The Effect of Critical Illness on Drug Distribution

Daniel Gonzalez[1], Daniela J Conrado[1], Ursula Theuretzbacher[2] and Hartmut Derendorf[1,*]

[1]*Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, USA;* [2]*Center for Anti-Infective Agents, Vienna, Austria*

Abstract: The complexity of managing critically ill patients has increased since the early establishment of intensive care units in the 1950s. Despite of the fact that the number of drugs available to clinicians has increased, the understanding of the pharmacokinetics of individual drugs in specific disease states is still a matter of concern. Among the pharmacokinetic processes which may be affected in this patient population, drug distribution is a very important one. Changes in drug distribution may cause inadequate drug exposure at the infection site and consequently influence clinical outcome. Since drug distribution is dependent on a plethora of factors, including the physicochemical characteristics of the drug, we will focus on the most common mechanisms responsible for altered tissue distribution. These include changes in protein binding, fluid shifts, and pH changes. Although less common, alterations in organ perfusion may also play a role, particularly in heart failure patients. Despite great advances in understanding the distribution of antibacterial drugs, further studies are needed to define the consequences of changed drug distribution in critically ill patients on dosing regimens and clinical outcome.

Keywords: Critical Illness, protein binding, pharmacokinetics, pharmacodynamics, antibiotics.

INTRODUCTION

The management of critically ill patients is both complex and challenging for a variety of reasons. Critically ill patients are often suffering from several life-threatening conditions, which may be associated with multiple organ failure. As a result, dysfunction in the organs involved in drug elimination may influence the pharmacokinetic properties of a drug and make dosing more complex. Organ impairment or failure may include changes in the absorption, distribution, metabolism, and excretion of the drug(s). Moreover, multiple drugs are often needed to manage the underlying condition(s) as well as provide supportive care. Thus, the critically ill are particularly susceptible to drug-drug interactions and adverse drug reactions that are caused by pharmacokinetic changes in the drugs being used.

The distribution of drugs is dependent on several factors, including physicochemical properties of the drug, the degree of binding to plasma and tissue proteins, permeability of the tissues, organ perfusion, and the involvement of drug transporters [1]. In general, alterations in tissue distribution resulting from a critical illness are more likely to be clinically significant for hydrophilic drugs which do not display useful intracellular penetration, and thus have a relatively low volume of distribution [2]. Ultimately, both drug specific properties and disease related changes will determine whether or not changes in a drug's volume of distribution (V_d) occur Fig. (**1**).

*Address correspondence to this author at the Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, USA;
Tel: +1-352-273-7856; Fax: +1-352-392-3249; E-mail: hartmut@ufl.edu

MECHANISMS INVOLVED IN ALTERED TISSUE DISTRIBUTION

Several mechanisms may be involved in altered tissue distribution in severely ill patients. The most common mechanisms are alterations in protein binding, fluid shifts, and changes in pH [1, 3]. Less common is a reduction in cardiac output as a result of heart failure. Often times it is a combination of these mechanisms which is responsible for the change in the tissue distribution of a drug. For example, renal failure may result in alterations in protein binding as well as result in fluid retention, thus altering total body water [4].

Protein Binding Changes

Many drugs bind to plasma proteins and are available in both a protein bound and unbound form in plasma. It is only the unbound drug which is able to diffuse into tissues, reach the site of action (assuming the site of action is located extravascularly), and bind to its receptor. The two most common plasma proteins involved in drug binding are albumin and α-1 acid glycoprotein (AAG) [5]. Alterations in protein binding can thus impact a drug's pharmacokinetics and pharmacodynamics [5, 6]. Some examples of antibiotics with a high degree of protein binding include ceftriaxone [2, 7], oxacillin, ertapenem [8], and daptomycin [9].

When protein concentrations in the blood are altered, the observed change often involves decreased levels of albumin (hypoalbuminemia) or elevated levels of AAG [10-14]. Several conditions (e.g. kidney and liver disease) in critically ill patients can affect protein concentrations by altering synthesis, catabolism, or promoting the movement of protein from the plasma to an extravascular site [11-18]. Altered protein binding may also be the result of an alteration in the binding affinity for its protein.

