuscular site. [d] See *Reference 5*. [e] Based on 2× the area for the 250-mg. i.v. dose. [f] Based on 4× the area for the 250-mg. i.v. dose.

tion administered *via* the same route as the test dosage form, and it is assigned an availability of 100%. According to this conception of availability, only drug that is absorbed, *i.e.*, that reaches the blood, is "available." Often for practical reasons with new drugs intended for oral administration in solid dosage forms, the standard dosage form will be an oral solution; occasionally, an intramuscular injection will be used as a standard for oral availability. The latter approach is inconsistent with the above definition of biological availability and may even be misleading, because extravascular parenteral administration is not always equivalent to 100% absorption efficiency.

This point is illustrated by the data in Table III in which areas under serum level curves for intramuscular ampicillin and dicloxacillin dosage forms are compared with the areas for equivalent doses administered intravenously. Absorption efficiencies can also be computed by dividing the $A_{max.}$ values from the Loo–Riegelman calculations (2) by the doses administered, and these values are included in Table III for comparison purposes. The results show that, compared to the intravenous standards, a 250-mg. intramuscular dose of dicloxacillin sodium solution is only about 75–76% absorbed, as previously reported (8); a 500-mg. intramuscular dose of ampicillin sodium solution is only about 77–78% absorbed. Many factors may be responsible for an apparent absorption of less than 100% following an intramuscular injection of a solution. In the case of the penicillins, some of the drug may have been decomposed chemically or enzymatically at the injection site. Or, a fraction of the dose may have been released from the injection site so slowly that it produced undetectable blood and urine levels of active drug. It is less likely that unabsorbed drug remained permanently bound to the muscle tissue, although this is also possible. Intramuscular ampicillin trihydrate suspensions are apparently less well absorbed than intramuscular ampicillin sodium solution, the suspensions having biological availabilities of 82–92% based on the intramuscular solution standard.

These results illustrate that the intramuscular route of administration can be misleading as a standard for evaluating the availability of an oral dosage form. In fact, an early report (9) suggested that dicloxacillin was 100% absorbed orally because urinary output was identical to that found after intramuscular administration. Although this is not true, it can be said that dicloxacillin is as available orally as it is intramuscularly. The rates of absorption *via* the two routes are markedly different (10).

To test the agreement between the experimental data and the biological availabilities and absorption rate constants calculated by the Loo–Riegelman method, an analog computer was programmed with the following model:



Scheme III

where "muscle" represents the amount of drug remaining at the intramuscular injection site; "blood" represents the amount of drug in the "central compartment" (11) (the blood level at any time can be calculated by dividing this amount by the volume of the central compartment, V_p); "tissues" represents the amount of drug in the body but outside the central compartment; "eliminated drug" represents the amount of drug that has disappeared from the body by metabolic and excretory pathways; and k_a, k_{12}, k_{21}, and k_{el} are the rate constants controlling transfer among the "compartments."

The following rate constants and volumes were used for ampicillin and dicloxacillin (5):

	Ampicillin	Dicloxacillin
k_{12}	1.7 $hr.^{-1}$	2.0 $hr.^{-1}$
k_{21}	1.6 $hr.^{-1}$	2.0 $hr.^{-1}$
k_{el}	2.0 $hr.^{-1}$	2.1 $hr.^{-1}$
V_p	9.5 l.	4.4 l.

For each dosage form, the absorption-rate constant, k_a, was taken from the last column of Table II; the dose administered was the $A_{max.}$ value from the Loo–Riegelman calculation (2). (Actually, $A_{max.}/V_p$ was put into the computer so that it generated blood concentrations directly.) In each case, a slight lag time was also introduced.

Figure 2 shows the results of a typical analog simulation. The solid line was generated by the computer (with a lag time of 0.2 hr.), and the solid points are 20-subject average serum concentrations of ampicillin activity following intramuscular administration of 500 mg. of ampicillin sodium solution. A similar figure was

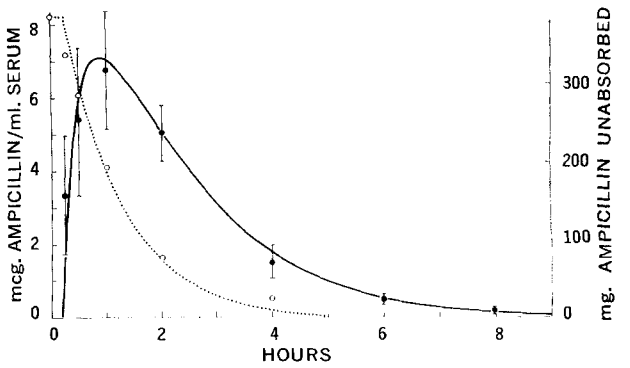


Figure 2—*A comparison between an analog computer-generated curve (solid line) using Scheme III and 20-subject average serum data points (●) (with standard deviations) following intramuscular administration of 500 mg. of ampicillin sodium solution. The dotted line is the analog computer-generated amount of ampicillin remaining unabsorbed and the open circles (○) are for this amount calculated by the Loo–Riegelman method (2).*

