Should Medications be Coadministered with Albumin in Hypoalbuminemic Patients

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Abstract

Protein binding significantly influences pharmacokinetic properties of drug distribution. Albumin accounts for approximately 60% of the total plasma protein by mass, thereby making it the major protein in the body. Hypoalbuminemia, a type of hypoproteinemia, is a condition of abnormally low blood albumin levels. Hypoaluminemia causes pharmacokinetic issues in regards to dosing a patient's medication. The purpose of this paper is to review the role of the coadministration of albumin in hypoalbuminemic patients to optimize pharmacotherapy.

Keywords: Hypoalbuminemia; Pharmacotherapy; Pharmacokinetics; Protein binding

Protein Binding

One of the factors that influence pharmacokinetic properties of drug distribution is protein binding. Medications that enter the body interact with tissue and plasma proteins. These interactions determine how the drug product will be distributed. Protein binding can be classified as irreversible and reversible. There are also varying degrees and percentages to which medications can be bound [1]. Irreversible protein binding occurs when the drug and protein molecule bind tightly via covalent bonds. Reversible protein binding, the more common of the two, occurs via weaker hydrogen bonding or Van der Waals forces.

Protein binding is of great importance in pharmacokinetics and drug dosing due to the fact that protein bound drug is therapeutically unavailable for its intended action. It is only the unbound portion of the drug that is pharmacologically active [2]. Thus, medications that are highly protein bound have a lower free fraction; the inverse relationship exists for minimally protein bound drugs.

As pharmacist knowledge of pharmacokinetics, including drugs that are highly protein bound and drugs that can cause proteinuria, is paramount. Drugs that are protein bound can be divided into three categories: those that are extensively bound (i.e., >90%; warfarin, furosemide, ceftriaxone, and diazepam), intermediate binding (phenytoin, phenobarbital, and theophylline), and those that are barely bound (i.e., <10%; gentamycin, metformin, lithium) to name a few [3]. However, in our reading, we found out that there is no set of standards for ranges of protein binding, but literature agrees as >90% as highly protein bound, and <10% as minimally bound.

Common plasma proteins include alpha 1-acid glycoprotein and albumin. Each of these proteins increase or decrease in concentration as a response to injury, infection, or inflammation. Alpha 1-acid glycoprotein, also known as orosomucoid, serves as an acute phase protein, that is associated with inflammatory and immunomodulating effects [4,5]. This protein binds and carries a variety of acidic, basic, and lipophilic drugs such as propranolol and lidocaine.

Albumin accounts for approximately 60% of the total plasma protein by mass, thereby making it the major protein in the body. The synthesis of albumin takes place in the liver. Many hormones, drugs, and other molecules are mostly bound to albumin in the bloodstream and must be released before biologically activity can occur [6]. Hypoalbuminemia, a type of hypoproteinemia, is a condition of abnormally low blood albumin levels. The causes for hypoalbuminemia can be redistribution of body fluid, decreased production and/or dilution of albumin, or increased loss of albumin through urine. Decreased plasma albumin concentration, fluid accumulation, and thromboembolism can result in patients with moderate to severe hypoalbuminemia (<2 mg/dL).

In critically-ill hospitalized patients, hypoalbuminemia is a common finding. In fact, a number of studies have indicated the presence of hypoalbuminemia is associated a with poorer prognosis [7,8]. Low albumin levels are often found in patients with liver diseases such as: cirrhosis and chronic hepatitis [9]. Hypoalbuminemia can also result when the kidney is damaged, in which protein is lost through the urine. Furthermore, low albumin levels (i.e., <3.5 mg/dl) can be an indicator of chronic malnutrition or protein losing enteropathy [10]. When a patient's disease state leads to moderate or severe hypoalbuminemia, the clinical course can be influenced.

Albumin is an important parameter for drug dosing as changes in the levels of protein available can alter the free fraction of drug in circulation. For example, sodium binds to albumin and hypoalbuminemia leads to an increase in free sodium. Due to the resulting decrease in the oncotic pressure, as a consequence of hypoalbuminemia, free sodium shifts to the interstitial space. As the sodium shifts, water follows which creates an increase in fluid accumulation in the interstitial space, hence edema.

