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Effect of Plasma Protein Binding of Drugs on Duration and Intensity of Pharmacological Activity

Keyphrases □ Plasma protein binding—effect on duration and intensity of pharmacological activity of drugs □ Binding, plasma protein—effect on duration and intensity of pharmacological activity of drugs □ Pharmacological activity—duration and intensity, effect of plasma protein binding of drugs

To the Editor:

There is increasing evidence that the pharmacological activity of drugs is a function of their free (not protein bound) concentration (1–4). It has also become apparent that the total clearance of drugs by the body is affected by the extent to which they are plasma protein bound (5–7). It is informative, therefore, to consider the effect of a change in plasma protein binding of a drug on the duration and intensity of its pharmacological activity, particularly since these indicators have been used to study drug interactions involving competitive displacement from plasma protein binding sites (8, 9).

It will be assumed as a matter of convenience that the free fraction of drug in plasma (f) is essentially constant over a wide concentration range (5, 6, 10), that the elimination of the drug is by apparent first-order kinetics and not affected by organ perfusion rate, that the drug is distributed in the body so rapidly as to justify the use of a one-compartment pharmacokinetic model, and that the only *direct* perturbation of the biological system is a change in f. Under these conditions:

$$\text{total clearance} = k''f \qquad \text{(Eq. 1)}$$

where k'' is the intrinsic clearance of the drug (5, 6). Also:

$$\text{total clearance} = V_d k_{app} \qquad \text{(Eq. 2)}$$

where V_d is the apparent volume of distribution of total (free and bound) drug, and k_{app} is the apparent first-order elimination rate constant. It is evident that an increase in f results in a corresponding increase in total clearance or $V_d k_{app}$. The quantitative effect of an increase in f on V_d is difficult to predict, but it appears to be smaller than the effect on k_{app} (6).

Figure 1 shows the effect of an increase in f from 0.01 to 0.03 on the time course of free and total drug concentrations after intravenous injection of 100 mg/kg of a drug with V_d = 0.20 liter/kg and k_{app} = 0.05776 hr^{-1} (equivalent to $t_{1/2}$ = 12 hr) under conditions where: (*a*) V_d increases to 0.25 liter/kg or (*b*) V_d is unaffected. In either case, it is evident that the increase in f causes an

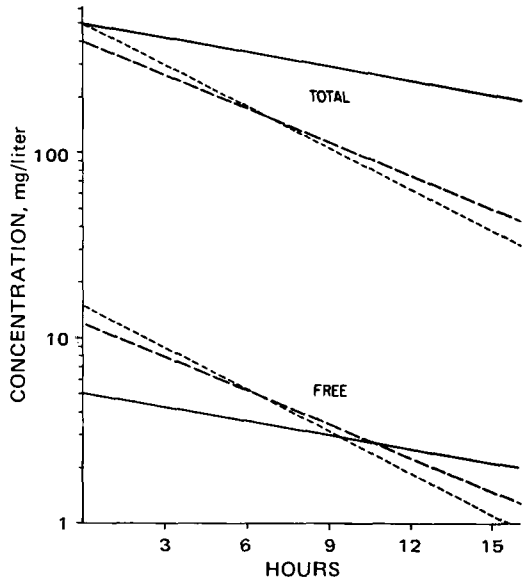

Figure 1—*Effect of a change in free fraction in plasma (f) on the time course of total and free drug concentrations in plasma after intravenous injection of 100 mg/kg. Key: continuous line, V_d = 0.20 liter/kg, $t_{1/2}$ = 12 hr, and f = 0.01; short stippled line, f increased to 0.03, and V_d unchanged; and long stippled line, f increased to 0.03, and V_d increased to 0.25 liter/kg. These simulations are based on the assumption that the total clearance increases proportionally with f.*

increase in the initial concentration of free drug but also a more rapid decline so that the free concentration when f = 0.03 will eventually be lower than when f = 0.01. This means that an increase in f will cause an increase in the intensity of the initial (maximum) pharmacological effect but that the duration of action may be increased *or* decreased, depending on the dose and the minimum effective concentration of free drug. For any one drug, an increase in f under the stated conditions may be expected to prolong the duration of pharmacological activity of small doses and to shorten the duration of action of large single doses.

It has been observed that the incidence of adverse

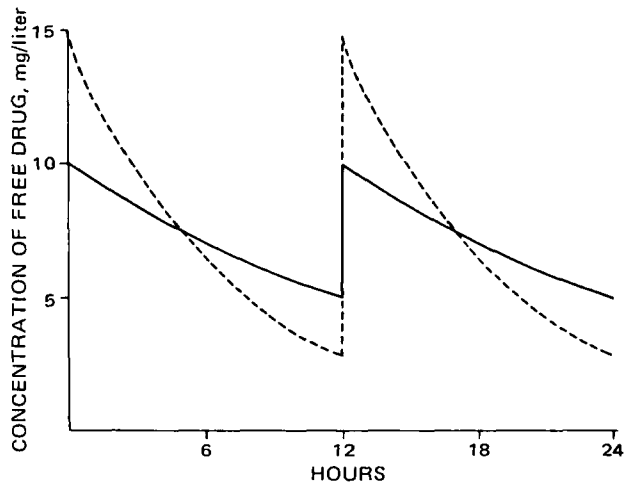

Figure 2—*Effect of a change in f on the time course of free drug concentrations in plasma at the steady state when 100 mg of drug/kg is administered intravenously every 12 hr. Key: continuous line, V_d = 0.20 liter/kg, $t_{1/2}$ = 12 hr, and f = 0.01; and stippled line, f increased to 0.03, V_d increased to 0.25 liter/kg, and $t_{1/2}$ decreased, therefore, to 5 hr.*

