

PROTEIN BINDING OF DRUGS,  
DRUG ENANTIOMERS, ACTIVE DRUG  
METABOLITES AND THERAPEUTIC  
DRUG MONITORING

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In the past, most people received uniform doses of most drugs. This led to large variation in intensity of effect. Subsequent research indicated most of this inter-individual variation in intensity of effect was due to inter-patient variation in drug elimination. This led to the concept of therapeutic drug monitoring where the patient's dose is individualized to achieve a desired therapeutic plasma level of the drug. Until recently, total drug plasma concentration (bound plus unbound) was used to individualize the dose. In the future, many predict that dosing schedules will be further refined and be guided by unbound drug concentration monitoring. This is in the hope of further narrowing inter-individual variation in response. The purpose of this chapter is initially to discuss studies comparing unbound and total drug concentration monitoring with intensity of effect to see how much clinical utility is really gained by introducing the extra analytical step necessary to measure free drug concentrations. Following this, protein binding of drugs and their active metabolites will be compared and finally protein binding of drug enantiomers (optical isomers) will be discussed.

Mungall et al. (1984) studied the relationship between steady-state unbound and total warfarin plasma levels and anticoagulant effect in 50 patients. As can be seen in Table 23.1, unbound warfarin plasma levels correlated with anticoagulant effect better than total levels. However, on the basis of regression analysis of the logarithm of the plasma level with anticoagulant effect, the correlation of unbound warfarin concentration ( $r = 0.5$ ) with effect was only slightly better than that of total concentration ( $r = 0.45$ ).

A comparison of total and unbound plasma carbamazepine concentrations with clinical toxicity (intermittent side effects which were

TABLE 23.1  
Warfarin Concentration and Anticoagulant Effect in 50 Patients

Dose (mg/day/m <sup>2</sup> )	Warfarin Plasma Levels		Prothrombin Ratio
	Total (μg/ml)	Free (ng/ml)	
3.04 ± 1.32*	1.64 ± 0.81	5.9 ± 2.5	< 1.5
2.99 ± 1.36	2.41 ± 0.99	9.4 ± 4.1	1.5-2.5
2.70 ± 1.39	2.46 ± 1.31	16.4 ± 5.7	> 2.5

\*Mean ± S.D.

Source:

Modified from Mungall et al. 1984.

not defined in article) was studied in nine patients receiving standard three times a day dosing regimens (Perucca 1984). While the side effects correlated strongly with unbound carbamazepine levels, this correlation was found to be only slightly superior to the correlation with total drug levels (Fig. 23-1).

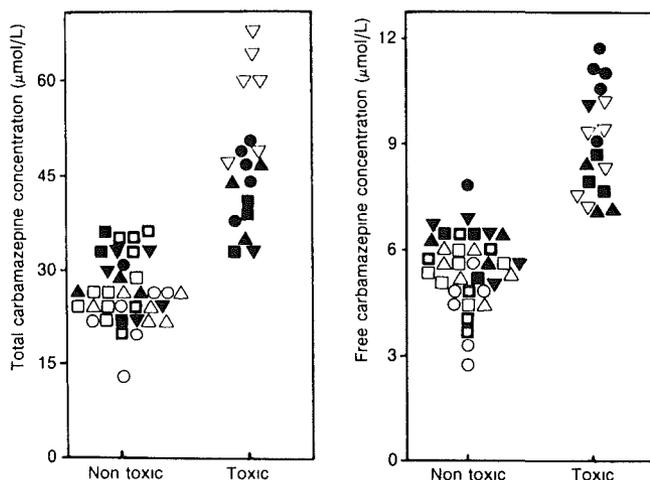


FIGURE 23-1

Relationship of total and free plasma carbamazepine concentrations with clinical toxicity in 9 patients. Each symbol represents 1 patient. Each patient was studied 6 times over the day in order to evaluate intermittent side effects.

Source: Perucca 1984. Reprinted with permission.

