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Theoretical changes in drug distribution resulting from changes in binding to plasma proteins and to tissues

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Concentrations of chlorpromazine fluctuate in the plasma of dogs and man after intravenous doses. The possibility that the fluctuations could arise from movement of the drug between tissue and plasma stores is examined theoretically. Calculations show that small changes in protein binding of drugs in plasma and tissues could cause redistribution of highly bound drugs between tissues and plasma. Redistribution would be greatest after changes in tissue binding of highly bound drugs. Fluctuations in chlorpromazine concentrations could be caused in this way.

Fluctuations were recently observed in concentrations of chlorpromazine in plasma of dogs and man after intravenous doses (Curry, Marshall & others, 1970; Curry, Derr & others, 1970). For example, concentrations were sometimes seen to increase by 50% within 10 min, and similar decreases could also occur.

A constant concentration of a drug in plasma could be considered to be maintained in a theoretical situation in which input and output were balanced. Increases could usually arise only as a result of absorption of previously unabsorbed drug; decreases would usually result from removal of drug by metabolism and excretion. However, after an intravenous injection there are no opportunities for changes in the rate of input of drug. Thus fluctuations can occur only by movement of the drug backwards and forwards between plasma and other tissues. The possibility that redistribution between tissue and plasma stores, caused by changes in binding, could be sufficient to cause fluctuations in concentrations of chlorpromazine in plasma was therefore investigated from a theoretical point of view.

The findings are in agreement with, but more extensive than, previous reports concerning the significance of binding in drug distribution (Brodie, 1966; Martin, 1965; Meyer & Guttman, 1968).

EXPERIMENTAL

Relations describing protein binding of drugs are derivable from the Law of Mass Action. The constant, Kap, for each set of binding sites is determined from the equation:

$$\text{Kap} = \frac{[\text{Db}]}{[\text{Df}]\,[\text{Pf}]}$$

in which: [Db] is the molar equilibrium concentration of bound drug; [Df] is the molar equilibrium concentration of unbound drug; and [Pf] is the molar equilibrium concentration of protein not associated with drug molecules. At equilibrium in the

body, a drug is distributed between plasma water, plasma protein, and tissues (including blood cells), largely by reversible processes. The total amount of drug in the body D, consists of the sum of drug in plasma water, [Df] V, drug bound to plasma proteins [Db] Vp, and drug in tissues, [Dt] Vt, where [Dt] is the concentration of the drug in tissues, and V, Vp and Vt are the values of the volume of distribution of the drug in plasma water, plasma, and tissues respectively. The concentration of drug in plasma [Dp] = [Df] + [Db].

In this theoretical study 10 μg of drug were distributed through 1 g of biological material (tissue volume 10 $\times$ plasma volume) with various degrees of binding. Excess albumin at a molar concentration of 6×10^{-4} was the plasma protein. Calculations were made of the distribution of a drug in this system in four theoretical sets of conditions, as defined in the figure legends.

RESULTS

The results of the calculations are shown in Figs 1–4. As an example, in Fig. 1, at each value of fraction bound, the points on the lines, multiplied by V, Vp or Vt, as applicable, add up to 10 μg. (The calibrations of the axes should be noted.) The different values of [Df], [Db] and [Dt] in different binding conditions result from defining one binding ratio, and varying another; changes in all three concentrations are necessary if equilibrium is to be preserved.

