Plasma protein binding displacement interactions — why are they still regarded as clinically important?

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Throughout the history of science and medicine, apparently plausible hypotheses have been put forward to explain observations which are subsequently found to be incorrect. However, it may take much longer to remove incorrect but attractive hypotheses from textbooks and current opinion than to establish them in the first place. One such false doctrine is related to the clinical relevance of plasma protein binding displacement interactions. Despite the theoretical and experimental data to the contrary, the concept that plasma protein binding displacement is a common cause of clinically significant interactions may still be widely taught in some medical schools, often appears in textbooks and is accepted by many in the medical community and by drug regulators. The purpose of this article is to review the likely clinical importance of plasma protein binding displacement interactions and to suggest an algorithm for investigating potential interactions. I also wish to encourage teachers of therapeutics and drug regulators to regard protein binding displacement with the minor degree of attention it deserves.

About 25–30 years ago, marked increases in prothrombin times were observed in patients who were taking phenylbutazone in addition to warfarin [1, 2]. Soon after, severe hypoglycaemia was described in patients taking sulphonamides in addition to tolbutamide [3]. In both cases the drug of interest is highly bound to plasma proteins, and in both cases it was correctly observed that the interacting drug displaced the drug of interest from plasma proteins and increased the free fraction in plasma. Although some authors suggested that other mechanisms might be responsible [2, 3], others

attributed the cause of the altered drug response to plasma protein displacement [4, 5]. Other examples of clinically significant drug interactions which have been attributed to plasma protein binding displacement are presented in Table 1.

Since the initial attribution of the interactions in Table 1 to plasma protein binding displacement, there have been two major reasons why many authors have doubted whether this attribution adequately explains the observed interactions. These have come from pharmacokinetic theory [6–11] and from the demonstration of other mechanisms for observed interactions (see Table 1).

The pharmacokinetic argument is as follows: imagine our drug of interest, drug A, is given chronically to steady-state. Then drug B, which increases the free fraction of A, is added. As it is the free concentration of A which is responsible for its effects, will not the effect of A be significantly increased? Acutely, the amount of drug A displaced will not only be available to interact with its receptor, but is also available to be distributed throughout the rest of the body. The extent of increase in the free concentration of A will be buffered by redistribution, with the increase being greatest for drugs with the smallest initial distribution volumes. As distribution of drug from plasma to its receptor is often not instantaneous but is characterised by a first-order process with comparable rate to general drug distribution, this will also reduce the extent of increase in the effect of A. However, any increase in free A following redistribution will also be available for drug elimination. For low clearance (restrictively cleared) drugs, where intrinsic clearance of free drug is the only determinant of mean

Table 1 Examples of clinically significant drug interactions which have been attributed to plasma protein binding displacement

<i>Drug of interest</i>	<i>Displacing drug</i>	<i>Other mechanisms responsible</i>	<i>References</i>
Warfarin	Phenylbutazone	Inhibition of metabolism	2, 13, 14, 15
	Clofibrate	? Pharmacodynamic	17, 34
	Chloral hydrate	Possible pure displacement; clinical significance disputed	20, 21
	Sulphamethoxazole	Inhibition of metabolism	35
	Sulphinpyrazone	Inhibition of metabolism	36
Tolbutamide	Sulphonamides	Inhibition of metabolism	16, 37
	Phenylbutazone	Inhibition of metabolism	37
	Salicylates	Pharmacodynamic	16
Chlorpropamide	Sulphaphenazole	Prolongation of half-life	16
	Dicoumarol	Prolongation of half-life	16
Methotrexate	Salicylate	Inhibition of renal clearance	38, 39
Phenytoin	Valproate	Inhibition of metabolism	40

steady-state free drug concentration, free concentrations of A will return to the pre-B level. Thus any increase in pharmacological effect of A will be transient and cannot be sustained. How do the pharmacokinetic parameters of A compare in the absence and presence of B? Viewed from free drug concentrations in plasma, B will cause the volume of distribution of A to decrease, due to the reduced binding to plasma protein which is counted as 'tissue' binding for free drug. As the clearance of free A is unaltered, there will be a small reduction in the half-life of free A. Viewed from total plasma concentrations of A, B will cause the volume of distribution to increase, as less drug will be in the plasma compared with tissues. However, the volume of distribution (V) will increase less than proportionately to the increase in free fraction as the volume of plasma water into which the drug distributes is not changed: $V = V_P + V_T \cdot f_u/f_{uT}$ [12], where V_P = plasma volume, V_T = volume of tissue water, f_u = fraction of unbound drug in plasma, f_{uT} = fraction of drug not bound to tissue components. As plasma clearance is directly proportional to free fraction, $CL = f_u \cdot CL_{u_{int}}$ [12] where CL = clearance, $CL_{u_{int}}$ = intrinsic drug clearance of unbound drug, it will increase more than V and so half-life will decrease. The changes in free and total drug concentration half-lives must be the same as the two concentrations are in dynamic equilibrium. Thus, the overall result of displacement is that it may cause a minor transient increase in free drug concentration and effect, but the mean steady-state free drug concentration will be unaltered. Free concentration may, however, fluctuate to a slightly greater extent during a dosing interval owing to the small decrease in half-life. Thus, except where the slightly greater peak/trough ratio might be clinically important, the lack of change in mean steady-state unbound drug concentrations should result in no change in drug response and no need to alter the dosing regimen.