1389-2010/11 $58.00+.00

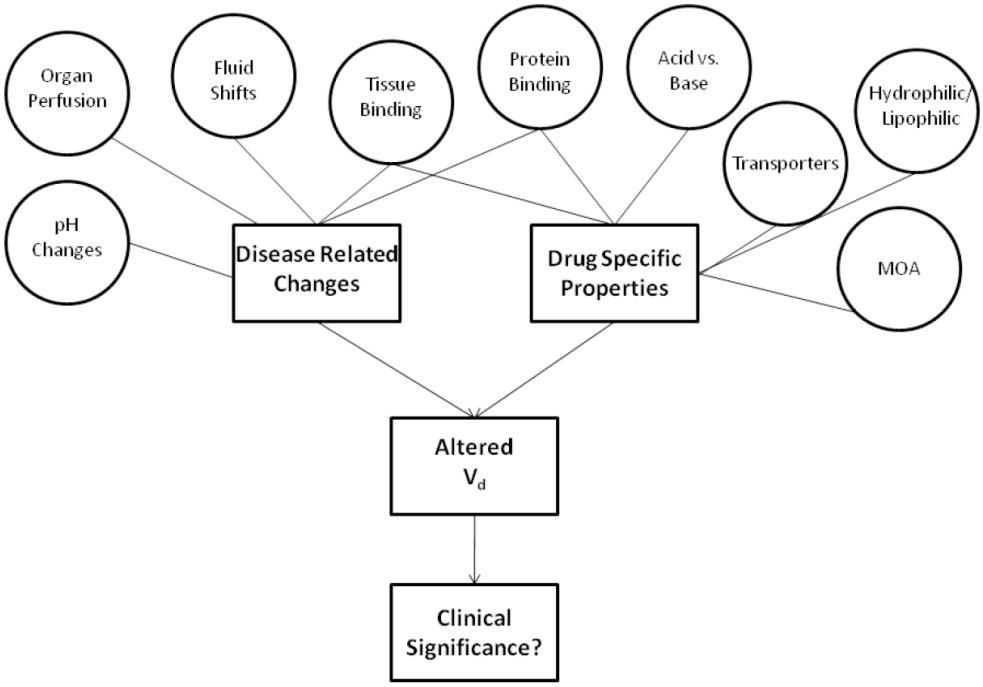

Fig. (1). Summary of disease and drug related factors which may be important in altered drug distribution. MOA= Mechanism of action, V_d=Volume of distribution

Changes in the binding affinity of the albumin molecule can be caused by chemical modification and include glycation (addition of carbohydrate groups) or carbamylation (nonenzymatic binding of cyanate) [19]. Conformational changes in the protein may also occur as a result of pH changes triggered by a disease state [19, 20]. For some disease states, an alteration in the protein binding may be caused by accumulation of endogenous substances (e.g. bilirubin, free fatty acids) which can compete with the drug for a binding site [19-22]. A decreased albumin-binding capacity may also be caused by changes in the amino acid composition and variations in the protein content as has been shown in uremic patients [23].

Binding of drugs to proteins can occur both in plasma as well as in the extracellular and intracellular compartments. For a highly bound drug, changes of a drug's V_d caused by a reduced plasma protein binding depend on the degree of protein binding in the tissues (both outside and inside cells). In critically ill patients, the degree of protein binding which occurs in extracellular and intracellular compartments may also change, or conversely, it may remain unaffected. Thus, it is the ratio of fraction unbound in plasma and tissues, f_{uP}/f_{uT}, which will determine the V_d.

Fluid Shifts

Critical illnesses can affect the distribution of drugs by promoting a significant shift of body fluids into the interstitium. Often these shifts occur due to increased capillary permeability, fluid retention, decreased oncotic pressure, and endothelial damage caused by the release of endogenous inflammatory mediators [1, 2, 24]. Since plasma proteins serve as the major source of oncotic pressure for the vascular space, hypoalbuminemia may promote movement of fluid into the extravascular space [12]. Disease states which can cause fluid shifts include liver cirrhosis, congestive heart failure, renal failure, trauma, and fluid resuscitation [13]. Mechanical ventilation may also trigger regulatory mechanisms which increase the intra- and extravascular volume as a result of an increase in the intrathoracic pressure [2, 3, 25]. Fluid shifts can manifest as edema, ascites, and pleural effusion [1]. Hydrophilic drugs (e.g. aminoglycosides, β-lactams, glycopeptides) which normally have a small V_d now have an additional "compartment" into which they can distribute, a manifestation often referred to as "third spacing" [1, 26]. An increased V_d has been observed for several antibiotics in critically ill patients [27-30]. A change in the apparent V_d may be clinically relevant for concentration dependent antibiotics (e.g. aminoglycosides), since the maximal concentration (C_{max}) may be decreased with an increase in V_d [1].

