Inter- and Intrasubject Variations in Drug Absorption Kinetics

By GERHARD LEVY and LEO E. HOLLISTER

Inter- and intrasubject variations in drug absorption kinetics were studied in 15 subjects who ingested 975 mg. of aspirin in compressed tablets on two separate occasions. The group included unusually rapid and unusually slow eliminators of salicylate. Average as well as individual absorption data could be described as first-order processes preceded by a short induction period. The magnitude of variations in rate constants and induction times between subjects and between tests in any one subject has been determined, and the possible existence of consistently slow and rapid drug absorbers has been examined. *In vitro* dissolution of drug from the dosage form was describable as a first-order process, and a quantitative correlation between *in vitro* dissolution and *in vivo* absorption data has been obtained. Acceptance of a given mathematical model, based on average data, as a description of drug absorption and elimination processes is justified only if the model fits the majority of the individual data. It also must be appreciated that considerable inter- and intrasubject variations in rate constants may exist.

THE RECENT development of convenient mathematical methodology for determining drug absorption rates (1) represents a major advance in biopharmaceutics. Different kinetic models for drug absorption processes, illustrated by several practical examples, have been presented (2). In the present report, studies are described which serve to extend these developments to a consideration of inter- and intrasubject variations in drug absorption kinetics and to the mathematical correlation of *in vitro* and *in vivo* drug-release data.

EXPERIMENTAL

Clinical Study.—Fifteen normal male subjects ingested 975 mg. aspirin[1] in the form of three compressed tablets on two occasions, usually about 1 week apart. The tablets were swallowed whole on an empty stomach with 240 ml. of water. Blood samples were obtained at 15, 30, 60, 90, 120, 180, and 240 minutes after drug ingestion. Serum salicylate levels were determined in duplicate by the colorimetric procedure of Trinder (3). Aspirin tablets used in all phases of the study were from a single lot of a national brand purchased on the open market.

Calculation of Absorption Rates.—The per cent of the dose absorbed at various times was calculated by the procedure of Wagner and Nelson (2)

$$\% \text{ Absorbed} = \frac{A}{A_\infty} \times 100 = \frac{C_T + K \int_{t=0}^{t=T} C\,dt}{K \int_{t=0}^{t=\infty} C\,dt} \times 100 \quad \text{(Eq. 1)}$$

where A is the cumulative amount of drug absorbed at any time T, A_∞ is the total amount of drug eventually absorbed, C_T is the drug concentration in serum at time T, and K is the first-order elimination rate constant for salicylate. Individual values of K were obtained from half-lives which were determined graphically from postabsorptive blood level data that yielded straight lines when the logarithm of serum salicylate concentration was plotted as a function of time, on the basis of the relationship

$$K = \frac{.693}{t_{1/2}} \quad \text{(Eq. 2)}$$

where $t_{1/2}$ is the half-life for elimination, expressed in units of time. Values for the integral in Eq. 1 were obtained by planimetry of respective areas under individual serum salicylate concentration *versus* time curves. In view of the known rapid and complete gastrointestinal absorption of aspirin when it is administered in conventional compressed tablets (4), A_∞ was assumed to equal the administered dose. Considerations concerning the use of the Wagner-Nelson method (1, 2) for the determination of aspirin absorption rates on the basis of salicylate blood levels have been discussed by Levy in a previous publication (5).

Dissolution Rate Determinations.—*In vitro* dissolution rates were determined by the method of Levy and Hayes (6) with the following modifications: the volume of 0.1 *N* HCl was increased to 350 ml., and data for tablets which formed a "mound" at the edge rather than in the center of the bottom of the beaker were excluded. Samples were analyzed as described previously (6).

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[1] Analysis of four individual tablets (no more were available) indicated an average aspirin content of 319 mg. per tablet (range: 315–328 mg.). In view of the small sample, the label claim (325 mg.) was accepted as accurate and was used in subsequent calculations.