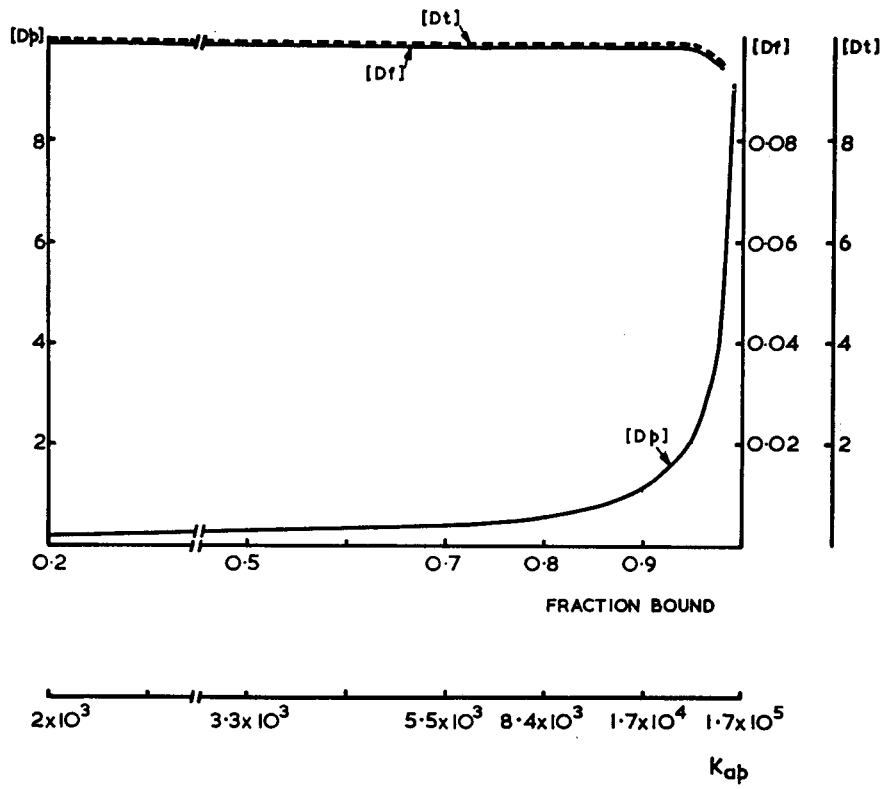

FIG. 1. Concentrations (μg/ml) of drug in plasma [Dp] and plasma water [Df], and mean concentration (μg/g) in tissues [Dt] for a model system (tissue volume ten times plasma volume), in which 10 μg of drug is distributed through 1 g of tissue and plasma, with a high degree of binding to tissues ([Dt] / [Df] = 100), and with varying degrees of binding to plasma protein.

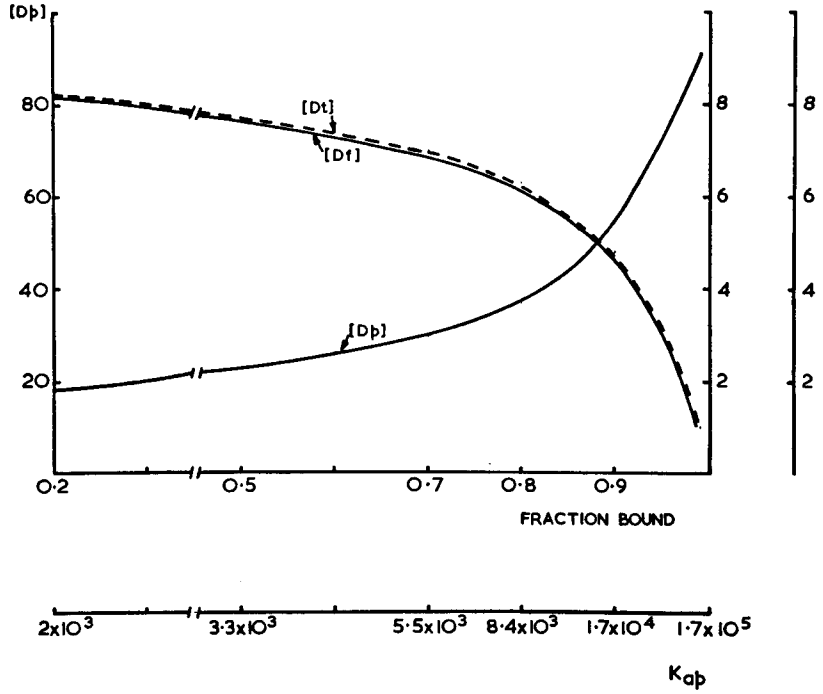

FIG. 2. Concentrations of drug in plasma, plasma water and tissues, for the model system of Fig. 1 with a low degree of binding to tissues ([Dt] / [Df] = 1), and with varying degrees of binding to plasma protein.