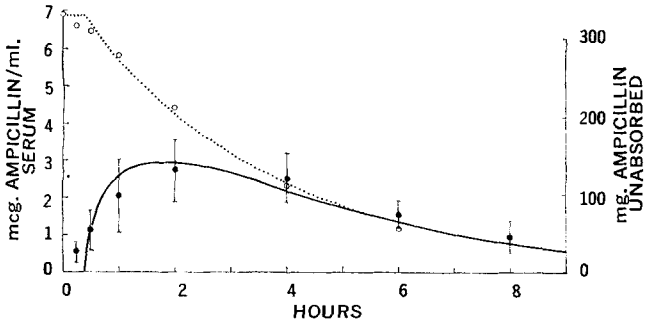


Figure 3—*A plot similar to that shown in Fig. 2 for 500 mg. of ampicillin trihydrate suspension administered intramuscularly.*

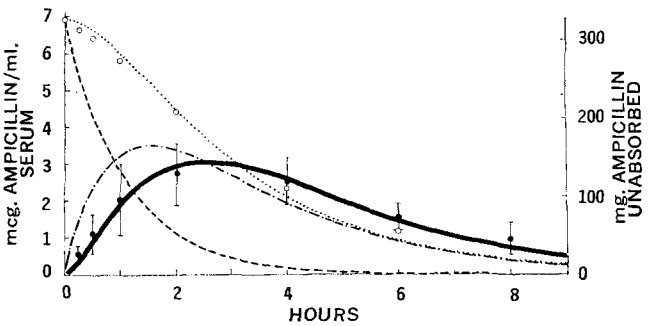


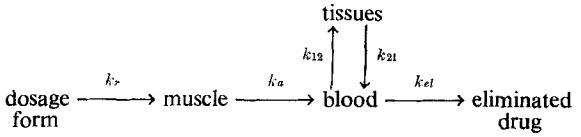
Figure 4—*A plot similar to that shown in Fig. 2 for 500 mg. of ampicillin trihydrate suspension administered intramuscularly. In this case, the mathematical model given by Scheme IV was used. The value of* $k_r = 0.45$ *hr.*$^{-1}$. *The lines (generated by the computer) are as follows:* ——, *serum level;* . . ., *amount of ampicillin remaining unabsorbed;* - - -, *amount of ampicillin remaining in the dosage form; and* - · - · - · -, *amount of ampicillin solution in the muscle.*

published previously (10) for intramuscular administration of 250 mg. of dicloxacillin sodium solution with lidocaine. These results suggest that previously published intravenous data for ampicillin and dicloxacillin (5) are consistent with the present intramuscular data for these drugs.

The dotted line in Fig. 2 is the analog computer estimate of the amount of drug remaining in the "muscle" compartment, and the open circles are the "amount remaining unabsorbed" as calculated by the Loo–Riegelman method (2). The agreement here suggests that the Loo–Riegelman calculation and the analog model are mutually consistent.

Figure 3 shows a comparison of the experimental blood levels (solid points) following intramuscular injection of 500 mg. of ampicillin trihydrate suspension and the theoretical blood curve (solid line) generated by the computer programmed with the model given by Scheme III using the absorption-rate constant given in Table II and a lag time of 0.35 hr. The dotted line is the analog computer estimate of the amount of drug remaining in the "muscle" compartment, and the open circles are the "amount remaining unabsorbed" as calculated by the Loo–Riegelman method (2). Although these lines agree fairly well with the experimental points, the overall shapes of the curves at early times are less than satisfactory. Many other absorption- and elimination-rate constants as well as many $A_{max.}/V_p$ values were tried with the program, but no combination fit the early blood points better than the combination of constants derived from the Loo–Riegelman calculations. In every case, the theoretical blood curve rose too rapidly at early times.

Absorption from a suspension depends upon both dissolution of the solid particles and subsequent absorption of the drug in solution. Therefore, the following modified model was tested:



Scheme IV

where "dosage form" represents the amount of ampicillin remaining in solid particles, "muscle" represents the amount of ampicillin solution remaining in the muscle, k_r is the first-order rate constant controlling dissolution of the solid drug, and k_a is the first-order rate constant controlling absorption of ampicillin in solution. This model is similar to a model used by Turco *et al.* (12) to describe plasma levels of sulfamethazine following oral administration of a suspension of the drug to humans. The absorption-rate constant, k_a, was set at 0.89 hr.$^{-1}$, the same rate constant that fits the 500-mg. ampicillin sodium solution data (Table II and Fig. 3); k_r was varied to give the best fit to the data points.

Figure 4 shows that, when k_r is set at 0.45 hr.$^{-1}$, the theoretical blood curve (bold solid line) agrees very well with the experimental blood concentrations (solid points) at all times without introducing a lag time. In addition, the theoretical "amount remaining unabsorbed" curve (dotted line) agrees with the amounts calculated by the Loo–Riegelman method (open circles). The latter curve is the sum of the amounts of drug in the "dosage form" and "muscle" compartments, and the curves for these compartments are also shown in Fig. 4 (dashed and dot-dashed lines, respectively).

It should be emphasized that, although Scheme IV fits the data very well, it was not the only model tested. Overall dissolution and absorption of suspensions may approximate a zero-order process, and many models were tested which involved pure zero-order and mixed zero- and first-order absorption mechanisms. None of the models tested agreed with the data points as well as the consecutive first-order model (Scheme IV), but this must not be construed as proof or disproof that the mechanism depicted by Scheme IV is or is not the true operating mechanism. These results prove only that Scheme III is probably an oversimplification for ampicillin trihydrate suspensions administered intramuscularly.

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