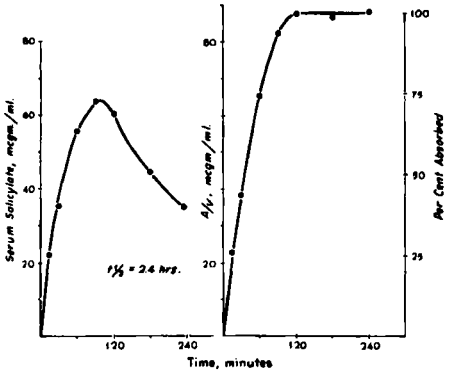

Fig. 1.—Serum salicylate concentration and per cent absorbed as a function of time after ingestion of 975 mg. aspirin by subject H, a rapid eliminator of salicylate.

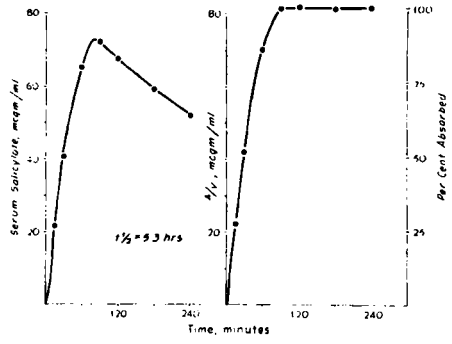

Fig. 2.—Serum salicylate concentration and per cent absorbed as a function of time after ingestion of 975 mg. aspirin by subject P, who eliminates salicylate at an average rate.

RESULTS AND DISCUSSION

Figures 1 to 3 illustrate how absorption rates were determined for each subject. The examples were chosen because they represent subjects who eliminate salicylate at an unusually rapid, average, and slow rate, respectively. Such pronounced inter-subject variations in salicylate elimination kinetics are in accord with the results of previous studies in our laboratories (7, 8). Excellent plateaus were obtained when values of A/V (cumulative amount absorbed/apparent volume of distribution) were plotted as a function of time, an indication of the accuracy of blood level data, the precision of planimetric measurements of areas under the blood level-time curves, and the applicability of apparent K value determinations.[2]

After calculation of individual values for per cent absorbed at various times after drug ingestion, the data were averaged and were plotted on semi-logarithmic paper as per cent unabsorbed *versus* time. Figure 4 represents the average of 30 individual values obtained from 15 subjects in two tests. The data can be described in terms of a first-order process preceded by an apparent induction phase which can be accounted for by a zero time shift. Specifically,

$$A_u = A_o e^{-.038(t-6)}, \quad \text{when } t \geq 6 \text{ minutes} \quad \text{(Eq. 3)}$$

or

$$\log A_u = -0.01(t - 6) + \log A_o, \quad \text{when } t \geq 6 \text{ minutes} \quad \text{(Eq. 4)}$$

where A_u is the amount unabsorbed at time t (expressed in minutes), and A_o is the administered dose. Figure 5 depicts the results obtained when average data from the two tests (15 individual values each) are plotted separately. The results of the two tests are essentially identical.

The impressive reproducibility of absorption kinetics in a group of only 15 subjects might lead one to conclude that the rate of drug absorption in

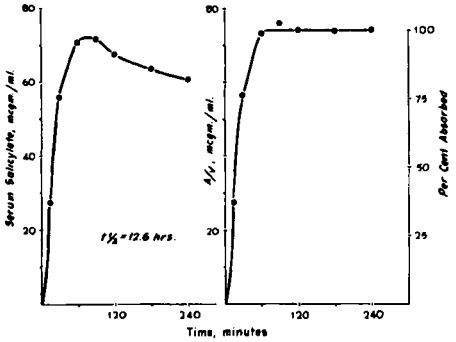

Fig. 3.—Serum salicylate concentration and per cent absorbed as a function of time after ingestion of 975 mg. aspirin by subject J, a slow eliminator of salicylate.

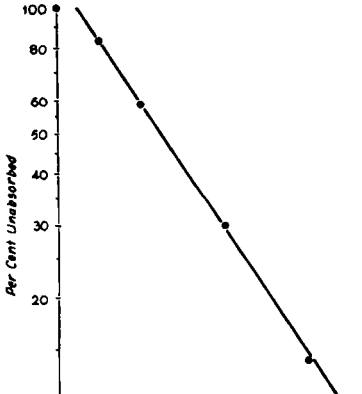

Fig. 4.—Rate of gastrointestinal absorption of aspirin after ingestion of 975 mg. aspirin as three tablets, expressed in terms of per cent unabsorbed as a function of time. Average of 30 determinations in 15 subjects.