Booker and Darcey (1973) compared unbound and total serum phenytoin concentrations with clinical toxicity (ataxia, nystagmus) in 25 non-uremic epileptic patients and observed that toxicity correlated much better with unbound than with total drug levels since there was much less overlap in unbound phenytoin serum levels between non-toxic and toxic patients compared to the overlap seen in total serum levels between these two groups. However, these findings were criticized by other investigators including Dr. Sjöqvist's group (Barth et al. 1976) on several grounds, including the fact that the ultrafiltration device used was technically unsatisfactory since the filter device adsorbed phenytoin (12 percent), caused a variable dilution of the filtrate and permitted albumin to leak into the filtrate (also see Perucca 1984). Interestingly, Barth et al. (1976) and Porter and Layzer (1975), using different ultrafiltration devices, observed a smaller inter-subject variation in unbound phenytoin fraction in a larger series of epileptic patients with normal renal function compared to that reported by Booker and Darcey (1973). This result also raises questions about the validity of the data presented by Booker and Darcey.

Recently, the relationship between unbound phenytoin and total drug plasma levels in non-uremic epileptic patients was studied by two different groups. Kilpatrick, Wanwimolruk, and Wing (1984) found that unbound phenytoin (mg/l) = 0.12 total phenytoin (mg/l) + 0.01 ( $r = 0.93$ ,  $p < 0.001$ ). In only 5 out of 46 patients did the unbound concentration better reflect the clinical status of the patient than did the total phenytoin concentration. A similar linear relationship between unbound and total phenytoin plasma levels was found in 56 non-uremic patients in a study by Rimmer et al. (1984) with an even better correlation ( $r = 0.99$ ). Thus, it is tempting to conclude that in non-uremic epileptic subjects total phenytoin concentration will accurately reflect drug levels in plasma water in most patients.

In uremic patients there is decreased plasma protein binding of phenytoin. Thus, the relationship between total and unbound phenytoin in these patients is altered from that seen in non-uremic patients. However, detailed studies with phenytoin have shown that the degree of decrease in protein binding is proportional to the severity of the impairment of renal function. Therefore, one can calculate the decrease in total phenytoin concentration (bound plus unbound) required to achieve phenytoin levels in plasma water similar to that seen in plasma water of non-uremic subjects (Reidenberg and Drayer 1984) possibly obviating the need for measuring unbound phenytoin levels in many uremic patients. This, however, is just a first approximation. One uremic patient taking phenytoin who developed a slight nystagmus had a plasma water phenytoin level of 0.6  $\mu\text{g/ml}$  which is well below that considered toxic in non-uremic subjects (Reidenberg

and Affrime 1973). This suggests that appropriate studies be done to determine whether the therapeutic range for phenytoin in plasma water of uremic patients is similar or dissimilar to that in non-uremic subjects.

The few studies reviewed here fail to support the idea that measuring unbound drug is clinically better than the current practice of measuring total (bound plus unbound) drug in plasma. There obviously is a need for more research in this area. As for now, I suggest that unbound drug level monitoring be used only for highly protein bound drugs when toxicity is observed with total plasma levels in or below the "usual" therapeutic range for total drug. This would allow differentiating drug toxicity from toxicity due to underlying disease.

The next topic to be discussed is protein binding of drugs and their active metabolites. Drug metabolites are generally more polar (have lower partition coefficients) and are less protein bound than their respective parent drugs (Fig. 23-2). For instance, lidocaine

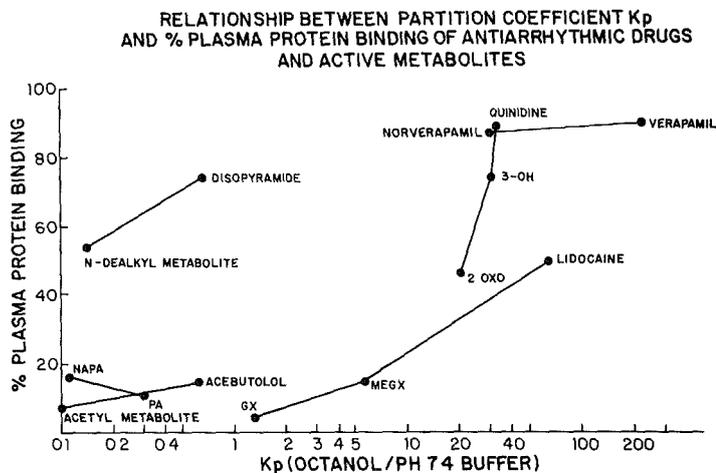


FIGURE 23-2

Relationship between partition coefficient  $K_p$  and percent plasma protein binding of antiarrhythmic drugs and active metabolites in man. Abbreviations: 3-OH, 3(s)-3-hydroxyquinidine; 2'OXO, 2'-oxoquinidine; PA, procainamide; NAPA, N-acetylprocainamide. MEGX and GX are metabolites of lidocaine with 1 less ethyl and 2 less ethyl groups respectively.