However, the clinician needs to be aware that displacement has occurred and to what extent when therapeutic drug monitoring is used so that the fall in total drug concentrations is not misinterpreted and the dose increased inappropriately.

Further examination of the two drug interactions quoted at the beginning of this article has shown that additional mechanisms are likely to be the major ones responsible for the exaggerated effect observed clinically. In addition to displacing warfarin from plasma proteins [13], phenylbutazone inhibits the metabolism of both S-warfarin and its less potent R-isomer [14, 15]. The combined effects of displacement and inhibition of metabolic clearance lead to complex effects on the kinetics of the two warfarin isomers. Similarly, sulphonamides reduce free tolbutamide clearance resulting in a sustained increase in hypoglycaemic effect [16]. However, confirmation that a pure protein binding displacement interaction produces no change in free concentration of the displaced drug comes from the warfarin-clofibrate interaction [17]. The interaction between the major metabolite of chloral hydrate, trichloroacetic acid, and warfarin has not been as thoroughly investigated but may be a pure displacement interaction. In their major and widely-quoted reviews on plasma protein binding displacement, Koch-Weser &

Sellers [18, 19] state that the effect of chloral is a transient increase of warfarin effect but the experimental evidence quoted does not clearly support this [20]. The clinical consequences of this interaction have been variously described as none [21] or frequently minimal or absent [22].

In their reviews, Koch-Weser & Sellers [18, 19] discuss and support the pharmacokinetic argument as to why the clinical consequences of displacement should be temporary. However, statements such as 'administration of strongly displacing drugs to chronically treated patients may markedly increase the concentration of free coumarin and cause severe hypoprothrombinaemia and bleeding' referenced to the warfarin-phenylbutazone interaction helped perpetuate the concept that displacement interactions are clinically significant. A table listing 'clinically important displacement interactions' referring additionally to the interactions between tolbutamide with phenylbutazone and sulphonamides contributed. Perhaps to redress this ambiguity, Sellers [7] subsequently published a paper entitled 'Plasma protein binding displacement interactions are rarely of clinical significance' but the concept has persisted.

When might a plasma protein binding displacement interaction be clinically significant? For low clearance drugs with a low therapeutic index and a small V , the temporary increase in drug concentration and the increased variation within a dosing interval might be clinically relevant. The drugs best fitting this description are warfarin ($f_u = 0.01$, $V = 9$ l), phenytoin ($f_u = 0.04$, $V = 35$ l) and tolbutamide ($f_u = 0.04$, $V = 10$ l) [23]. However, for high clearance (flow-limited) drugs given i.v., the above pharmacokinetic argument does not apply. For these compounds, increased free concentrations following displacement will not be adequately compensated by increased clearance, as both free and bound drug are already available for elimination. In the case of a highly protein bound high-clearance drug, a clinically significant interaction is possible. However, there are few examples of such drugs administered on a repeated-dose basis; one example is lignocaine. For high clearance drugs given orally, the 'well-stirred' hepatic model [24] predicts that although clearance increases only marginally with increasing free fraction, bioavailability will be reduced, hence average steady-state unbound concentrations should be unchanged [12].

How well are pharmacokinetic and clinical consequences of protein binding displacement explained in modern clinical pharmacology texts? I surveyed the section on protein binding displacement in a selection of clinical pharmacology texts available in the library of a major teaching hospital. Most had a thorough and adequate explanation [23, 25–28] but in some the reader would still be misled or confused. Examples of unsatisfactory explanations include a good discussion in the text but with the use of a diagram of the phenylbutazone/warfarin interaction as an example of a displacement interaction [29]; mentioning only the buffering effect of distribution without mentioning the effect of clearance [30]; mentioning that increased free concentrations due to displacement are temporary without an explanation of the reasons [31, 32] and the statement 'the net effect [of displacement] is that the biological action may be

Figure 1 Algorithm for determining clinical significance of potential protein binding displacement interactions.

increased' but the total plasma concentration . . . decreased [33]. It is also my personal experience working in drug development that many physicians in the pharmaceutical industry and academic clinical investigators regard protein binding displacement as clinically important. For example, during the clinical development of a highly-bound wide therapeutic index anti-infective compound, some investigators wished to exclude patients on any highly bound drug (even with a high therapeutic index) because of concern about clinically important displacement interactions. Despite demonstrating efficacy in an otherwise fatal disease, regulators expressed considerable concern about the need for clinical studies examining potential displacement interactions with this compound. It is also my experience teaching medical students that the suggestion that protein binding displacement is unlikely to have clinical consequences comes as a complete surprise and is initially regarded as

heresy. Thus, despite the academic clinical pharmacology community having put the clinical relevance of protein binding displacement in its appropriate (and minor) place I believe that there is ample evidence that this message has not reached the wider clinical community.

For those who are interested in improving patient therapy and those who are developing and regulating drugs I suggest the algorithm shown in Figure 1 for the investigation of protein-binding displacement interactions. I question the investigation of potential interactions which are not likely to improve the care of our patients, and the practice of drug regulators to routinely 'require' such studies in man in the development of highly bound drugs. However, when displacement does occur and drug concentrations are measured, it is important for binding to be measured so that the mechanism and extent of the interaction can be understood.

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