Interfacial Properties of Phenothiazine Derivatives

Sir:

Recent publications have indicated that chlorpromazine and other phenothiazine derivatives accumulate at biological membranes (1–3), and that these membranes might be the site of pharmacological activity. This view is strengthened by recent work, which has demonstrated the active role of mitochondrial phospholipid membranes during oxidative phosphorylation (4), and by the fact that chlorpromazine has been shown to interfere with electron transport by uncoupling oxidative phosphorylation (5, 6). Since the accumulation of a drug at a membrane depends on its ability to be adsorbed at interfaces, we have initiated a study of the interfacial properties of various phenothiazine derivatives at the air-water interface and at interfaces covered with insoluble monomolecular films, which simulate the oriented structure of biological membranes.

We have measured the surface tension of chlorpromazine[1] (CPZ), chlorpromazine sulfoxide (CPZ-O), and trifluoperazine[2] (TFP) at 25°, using the Wilhelmy plate method (7). The solutions were prepared in a Sorenson buffer at pH 6.9 and at an ionic strength of 0.04. A plot of surface tension *versus* the logarithm of molar concentration is shown in Fig. 1. The differences in surface activity are quite large and the order appears to parallel that of accumulation at biological membranes (2). Since an increased fraction of undissociated molecules generally increases the surface activity of acidic and basic substances at liquid interfaces, the differences between TFP and the other substances may be attributed, in part, to differences in the degree of dissociation; the two pKa values for TFP are about 2.7 and 7.2 (8) while those of CPZ and CPZ-O are about 8.2 (8) and 8.5 (9), respectively. The importance of the undissociated species was observed at a pH of 2.3 where the drugs are dissociated to a great extent. Here, there is no surface activity below a concentration of 1.0×10^{-3} *M*. The almost complete lack of adsorption of CPZ-O is probably due to the sulfoxide group which is too polar to be oriented toward air at

[1] Marketed as Thorazine Hydrochloride by Smith Kline & French Laboratories.

[2] Marketed as Stelazine Dihydrochloride by Smith Kline & French Laboratories.

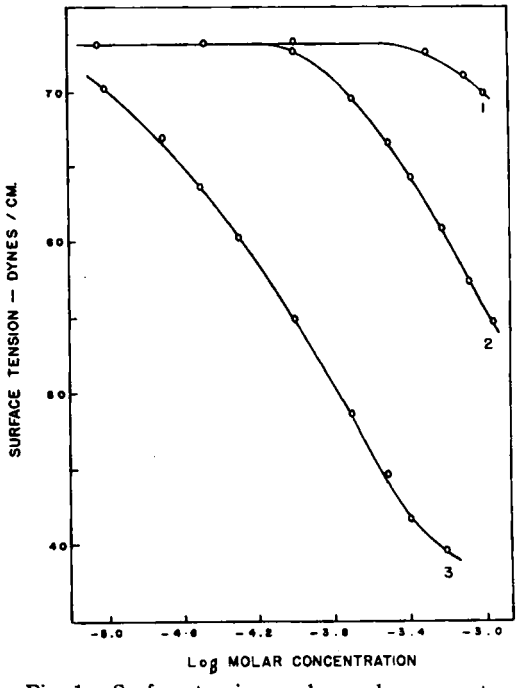

Fig. 1.—Surface tension *vs.* log molar concentration for: *1*, chlorpromazine sulfoxide; *2*, chlorpromazine; *3*, trifluoperazine in Sorenson buffer, pH 6.9 and ionic strength 0.04, at 25°C.