Fluid shifts can also be caused by the supportive care given to the patient. For example, one study compared the pharmacokinetics of amikacin in critically ill patients receiving parenteral nutrition versus fluid therapy only [31]. Patients receiving total parenteral nutrition had a significantly increased V_d and lower C_{max}. This greater V_d may be attributed, at least in part, to a significantly greater fluid input in this patient group. Since amikacin is an aminoglycoside and its antimicrobial effect is concentration dependent, such a change in peak concentration, may warrant an increase in its dose. Unfortunately, clinical studies that correlate changed distribution of antibiotics to clinical outcome are scarce.

pH Changes

The disposition (distribution and clearance) of a drug may be affected by changes in pH caused by critical ill-

nesses. Acidosis and alkalosis may be caused by conditions such as respiratory failure, shock states, renal failure, and central nervous system dysfunction [2, 3]. Alterations in pH affect membrane permeability and thus, the tissue distribution of drugs by altering the degree of ionization of the drug. The extent to which pH changes are relevant will be dependent on the pKa of the drug and the degree to which pH changes. The influence of pH on the ionization and the distribution of antibacterial drugs was shown in an early study that examined the permeability of the blood-CSF barrier for sulfonamide drugs with different pKa values [32].

DISEASE STATES RESPONSIBLE FOR ALTERED TISSUE DISTRIBUTION

Renal Failure

Among the factors that affect the V_d, total body water, blood pH, plasma protein binding, and tissue protein binding (extra-and intra-cellular compartments) may be altered in patients with renal failure. Acute renal failure (ARF), which is characterized by fluid retention [33, 34], causes a change in total body water and thereby may alter the V_d of drugs. Another manifestation of ARF is metabolic acidosis [35], which can modify the ionized fraction of some drugs in the blood. Since ionized molecules, and more specifically, those with a large molecular weight, do not diffuse across the lipid-based cellular membrane as easily, an alteration in the ionized state may affect the extent of drug distribution.

In chronic kidney disease, where both the glomeruli and tubules are affected, an excessive filtration of protein can result in a marked loss of albumin from the body [36]. In end stage renal disease (ESRD) patients who are treated with hemodialysis, additional mechanisms are reported to cause hypoalbuminemia. Albumin synthesis is regulated in part by nutrition [12], but malnutrition itself does not seem to be the preponderant factor responsible for hypoalbuminemia in this population. Some authors suggest that the hypoalbuminemia in hemodialysis patients, where dialyzer membranes are not extensively used, is probably a consequence of an inflammatory response. Indeed, the increase in the levels of acute phase proteins (APP), such as AAG, was positively correlated with albumin catabolic rate in patients on hemodialysis [37].

The degree to which acidic drugs bind to albumin is usually decreased in ESRD patients, but the observed reduction is often greater than can be explained by hypoalbuminemia alone. Competition between drugs and their accumulated metabolites [38, 39], and/or drugs and accumulated protein-bound uremic substrates [40, 41], may decrease the plasma protein binding. The latter deserves special consideration given that removal of protein-bound uremic compounds with conventional hemodialytic strategies is suboptimal [42, 43]. As discussed earlier, structural changes to albumin, such as carbamylation, appear to be an interesting secondary contribution for decreased binding of acidic drugs in uremia [23, 44]. A reduction in plasma protein binding in patients with chronic kidney disease has been reported for dicloxacillin, sulfamethoxazole [45], ceftriaxone [46], cefazolin and other cephalosporins [47]. Conversely, it appears that the effect of renal failure on plasma protein binding of basic and neutral drugs is heterogeneous. Basic drugs such as erythromycin often display saturable binding to AAG, which has been reported to be significantly higher in uremic patients [37, 48, 49].

Hepatic Failure

The major factors which influence drug distribution in patients with hepatic failure are an increase in total body water and a decrease in plasma protein binding. Patients with edema and ascites, both physical signs of advanced chronic hepatic disease, have an increase in extravascular volume. Drugs that are distributed in total body water or extracellular fluid, hence, will distribute into a larger volume, and peak levels with conventional doses are likely to be subtherapeutic. Aminoglycosides, for instance, are able to pass into ascitic fluid; as a result, an increased V_d has been observed in this patient population [50-52].

Since the liver synthesizes most plasma proteins, hepatic impairment, especially chronic disease, can result in reduced protein levels in the body. Cirrhosis, for example, may alter the binding of drugs in plasma by decreasing albumin and/or AAG concentrations [53-55]. An increase in unbound plasma concentrations was reported for alfentanil [56], lidocaine [53], tolbutamide [57, 58], diazepam [57,59], phenytoin and morphine [60] when administered to patients with hepatic disease.

Cardiac Failure

Among the multiple factors which can influence drug distribution in patients with cardiac failure, reduced cardiac output and regional blood flow deserve special consideration. The decline in blood flow to the renal, hepatic, and peripheral vascular beds, a consequence of the compensatory peripheral vasoconstriction, is proportional to the decrease in cardiac output; on the other hand, perfusion of the heart and brain is maintained by autoregulation and these organs may receive a relative increased proportion of the cardiac output [61]. As a consequence, the V_d of drugs that are rapidly distributed to the peripheral tissues, such as lidocaine [62, 63], is decreased. Higher plasma concentrations in combination with preferential flow, make the myocardium and central nervous system more susceptible to toxic effects; indeed, a single dose of lidocaine administered during acute cardiac failure has been reported to cause seizures in patients [64].

