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Pharmacokinetic effects of altered plasma protein binding of drugs in renal disease

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SUMMARY

The measurement of plasma drug concentrations provides no insight into the relationship between the free and the plasma-protein-bound fractions of drugs. Plasma protein binding may decrease in renal disease due to uremia, hypoalbuminemia, or due to drug interactions. Decreased plasma protein binding leads to an increase in free plasma fraction causing an increase in volume of distribution and a shorter elimination half life. The increase in the apparent volume of distribution and the shorter elimination half life cause a decrease in total plasma concentration. Therefore, the free drug concentration is more reliable than the total plasma concentration for therapeutic drug monitoring. However, the free amount in plasma and in tissue and the tissue-bound amount remain unchanged under steady state conditions. Thus, a decrease in plasma protein binding in renal disease usually does not lead to increased drug toxicity, and alteration of drug dosage is not required, although the total plasma concentration may be found to be considerably lower than normal. In addition to plasma protein binding, alteration of tissue binding must also be considered for the determination of the appropriate dosage of some drugs in renal disease.

INTRODUCTION

The measurement of drug concentrations in plasma is the most important basis for pharmacokinetic evaluation and clinical monitoring of drugs. However, the total concentration of drugs is usually measured in plasma, and no information is provided about free and protein-bound drug levels.

In this paper the basic pharmacokinetic principles of altered plasma protein binding will be derived from albumin binding since alteration of albumin binding is the most important phenomenon of protein binding in renal disease (Bowmer 1982, Clegg 1982, Robertz 1983, Lichtenwalner 1982, 1983). The pharmacokinetic principles derived for decreased albumin binding may be applied to alteration of drug binding to other proteins too.

In renal disease, plasma protein binding of drugs is subject to various alterations (Table I). Plasma protein binding of cationic (basic) drugs can be increased in renal failure (Piafsky 1980). Cationic (basic) drugs such as quinidine, propranolol, chlorpromazine, desmethylimipramine, d-tubocurarine and trimetoprim are bound to α_1-acid glycoprotein, transcortin, lipoproteins, gammaglobulin and red blood cells (Piafsky 1980). Plasma protein binding of drugs bound to α_1-acid-glycoprotein may be increased in systemic inflammatory disease, as often observed in nephrological patients (Schneider 1982).

Plasma albumin is the binding protein for all anionic (acidic) and neutral drugs (Piafsky 1980). The decrease in the plasma protein binding of drugs bound to albumin is more pronounced than the increase in the binding of cationic (basic) drugs. Plasma albumin binding of drugs may decrease in renal failure due to hypoalbuminemia in severe nephrotic syndrome as observed in digitoxin, prednisolone, phenytoin and clofibrate (Gugler 1975, Storstein 1977, Frey 1982). Additionally, drug binding to albumin is decreased due to competitive inhibition by uremic toxins and decreased drug-albumin affinity (Bowmer 1982, Robertz 1983, Lichtenwalner 1982, 1983). This leads to a binding defect of anionic (acidic) or neutral drugs such as digoxin and most probably digitoxin, in phenytoin, dicumarol, warfarin, morphine, diazepam, n-desmethyldiazepam, chlroam-

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Table I: Protein binding (PB%) in normal (norm) renal function, end stage renal disease (ESRD), during hemodialysis (HD) and in nephrotic syndrome (NS), where PB% = (1-fp)100

