Protein Binding

<table>
<tr><td>Plasma Protein Binding</td><td colspan="4">

Almost all drugs are bound to plasma proteins to some extent
Drug-protein complexes are large & do not readily cross membranes
ONLY unbound/free drug can diffuse through capillary walls, produce pharmacologic effect, be metabolized & excreted
Plasma protein binding profile of drug determines extent of its drug distribution & elimination rate
Drugs which compete for same plasma protein binding site may displace each other (drug-drug interaction)

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<tr><td>Reversible & Irreversible Binding</td><td colspan="4">

Most drugs reversibly bind to proteins via electrostatic forces
Free Drug + Free Protein ⇌ Drug-Protein Complex
To maintain equilibrium between free & bound drug, if a free component goes away, a bound component will be released
Irreversible binding is less common & results in drug inactivation (e.g. cisplatin)

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<tr><td rowspan="5">Examples of Plasma Proteins</td><td rowspan="3">Albumin (quantitatively most important)</td><td colspan="3">

Generally acidic drugs bind more avidly to albumin
Low albumin levels (called hypoalbuminemia) = ↑Free Fraction of Drug in body

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<tr><td rowspan="2">Main Drug Binding Sites on Albumin</td><td>Site I</td><td>

Phenytoin,
Sulphonamides

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NSAIDs
Valproate

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<tr><td>Site II</td><td colspan="2">

Penicillins
Benzodiazepines
Probenecid

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<tr><td>α_1-acid-glycoprotein (reactive protein)</td><td colspan="3">

Binding to this protein is quantitatively less important since conc. are typically 100X less than that of albumin
Reactive protein that may increase several-fold in presence of acute inflammation/stress (e.g. myocardial infarction)
Mostly binds basic drugs (e.g. lignocaine)
Elevated conc. of α_1-acid-glycoprotein = ↓Free Fraction of Drug in body

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<tr><td colspan="4">Lipoproteins</td></tr>
<tr><td colspan="4">Specific protein carriers (e.g. thyroxine binding globulin, cortisol binding globulin)</td></tr>
<tr><td rowspan="3">Free Conc. & Free Fraction</td><td colspan="4">

In most cases, drug conc. at therapeutic doses are well below those of binding proteins & free drug fraction is constant

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<tr><td colspan="4">Total Drug Conc. (C_t) = C_f + C_b
Free Drug Conc. (C_f) = C_t * (1 - %Protein Bound/100)
Free Drug Fraction = C_f/C_t</td></tr>
<tr><td>E.g. Drug A 80% Protein Bound</td><td>100mg Dose
Total drug conc. = 10 mg/L
Free drug conc. = 2 mg/L
Free drug fraction = 0.20</td><td colspan="2">200mg Dose
Total drug conc. = 20 mg/L
Free drug conc. = 4 mg/L
Free drug fraction = 0.20</td></tr>
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Situations that can bring about a change in free drug fraction

<table>
<tr><td rowspan="3">Change in no. of plasma protein binding sites</td><td rowspan="2">↓Plasma Proteins</td><td colspan="2">• ↓No. of Binding Sites = ↑Free Fraction of Drug</td></tr>
<tr><td>Causes of ↓Plasma Proteins</td><td>• ↓Production (e.g. due to liver failure)
• ↓Intake (e.g. due to malnutrition, cachexia)
• ↑Elimination (loss via kidneys, e.g. nephrotic syndrome)
• Redistribution (trauma)</td></tr>
<tr><td>↑Plasma Proteins</td><td colspan="2">• ↑No. of Binding Sites = ↓Free Fraction of Drug
• e.g. Elevated α_1-acid-glycoprotein during an acute stressor</td></tr>
<tr><td>Δ in 'apparent' affinity of drug for plasma protein</td><td>↓Apparent Binding Affinity</td><td colspan="2">• ↑Free Fraction of Drug (e.g. Drug A in below example)
• e.g. Due to reversible competitive drug interactions (Drug B displaces drug A from binding sites)</td></tr>
<tr><td>Development of saturable protein binding (at higher drug doses)</td><td colspan="3">• For a few drugs, clinically used dose may be sufficiently large to saturate protein binding sites for that drug (Corticosteroids (e.g. prednisolone), Valproate, Cefazolin)
• At saturating doses, free fraction of that drug will be much greater than expected (Free drug conc. increases linearly with dose, but there is a less than linear increase in total drug conc. as saturation occurs, causing free drug fraction to increase)</td></tr>
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Clinical Significance of Changes in Drug Binding to Plasma Protein

- **No clinical significance** at all except for a <u>few rare theoretical exceptions</u> to this
- Changes in drug binding to plasma protein will **alter free fraction of a drug & total drug conc.** but **once steady state has been re-established, free drug conc. will return to as before** (with **no lasting change in drug effect**)
- There is **no significance of alterations** to plasma protein binding/plasma protein binding interactions **unless measuring total drug conc. & adjusting drug dosage accordingly** (e.g. **performing TDM**)

<table>
<tr><td rowspan="2">Reasons why it is not Clinically Significant

In nearly all cases where a clinically important protein binding interaction has been postulated, other mechanisms, have since been shown to be in vivo cause of increased drug effect (e.g. Due to metabolic inhibition rather than a change in free drug conc.)</td><td>If ↓Protein Binding</td><td>• Momentarily ↑Free Drug Conc. = ↑Free Drug available for distribution (V_d) & clearance (CL) processes = ↑V_d & ↑CL = ↓Free Drug Conc. (back to starting conc.)
• Result: ↑Free Fraction of Drug & ↓Total Drug Conc. but no change in free drug conc. when steady state is re-established
• At re-establishment of steady state, free drug conc. is the same as originally = Same drug therapeutic effect</td></tr>
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		• At re-establishment of steady state, free drug conc. is the same = Same drug therapeutic effect
Theoretical Exceptions	• Transient change in free drug conc. before steady-state is re-established = Excess drug effect/SE/inefficacy (very rare) (e.g. anaesthetics: thiopentone, diazoxide) ○ May be a consideration in determining a loading dose but will not affect chronic dosing	
	Drugs with very High CL (CL >30 L/h)	• E.g. IV lignocaine (Often drug dose is titrated to effect anyway) • Some drugs are cleared so rapidly that elimination process actually "drags" drug from its plasma protein binding site as it goes passed in blood • **Drug CL** is **dependent only on blood flow to eliminating organ** & is **not affected by extent of protein binding of drug** • Drug CL may not rise/fall to compensate for a change in free drug conc, since elimination organ is bypassed by drug • Very few clinical examples of this