[2] It was found recently that elimination of salicylate given in 1-Gm. (aspirin) doses involves initially parallel first-order and zero-order processes (Levy, G., to be published). This cannot be recognized readily from salicylate plasma level *versus* time data, which appear linear rather than curved, when plotted semilogarithmically. Therefore, first-order elimination rate constants (K) referred to in this paper must be considered apparent values. Their use in calculations of salicylate absorption and elimination kinetics does not introduce any significant errors, except in the terminal phase of salicylate elimination.

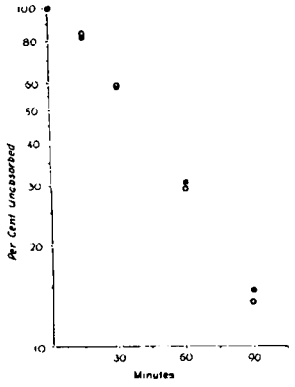

Fig. 5.—Rate of gastrointestinal absorption of aspirin after ingestion of 975 mg. aspirin as three tablets, expressed in terms of per cent unabsorbed as a function of time. Average of 15 determinations in 15 subjects. Key: ●, first test; ○, second test.

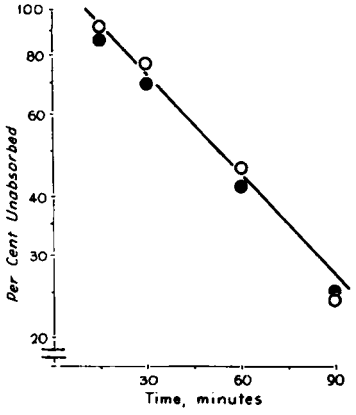

Fig. 6.—Example of consistently slow absorption: rate of gastrointestinal absorption of aspirin after ingestion of 975 mg. aspirin as three tablets, expressed in terms of per cent unabsorbed as a function of time. Results of two separate tests in subject A.

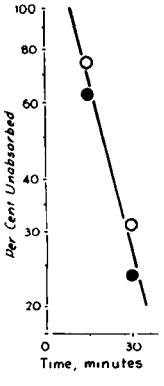

Fig. 7.—Example of consistently rapid absorption: rate of gastrointestinal absorption of aspirin after ingestion of 975 mg. aspirin as three tablets, expressed in terms of per cent unabsorbed as a function of time. Results of two separate tests in subject J.

any one individual is quite consistent in separate experiments. However, such was generally not the case. The group of subjects in the two tests included individuals who behaved as consistently slow absorbers, consistently rapid absorbers, and some who exhibited pronounced differences in absorption kinetics on the two occasions. To illustrate, Fig. 6 shows data representative of an individual who absorbed the drug at a consistently low rate (relative to the average), while Fig. 7 represents data indicative of consistently rapid drug absorption. On the other hand, pronounced differences in absorption kinetics are apparent in the results depicted in Figs. 8–10. These figures were chosen because they illustrate various types of intrasubject variations observed in the present study: (*a*) similar rate constants but different induction times (Fig. 8), (*b*) similar induction times but different rate constants (Fig. 9), and (*c*) different induction times and different rate constants (Fig. 10).