	norm	*ESRD*	*HD*	*NS*	
azlocillin	28%	25%			Reidenberg 1984
bilirubin		decreased			Reidenberg 1984
captopril	24%	18%			Yeung 1983
cefazolin	84%	73%	22%		Greene 1977
cefoxitin	73%	20%			Garcia 1979
chloramphenicol	53%	45%	30%		Piafsk
					Blouin 1980
chlorpromazine	98	98%			Piafsk 1980
clofibrate	96%			89%	Gugler 1975
clonidine	30%	30%			Hulter 1979
					Bennett 1980
congo red		decreased			Reidenberg 1984
dapsone		normal			Reidenberg 1984
desipramine	80%	normal			Reidenberg 1984
n-desmethyldiazepam	98%	94%			Piafsky 1980
desmethylimipramine	89%	88%			Reidenberg 1971
diazepam	99%	94%			Piafsk 1980
diazoxide (30 μg/ml)	92%	86%	83%		Pearson 1976
(300 μg/ml)	77%	72%			O'Malley 1975
dicloxacillin	96%	91%			Reidenberg 1984
diflunisal	88%	56%		39%	Verbeeck 1980
digitoxin	97%	96%	90%	96%	Storstein 1977
digoxin	25%		22%		Storstein 1977
doxycycline	88%	71%			Houin 1983
erythromycin	75%	77%			Iliopoulou 1982
etomidate	75%	57%			Reidenberg 1984
fluorescein	86%	decreased			Reidenberg 1984
furosemid	96%	94%		93%	Rane 1978
indomethacin		normal			Reidenberg 1984
maprotiline	90%	normal			Reidenberg 1984
β-methyldigoxin	30%		19%		Kramer 1974
methyl orange		decreased			Reidenberg 1984
methyl red		decreased			Reidenberg 1984
morphine	35%	31%			Piafsky 1980
nafcillin	88%	81%			Lichtenwalner 1982
naproxen	75%	21%			Anttila 1980
oxazepam	95%	88%			Greenblatt 1983
papaverine	97%	94%			Belpaire 1977
penicillin G	72%	36%			Lichtenwalner 1982
pentobarbital	66%	59%			Reidenberg 1984
phenobarbital	55%	decreased			Reidenberg 1984
phenol red		decreased			Reidenberg 1984
phenylbutazone	97%	88%			Belpaire 1977
phenytoin	90%	80%	93%	81%	Steele 1979
					Richens 1979
					Adler 1979
pindolol	41%	normal			Reidenberg 1984
prazosin	95%	92%			Reidenberg 1984
prednisolone (50 mg)	74%		65%	64%	Frey 1982a,b
(15 mg)	87%	88%		85%	Bergrem 1983
d-propoxyphene	76%	80%			Giacomini 1978
propranolol	88%	89%	90%		Piafsk 1980
quinidine	88%	86%	88%		Piafsky 1980
					Kessler 1981
					Lichtenwalner 1982
salicylate	94%	85%			Lichtenwalner 1982
sulfadiazine		decreased			Reidenberg 1984
sulfamethoxazole	74%	50%			Lichtenwalner 1982
sulfonamides		decreased			Reidenberg 1984
strophantin	1%		2%		Kramer 1974
theophylline	60%	decreased			Reidenberg 1984
thiopental	72%	44%			Reidenberg 1984
thyroxine		decreased			Reidenberg 1984
triamterene	81%	61%			Piafsk 1980
trimethoprim	70%	68%		70%	Piafsk 1980
					Lichtenwalner 1982
tryptophan	75%	decreased			Reidenberg 1984
d-tubocurarine	44%	41%			Piafsk 1980
valproic acid	85%	decreased			Reidenberg 1984
verapamil	90%	normal			Reidenberg 1984
warfarin	99%	98%			Odar-Cederlöf 1977

phenicole, triamterene, papaverine, doxycycline, captopril, and desmethylimipramine (Reidenberg 1971, Storstein 1977, Odar-Cederlöf 1977, Bachmann 1977, Piafsky 1980, Clegg 1982, Houin 1983, Yeung 1983).

Finally, plasma protein binding may be decreased due to drug interaction with heparin given regularly on hemodialysis. Heparin decreases albumin binding of drugs by itself as well as by liberation of free fatty acids (Naranjo 1982). Decreased plasma protein binding due to heparinization has been observed in digoxin, digitoxin, cefazolin, propranolol, quinidine, diazepam, chlordiazepoxide, oxazepam and quinidine (Storstein 1977, Greene 1977, Piafsky 1980, Kessler 1981, Schneider 1982, D'Arcy 1982).

Free plasma fraction

The usually measured plasma concentration (C) comprises the free (Cf) and bound (Cb) drug concentrations.

$$C = Cf + Cb \quad (1)$$

Thus the free plasma fraction (fp) is defined.

$$fp = \frac{Cf}{C} \quad (2)$$

Drug binding to albumin can be derived from the law of mass action (Kragh Hansen 1981). If binding capacity is not saturated, the free plasma fraction (fp) depends on the plasma albumin concentration (Calb), the drug-albumin association constant (Ka), the number of binding sites (n) of each albumin molecule, and on the molecular weight of albumin (MW = 69000 g/Mol) according to the definition of the association constant.

$$fp = \frac{1}{1 + Calb \frac{n\ Ka}{MW}} \quad (3)$$

The free plasma fraction (fp) will increase if plasma protein binding decreases. A decrease in plasma protein binding due to a decrease in the association constant in uremia is observed in phenytoin (Odar-Cederlöf 1974, Richens 1979, Kinniburgh 1981). A decrease in plasma protein binding due to a decrease in albumin concentration in nephrotic syndrome is observed in digitoxin (Storstein 1977).