Source: Drayer DE 1984. "Clinical consequences of the lipophilicity and plasma protein bindings of antiarrhythmic drugs and active metabolites in man." Annals of the New York Academy of Sciences 432: 45-56. (Reprinted with permission.)

is more lipophilic (partition coefficient  $K_p = 65$ ) than its two dealkylated metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) and is most strongly bound to plasma proteins in normal subjects (50 percent bound). GX is the least lipophilic ( $K_p = 1.3$ ) of these three compounds and is least strongly bound to plasma proteins (only 5 percent). MEGX is of intermediate polarity and protein binding. Similarly, quinidine is more lipophilic ( $K_p = 36$ ) than two of its oxidized metabolites [2'-oxoquinidinone and (3S)-3-hydroxyquinidine] and is 89 percent bound to plasma proteins in normal subjects. 2'-Oxoquinidinone is the least lipophilic of these three compounds ( $K_p = 21$ ) and is only 46 percent bound. (3S)-3-Hydroxyquinidine is of intermediate polarity ( $K_p = 31$ ) and protein binding (74 percent). Therefore, the contribution of the active drug metabolites listed in Figure 23-2, to parent drug therapy will be erroneously estimated, if one compares the concentration of the metabolite in plasma to that of the parent drug ignoring differences in plasma protein binding. An exception to this generalization is that N-acetylprocainamide ( $K_p = 0.31$ ) is slightly more lipophilic than procainamide ( $K_p = 0.11$ ) but is slightly less protein bound than the parent drug (11 percent versus 16 percent).

Similarly, the partial biotransformation of benzodiazepines in man is shown in Figure 23-3. Notice that the successive addition of one oxygen atom and then two oxygen atoms to the medazepam molecule to yield diazepam and temazepam, respectively, markedly increases the polarity of the molecule ( $K_p$  decreases). However,

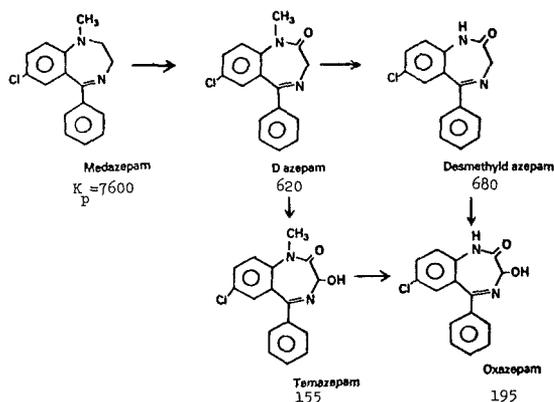
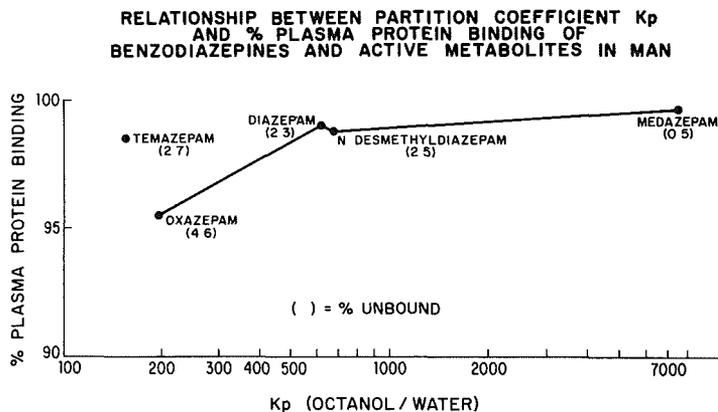


FIGURE 23-3

Partial biotransformation of benzodiazepines in man.  $K_p$  is the partition coefficient.