Interestingly, the individual showing rapid absorption (Fig. 7) happens to be an unusually slow drug eliminator (Fig. 3). The unusually rapid drug eliminator (Fig. 1) absorbed aspirin at a slow, though variable rate (Fig. 9). Using data from these two subjects, it is possible to demonstrate the profound intersubject variations in drug absorption and elim-

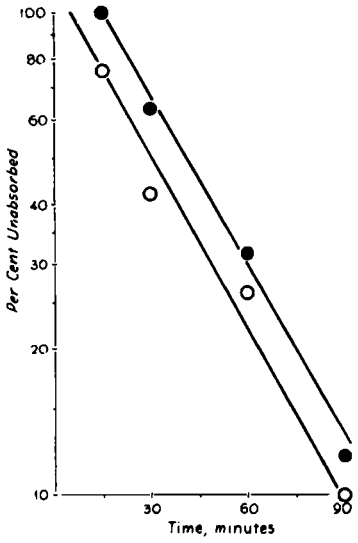

Fig. 8.—Example of variable absorption evidenced by differences in induction times: rate of gastrointestinal absorption of aspirin after ingestion of 975 mg. aspirin as three tablets, expressed in terms of per cent unabsorbed as a function of time. Results of two separate tests in subject L.

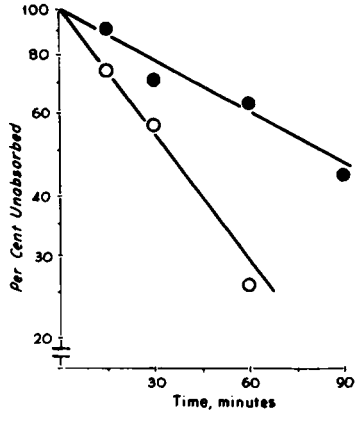

Fig. 9.—Example of variable absorption evidenced by differences in first-order rate constants: rate of gastrointestinal absorption of aspirin after ingestion of 975 mg. aspirin as three tablets, expressed in terms of per cent unabsorbed as a function of time. Results of two separate tests in subject H.

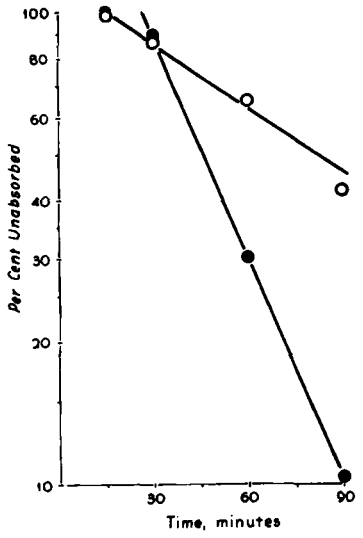

Fig. 10.—Example of variable absorption evidenced by differences in induction times and first-order rate constants: rate of gastrointestinal absorption of aspirin after ingestion of 975 mg. aspirin as three tablets, expressed in terms of per cent unabsorbed as a function of time. Results of two separate tests in subject S.

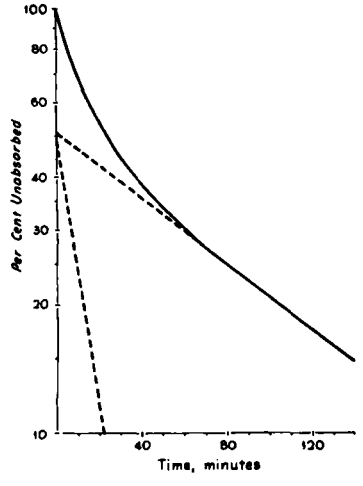

Fig. 11.—Solid line depicts per cent unabsorbed as a function of time for the hypothetical case where average data from two subjects absorbing drug by a first-order process with half-lives of 10 minutes and 80 minutes, respectively, are plotted. Stippled lines indicate rates of component processes if average data are interpreted (mistakenly) to represent two parallel first-order processes.

ination kinetics which may be encountered clinically. Since, in the present study, drug absorption and elimination can be represented as two consecutive first-order processes

$$\frac{dA_b}{dt} = k_a A_u - K A_b \qquad \text{(Eq. 5)}$$

which, upon integration, evaluation of the constant of integration at zero time, and rearrangement yields

$$A_b = \frac{A_o k_a}{K - k_a} (e^{-k_a t} - e^{-Kt}) \qquad \text{(Eq. 6)}$$

where A_b is the amount of drug in the body (exclusive of the gastrointestinal tract) at time t, k_a is the first-order absorption rate constant, and the other symbols have the meanings assigned to them previously. A_b is related to drug concentration in serum (C) in the following manner