Volume of distribution

The volume of distribution is a parameter representing the relationship between the plasma concentration and the total amount in the body. The volume of distribution can be expressed in terms of physiological body compartments: plasma volume (Vp) and the tissue water volume (Vt) (Wilkinson 1975) (Figure 1):

$$Vd = Vp + Vt \frac{fp}{ft} \quad (4)$$

The plasma volume (Vp) is considered to be 4% of the body weight or 2.5 liters, whereas tissue water (Vt) is considered as 60% of the body weight or 40 litres, and both spaced are considered to be physiological constants (Tozer 1981). Total body water comprises intracellular as well as extracellular water space. For drugs distributed exclusively in the extracellular space, as is the case for many antibiotics, the tissue water (Vt) corresponds to the extracellular space only, which is only 20% of the body weight or 13 liters.

An increase in the free plasma fraction (fp) will lead to an increase in the volume of distribution (Vd) if the free tissue fraction (ft) remains unchanged. An increase in the volume of distribution in uremia is observed in phenytoin, dicumarol and prednisone (Odar-Cederlöf 1974, Martin 1977, Bachmann 1977, Frey 1982). An increased volume of distribution in patients with nephrotic syndrome is observed in digitoxin (Storstein 1977).

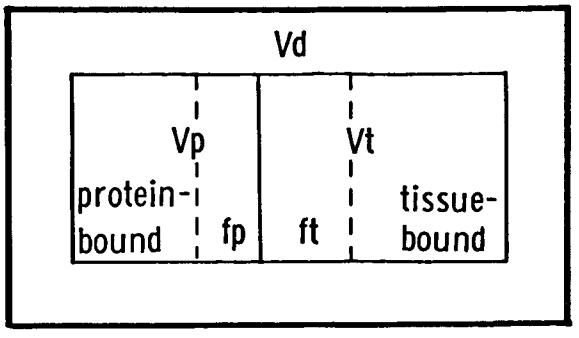

Fig. 1: Volume of distribution (Vd) is a function of plasma volume (Vp), tissue water (Vt), and free fraction of drug in plasma (fp) and tissue (ft) (Wilkinson 1975).

Elimination half life

To derive the effect of plasma protein binding on elimination, a basic assumption must be made: according to this assumption, it is only the free plasma fraction which is available for elimination. This assumption is proven by the kinetics of disopyramide and prednisolone (Giacomini 1982, Frey 1982). An increase in the free plasma fraction due to decreased plasma protein binding will lead

to an acceleration of the elimination half life from ($T_{1/2}$) to ($T_{1/2*}$).

$$\frac{T_{1/2*}}{T_{1/2}} = \frac{fp \quad Vd*}{fp* \quad Vd} \qquad (5)$$

The elimination half life ($T_{1/2}$) will decrease if the increase in the free plasma fraction (fp) is not equalized by an increase in the volume of distribution (Vd) according to equation 4. The elimination half life ($T_{1/2}$) will be accelerated as required for the additional removal of the amount released from plasma protein binding (Figure 2). A faster elimination half life in patients with nephrotic syndrome has been observed in digitoxin (Storstein 1977).

Equation 5 can be derived from the concept of free plasma clearance (Levy 1974 and 1976). Additionally, it can be shown that equation 5 also holds true for the post-distributive phase in the case of 2-compartment kinetics.

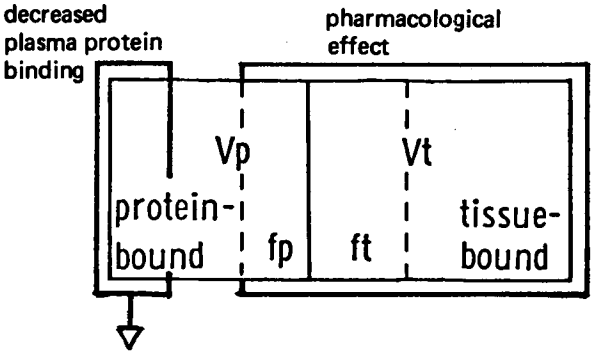

Fig. 2: A decrease in plasma protein binding causes no alteration in pharmacological effect. The volume of distribution increases, since the plasma concentration is smaller in relation to the remaining amount in the body. The elimination half-life is faster as required for the additional elimination of the amount released from plasma protein binding.