Heart failure, the end stage of a number of cardiovascular disorders, has been reported to be associated with albuminuria [65, 66] and microalbuminuria [67]. Albuminuria may occur in cardiac failure as a manifestation of widespread vascular damage induced by common cardiovascular risk factors [68]. Conversely, an increase in AAG can occur in those patients with congestive heart failure. An increase in binding has been observed for pindolol [69] and disopyramide [70].

Systemic Inflammatory Response Syndrome

Trauma, localized or generalized infection, thermal injury, and sterile inflammatory processes may trigger a host systemic inflammatory response syndrome (SIRS) [71], which is induced and sustained by a cascade of inflammatory mediators. The local and systemic release of pro-

inflammatory cytokines induces an acute phase reaction in the liver, resulting in an enhancement of tissue protective mechanisms. The synthesis of positive APP in hepatocytes, such as AAG is increased, whereas the production of negative APP, such as albumin, is reduced [72]. Activation of neutrophils, monocytes/macrophages, and lymphocytes produce injury to the endothelium, with a consequent increase in endothelial permeability. This then leads to hypovolemia, which causes a drop in cardiac output, tissue hypoperfusion, and leakage of plasma proteins into the interstitial space. Thus, the V_d can be altered by both a change in the plasma protein binding as well as a result of fluid shifts. In a study involving head trauma patients, hypoalbuminemia was evident after 2-3 days, with levels normalizing within 1 month Fig. (**2**) [73].

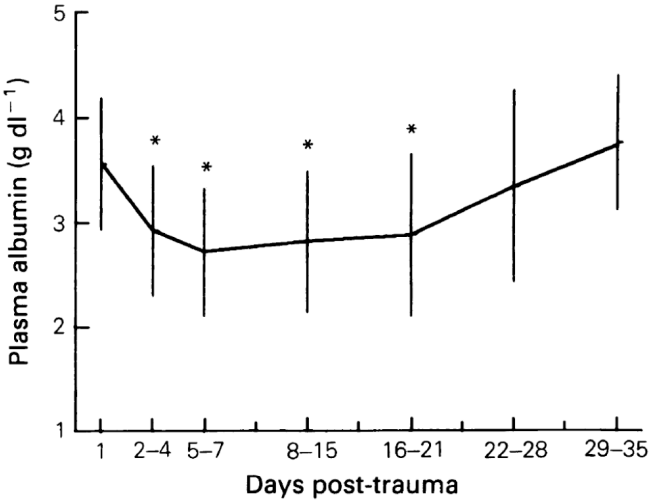

Fig. (2). Alteration in mean (± s.d.) plasma albumin concentration after head injury (n = 130). *Statistically significant ($p<0.05$, ANOVA and Dunnet`s multiple comparison test (reference 73). *Permission to reuse this figure has been obtained and payment organised through Mr. Mahmood Alam.*

Severe burn injury is a classical etiology of non-septic SIRS. Among the studies examining the pharmacokinetics of β-lactams in burn patients, ceftazidime has received the most attention. Different authors reported a greater Vd in adult burn patients than in healthy subjects [74-76]. Similarly, for aminoglycosides, such as gentamicin, tobramycin and amikacin, a larger Vd was reported in burn patients [77-79]. The significance of taking protein binding into account when evaluating the pharmacokinetics of drugs that are highly bound to proteins in burn patients was seen with alfentanil. In burn patients, a two-fold decrease in the V_d was correlated with the significant decrease in the free fraction of alfentanil due to increase in the concentration of AAG [80].

SIRS can also occur in patients who are septic [71]. The increased V_d of aminoglycosides observed in patients with sepsis or septic shock has been attributed to increased capillary permeability and consequent extravascular fluid sequestration, especially following vigorous fluid resuscitation [81-87]. Therefore, higher peak serum concentrations, balanced against a potential increase in toxicity, must be considered in order to treat this condition effectively. An increase in V_d was observed for cefpirome when administered in septic patients [88]; similar to aminoglycosides, cefpirome is a hydrophilic and low protein-bound antibiotic, which distributes throughout the extracellular water. Ceftriaxone, which is >90% protein-bound in non-critically ill patients, had a 50% increase in V_d in critically ill patients with severe sepsis; however, it was associated to the marked hypoalbuminemia observed in those group of patients [89]. The difference in protein binding between patients with normal renal function and renally impaired subjects, as well as the concentration dependent binding of this drug were observed in this study Fig. (**3**).

