Protein binding changes and drug interactions: What do we know?

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Mr. S, age 47, weighs 209 lb and has a history of seizure disorder, bipolar disorder not otherwise specified, hypertension, and type 2 diabetes mellitus. He presents to the emergency department after not taking his medications for 2 days while on vacation. He has increased energy, decreased sleep, and pressured speech, and insists on walking for up to 10 hours per day "in preparation for a marathon," even though he has a 4-cm foot ulcer. His family reports that he had been compliant with his medications until the present incident.

Mr. S has no known drug allergies. His medications include oral divalproex sodium delayed release (valproic acid [VPA]), 1,000 mg twice a day, oral lisinopril, 20 mg every morning, and insulin glargine, 22 units subcutaneously every evening.

A complete blood count, basic metabolic panel, creatine kinase level, VPA level, and urine drug screen are ordered. Relevant results include a serum creatinine level of 1.4 mg/dL (normal range: 0.6 to 1.2 mg/dL), a glucose serum level of 188 mg/dL (normal range: 70 to 100 mg/dL), and a VPA level of 23 mcg/mL (therapeutic range: 50 to 125 mcg/mL). A liver function panel is within normal limits: albumin level of 3.9 g/dL, aspartate aminotransferase level of 18 IU/L, and alanine aminotransferase level of 14 IU/L. In light of Mr. S's seizure history, neurology is consulted and the decision is made to continue treating him with VPA because he has been seizure-free for 4.5 years and this medication has also helped with his bipolar disorder.

Mr. S is admitted to the hospital and his home medications are resumed at the current doses. On hospital Day 3, Mr. S's VPA level is 62 mcg/mL, his obsession with a marathon has remitted, and his sleep pattern has normalized. Infectious disease and podiatry services are consulted for his diabetic foot infection, which has ulcerated down to the bone. IV ertapenem, 1,000 mg/d, is initiated with plans for debridement the following week. Two days later, Mr. S has a witnessed seizure; his VPA level is 9 mcg/mL.

A common question asked of pharmacists is, "Will protein binding changes affect drug dosages?" In this article, I describe how protein binding changes may occur, and the complexity of the dynamic. Being

Practice Points

- **A bound drug is inactive; a free drug exerts its activity.**
- **The free drug distributes from the vasculature into the organs and tissues or may be metabolized and eliminated.**
- **A bound drug may act as a reservoir.**
- **If a medication is extensively bound, a small change can have a significant impact.** For example, if a drug is 99% bound, then 1% of it is unbound. If that drug is displaced and is now only 98% bound, then 2% is unbound, which results in a doubling of available medication.

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Table

Examples of medications that are >90% protein-bound (not inclusive)

Category	Medication(s)
Antibiotics	Ceftriaxone, doxycycline, ertapenem
Antidepressants	Duloxetine, fluoxetine, nortriptyline, sertraline
Antipsychotics	Chlorpromazine, clozapine, haloperidol
Anxiolytics	Chlordiazepoxide, diazepam, lorazepam
Cardiac	Amiodarone, bumetanide, furosemide, nicardipine, verapamil, warfarin
Chemotherapy	Paclitaxel, tamoxifen
Diabetes	Glipizide
Pain	Bupivacaine, buprenorphine, ibuprofen
Seizure	Phenytoin, valproic acid

Source: Reference 1

highly bound to a protein typically does not mean all medications will interact, but some interactions can be important. This article does not cover medications that bind to hormones.

Why is protein binding important? When a medication is bound to plasma protein, it is not free to act. There can be a delay in therapeutic effect (because no drug is available to react), delayed elimination, or possibly displacement of another protein-bound medication. Additionally, medications tend not to cross the blood-brain barrier or be eliminated when bound. For example, if a drug is 99% bound (leaving 1% free) and displacement now leaves 2% of the drug free, this event has doubled the amount of free drug. As the unbound medication is eliminated, the drug that is bound to the protein can act as a reservoir. A dynamic relationship exists between bound drug, unbound drug, and rate of elimination.

Which proteins do drugs commonly bind to? The proteins often associated with binding include albumin, alpha-1-acid glycoprotein (AAG), and lipoproteins. Albumin comprises 60% of total plasma protein in the plasma. Lipoproteins include very high-density lipoprotein (VHDL), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL).[1] Medications that bind to lipoproteins include cyclosporine, tacrolimus, and propofol.[2]

What common disease states can cause hypoalbuminemia? Many disease states can result in low albumin levels. The most common ones are malnutrition, malignancies, stress, injury, burns, pregnancy, and diabetes.[3] When there is less albumin to bind to, free drug levels may be increased.