Steady state plasma concentration

Usually, the measured plasma concentration comprises the free and bound plasma fractions of drugs. The plasma concentration which is usually measured in clinical practice is the minimal steady state concentration. This minimal steady state concentration (C_{min}) is the plasma concentration after multiple dosing just before the next dose is applied. It depends on the bioavailability (F; for intravenous dosing, F = 1), on the dose (D), the volume of distribution (Vd), the elimination half life ($T_{1/2}$), and on the dosage interval (Tau).

$$C_{min} = \frac{F \; D/Vd}{\exp(\frac{\ln 2}{T_{1/2}} Tau) - 1} \qquad (6)$$

If plasma protein binding decreases, the free plasma fraction and the volume of distribution (Vd) increase, and the elimination half life ($T_{1/2}$) decreases. Consequently, the steady state plasma concentration (C_{min}) will decrease.

Decreased plasma levels due to uremia are observed in phenytoin and due to hypoalbuminema in digitoxin (Adler 1979, Storstein 1977). In patients with severe hypoalbuminemia during repetitive plasma exchange, we observed a reduced steady state plasma concentration of digitoxin, which was in complete agreement with the values calculated by the simultaneous use of equations 3, 4, 5 and 6 (Keller 1984).

Dosage recommendations

The question arises whether the decrease in plasma protein binding and the consequent decrease in steady state plasma concentrations requires an increase in drug dosage to achieve therapeutic drug action. Either drug dosage must be changed or drug levels lower than normal must be considered to be therapeutic in the case of reduced plasma protein binding.

It is the aim of drug dosage to achieve the same therapeutic effect in the case of altered plasma protein binding as in normals. The relation between dose and effect or the relation between pharmacokinetics and pharmacodynamics is rather complex (Holford 1982), but it can be postulated that the pharmacological effect is a function either of the free amount in plasma, of the free amount in tissue, or of the tissue-bound amount. Only the plasma-protein-bound amount will not be related to drug action (Figure 2).

From the above equations – and if the dosage is constant (D* = D) – it can be derived that, under steady state conditions, there is a constant relationship between the free plasma fracion (fp) and the total plasma concentration (C) and free plasma concentration remains unchanged by plasma protein binding (Cf = fp* C* = fp C = const.). The free plasma fraction (fp) will increase only in relation to and at the expense of the total plasma concentration (C). From this fundamental relationship, four important clinical conclusions can be derived.

First, the action of drugs very often is considered to be related to the area under the plasma concentration time curve (AUC). A decrease in plasma protein binding will lead to a decrease in the total AUC, but it can be shown that under steady state conditions the free area (fp AUC) remains constant when plasma protein binding changes (fp* AUC* = fp AUC = const.).

Secondly, under steady state conditions, the free amount in plasma remains constant, since the plasma volume can be considered to be constant (fp C Vp = const.) (Greenblatt 1982).

Third, it can be shown that, under steady state conditions, the free amount in tissue (ft T) remains constant if the free tissue fraction (ft) does not change.

$$ft\ T = fp\ C\ Vt = const. \quad (7)$$

Fourth, the tissue-bound amount (Tb) will be constant if tissue binding (ft) remains unchanged.

$$Tb = fp\ C\ Vt\ (\frac{1}{ft} - 1) = const. \quad (8)$$

Therefore, an alteration of plasma protein binding does not require the alteration of drug dosage as far as drug action is related to either the free area, the free amount in plasma, the free amount in tissue, or the tissue-bound amount. In the case of decreased plasma protein binding, the same therapeutic effect is achieved by unchanged dosage, although plasma concentrations may decrease considerably.

If an alteration of plasma protein binding occurs instantaneously, the free amount in plasma will increase before it can be removed by accelerated elimination. Thus toxic tissue levels may be produced by an increase in the free amount in plasma due to the release from protein binding and subsequently movement from plasma into tissue (Levy 1976). This maximal increase in the amount in tissue can be predicted from the increase in the free plasma fraction (fp). The instantaneous increase in the amount in tissue ($T^* - T$) will be restricted to the amount effectively liberated from plasma protein binding which is usually only a small fraction of the total amount in the body and risk of intoxication will be limited.

$$T^* - T = C\ Vp\ (1 - \frac{fp}{fp^*}) \quad (9)$$

It is the clinically most important conclusion of this paper that alteration of plasma protein binding per se does not require alteration of drug dosage. Renal disease is very often associated with alteration of elimination and distribution, which requires considerable alteration of drug dosage. Alteration of dosage is needed if uremia leads to changes in receptor sensitivity or retention of active metabolites. However, alteration of plasma protein binding alone does not require alteration of drug dosage.

