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Received July 16, 1970.
Accepted for publication August 21, 1970.
This investigation was supported in part by Grant AFOSR-914 from the U. S. Air Force Office of Scientific Research and Grant NB-01966 from the National Institute of Neurological Diseases and Stroke of the National Institutes of Health.

Apparent Dose-Dependent Elimination Kinetics as an Experimental Artifact

Keyphrases ☐ Dose-dependent elimination kinetics, apparent—experimental artifact consideration ☐ Plasma concentration—experimental blank errors

Sir:

It is now known that the kinetics of elimination of several drugs are dose dependent. The decline in the plasma concentrations of some drugs is exponential throughout, but the apparent first-order rate constant for this process descreases with increasing dose (1). The elimination of other drugs involves one or more saturable processes, and semilogarithmic plots of plasma concentrations as a function of time curve downward until they attain an exponential phase which is reached at the same concentration irrespective of the dose (2). In view of the great interest and investigative activity in the area of dose-dependent pharmacokinetics, it is appropriate to point out that errors in blank corrections can artifactually lead to the conclusion that an entirely linear, dose-independent system is in fact dose dependent and nonlinear.

Figure 1 shows hypothetical plasma concentrations obtained after intravenous injection of 1, 3, and 10 weight units of a drug which is actually eliminated by apparent first-order kinetics ($t_{1/2}$ = 2.0 hr.), with the plasma concentration data describable by means of a one-compartment open model. However, the data points in the figure are, in each case, 2 mg./l. lower than the "real" concentrations. This would be so if, for a number of possible reasons, a 2 mg./l. error in the blank value determination would have occurred. The data points thus obtained can be fitted readily to straight lines which yield a decreasing half-life with increasing dose. In the example shown, there is an almost 50% change in the apparent half-life.

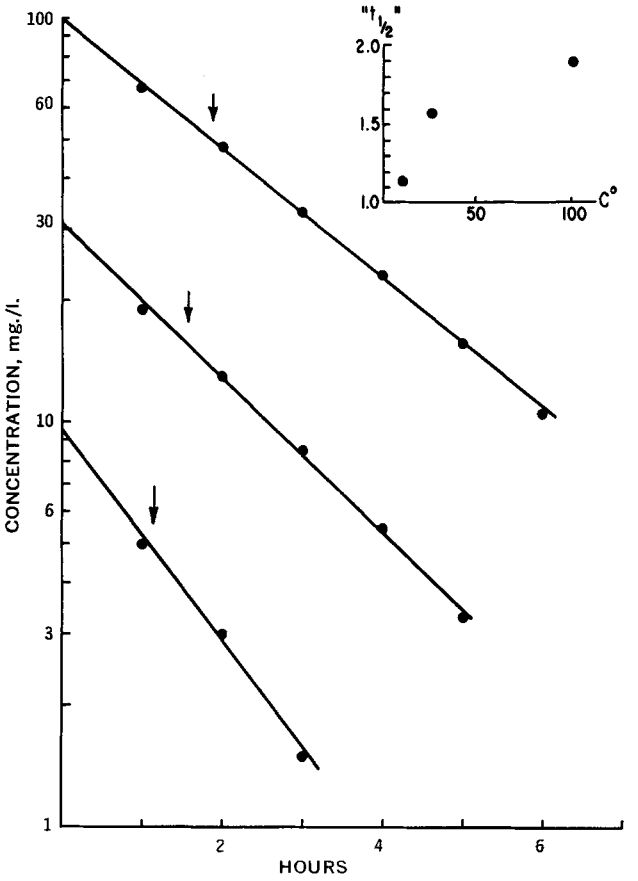

Figure 1—*Hypothetical plasma concentration data obtained after intravenous injection of 1, 3, and 10 weight units of a drug which is eliminated by apparent first-order kinetics* ($t_{1/2}$ = 2 hr.), *if the blank correction is 2 mg./l. too large. Arrows indicate apparent half-life. Inset: Relationship between initial plasma concentration* (C_0) *and apparent half-life* ("$t_{1/2}$").

If plasma concentrations are determined over a wide concentration range, an error in the blank correction can lead to the erroneous conclusion that elimination involves a combination of parallel linear and saturable (*i.e.*, capacity-limited) processes. Such systems may show an initial exponential concentration decline phase at high concentrations, a subsequent downward curvature, and finally another exponential phase which is steeper than the initial exponential phase (2). This pattern is evident in Fig. 2; the figure shows hypothetical plasma concentration data at two doses (differing 10-fold) of a drug, which is actually eliminated by apparent first-order kinetics but where an error of 3 mg./l. in the blank correction causes appreciable deviations from linearity. In this example, parallel straight lines may be fitted erroneously to the two sets of terminal data points, suggesting that the elimination kinetics above a plasma concentration of about 10 mg./l. are capacity limited.