Patients Requiring Fluid Resuscitation

Aggressive fluid resuscitation and consequent expansion of the extracellular water may result in an increased V_d for some drugs used in critically ill patients. For lipophilic drugs which are taken up intracellularly, a decrease in the interstitial fluid concentrations is expected to be temporary since this decrease would trigger a redistribution process between the intra- and intercellular compartments until a new equilibrium state be achieved. Nevertheless, this re-equilibration does not occur for hydrophilic drugs because their distribution is limited to the extracellular compartment. Since the interstitial space is the target site for most bacterial infections, this issue may be of clinical relevance for hydrophilic antimicrobial agents, such as β-lactams, aminoglycosides and glycopeptides. In fact, a study assessing the tissue distribution of piperacillin by microdialysis showed that the target site concentrations of the drug were markedly lower in cardiac surgical patients when compared to healthy subjects, possibly due to the administration of large amount of fluids Fig. (**4**) [90]. This reduction in target site concentrations could promote the development of resistant strains. The reduced tissue concentrations were observed despite a decrease in protein concentrations, which is likely attributed to the low protein binding of piperacillin(~30%) and the overwhelming effect of fluid shifting. A case report describing a post-trauma critically ill patient receiving extended amikacin treatment showed that the administration of copious quantities of intravenous fluid resulted in an increased V_d of the antibiotic with extensive daily fluctuations in drug concentrations [91]. Similarly, a large V_d for vancomycin was observed in critically ill infants receiving an aggressive fluid resuscitation, which helped confirm the importance of therapeutic drug monitoring [92].

CONCLUSIONS

Several mechanisms may be responsible for altered drug distribution in critically ill patients. Changes in protein binding, fluid shifts, and pH changes are the most common. These changes will be most relevant for hydrophilic drugs, which in healthy subjects, have a relatively low V_d. The significance of changes in protein binding, either by alteration in protein concentrations or binding affinity, will depend on the degree to which a drug is protein bound, the number of binding sites on the protein, the equilibrium dissociation constant, and the total drug concentration. As one would expect, changes in protein binding would be most relevant for highly bound drugs. Fluid shifts are observed in several

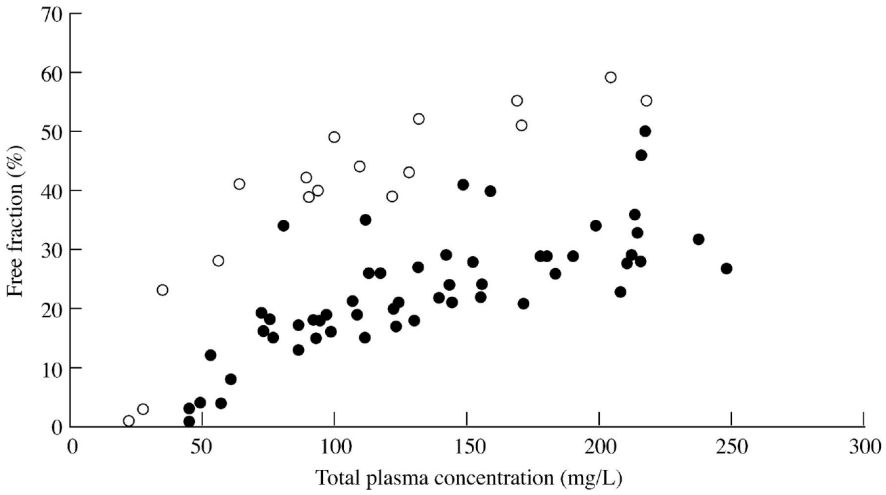

Fig. (3). Scatter graph which shows the relationship between ceftriaxone concentration (mg/L) and free fraction of the drug in subjects with normal renal function (closed circle) and impaired renal function (open circle) (reference 89). *Permission to reuse this figure has been obtained and payment organised through Mr. Mahmood Alam.*