Body fluids are located in two compartments, intracellular space (inside the cell), and extracellular space (outside of the cell). Intracellular Fluid (ICF) is located primarily in the skeletal muscle

mass and constitutes approximately 40% of the total body weight. This can also be interpreted as 70%, or two thirds, of the total body fluid/water. Extracellular Fluid (ECF) accounts for approximately 20% of the body weight. This can also be interpreted as 30%, or one third, of the total body fluid/water [11]. Fluid spacing is a term used to classify the distribution of water in the body. There are three main definitions as it relates to fluid spacing. They are listed as follows:

1. **First spacing:** Describes normal distribution of fluid in the body in both the intracellular and extracellular fluid compartments.
2. **Second spacing:** Describes the excess accumulation of fluid in the interstitial spaces, also known as edema.
3. **Third spacing:** The unusual accumulation of extracellular fluids in a transcellular space. It occurs when fluid accumulates in areas that normally have no fluid or minimal amount of fluid, such as with ascites, and edema associated with burns. In extreme cases third, spacing can cause a relative hypovolemia (Figure 1) [12,13].
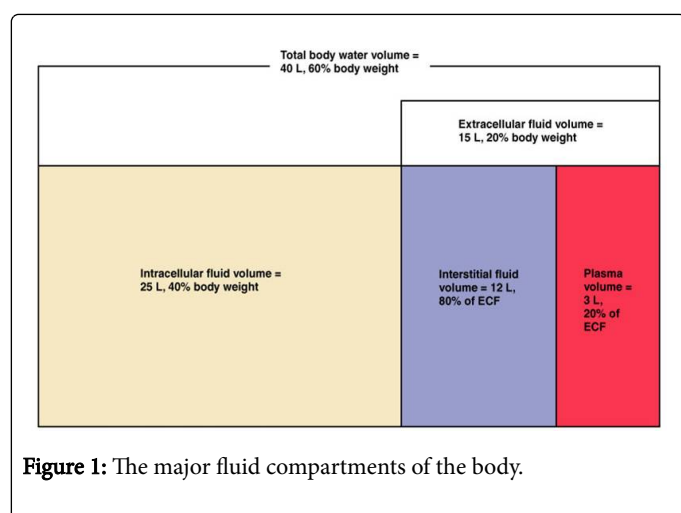

Figure 1: The major fluid compartments of the body.

Correction Factors

When dosing medication, it is important to consider the extent of protein binding and therapeutic index. As stated, medications that are highly protein bound have a lower free fraction available for pharmacological activity. Therefore, such medications may require decreased dosing in hypoalbuminemic patients.

Like sodium, calcium is an electrolyte which is bound to albumin. The commonly accepted reference range of calcium is between 8.5 mg/dL to 10.6 mg/dL, with slight variations between institutions. Calcium is a key physiological component for cell division, cardiac contractility, neuronal excitability and a wide range of other functions. Laboratory reports of total calcium concentrations include the free serum calcium as well as the calcium bound to protein measurements. Whether the free or bound concentration of calcium is reported is institution specific. Fluctuations in serum albumin will lead to variations in measured calcium. However, the perceived change in calcium is not indicative of the actual concentration. The total serum calcium will increase 0.8 mg/dL for every 1 g/dL rise in serum albumin and will fall 0.8 mg/dL for every 1 g/dL fall in serum albumin. There is a corrected calcium adjustment calculated using the following formula: Corrected calcium (mg/dL)=measured total serum calcium (mg/dL)+[4.0-serum albumin (g/dL) × 0.8] [14,15]. This formula is widely used for the approximation of serum calcium in the presence of hypoalbuminemia, providing clinicians with information to appropriately treat patients.

The relationship between albumin and its substrates is crucial to understand in order to determine and approximate dosing parameters. Medications that are known to be of Narrow Therapeutic Index (NTI) and highly protein bound must be monitored in order to avoid toxicity. While there are various definitions, the FDA defines a narrow therapeutic range drug as "containing certain drug substances subject to therapeutic drug concentration or pharmacodynamics monitoring, and/or where product labeling indicates a narrow therapeutic range designation." An updated definition for NTI medications was proposed at the Generic Pharmaceutical Association Fall 2011 Technical Workshop and is as follows "Narrow therapeutic index (NTI) drugs are defined as those drugs where small differences in dose or blood concentration may lead to dose and blood concentration dependent, serious therapeutic failures or adverse drug reactions. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening, possibly resulting in hospitalization, disability, or even death" [16,17]. Phenytoin is a documented NTI medication, extensively bound to the protein albumin. For critically-ill patients with hypoalbuminemia that are being treated with phenytoin, there are dosing adjustments available. The Sheiner-Tozer equation, assuming renal function is not impaired, is as follows: Corrected phenytoin (mg/L)=Observed phenytoin (mg/L) (0.2 × albumin [g/dL])+0.1; with the albumin coefficient changing to 0.1 in cases of renal disease and 0.25 for elderly patients. This formula has been evaluated for this ability to accurately provide clinicians with an approximate phenytoin concentration in instances where direct measurement of free phenytoin is unavailable [18,19].