The potential artifacts outlined in this article necessitate that considerable attention be directed to the correct determination of blank values. The magnitude

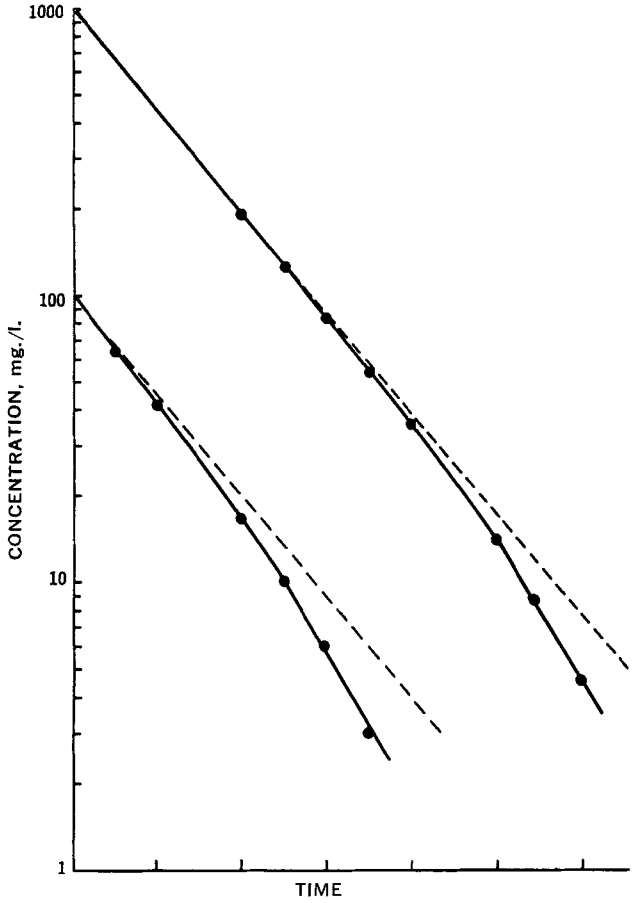

Figure 2—*Hypothetical plasma concentration data* (●) *obtained after intravenous injection of two different doses of a drug which is eliminated by apparent first-order kinetics, if the blank correction is 3 mg./l. too large. The dashed lines represent the correct curve. Note the apparent parallelism of the straight lines fitted to the last three points of each set of data.*

and variability of the blank, relative to the lower range of drug concentrations encountered in the investigation, must be carefully considered in the pharmacokinetic analysis of the data. It is recommended that apparent dose-dependent changes in elimination-rate constants, as shown in Fig. 1, be tested statistically for lack of parallelism of the respective log concentration *versus* time curves *in the same concentration range.* Where plasma concentration data show the pattern presented in Fig. 2, it is best to focus attention on the plasma concentration and/or urinary excretion pattern of the metabolite that is presumed to be subject to capacity-limited formation.

An underestimation of blank values, resulting in higher than correct drug concentration data, has exactly the opposite effects as those described here. Apparent first-order elimination-rate constants may be mistakenly assumed to increase with increasing dose [a type of kinetics that can actually occur due to dose-dependent distributional effects (3)], and a decrease in the slope of log drug concentration *versus* time curves with decreasing concentration might be treated as a linear multicompartment model or be interpreted as suggesting saturation of a renal tubular reabsorption process [a type of kinetics that can, in fact, occur (4)]. Thus, one must be concerned not only with the specificity and sensitivity of an analytical method but also with the possibility of systematic errors in the blank correction.

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Received July 15, 1970.
Accepted for publication August 20, 1970.
Supported in part by Grant 5 RO1 FD00015 from the National Institutes of Health.

Flocculation Theory and Polysorbate 80–Sulfaguanidine Suspensions

Keyphrases □ Flocculation theory—sulfaguanidine–polysorbate 80 suspension □ Sedimentation height—sulfaguanidine–polysorbate 80 suspension

Sir:

Flocculation has been defined as an open network structure formed by aggregated suspension particles (1). Three possible mechanisms by which such a structure can occur are: (*a*) aggregation in the secondary minimum which can theoretically result when the forces of attraction exceed the forces of repulsion (2, 3); (*b*) adsorption bridging—the aggregation of particles whose surface sites are occupied by segments of extended macromolecules; the extended molecules act as bridges between particles (4); and (*c*) chemical bridging—the aggregation by chemical reaction between adsorbed ions extending from the particle surface and media precipitation ions (5, 6).

In a study of the aggregation of a sulfaguanidine suspension with particles wetted by polysorbate 80, it was reported that the addition of increasing amounts of aluminum chloride produced a "flocculated system" which showed a steady increase in sedimentation height (7). A maximum volume was reached, and further additions of salt produced no change in sedimentation height.

Aluminum chloride at the concentrations used in the report could not react with the nonionic surfactant in a manner similar to those interactions that cause flocculation by chemical bridging.

Polysorbate 80 has never, in our experience, shown the characteristics exhibited by macromolecules that produce floccules in suspensions; therefore, it seemed