For drugs highly bound to plasma protein (fraction bound = 0·95) and highly bound to tissues ([Dt] / [Df]) = 100, a small change (± 0·01) in fraction bound could cause much redistribution between tissues and plasma (Fig. 1). However,

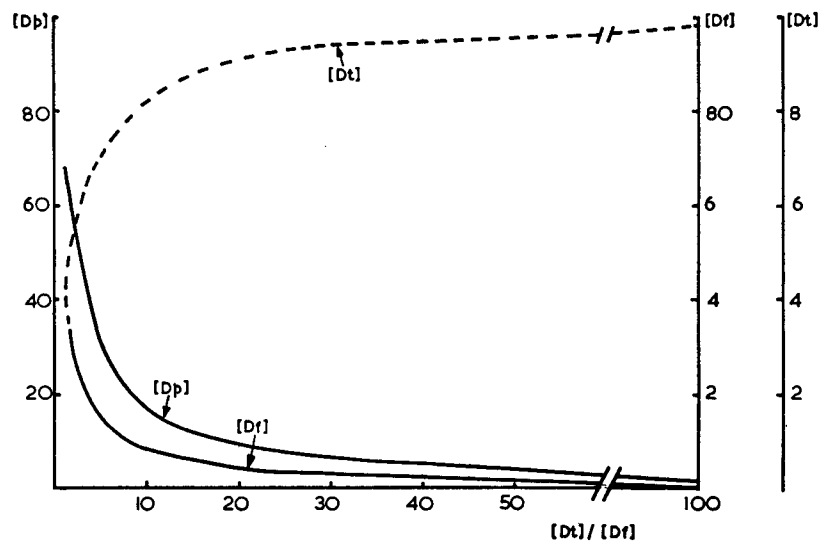

FIG. 3. Concentrations of drug in plasma, plasma water and tissues, for the model system of Fig. 1, with a high degree of binding to plasma protein (fraction bound = 0·95; Kap = 3·3 × 10^{-4}) and with varying degrees of binding to tissues.

because the tissue compartment is relatively large, the concentrations in tissues and plasma water would change less than might be expected. Thus drug concentrations at active sites in tissues might be relatively unchanged, in spite of large changes in concentrations in plasma. With drugs with lower binding to tissues ([Dt] / [Df]) = 1, concentrations in tissue and plasma water would change more with small changes in plasma protein binding (Fig. 2). Concentration changes in plasma would be correspondingly less. After changes in tissue binding, the redistribution would be greatest at lower tissue to plasma water concentration ratios (Figs 3 and 4). Considering all four situations, redistribution would be most marked after small changes in *tissue* binding of drugs *highly* bound to plasma protein.