**FIGURE 23-4**

Relationship between partition coefficient  $K_p$  and percent plasma protein binding of benzodiazepines and active metabolites in man.

notice that demethylation of the diazepam and temazepam, which is also an oxidative process, in these cases makes the molecule slightly more lipophilic (slight increase in  $K_p$ ), not more hydrophilic. Thus, this is an exception to the rule that biotransformation increases the hydrophilicity of the drug molecule. The relationship between partition coefficient ( $K_p$ ) and percent plasma protein binding of these compounds is shown in Figure 23-4. Medazepam is the most lipophilic ( $K_p = 7600$ ) compound in this series and is most strongly bound (0.5 percent unbound) to plasma proteins. Oxazepam is the least lipophilic ( $K_p = 200$ ) (most polar) and is least strongly bound (4.6 percent unbound or a nine-fold increase). Diazepam and N-desmethyldiazepam are of intermediate polarity and protein binding. Unexplainably, temazepam is an exception in that its protein binding is far too high for its degree of polarity ( $K_p$ ).

In the United States in 1982, 12 of the 20 most prescribed drugs and 114 of the top 200 drugs prescribed contained at least 1 asymmetric center (Wainer and Doyle 1984). Many of these drugs are given as racemic mixtures. A valid question for therapeutic drug monitoring in this instance is: Should we continue the current practice of measuring total drug plasma levels (sum of the individual enantiomer plasma levels) and determining total drug pharmacokinetics or should the enantiomers be separated and quantitated individually? I suggest the latter for the following reasons: Drugs given as racemic mixtures usually have the therapeutic activity residing mainly in one of the enantiomers. The other enantiomer can have undesirable properties (see Table 23.2), have different therapeutic

TABLE 23.2

## Undesirable Activity of the Non-therapeutic Enantiomer of Optically Active Drugs Administered as Racemates

1. At equianesthetic doses in man, (-)ketamine produces more cardiovascular stimulation and more spontaneous motor activity than (+)ketamine (White et al. 1979).
2. Although both enantiomers of thalidomide are equally sedating in the mouse (Fabro, Smith, and Williams 1967), only the l-enantiomer and its glutamic acid metabolite are teratogenic in this species and also in rats (Blaschke et al. 1979; Ockenfels and Kohler 1970; Kohler, Meise, and Ockenfels 1971).
3. Although the l-enantiomer of pentazocine is more potent in man as an analgesic and a respiratory depressant, the d-enantiomer causes more subjective feelings of anxiety (Forrest et al. 1969; Bellville and Forrest 1968).
4. (+)Barbiturates may cause CNS excitation while (-)barbiturates are sedatives (Ho and Harris 1981). For example, the (-)enantiomer of pentobarbital is a more potent sedative in man than the (+)isomer. Sedation with the (+)stereoisomer, however, is accompanied by symptoms of hyper-irritability (hiccups, involuntary twitching) and a higher degree of confusion during recovery (Jim Perel, personal communication).
5. Many of the serious side effects (granulocytopenia, for example) encountered with d, l-dopa in man were not seen with levodopa and therefore can be attributed to the d-enantiomer (Cotzias, Papavasiliou, and Gellene 1969). For this reason, the racemate is no longer given.

activities (see Table 23.3), or be pharmacologically inert. For drugs administered as a racemic mixture and eliminated mainly by biotransformation, individual enantiomers can have different pharmacokinetic parameters (Low and Castagnoli 1978). For example, most of the therapeutic activity of propranolol resides in the (-)enantiomer. The clearance of this optical isomer is 1000 ml/min compared to 1200 ml/min for the (+)enantiomer (Olanoff et al. 1984). More dramatically, the plasma clearance for (-)verapamil, the therapeutic isomer, is about twice that of the (+) isomer (1400 ml/min versus 800 ml/min (Eichelbaum, Mikus, and Vogelgesang 1984), and the plasma clearance of (-) warfarin, the therapeutic isomer, is 1.6 times that of the (+)enantiomer (2.1 ml/hr/kg versus 1.3 ml/hr/kg)

