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The Importance of Protein Binding in Drug Monitoring

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Abstrak: Ikatan obat dengan protein dalam darah umumnya tidak mempengaruhi efek terapinya. Selama tidak ada pergeseran ikatan, akibat obat lain yang afinitasnya lebih besar terhadap protein atau perubahan kondisi pasien. Terjadinya pergeseran ikatan yang mengakibatkan peningkatan konsentrasi obat tidak terikat juga akan dikompensasi dengan peningkatan volume distribusi sehingga konsentrasi obat tidak terikat kembali normal. Akan tetapi dalam prosedur monitoring obat yang ditetapkan adalah konsentrasi oba total, sehingga salah interprestasi bisa terjadi.

Kata kunci: ikatan obat-protein, monitoring obat, konsentrasi obat tidak terikat, konsentrasi obat total

INTRODUCTION

Even though Drug Monitoring has been a standard of practice for clinical activity in hospitals foreign countries, in Indonesia, this service has not been applied yet. Due to high cost or lack of competent pharmacist, this service has not yet been put into practice until now. Since clinical pharmacy services are starting to be implemented in several hospitals in this country, hopefully, this topic could help pharmacist to understand the problem of drug monitoring. The purpose of this article is to review the impact of drug protein binding changes caused by drug displacement or disease condition and the significance of these changes in drug monitoring.

DRUG-PROTEIN BINDING

Protein binding is a reversible process of drug and protein interaction in plasma. This includes the reversible interaction of drugs with red blood cell and tissue membranes and other blood constituents [1]. It can be described as:

Free drug + Free protein ↔ drug-protein complex...[1]

The major protein binding in plasma is albumin, á$_1$-acid glycoprotein and lipoprotein. The extent of drugs bound to protein varies widely. Some, like caffein, procainamide and digoxin, are poorly, while others, like phenytoin and warfarin are strongly bound (Table 1). Wide differences in the degree of protein binding can also occur for the same drug within population[2].

Drug protein binding depends on four major factors. They are the affinity between drug and protein, the concentration of the drug, the concentration of protein and the presence of other substances which can either compete for the binding site (drug displacer) or through an allosteric effect, so altering drug binding. Any one or all of these factors can vary as function of genetics, age, disease, drug administration and environmental factor[3].

In most cases, drug concentrations at therapeutic doses are well below those of the binding protein

Table 1 Selected drugs exhibiting >90% plasma protein binding in healthy volunteers [2]

Drug	%Bound
Amitriptylin	96 ± 8
Atenolol	96
Diazepam	98.7 ± 0.2
Digitoxin	90 ± 2
Furosemide	95.9 ± 2.0
Imipramine	94
Lorazepam	93 ± 2
Nortriptyline	94.5 ± 0,6
Phenytoin	99
Valproic acid	93 ± 4
Warfarin	99

Table 2. Examples of therapeutic setting in which drug plasma binding in plasma may vary [2]

Condition	Therapeutic setting
Binding decreased	Burn, Bacterial pneumonia, Cirrhosis of liver, Cystic fibrosis, GI disease, Liver abscess, Severe malnutrition, Pancreatitis, Renal failure, Pregnancy, Surgery, Trauma
Binding increased	After dialysis, Renal transplant, Psychosis, Neurosis, Paranoia, Benign tumor

and the unbound fraction is constant across the therapeutic range of drug concentration[1]. However, the concentration of $á_1$-acid glycoprotein is relatively low, and saturation of the binding sites can occur in the therapeutic range. For example, the unbound disopyramide increases linearly with dose, while the total concentration increases less than proportionate because of saturation resulting increase in unbound fraction[4]. Albumin concentrations are high, and saturation rarely occurs with drugs binding to this protein. An exception is salicylate, which has high therapeutic concentration[3]. The concentration of albumin is decreased in liver and renal disease resulting in decreased drug binding[7]. $Alpha_1$-acid glycoprotein is an acute phase reactant and concentrations increase in rheumatoid arthritis and post-myocardial infarction resulting in increased drug binding in these situations[4].

The binding affinity can be changed due to competition from endogenous compounds such as fatty acids, or from other drugs competing for the same protein binding sites[4].

PHARMACOKINETIC CONSEQUENCES

Many studies have been made to measure protein-binding interactions based on 'test tube' experiments. For example, warfarin is about 98% bound and 2% unbound (F=0.02). If competing drug reduces the binding from 98% to 96%, the *in vitro* unbound fraction rises from 0.02 to 0.04, a twofold increase. If nothing else happened, this would represent a twofold increase in the unbound concentration. *In vivo*, however, two compensating mechanisms operate. They are volume distribution (Vd) and clearance (Cl)[10].