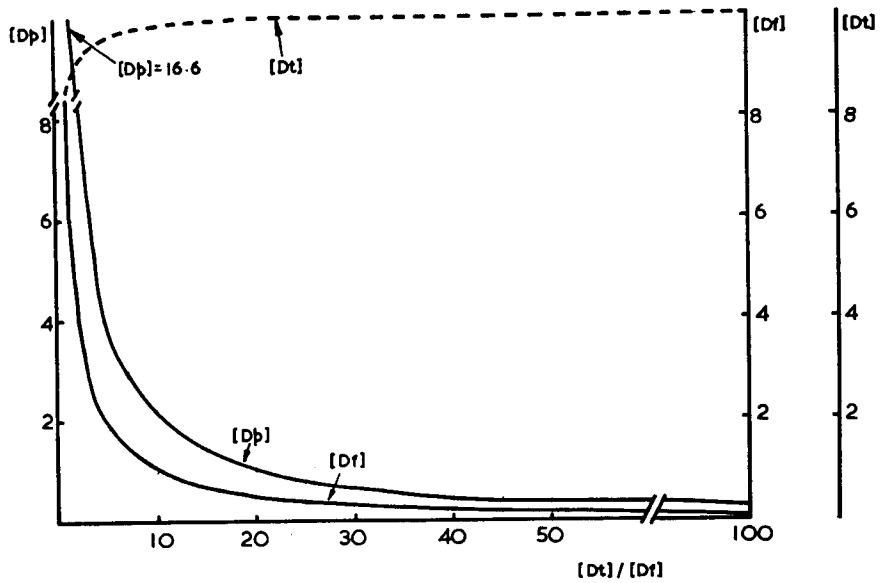

FIG. 4. Concentrations of drug in plasma, plasma water and tissues, for the model system of Fig. 1, with a degree of binding to plasma protein lower than in Fig. 3 (fraction bound = 0·5; Kap = $3{\cdot}3 \times 10^{-3}$), and with varying degrees of binding to tissues.

DISCUSSION

Pharmacological effects are sometimes related to concentrations of drugs in plasma or plasma water (Brodie, 1967). Redistribution of the type discussed theoretically, would affect concentrations of drugs in plasma, and would affect the amount of drug in plasma as a proportion of the amount in the whole body. The result would be an increased complexity of the relation between concentrations in plasma and at receptor sites on the one hand, and between concentrations in plasma and pharmacological effects on the other.

The model used can be criticized as being an oversimplification of what must be in nature a highly complicated system. For example, the chosen figure of $10 \times$ Vp for Vt is, at best, an estimate of the mean value for the volume of tissue which a drug penetrates. Equally, different tissues can carry different concentrations of drugs and the use of a mean value for [Dt] is undoubtedly an over-simplification. An infinite number of permutations of tissue and plasma binding is theoretically possible, yet only four combinations were considered in the present study. Finally plasma protein is not entirely albumin. However, the model was used to facilitate the

examination of the possibility of redistribution. To have considered each tissue individually and to have considered a large number of combinations of binding would have been a task of theoretically infinite proportions and the results would have made little difference to the conclusions.

The model was for no particular drug, as it represented a theoretical situation. Nevertheless, the diagrams were designed so that in a situation in which [Dp], [Df] and [Dt] are known for a chosen drug, it will be possible to estimate the likely influence of small changes in binding on distribution of the compound. The model could be used in the determination of changes in the distribution of one drug resulting from a change in binding, and for comparison of two drugs with different binding.

Changes in binding with concentration have been observed with phenylbutazone (Brodie & Hogben, 1957). Interspecies variations in binding have been observed with acidic drugs (Anton, 1960; Sturman & Smith, 1967), and with basic drugs (Borgå, Azarnoff & Sjöqvist, 1968; Curry, 1970). Differences between individuals have been recorded with thiopentone (Dayton, Perel & others, 1967), and with chlorpromazine (Curry, 1970). The possibility of variation within individuals appears not to have been explored.

Binding can be affected by minor changes in pH of plasma, and of intracellular fluid, by changes in concentrations of interfering substances, or by physical changes in the proteins or protein complexes to which drugs bind. Additionally, outside the limits of the model discussed in this report, differences in fraction bound can follow from changes in protein concentrations.

Chlorpromazine is a highly bound drug (the fraction bound to plasma protein is as high as 0·98 in man; the value for the ratio of average concentration in tissues to concentration in plasma water is 140) (Curry, 1970; Curry, Derr & others, 1970). Fluctuations in concentrations in plasma could apparently be caused by redistribution resulting from small changes in binding.

Acknowledgements

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