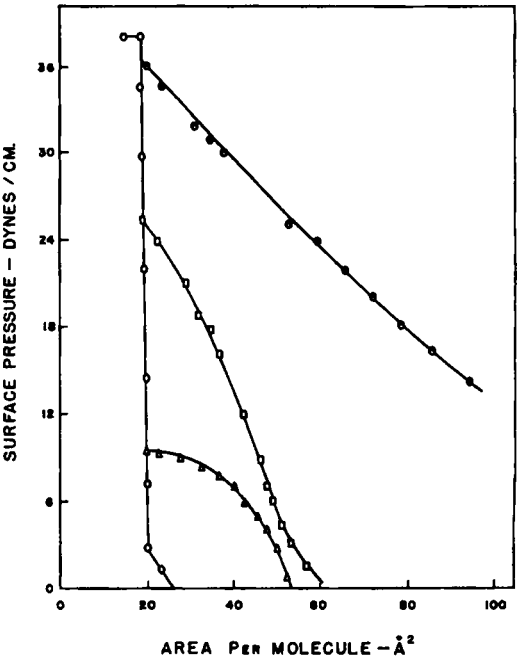

Fig. 2.—Surface pressure *vs.* area per molecule for stearic acid spread on: Sorensen buffer, pH 6.9 and ionic strength 0.04 (○); buffer plus 10^{-5} *M* chlorpromazine (□); buffer plus 10^{-5} *M* chlorpromazine sulfoxide (△); buffer plus 10^{-5} *M* trifluoperazine (●), at 25°C.

the interface. This lack of adsorption was also noted for trifluoperazine sulfoxide.

We have also measured the interfacial activity of these compounds in the presence of insoluble monomolecular films which were spread on a Langmuir-type balance (10). Figures 2 and 3 show the relationship between surface pressure (surface tension of solvent-surface tension of the film) and the area per molecule for stearic acid and L-α-dipalmitoyl lecithin spread on the same buffer solution as used previously, with and without dissolved drug. A concentration of 1.0×10^{-5} M was chosen since little, if any, surface activity was previously noted at the air-water

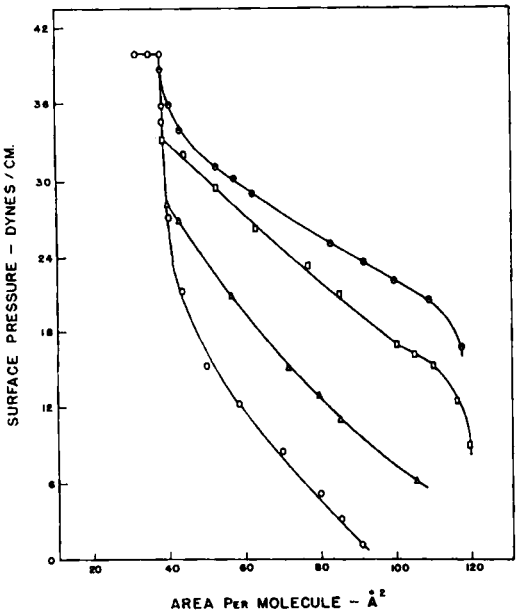

Fig. 3.—Surface pressure *vs.* area per molecule for L-α-dipalmitoyl lecithin spread on: Sorenson buffer, pH 6.9 and ionic strength 0.04 (○); buffer plus 10^{-5} M chlorpromazine (□); buffer plus 10^{-5} M chlorpromazine sulfoxide (△); buffer plus 10^{-5} M trifluoperazine (◓), at 25°C.

interface, whereas adsorption at membranes (2) and biological activity (5) have been reported.

The marked development of surface pressure at areas per molecule where stearic acid and lecithin exhibit none indicates penetration of the film by the dissolved drugs. Cockbain and Schulman (11) have studied the penetration of soluble surfactants into insoluble films and have indicated that the extent of the penetration and the strength of the resulting mixed film depends on such factors as, the chemical nature and the number of polar groups in the two molecular species, the van der Waals forces between nonpolar groups, the surface pressure of the insoluble film, the concentration of dissolved compound, the pH and ionic strength of the underlying solution, and the stereochemical configuration of the two molecular species in both polar and nonpolar groups. They concluded that in order to form a strong mixed film two strong points of contact must be made between polar and nonpolar portions of the molecules involved.

As can be seen in Figs. 2 and 3, penetration occurs to a great extent at higher areas per molecule but as the film is compressed to lower areas the drugs are ejected from the film. The relative surface pressure developed at the same area per molecule, and the ability to resist ejection, therefore, are measures of the interfacial activity of these drugs at a particular membrane under a given set of conditions. In view of this, it is interesting to note the differences between the three compounds studied and the correlation with earlier studies (2, 3).

Thus, it is apparent that at concentrations where biological activity is observed, a drug may be quite surface active at an insoluble monomolecular film, and yet, exhibit no activity at the air-water interface. It is also apparent that modification in the structure of the hydrophobic and hydrophilic portions of the drug can greatly alter its ability to accumulate at a particular interface.

Further studies, utilizing other films and drugs are being conducted. In addition, the effects of pH, ionic strength, and drug concentration are being considered.

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