$$\frac{A_b}{V} = C \qquad \text{(Eq. 7)}$$

where V is the apparent volume of distribution. In the case of the individual (subject J) who yielded the experimental values shown in Figs. 3 and 7 (rapid absorption and slow elimination),

$$A_b = -1.0\, A_o(e^{-.060(t-9)} - e^{-.00092(t-9)}) \qquad \text{(Eq. 8)}$$

while in the case of subject H, who absorbed the drug slowly and eliminated it rapidly (Fig. 1 and first test in Fig. 9),

$$A_b = -2.3\, A_o(e^{-.0085(t-1)} - e^{-.0048(t-1)}) \qquad \text{(Eq. 9)}$$

The expressions are not applicable when t <9 minutes and <1 minute, respectively.

An even greater difference is obtained in expressions for calculating serum salicylate concentrations (C, in micrograms per milliliter) rather than amount of drug in the body (A_b). Instead of Eq. 8, one obtains

$$C = -.76 \times 10^{-4}\, A_o(e^{-.060(t-9)} - e^{-.00092(t-9)}) \qquad \text{(Eq. 8a)}$$

while

$$C = -2.1 \times 10^{-4}\, A_o(e^{-.0085(t-1)} - e^{-.0048(t-1)}) \qquad \text{(Eq. 9a)}$$

takes the place of Eq. 9. The greater difference is due to the fact that absolute apparent volumes of distribution in the two subjects differ appreciably (subject J: 13,200 ml.; subject H: 11,100 ml.).

It is not too difficult to develop suitable kinetic models to fit most curves representing cumulative amount (or per cent) absorbed *versus* time, since such curves are generally smooth rather than undulating and since they reach a plateau or asymptotic value. It should be recognized, however, that kinetic models derived from average data may be completely meaningless since they may fit only these and none of the individual data. Kinetic models become meaningful only if they can describe the majority, if not all, of the *individual* data. While individual rate constants may vary, all or most of the individual data should be describable, within reasonable limits, by one and the same general type of mathematical expression. Such is the case with the data reported here—the average and the individual data can be described as first-order processes.

From a theoretical point of view, a mathematical expression which describes adequately all individual data need *not* necessarily fit the average data. To illustrate, one may consider the hypothetical case of two subjects, a rapid and a slow absorber.[3] Both subjects absorb a drug in a manner describable as a single first-order process but with half-lives of 10 minutes and 80 minutes, respectively. These are

[3] One may also consider a group of subjects showing bimodality in drug absorption rates, perhaps due to its composition with respect to age, sex, or state of health.

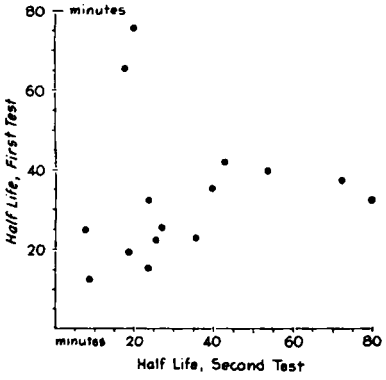

Fig. 12.—Scatter plot of individual half-lives for aspirin absorption (based on absorption rates and neglecting induction times) in two separate tests.

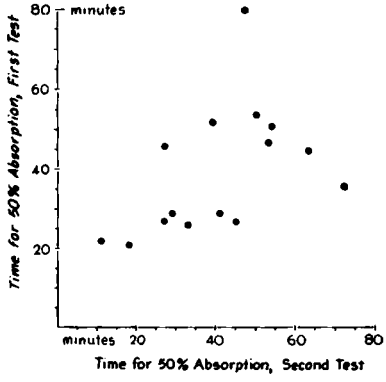

Fig. 13.—Scatter plot of individual times for 50% aspirin absorption (reflecting absorption rates and induction times) in two separate tests.