(Wingard, O'Reilly, and Levy 1978). Large inter-individual variation in the plasma ratio of tocainide enantiomers have been observed [S(+)/R(-) varies from 4:1 to 1.3:1, Sedman, Bloedow, and Gal 1984], while the (-)/(+) propranolol enantiomer ratio in plasma of different subjects varies from 2:1 to 1:1, 2 hr after the propranolol dose (Von Bahr, Hermansson, and Tawara 1982). Therefore, since many drug enantiomers have different pharmacologic effects and there seems to be substantial inter-subject variation in the plasma ratios of individual drug enantiomers, if therapeutic drug monitoring is proposed for these drugs it probably is a good idea for individual drug enantiomer levels to be determined and correlated with effect to see if any extra clinical benefit is gained.

In a previous section, the influence of drug polarity on drug protein binding was discussed. However, for drugs that bind to albumin the situation is more complex. There are two high affinity binding sites of most drugs to human serum albumin, the warfarin site (or site I) and the benzodiazepine and indole site (site II) (Fehske, Müller, and Wollert 1981; Jahnchen and Müller 1983). Drugs that bind to site II do so in a highly stereoselective manner. For example, the essential amino acid L-tryptophan binds to this site with an affinity about 100 times greater than D-tryptophan (McMenamy and Oncley 1958). Similar to this, several chiral benzodiazepine derivatives also interact with this site in a highly stereoselective manner (Jahnchen and Müller 1983). For example, the d-enantiomer of oxazepam hemisuccinate binds 90 percent to 1 percent human serum albumin compared to only 45 percent for the l-form (Müller and Wollert 1975).

TABLE 23.3

Drug Optical Isomers Which Have Different Therapeutic Effects

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1. Labetalol contains two asymmetric carbons and the clinical formulation consists of equal proportions of four optical isomers. The RR isomer produces most of the  $\beta$ -adrenoceptor blockade and the SR isomer produces most of the alpha-blockade in anesthetized dogs (McNeil and Louis 1984).
  2. The l-enantiomer of propranolol displays mainly  $\beta$ -adrenoceptor blocking activity while the d-enantiomer has direct electrophysiological actions similar to those of quinidine (Iansmith, Nash, and Bandura 1983).
  3. The (+)enantiomer of tranylecypromine is a more powerful monoamine oxidase inhibitor in human brain while the (-)isomer is more effective as an inhibitor of neuronal uptake of catecholamines (Nickolson and Pinder 1984).
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TABLE 23.4

Human Plasma Protein Binding of the Therapeutic and Non-Therapeutic Optical Isomers of Acidic Drugs

Drug	Unbound Fraction $\times$ 100		Reference
	Therapeutic Optical Isomer	Non-therapeutic Optical Isomer	
Moxalactam	(R) 47	(S) 32	Yamada et al. 1981
Phenprocoumon	(-)* 0.72	(+) <sup>†</sup> 1.07	Schmidt and Jahnchen 1978
Warfarin	(-) 0.9	(+) 1.2	Yacobi and Levy 1977

\*(-) indicates levorotatory isomer.

<sup>†</sup>(+) indicates dextrorotatory isomer.

Also, the R-enantiomer of 3-methyldiazepam binds to human serum albumin to a much greater extent than the S-form (82 percent versus 47 percent) (Alebic-Kolbah et al. 1979).

Binding of acid drugs whether to site I on albumin or to human plasma proteins (Table 23.4) is stereoselective but to a smaller extent. For example, S(-) phenprocoumon binds to 0.2 percent human serum albumin slightly greater than the R(+) enantiomer (94 percent versus 91 percent) (Brown et al. 1977). Also, another example of the stereoselective binding of an acidic drug (a barbiturate) to human albumin is that of N-methyl-5-cyclohexenyl-5-ethylbarbital where the therapeutic (-) isomer binds 63 percent to 4 percent human serum albumin compared to 73 percent for the nontherapeutic (+)enantiomer (Buch et al. 1970). For the three acidic drugs listed in Table 23.4, there is about a 30 percent excess in the unbound fraction of one of the drug enantiomers to human plasma proteins compared to the other optical isomer.