Alteration of drug dosage is not required even if the total plasma concentration is decreased. This limits the value of measuring the total plasma concentration for therapeutic drug monitoring, and measurement of free plasma concentration has been recommended (Levy 1984). But the evaluation or free plasma concentration by ultracentrifugation of equilibrium dialysis reuqires much technical effort and may be necessary only when alteration of plasma protein binding is suspected (Rimmer 1984).

Clinical investigations on prednisolone, fentanyl, phenytoin, warfarin, and clofibrate also led to the conclusion that an alteration of plasma protein binding requires no alteration of drug dosage (Frey 1982, Bergrem 1983, Holley 1982, Odar-Cederlöf 1977, Adler 1979, Bachmann 1977, Gugler 1975).

The effect of many drugs, for example, antibiotics is usually related to the free plasma concentraiton and to the free amount in tissue (Singhvi 1978). Many other drugs, however, such as digoxin and digitoxin, act upon a specific receptor at the target organ. It is an important question whether the effect of receptor-active drugs is related to the free concentration in plasma or to the tissue bound amount. Physiologically, the receptor is located in the tissue, but the tissue bound amount depends not only on the free plasma concentration but also on the tissue binding represented by the free tissue fraction. The volume of distribution for digoxin and digitoxin is reduced in uremia, indicating displacement of digoxin and digitoxin from tissue receptors by uremic toxins which also displace them from plasma proteins (Aronson 1983). Therefore, dosage recommendations for drugs acting at specific tissue receptors must be based on the free plasma concentrations as well as on tissue binding. Reduced tissue binding usually requires a dosage reduction.

Bioavailability

Bioavailability indicates the rate and extent of drug absorption and usually depends on the galenic properties of the drugs. However, some drugs are subjected to extensive presystemic elimination after oral dosing due to a first pass effect (Rowland 1972). Reduced bioavailability due to a first pass effect depends on liver blood flow (Q) and intrinsic clearance constant (Cl_{int}) and may be decreased if free plasma fraction (fp) increase (Wilkinson 1975).

$$F = \frac{Q}{Q + fp\ Cl_{int}} \quad (10)$$

The most important representative of an extensive first pass effect are propanolol and lidocaine, but relevant effects of altered plasma protein binding on bioavailability are not observed.

Saturable protein binding

The basic statement that the free plasma concentration is constant under steady state conditions is not in contradiction to nonlinear plasma protein binding. Theoretically, plasma protein binding may be nonlinear, because both the free and bound plasma concentrations show a nonlinear relation to the total amount in the body.

Actually, however, nonlinear plasma protein binding means that the bound plasma concentration is related nonlinearly to the total amount in the body, and the relationship between the total plasma concentration and the total amount is nonlinear due to saturation of the bound plasma concentration (McNamara 1983). Thus, the kinetics of the free plasma concentration may be linear, and a linear relation between dose and drug action can be assumed (Lima 1983).

Nonlinear and concentration-dependent plasma protein binding is observed in prednisolone and other corticosteroids, in disopyramid, catecholamines, phenylbutazone, naproxen, propranolol, ceftriaxone, and amide type local anesthesics (Frey 1982, Giacomini 1982, McNamara 1983). Alteration of prednisolone dosage was not required in patients with severe nephrotic syndrome (Frey 1982, Bergrem 1983).

Nonlinear elimination

Many drugs are eliminated by hepatic metabolism, obeying nonlinear and saturable Michaelis Menten kinetics, but even nonlinear and saturable elimination kinetics are in conformity with the basic statement that the free plasma concentration remains constant under steady state conditions (Bachmann 1982). In nonlinear kinetics, the parameter elimination half life can be considered to depend on the concentration (C) and on metabolism constants ($V_m K_m$).

$$T_{1/2} = \ln 2 \frac{K_m + C}{V_m} \qquad (11)$$

Still under nonlinear conditions, the elimination half life ($T_{1/2}$) as defined above depends on the free plasma fraction (fp) and the volume of distribution (Vd), and it can be shown that equation 5 is also valid if elimination kinetics are nonlinear.

Elimination of phenytoin follows nonlinear kinetics and the observed decrease in elimination half life in uremia can be evaluated by the present linear equations (equations 4 and 5), although the elimination is saturable, and the elimination half life is concentration-dependent (Richens 1979).

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