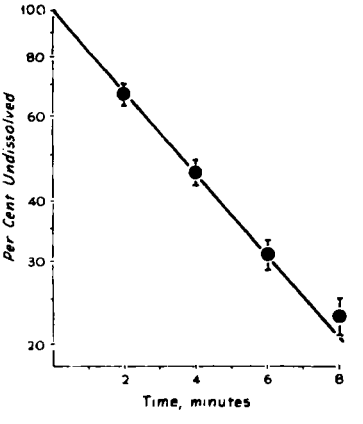

Fig. 14.—*In vitro* dissolution rate of aspirin from compressed tablets (the same lot as the tablets used in the clinical study). Average of six tablets. Vertical bars indicate ± one standard deviation.

realistic values, as evident from data shown in a subsequent figure. A semilogarithmic plot of average per cent unabsorbed as a function of time would yield the concave curve shown in Fig. 11. This curve can be resolved readily to yield two component first-order processes, and thus one may conclude that absorption occurred by two parallel first-order processes. Yet this kinetic model is unrealistic and meaningless because it fits only the average data—examination of individual data would show that absorption is describable as one exponential process.

Van Liew has shown that the sum of several exponential processes with different rate constants may yield a concave curve when plotted on semilogarithmic paper (9). The concavity from a single-mode distribution is determined by the relative magnitude of the standard distribution (SD) and the mean of the distribution. The smaller the SD/mean ratio, the more nearly the composite curve resembles a single exponential process. The straightness of the line in Fig. 4 can be explained in this manner.

The degree of correlation of individual absorption rates during the first test with rates during the second test has been examined in two ways: (*a*) by neglecting the respective induction times and plotting individual half-lives ($t_{1/2}$) for absorption rates in the first test against half-lives in the second test (Fig. 12) and (*b*) by plotting individual times for 50% drug absorption in the first test against those in the second test (Fig. 13). The latter values are a function not only of absorption rate constants but also of the respective induction times. Neither of the data depicted in the two plots yielded statistically significant correlation coefficients. There is an indication that about half of the 15 subjects absorbed drug at individually similar rates in separate tests, while the other half consisted of subjects with pronounced individual variability with respect to the rate of drug absorption. However, this suggestion should be considered as highly speculative, at least until additional data become available.[4]

Extensive studies have shown that the gastrointestinal absorption of aspirin administered in tablet form is rate-limited by the dissolution of drug in gastrointestinal fluids (10). It is reasonable to assume when absorption rate is dissolution rate dependent that the kinetic model which fits the drug absorption process will, in most instances, also apply to the *in vivo* dissolution process. As an extension of this reasoning, the suggestion may be made that a useful *in vitro* dissolution rate test for a given dosage form should yield data which are describable by the same kinetic model as the *in vivo* dissolution process and the *in vivo* absorption process.[5]

Results of dissolution-rate studies of aspirin tablets used in the clinical phase of this investigation are depicted in Fig. 14. Like the *in vivo* absorption process, the *in vitro* dissolution can be described by first-order kinetics, *viz.*,

$$a = a_o e^{-.20t} \qquad \text{(Eq. 10)}$$

or

$$\log a = -.085t + \log a_o \qquad \text{(Eq. 11)}$$

where a_o is the initial amount of drug in the tablet, and a is the amount of drug remaining undissolved at time t (which is expressed in minutes). The Levy-

[4] In some instances, variability in absorption rates can be due to variations in release properties of the dosage form. This was not a factor in the present study.

[5] It is emphasized that this statement applies only to cases where absorption rate is dissolution rate-limited. It must be appreciated also that this reasoning should be interpreted against the background of physiologic realities which may modify the suggested relationship in specific instances.

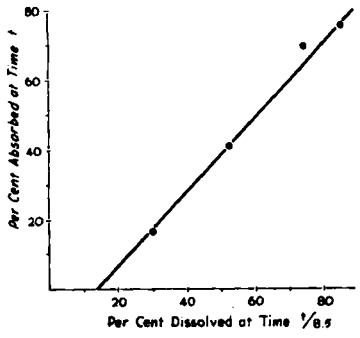

Fig. 15.—Plot of per cent aspirin absorbed at time t after drug administration *vs.* per cent dissolved *in vitro* at time $t/8.5$.

