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SHORT COMMUNICATION

The binding of polyphosphates by phenothiazines and related compounds: A possible relationship to clinical potency as tranquilisers

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IT HAS been demonstrated that phenothiazine derivatives, and compounds related to imipramine are able to form insoluble complexes with polyphosphates of biological interest.[1] The formation of these complexes probably results from the interaction of the cationic groups of the side chain of the drugs with the negatively charged phosphate groups of the polyanion. The reaction, (i.e. the formation of stable precipitates when drug and polyphosphate are mixed) can be studied by simple nephlometric methods.[1]

When the effect of drug concentration on the formation of these complexes is examined, inflected concentration curves are obtained (Fig. 1) and the degree of inflection of these curves is related to the

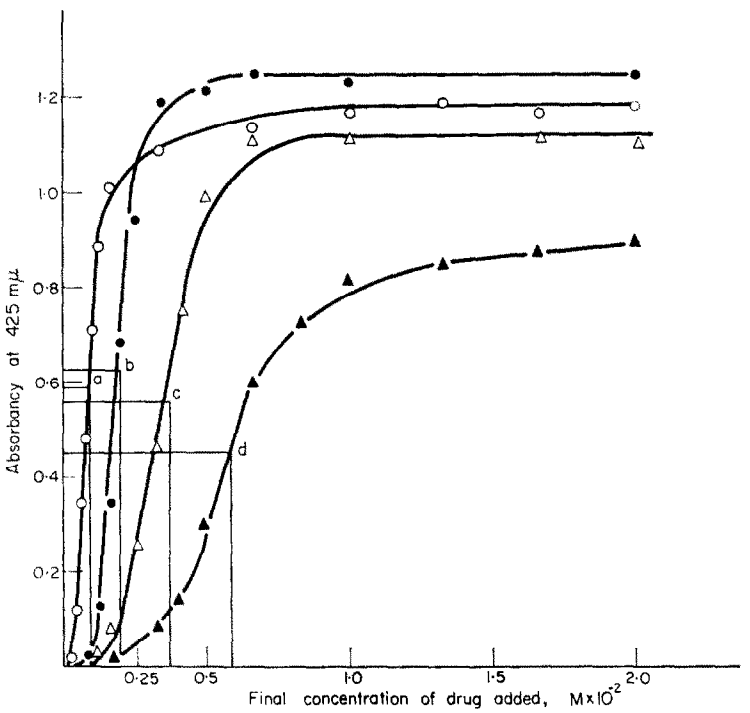

FIG. 1. The effect of drug concentration upon the interaction between drug and yeast polyphosphate. A high polymer yeast polyphosphate[1] was employed at a concentration equivalent to 2×10^{-4} M orthophosphate. The polyphosphate was dissolved in 1·0 ml glass-distilled water, and added to the drug, dissolved in 2·0 ml glass-distilled water, in a test tube and mixed with thorough shaking. The absorbency was read after 7 min in a cell with a 1-cm light path at 425 mμ. The pH of the reaction mixture was 5·0. All compounds were in the hydrochloride form. The points of half maximum precipitation for these four compounds are indicated by the letters a, b, c, d.

○, Thioproprazate = ●, Chlorpromazine = △, L-methotrimeprazine = ▲, Amitryptylene.

structure of the drug used.[1] Inspection of a series of such curves (obtained from twenty four compounds) suggests that the degree of inflection of the concentration curve may be related to the clinical potency of the compound as a tranquiliser.

A simple estimate of the degree of inflection of the concentration curve is given by that concentration of drug that will produce half the maximum degree of precipitation of polyphosphate—drug complex (Fig. 1). The degree of maximum precipitation is usually not difficult to determine, except in the case of the more potent tranquilisers with substituted side-chains. Here an optimum concentration of drug may be found, which, if exceeded, leads to the re-solution of the insoluble complex.

In a series of eleven compounds it is found that a broad correlation exists between the clinical effectiveness of a compound as a tranquiliser and the concentration of that drug needed to produce half-maximum precipitation with polyphosphate (Table 1).

TABLE 1. THE RELATIONSHIP BETWEEN THE EFFECTIVENESS OF A DRUG AS A TRANQUILISER, AND ITS CAPACITY TO FORM INSOLUBLE COMPLEXES WITH YEAST POLYPHOSPHATE

Concentration of drug needed to produce half-maximum precipitation with yeast polyphosphate (M)		Tranquilising potency of the drug on disturbed psychotics
Trifluoperazine	$6{\cdot}6 \times 10^{-4}$	Trifluperazine
Prochlorperazine	$6{\cdot}6 \times 10^{-4}$	Thioproperazine
Thioproprazate	$8{\cdot}3 \times 10^{-4}$	Thioproprazate
Thioproperazine*	10^{-3}	Prochlorperazine
Chlorpromazine	$2{\cdot}2 \times 10^{-3}$	Chlorpromazine
L-methotrimeprazine	$3{\cdot}7 \times 10^{-3}$	Promazine
Promazine	$4{\cdot}7 \times 10^{-3}$	Promethazine
Amitryptylene	$6{\cdot}0 \times 10^{-3}$	L-methotrimeptrazine
Promethiazine	$6{\cdot}6 \times 10^{-3}$	Amitryptrylene
Imipramine	9×10^{-3}	Imipramine
Chlorpromazine sulphoxide about 2% of the capacity of chlorpromazine to precipitate with polyphosphate		Chlorpromazine sulphoxide

All compounds used in the precipitation test were employed as their hydrochlorides, with the exception of prochlorperazine and thioproperazine methanesulphonates. Experimental conditions were as those described in Fig. 1.

* absorbency measured at 580 mμ

These drugs are known to be surface-active, and this surface activity is related to their potency as tranquilisers.[2] The same compounds also interfere with water and ion transport across biological membranes.[3, 4, 5] The mechanism of interaction of these compounds with negatively charged polyphosphates may reflect their mechanism of action with negatively charged cell membranes.

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