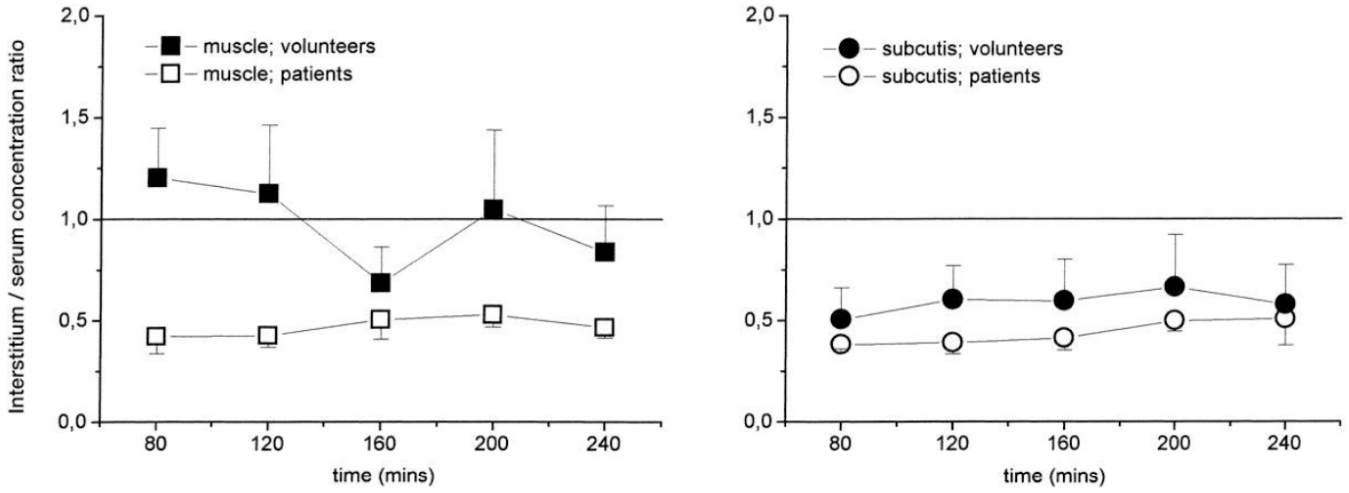

Fig. (4). Time-course for interstitium-to-serum concentration ratios of piperacillin for skeletal muscle (left) and adipose tissue (right) in healthy controls and in otherwise healthy subjects scheduled for aortic valve replacement (reference 90). *Permission to reuse this figure has been obtained and payment organised through Mr. Mahmood Alam.*

disease states, and can alter drug distribution by presenting a larger volume of fluid for the drug to distribute into. Ultimately, the relevance of these changes will depend on whether unbound drug concentrations change at the site of action and on the mechanism of action of the drug.

ACKNOWLEDGEMENT

D.J.C. would like to thank the financial support given by Conselho Nacional de Desenvolvimento Cientifico e Technologico (CNPq), Brasilia, Brazil.

REFERENCES

[1] Boucher, B.A.; Wood, G.C.; Swanson, J.M. Pharmacokinetic changes in critical illness. *Crit. Care Clin*., **2006**, *22*, 255-271.

[2] Roberts, J.A.; Lipman, J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit. Care Med*., **2009**, *37*(3), 840-851.

[3] Verbeeck, R.K.; Musuamba, F.T. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. *Eur. J. Clin. Pharmacol*., **2009**, *65*(8), 757-773.

[4] Power, B.M.; Forbes, A.M.; van Heerden, P.V.; Ilett, K.F. Pharmacokinetics of drugs used in critically ill patients. *Clin. Pharmacokinet*., **1998**, *34*(1), 25-56.

[5] Schmidt, S.; Gonzalez, D.; Derendorf, H. Significance of protein binding in pharmacokinetics and pharmacodynamics. *J. Pharm. Sci*., **2010**, *99*(3), 1107-1122.

[6] Benet, L.Z. and Hoener, B.A. Changes in plasma protein binding have little clinical relevance. *Clin. Pharmacol. Ther.,* **2002**, *71*(3), 115-121.

[7] Popick, A.C.; Crouthamel, W.G.; Bekersky I. Plasma protein binding of ceftriaxone. *Xenobiotica*, **1987**, *17*(10), 1139-1145.

[8] Majumdar, A.K.; Musson, D.G.; Birk, K.L.; Kitchen, C.J.; Holland, S.; McCrea, J.; Mistry, G.; Hesney, M.; Xi, L.; Li, S.X.; Haesen, R.; Blum, R.A.; Lins, R.L.; Greenberg, H.; Waldman, S.; Deutsch, P.; Rogers, J.D. Pharmacokinetics of ertapenem in healthy young volunteers. *Antimicrob. Agents Chemother*., **2002**, *46*(11), 3506-3511.

[9] Woodworth, J.R.; Nyhart, E.H. Jr.; Brier, G.L.; Wolny, J.D. Single-dose pharmcokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. *Antimicrob. Agents Chemother*., **1992**, *36*(2), 318-325.

[10] MacKicha, J.J. In: *Influence of Protein Binding and Use of Unbound (Free) Drug Concentrations*. Burton, M.E.; Shaw, L.M.;

Schentag, J.L.; Evans, W.E. Eds., Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring, 4th Ed., Philadelphia: Lippincott Williams & Williams., **2005**, p 82-120.

[11] Haller, C. Hypoalbuminemia in renal failure: pathogenesis and therapeutic considerations. *Kidney Blood Press Res*., **2005**, *28*(5-6), 307-310.

[12] Kaysen, G.A. Biological basis of hypoalbuminemia in ESRD. *J. Am. Soc. Nephrol*., **1998**, *9*(12), 2368-2376.