Use of Albumin

Although correction equations are available for a few albumin-bound medications, perhaps administration of albumin with the drug will eliminate the need for correction. For further examination of coadministration of medication with albumin, furosemide can be evaluated.

Treatment considerations for hypoalbuminemic patients should address the underlying causes or disease state(s). Nevertheless, adjustment of medications, nutritional support, maintenance of adequate colloid oncotic pressure, and prevention of thromboembolism are also as important. According to current practice, albumin is not typically indicated for correcting hypoalbuminemia [20]. The administration of albumin has not been shown to reduce mortality in patients [21]. Albumin administration may result in immediate allergic-type reactions such as fever, nausea, vomiting, and urticaria. Rapid infusions of albumin (20-50 mL/min) can cause a sharp decrease in systemic blood pressure and induce congestive heart failure, especially in elderly patients and those who are at risk [22].

When a patient is critically-ill, fluid resuscitation may be indicated to stabilize for hemodynamic stabilization. At times, aggressive fluid resuscitation can lead to fluid overload. Often times, furosemide is the diuretic of choice in patients experiencing hypervolemia. Critical illness can also result in malnutrition and hypoproteinemia, decreasing oncotic pressure and shifting fluid into the third space, worsening edema [23]. Furosemide is an effective selection for removing excess fluid. Unfortunately, when the goal is to remove trapped in the third space, the effects of the diuretic are not as profound. For these cases, it

is theoretically plausible that the addition of human albumin to furosemide will improve diuresis.

A retrospective study was conducted to determine if there was a difference in the effectiveness of furosemide on diuresis when coadministered with albumin. The primary endpoints of the study were net fluid loss and urine output. The conclusion determined that addition of albumin did not enhance diuresis [24]. Furthermore, a separate study determined that there was no difference in the pharmacokinetics of furosemide when administered with albumin versus administration of furosemide alone [25]. However, we found two small studies that have concluded positive results when coadministering albumin with furosemide. In patients experiencing acute respiratory distress, the addition of albumin to furosemide improved oxygenation, fluid balance, and hemodynamic stability [26,27]. These results suggest the use of albumin for diuresis in critically-ill patients. Overall, the results of various trials regarding the administration of albumin and furosemide are inconclusive.

Promising developments are on the horizon as albumin has been used as a vehicle in drug delivery systems due to its bio-acceptable and biodegradable properties. Under investigation for rheumatoid arthritis, albumin-based delivery systems are showing potential to provide an improved therapeutic response. Aspirin is a common anti-inflammatory and anti-platelet agent widely used for various conditions. However, delivery of the drug to the effective site has proven to be difficult. In arthritis, the delivery of aspirin into the intra-articular space has been made possible by using an aspirin-albumin nanoparticle as a coacervate [28]. An albumin-methotrexate conjugate is currently in clinical trials and has produced positive preliminary results in reducing cartilage degradation in a humanized rheumatoid arthritis mouse model. Applications of albumin conjugates are most studied in cancer research, with several approved agents. The albumin-paclitaxel nanoparticle, Abraxane®, was first approved January 7th, 2005. Diabetes is also an emerging area for the study for albumin conjugates, with marketed medications [29]. As it relates to antibiotics, studies have shown that correcting hypoalbuminemia in critically-ill patients has indicated a decrease in effectiveness of antibiotics. This is due to the fact that hypoalbuminemia would increase the apparent total volume of distribution (Vd) and clearance (CL) of the drug, which translates to decreasing the pharmacodynamic activity of the antibiotics [30].

When considering the pharmacist's hierarchy of medication use deliberations (safety, efficacy, cost), our review of literature has shown a possible benefit of the coadministration of albumin with furosemide in critically-ill patients with acute lung injury. An associated safety concern is congestive heart failure. Yet, there has been no demonstration of a decreased mortality risk. The average wholesale price for a 50 mL vial of 25% albumin is approximately $70 whereas a 40 mg injection of furosemide is approximately $8 [31]. Thereby increasing the cost of treatment approximately 10 times. As further studies are conducted where improved outcomes can be attributed to the use of albumin, recommendations for its use may eventually be expanded to non-ICU settings. Further studies should continue to be conducted.

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