effects of certain drugs increases with a decrease in the concentration of albumin in plasma (11, 12). Since f increases with decreasing albumin concentration, it has been suggested that the increased incidence of adverse effects of drugs in patients with hypoalbuminemia may be due to decreased binding of such drugs to plasma proteins, among other factors (11, 12). The "average" steady-state concentration of total drug in plasma ($\bar{C}_p$) is:

$$\bar{C}_p = R/\text{total clearance} \qquad \text{(Eq. 3)}$$

where R is the dosing rate (13). Therefore, according to Eq. 1:

$$f\bar{C}_p = R/k'' \qquad \text{(Eq. 4)}$$

which shows that the average steady-state concentration of free drug should be unaffected by a change in f. This effect was demonstrated experimentally (14, 15). Based on these considerations, it has been stated that a change in f should not affect the intensity of pharmacological activity of a drug during the steady state. However, this conclusion is not necessarily correct.

Figure 2 shows the time course of steady-state free drug concentrations for the hypothetical drug described in Fig. 1 under conditions when $f = 0.01$ or 0.03 and V_d is 0.20 or 0.25 liter/kg. While the average concentration of free drug (area under the curve divided by dosing interval) is equal under both conditions, its maximum concentration is substantially higher when $f = 0.03$. Consequently, it is entirely feasible that an increase in f results in an increased incidence of adverse effects[1].

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[1] *Note added in proof:* Consistent with the theoretical predictions in this communication, it was recently reported [R. Gugler and D. L. Azarnoff, *Clin. Pharmacokinet.*, **1**, 25(1976)] that the maximum plasma concentration of free phenytoin is higher and the minimum plasma concentration is lower in nephrotic patients with hypoalbuminemia (phenytoin free fraction = 0.19) than in normal subjects (phenytoin free fraction = 0.10) at the steady state during multiple dosing of phenytoin. The incidence of adverse effects of phenytoin is increased in patients with hypoalbuminemia (12).

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Appearance of Myelin Forms in Rheopexic Dispersions of Dioctyl Sodium Sulfosuccinate

Keyphrases ☐ Dioctyl sodium sulfosuccinate—rheopexic dispersions, formation of micelles ☐ Micelles—formation in rheopexic dispersions of dioctyl sodium sulfosuccinate ☐ Dispersions, rheopexic—dioctyl sodium sulfosuccinate, formation of micelles ☐ Rheopexic dispersions—dioctyl sodium sulfosuccinate, formation of micelles ☐ Surfactants—dioctyl sodium sulfosuccinate, rheopexic dispersions, formation of micelles

To the Editor:

The detection of long tubular structures visible under the electron microscope has been reported for aqueous dispersions of many phospholipids (1). These observable structural units have been described variously as "myelin forms" and "micelles." Stoeckenius (2) and Fernandez-Moran (3) detected, identified, and described myelin forms of phospholipids under the electron microscope at magnifications of 400,000–1,250,000×.

During work on the development of rheopexy in dispersions of dioctyl sodium sulfosuccinate in normal saline (4), the pronounced development of myelin forms was observed under the light microscope at 430× after a shear stress was applied. The dispersion consisting of

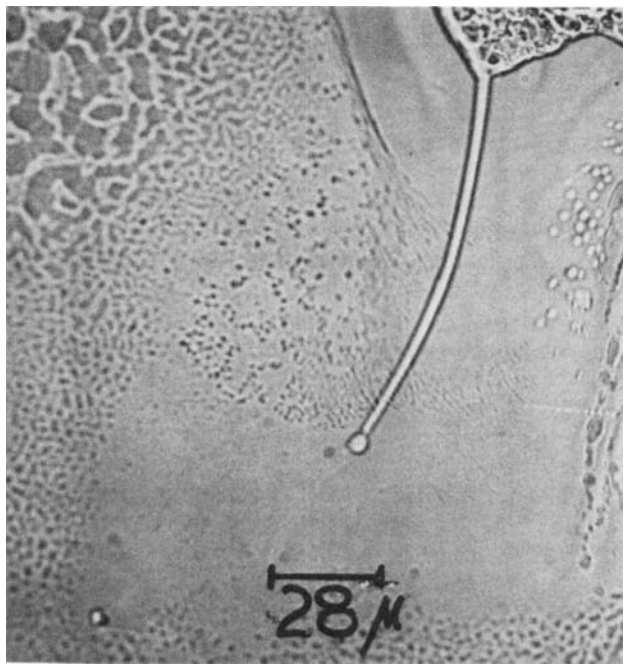

Figure 1—*Single tubular body thought to be a myelin form or micelle (430×).*