When the patient receives a highly bound drug and the albumin concentration is decreased resulting from liver disease, the unbound fraction (fu) will accordingly increase.

$$\text{Fraction unbound (fu)} = \frac{\text{Unbound drug concentration (Cu)}}{\text{Total drug concentration (Ct)}} \quad \ldots\ldots (2)$$

Looking at equation 2, unbound fraction (fu) and unbound concentration (Cu) are dependent variables, while the total concentration is independent. If the fu increases, the Cu also increases. However, from a distribution standpoint, it is Ct, which is dependent to the other two parameters (fu and Cu). Unbound fraction (fu) depends on the physicochemical interaction of drug with protein as explained in page 1 about four major factors determine the drug protein binding. While Cu depends on the balance between the rate at which the drug enters the body and the rate of unbound elimination by direct excretion or by biotransformation[6].

$$Cu = \frac{D/\tau}{CLu} \quad \ldots\ldots (3)$$

D = dosage,
ô = frequency of administration,
Clu = clearance of unbound drug.

It can be seen that an alteration of fu either caused by drug displacer or by hipoalbuminemia, but whatever the reason, it has no effect on Cu at steady state as long as D and ô remain the same.

Since only the unbound drug (Cu) is thought to be able to diffuse across membranes and to interact with an effector site to produce a response; therapeutic or toxic[1], therefore, there is no need to change the dose concerning alteration of protein binding.

IMPLICATION OF PROTEIN BINDING IN DRUG MONITORING

It is easy to find greatly exaggerated concerns about transcendency of changes in the plasma protein binding of drugs in literature. It is also worth mentioning that an early review of the true significance of the problems posed by interactions at this level was appropriately entitled 'Plasma protein binding is rarely of clinical significance' [10]. Since determination of total concentration (Ct) is cheap and simple, all hospitals prefer to use it as drug monitoring rather than unbound concentration (Cu). The use of total concentration (Ct) despite of Cu is becoming a greater clinical interest in relation to protein binding alteration.

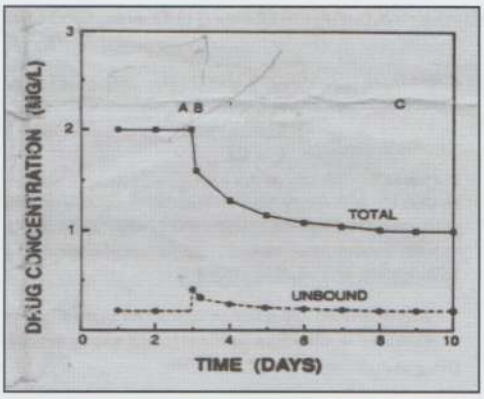

Figure 1. The correlation between unbound fraction and unbound drug. When the unbound fraction increases, the unbound drug also increases, which directly will be redistributed (increase Vd) and eliminated more rapidly (increase CL) until unbound concentration at steady state returns to the starting point.

SEQUENCE OF EVENTS FOLLOWING DISPLACEMENT OF A HIGHLY PROTEIN BOUND DRUG

Initially, the total concentration (Ct) is 2 mg/l and the unbound concentration (Cu) 0,2 mg/l giving an unbound fraction of 0.1. Displacement occurs at A with addition of a displacing drug which is then continuously present. The unbound fraction increases to 0.2 and the unbound concentration doubles to 0.4 mg/l with no change in total concentration.

At B, redistribution occurs over minutes to hours resulting in decreases in both total and unbound concentrations. The clearance of unbound drug is not changed so the unbound concentration (Cu=Dose rate/CLu) falls back to the initial value over 3-5 t½ (half life is 24 hr in this case).

At C, the final situation in the presence of displacing drug, Ct is reduced by 50% to 1 mg/l, Cu is the same as initially at 0.2 mg/l and fu increased from 0.1 to 0.2. There is no change in drug effect. The example is based on warfarin displacement interactions except that the unbound fraction has been increased from 0.02 to 0.2 for graphical clarity. As stated before that if the unbound fraction in blood increases either because of competitive displacement or hipoalbuminemia, Cu remains the same, however, Ct measured in drug monitoring is decreased. This could be explained through this equation.

$$CL = fu \times CLu \quad \cdots\cdots (4)$$

For drug with low hepatic extraction ratio, unbound fraction (fu) is a factor in the clearance of total drug, but clearance of unbound drug is determined only by intrinsic clearance and does not depend on protein binding[6]. On the other hand, clearance is also a factor of volume distribution (Vd) and constant of elimination (k) as shown in equation 5[7]. Therefore, when the unbound fraction increases, the unbound drug also increases, which directly will be redistributed (increase Vd) and eliminated more rapidly (increase CL) until unbound concentration at steady state returns to the starting point (Figure 1).

$$CL = k \times Vd \quad \cdots\cdots (5)$$

The increase of Vd causes the decrease of Ct, as seen in equation 6. Vd is a parameter relating to the concentration of a drug in the blood to the total amount of the drug in the body[6].

$$Vd = \frac{Ab}{Cp} \quad \cdots\cdots (6)$$

In short, monitoring total concentration of drug highly bound to protein and having low hepatic extraction ratio, the alteration of drug protein binding may lead to misinterpretation by increasing the dose.

CONCLUSION

Since total drug concentration is being evaluated in the hospital, consideration of measuring free concentration for highly bound drug (fu<0.3-0.4) is warranted for the following circumstances: plasma protein binding of drug is known to be varied considerably between normal patients, in patients who are likely to have altered binding of the drug (renal disease, pregnancy), when the extent of binding varies with the total drug concentration (eg. Salicylate).

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