Can AAG levels change with disease states as well? Because AAG accounts for a lower percentage of total plasma protein than albumin, there may be less clinical concern regarding AAG. AAG levels usually do not drop, but instead can become elevated during times of trauma, inflammation, and acute myocardial infarction. This could result in increased binding of the free drug.[4]

Which medications bind to red blood cells (RBCs)? There are several locations for drugs to bind to RBCs, including to hemoglobin and the plasma membrane. Medications that commonly bind to RBCs

Clinical Point

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Clinical Point

Using VPA and ertapenem together is discouraged because seizures have been reported

Related Resource

- DrugBank. www.drugbank.ca. Canadian Institutes of Health Research.

Drug Brand Names

Amiodarone • Cordarone, Pacerone
Bumetanide • Bumex
Bupivacaine • Marcaine, Sensorcaine
Buprenorphine • Belbuca, Subutex
Ceftriaxone • Rocephin
Chlordiazepoxide • Librium
Chlorpromazine • Thorazine
Clozapine • Clozaril
Cyclosporine • Gengraf, Neoral
Diazepam • Valium
Doxycycline • Acticlate, Doryx
Duloxetine • Cymbalta
Ertapenem • Invanz
Fluoxetine • Prozac, Sarafem
Furosemide • Lasix
Glargine (Insulin) • Lantus, Toujeo
Glipizide • Glucotrol
Haloperidol • Haldol
Ibuprofen • Advil, Motrin
Imipramine • Tofranil
Lacosamide • Vimpat
Lisinopril • Prinivil, Zestril
Lorazepam • Ativan
Nicardipine • Cardene
Nortriptyline • Pamelor
Paclitaxel • Abraxane, Taxol
Phenytoin • Dilantin, Phenytek
Piperacillin-tazobactam • Zosyn
Propofol • Diprivan
Sertraline • Zoloft
Tacrolimus • Prograf
Tamoxifen • Soltamox
Valproic acid • Depakene, Depakote
Verapamil • Calan, Verelan
Warfarin • Coumadin, Jantoven

include barbiturates, chlorpromazine, imipramine, and phenytoin.[5]

What are common highly-bound medications? The ***Table***[1] (***page 39***) provides examples of medications that are >90% protein-bound. However, this information may be misleading because many medications are highly bound. Zhang et al[1] compiled binding data for 222 drugs, half of which bind 90% to 100%. However, the literature does not indicate that they all have clinically significant interactions. Benet and Hoener[6] discuss how factors other than protein binding affect potential drug interactions, and the complexity of the body's ability to compensate for increased free drug. Medication characteristics that may contribute to producing a significant interaction include, but are not limited to:

- free vs protein-bound drug in the plasma or tissue
- volume of distribution
- organs affected
- hepatic bioavailability
- drug clearance.

For example, VPA is 93% protein-bound and phenytoin is 91% protein-bound.[1] However, this interaction is affected by more than just protein binding. VPA not only displaces the protein-bound phenytoin, but also inhibits its metabolism, which together result in increased free phenytoin levels.

Another area of concern is a critically ill patient who has a change in his or her pH. Medications that are highly bound and have high clearance rates may be affected. This is of particular concern when prescribing antibiotics that are time-dependent, such as beta-lactams.[3]

What happened to Mr. S? Mr. S likely experienced a drug–drug interaction that resulted in a subtherapeutic VPA level and subsequent seizure. Case reports have shown evidence that the carbapenem class of antibiotics, which includes ertapenem, interacts with VPA.[7] Proposed mechanisms include a lowering of VPA serum levels due to a redistribution of the VPA onto the RBCs due to carbapenem. Other theories include the possibility that carbapenems may limit oral VPA absorption, decrease VPA enterohepatic recirculation, and increase VPA metabolism.[7] Using VPA and ertapenem together is discouraged because seizures have been reported among patients receiving this combination. If it is medically necessary to administer VPA and ertapenem, closely monitor VPA levels. In Mr. S's case, another broad-spectrum antibiotic, such as piperacillin-tazobactam, could have been used, for his diabetic foot infection.

While many medications may have high protein binding, there are few clinically important known interactions. However, our understanding of the relationship between protein binding and drug interactions may improve with additional research.

CASE CONTINUED

Under neurology's care, lacosamide is added for treatment of Mr. S's seizures. No more seizures are noted during the remainder of his hospitalization. Infectious disease services change his antibiotic to piperacillin-tazobactam. Mr. S continues to progress well and is discharged to a rehabilitation center 2 days later.

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