In contrast, the binding of basic drugs is relatively non-stereoselective whether to  $\alpha_1$ -acid glycoprotein or human plasma proteins (Table 23.5). For example, both enantiomers of ketamine bind 55 percent to 0.2 percent  $\alpha_1$ -acid glycoprotein (Dayton et al. 1983), while (-)propranolol binds to 0.66 gm/liter  $\alpha_1$ -acid glycoprotein to a slightly greater extent than (+)propranolol (87 percent versus 84 percent) (Walle et al. 1983). For six of the nine basic drugs listed in Table 23.5, there is no difference in the protein binding of the drug enantiomers to human plasma proteins (verapamil,

TABLE 23.5

Human Plasma Protein Binding of the Therapeutic and Non-Therapeutic Optical Isomers of Basic Drugs

Drug	Unbound Fraction × 100		Reference
	Therapeutic Optical Isomer	Non-therapeutic Optical Isomer	
Amphetamine	(+)† 84	(-)‡ 84	Wan et al. 1978
Disopyramide	(-) 39 <sup>a, b</sup>	(+) 27 <sup>a, b</sup>	Cook et al. 1982; Burke et al. 1980
Fenfluramine	(+) <sup>d</sup> 2.8	(-) 2.9	Caccia et al. 1979
Methadone	(-) 12.4	(+) 9.2	Romach et al. 1981
Propoxyphene	(+) 1.8	(-) 1.8	Dr. H. Sullivan*
Propranolol	(-) 11	(+) 12	Albani et al. 1984
Quinidine	quinidine 13	quinine <sup>c</sup> 14	Notterman et al. 1984
Tocainide	(-) 86-91	(+) 83-89	Sedman et al. 1982; Sedman et al. 1984
Verapamil	(-) 11	(+) 6.4	Eichelbaum et al. 1984

\*Personal communication, Lilly Research Laboratories.

†(+) indicates dextrorotatory isomer.

‡(-) indicates levorotatory isomer.

<sup>a</sup>At present the anti-arrhythmic activity of the individual enantiomers of disopyramide is unknown (Pollick et al. 1982). However, (+)disopyramide is about 4 times more potent than (-)disopyramide as an anticholinergic agent (Giacomini et al. 1980) which in this instance is an undesirable property.

<sup>b</sup>At 2 µg/ml disopyramide in plasma.

<sup>c</sup>Non-therapeutic as an anti-arrhythmic drug.

<sup>d</sup>Although several studies (referenced in Caccia et al. 1979) indicate that the enantiomers of fenfluramine have different pharmacologic effects, it is not clear which one is the therapeutic isomer.

disopyramide, and methadone are exceptions). Thus, the high affinity binding sites on albumin have more receptor-like properties than the binding sites on alpha<sub>1</sub>-acid glycoprotein, since the former can much better differentiate between enantiomers. This property is unexpected since these albumin sites bind drugs whose chemical structures are very different.

One last point about optically active drugs marketed as racemic mixtures should be mentioned. In reality, two separate drugs are being given at the same time with different pharmacologic effects and pharmacokinetics. This situation probably is not desirable for most racemic mixtures especially if therapeutic and unwanted properties reside in different enantiomers. Therefore, it would appear desirable to evaluate the pharmacologic effects of each of the enantiomers of a racemic mixture to see if the risk/benefit ratio of the mixture can be improved by the use of only one of the enantiomers. A sad thought is that if the situation for thalidomide in the mouse presented in Table 23.2 was representative of that in man, then the thalidomide disaster could have been avoided if only the d-enantiomer had been marketed.

#### FUTURE TRENDS

The analytical technology enabling drug concentration monitoring in plasma water to be more easily carried out is rapidly evolving (Levy et al. 1984). Also the technology (for instance, high pressure liquid chromatography) necessary to routinely separate and quantitate individual drug enantiomers may soon be at hand (Wainer and Doyle 1984) allowing a complete pharmacokinetic profile, including protein binding, of the individual drug stereoisomers to be more readily determined. Therefore, I anticipate many more studies seeking to determine whether routine unbound plasma level monitoring of a drug, or of an individual drug enantiomer, is clinically more valuable than total drug concentration monitoring, the ultimate goal being to better individualize the patient's drug dose.

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