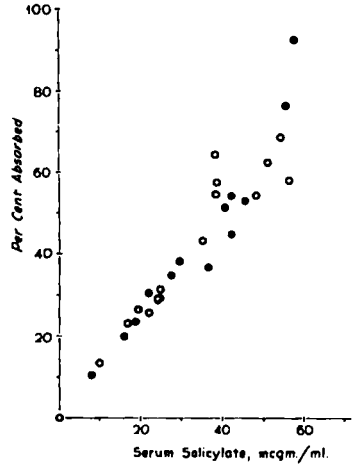

Fig. 16.—Scatter plot of per cent aspirin absorbed *vs.* serum salicylate concentration 30 minutes after ingestion of 975 mg. aspirin. Shown are 30 values from 15 subjects. Key: ●, first test; ○, second test.

Hayes dissolution-rate procedure (6) was modified in this study to obtain greater precision and to reduce saturation effects which became apparent in a previous study (5). Improvement in precision was obtained by excluding data from tablets which formed a "mound" at the edge rather than in the center of the bottom of the beaker,[6] while saturation effects due to concentration build-up in the terminal phase of the dissolution process were reduced by increasing the volume of solvent from 250 ml. to 350 ml.

The first-order rate constant for *in vitro* dissolution was about 8.5 times as great as the first-order rate constant for *in vivo* absorption. This may be a reflection of more intensive agitation of dissolution medium in the *in vitro* test. Using a procedure applied previously by Levy (5), a plot of per cent absorbed *in vivo* at time t *versus* amount dissolved *in vitro* at time $t/8.5$ was constructed and is shown as Fig. 15. The data fit satisfactorily a regression line of slope unity having an intercept at 14% dissolved *in vitro*, and thus can be expressed by

$$\%\text{ of dose absorbed at time } t = \%\text{ of dose dissolved } \textit{in vitro} \text{ at } t/8.5 - 14\% \quad \text{(Eq. 12)}$$

which describes drug absorption up to 86% of the dose. This may be compared with the expression

$$\%\text{ of dose absorbed at time } t = \%\text{ of dose dissolved } \textit{in vitro} \text{ at } t/3 - 10\% \quad \text{(Eq. 13)}$$

which Levy obtained from data on other subjects using different aspirin tablet preparations (5). In each case the data fitted a slope of unity, and in each case similar intercepts on the per cent dissolved axis were obtained. These reflect the induction time in drug absorption evident in Fig. 4. Levy and Jusko (11) have shown in experiments with rats that this induction time is due to initial accumulation of salicylate in the gastrointestinal wall which prevents or reduces markedly the entry of drug into the circulation during the first few minutes after drug administration. The question of why the intensity factor (the divisor of t) should differ almost threefold in the two studies remains. This could, of course, be due to the different subjects and clinical environments involved, but the differences also might be related to the fact that subjects in the present study participated for the first time in a test which involves intensive blood sampling, while subjects in the previous study were indoctrinated and experienced by participation in previous tests (12). Stress and apprehension are known to affect not only gastric motility but also gastric pH (13) and may modify *in vivo* dissolution and, therefore, the rate of absorption.

Finally, it is of interest to evaluate the data in terms of some of their practical implications with respect to comparative studies of absorption rates of drugs (particularly salicylates) administered in different dosage forms. How well do the "raw" blood level values reflect drug absorption rate? Using serum salicylate concentration and per cent absorbed values at 30 minutes (which is the approximate average midpoint for drug absorption in the entire group and shows the greatest spread of individual values), blood level and per cent absorbed values correlated very well (Fig. 16). This only can be the case if the subjects have similar absolute apparent volumes of distribution. Indeed, calculations based on A_∞/V values showed that 13 of the 15 subjects had apparent volumes of distribution which fell within ±10% of the mean value for the group. This fortunate occurrence would not happen if the subjects differ widely in respective body weights[7] or in relative volumes of distribution.[8] For example, the relative volume of distribution of salicylate in arthritics differs from that in normal subjects (14), due to changes in plasma protein composition characteristic of the arthritis syndrome. Consequently, salicylate blood levels from equal doses of drug are lower in arthritics than in normal subjects (14). The same is true in many other clinical situations, like infec-

[6] Data from four out of 10 tablets were excluded in this experiment. Results of all 10 dissolution determinations also fitted first-order kinetics, but standard deviations were considerably larger due to the slower dissolution of tablets which mounded at the edge. Rate constants were 0.20 minute^{-1} and 0.17 minute^{-1} based on the average of six and 10 determinations, respectively.