[13] Yogaratnam, D.; Miller, M.A.; Smith, B.S. The effects of liver and renal dysfunction on the pharmacokinetics of sedatives and analgesics in the critically ill patient. *Crit. Care Nurs. Clin. N. Am,* **2005**, *17*(3), 245-250.

[14] Sharma, S.; Kumar, A. Antimicrobial management of sepsis and septic shock. *Clin. Chest Med.,* **2008**, *29*(4), 677-687.

[15] Don, B.R.; Kaysen G. Serum albumin: relationship to inflammation and nutrition. *Semin Dial.,* **2004**, *17*(6), 432-437.

[16] Fournier, T.; Medjoubi-N, N.; Porquet, D. Alpha-1-acid glycoprotein. *Biochim. Biophys. Acta,* **2000**, *1482*(1-2), 157-171.

[17] Israili, Z.H.; Dayton, P.G. Human alpha-1-glycoprotein and its interactions with drugs. *Drug Metab. Rev.,* **2001**, *33*, 161-235.

[18] Croce, M.V.; Price, M.R.; Segal-Eiras, A. Association of a alpha1 acidic glycol`protein and squamous cell carcinoma of the head and neck. *Pathol. Oncol. Res.,* **2001**, *7*(2), 111-117.

[19] Meijers, B.K.; Bammens, B.; Berbeke, K.; Evenepoel, P. A review of albumin binding in CKD. *Am. J. Kidney Dis.,* **2008**, *51*(5), 839-850.

[20] Hinderling, P.H.; Hartmann, D. The pH dependency of the binding of drugs to plasma proteins in man. *Ther. Drug Monit*., **2005**, *27*(1), 71-85.

[21] Craig, W.A.; Welling P.G. Protein binding of antimicrobials: Clinical pharmacokinetic and therapeutic implications. *Clin. Pharmacokinet.,* **1977**, *2*(4), 252-268.

[22] Craig, W.A.; Suh, B. Changes in protein binding during disease. *Scand. J. Infect. Dis.,* **1978**, *14*, 239-244.

[23] Boobis, S.W. Alteration of plasma albumin in relation to decreased drug binding in uremia. *Clin. Pharmacol. Ther.*, **1977**, *22*(2), 147-153.

[24] Suzuki, A.; Ishihara, H.; Hashiba, E.; Matsui, A.; Matsuki, A. Detection of histamine-induced capillary protein leakage and hypovolaemia by determination of indocyanine green and glucose dilution method in dogs. *Intensive Care Med*., **1999**, *25*(3), 304-310.

[25] Conil, J. M.; Georges, B.; Lavit, M.; Laguerre, J.; Samii, K.; Houin, G.; Saivin, S. A population pharmacokinetic approach to ceftazidime use in burn patinets : Influence of glomerular filtration, gender and mechanical ventilation. *Br. J. Clin. Pharmacol.*, **2007**, *64*(1), 27-35.

[26] Scaglione, F.; Paraboni, L. Pharmacokinetics/pharmacodynamics of antimicrobials in the intensive care unit: setting appropriate dosing regimens. *Int. J. Antimicrob. Agents*, **2008**, *32*(4), 294-301.

[27] Brink, A.J.; Richards, G.A.; Schillack, V.; Kiem, S.; Schentag, J. Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. *Int. J. Antimicrob. Agents*, **2009**, *33*(5), 432-436.

[28] Hanes, S.D.; Wood, G.C.; Herring, V.; Croce, M.A.; Fabian, T.C.; Pritchard, E.; Boucher, B.A. Intermittent and continuous ceftazidime infusion for critically ill trauma patients. *Am. J. Surg.*, **2000**, *179*(6), 434-440.

[29] Etzel, J.V.; Nafziger, A.N.; Bertino, B.S. Jr. Variation in the pharmacokinetics of gentamicin and tobramycin in patients with pleural effusions and hypoalbuminemia. *Antimicrob. Agents Chemother*., **1992**, *36*(3), 679-681.

[30] Beckhouse, M.J.; Whyte, I.M.; Byth, P.L.; Napier, J.C.; Smith, A.J. Altered aminoglycoside pharmacokinetics in the critically ill. *Anaesth. Intensive Care*, **1988**, *16*(4), 418-422.

[31] Tormo, C.; Abad, F.J.; Ronchera-Oms, C.L.; Parra, V.; Jimenez, N.V. Critically-ill patients receiving total parenteral nutrition show altered amikacin pharmacokinetics. *Clin. Nutr*., **1995**, *14*(4), 254-259.

[32] Rall, D.P.; Stabenau, J.R.; Zubrod, C.G. Distribution of drugs between blood and cerebrospinal fluid: general methodology and effect of pH gradients. *J. Pharmacol. Exp. Ther.*, **1959**, *125*(3), 185-193.