[7] Evaluation of drug absorption from compressed tablets and many other pharmaceutical dosage forms does not permit individual adjustment of doses to obtain a constant dose on a milligram per kilogram body weight basis.

[8] The average body weight of the 15 subjects was 71 Kg. (SD 8.5 Kg.), and the average relative volume of distribution was 170 ml./Kg. (SD 15.4 ml./Kg.).

TABLE I.—COEFFICIENTS OF VARIATION CALCULATED FROM SERUM SALICYLATE CONCENTRATION AND PER CENT ABSORBED DATA[a]

Time, Min.	First Test S.S.	First Test P.A.	Second Test S.S.	Second Test P.A.	Combined Tests S.S.	Combined Tests P.A.
15	69	66	94	105	83	90
30	53	51	44	52	48	51
60	24	22	28	28	25	25
90	19	13	18	15	18	14

[a] S.S., Coefficients based on serum salicylate concentration; P.A., coefficients based on per cent absorbed.

tion, where plasma albumin concentration is greatly reduced (15). It is also to be expected that correlation of blood level and per cent absorbed data would be poor when drug absorption rate is not considerably higher than the rate of drug elimination (assuming that elimination rate shows the usual intersubject variability).

From a similar point of view, it is of interest to compare the homogeneity of per cent absorbed values to that of blood level data. Considering the possible intersubject variations in volume of distribution and elimination rate, one would expect that actual absorption data would be more homogenous than blood level data (which would reflect also the variations in V and K values). As shown in Table I, coefficients of variation of blood level data and of absorption data obtained in the present study were generally the same, except for the greater homogeneity of absorption data when absorption was near completion (90 minutes). The latter tendency reflects the intersubject differences in elimination rates, which become most apparent in the post-absorption period. The reasons for the lack of greater homogeneity of absorption data (compared to blood level data) in the present study can be attributed to the similarity of volumes of distribution among the test subjects and also the rapid gastrointestinal absorption (compared to elimination) of aspirin. The chance exists also that in this relatively small group of subjects a fortuitous occurrence of opposite effects in any given subject may have dampened the blood level variations. In general, however, and particularly in situations where a greater diversity of V and K values is encountered and where k_a is not much greater than K, the use of actual absorption values should yield more homogenous data than are obtained by use of blood level values. This would permit a more sensitive statistical comparison of drug absorption from different dosage forms and would provide a more direct indication of absorption rates.

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Metal-Acid Complexes with Members of the Tetracycline Family I

Introduction

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Metal-acid complexes with a number of members of the tetracycline family have been prepared for chemical and biological evaluation. The studies reported here indicate that these preparations exhibited properties not displayed by the uncomplexed antibiotic. The most interesting properties characteristic of selected complexes in this series include enhanced solubility at pH 4.0–7.0, enhanced alkaline stability, reduced acute toxicity, reduced tissue irritation and rapid tissue diffusion, and enhanced blood levels.

THIS PUBLICATION is the first in a series describing the pharmaceutical properties of metal-acid complexes with members of the tetracycline family. The experimental data reported in this and subsequent publications have been obtained over the last 5 years through the cooperative efforts of a large number of investigators.

Many metal-acid complexes have been prepared having the following general formula: (tetracycline - group antibiotic) - (aluminum)a-(calcium)b-(gluconic acid)c, where a, b, and c vary widely. As the molar ratios of the constituents are varied, the pharmaceutical proper-

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6-Demethylchlortetracycline, chlortetracycline, and tetracycline are marketed as Declomycin, Aureomycin, and Achromycin, respectively, by the American Cyanamid Co., Pearl River, N. Y. 5-Hydroxytetracycline is marketed as Terramycin by the Chas. Pfizer Co., New York, N. Y.