[33] Much, W.E.; Wilcox, C.S. Disorders of body fluids, sodium and potassium in chronic renal failure. *Am. J. Med.*, **1982**, *72*(3), 536-550.

[34] Schrier, R.W.; Wang, W.; Poole, B.; Mitra, A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. *J. Clin. Invest.*, **2004**, *114*(1), 5-14.

[35] Rocktaeschel, J.; Morimatsu, H.; Uchino, S.; Goldsmith, D.; Poustie, S.; Story, D.; Gutteridge, G.; Bellomo, R. Acid-base status of critically ill patients with acute renal failure: analysis based on Stewart–Figge methodology. *Crit. Care*, **2003**, *7*(4), R61-66.

[36] Kaysen, G.A. Plasma composition in the nephrotic syndrome. *Am. J. Nephrol.*, **1993**, *13*(5), 347-359.

[37] Kaysen, G.A.; Dubin, J.A.; Muller, H.G.; Mitch, W.E.; Rosales, L.M.; Levin, N.W. Relationships among inflammation nutrition and physiologic mechanisms establishing albumin levels in hemodialysis patients. *Kidney Int.*, **2002**, *61*(6), 2240-2249.

[38] Verbeeck, R.K.; Branch, R.A.; Wilkinson, G.R. Drug metabolites in renal failure: pharmacokinetic and clinical implications. *Clin. Pharmacokinet.*, **1981**, *6*(5), 329-345.

[39] Reidenberg, M.M. and Drayer, D.E. Drug metabolism and active drug metabolites in renal failure. *J. Dial.*, **1977**, *1*(4), 313-318.

[40] Meyer, T.W.; Hostetter, T.H. Uremia. *N. Engl. J. Med.*, **2007**, *357*(13), 1316-1325.

[41] Vanholder, R.; De Smet, R.; Lameire, N. Protein-bound uremic solutes: the forgotten toxins. *Kidney Int.*, **2001**, *78*(Suppl.), S266-270.

[42] Lesaffer, G.; De Smet, R.; Lameire, N.; Dhondt, A.; Duym, P.; Vanholder, R. Intradialytic removal of protein-bound uraemic toxins: role of solute characteristics and of dialyser membrane. *Nephrol. Dial. Transplant.*, **2000**, *15*(1), 50-57.

[43] Bammens, B; Evenepoel, P.; Verbeke, K.; Vanrenterghem, Y. Removal of middle molecules and protein-bound solutes by peritoneal dialysis and relation with uremic symptoms. *Kidney Int.*, **2003**, *64*(6), 2238-2243.

[44] Erill, S.; Calvo, R.; Carlos, R. Plasma protein carbamylation and decreased acidic drug protein binding in uremia. *Clin. Pharmacol. Ther.*, **1980**, *27*(5), 612-618.

[45] Craig, W.A.; Evenson, M.A.; Sarver, K.P.; Wagnild, J.P. Correction of protein binding defect in uremic sera by charcoal treatment. *J. Lab. Clin. Med.*, **1976**, *87*(4), 637-647.

[46] Stoeckel, K.; McNamara, P.J.; Hoppe-Seyler, G.; Blumberg, A.; Keller, E. Single-dose ceftriaxone kinetics in functionally anephric patients. *Clin. Pharmacol. Ther.*, **1983**, *33*(5), 633-641.

[47] Craig, W.A.; Welling, P.G.; Jackson, T.C.; Kunin, C.M. Pharmacology of cefazolin and other cephalosporins in patients with renal insufficiency. *J. Infect. Dis.*, **1973**, *128* (Suppl), S347-345.

[48] Henriksen, H.J.; Petersen, M.U.; Pedersen, F.B. Serum alpha-1-acid glycoprotein (orosomucoid) in uremic patients on hemodialysis. *Nephron,* **1982**, *31*(1), 24-26.

[49] Vasson, M.P.; Baguet, J.C.; Arveiller, M.R.; Bargnoux, P.J.; Giroud, J.P.; Raichvarg, D. Serum and urinary alpha-1 acid glycoprotein in chronic renal failure. *Nephron*, **1993**, *65*(2), 299-303.

[50] Sampliner, R.; Perrier, D.; Powell, R.; Finley, P. Influence of ascites on tobramycin pharmacokinetics. *J. Clin. Pharmacol.*, **1984**, *24*(1), 43-46.

[51] Lanao, J.M.; Dominguez-Gil, A.; Macias, J.G.; Diez, J.L.; Nieto, M.J. The influence of ascites on the pharmacokinetics of amikacin. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **1980**, *18*(2), 57-61.

[52] Hodgman, T.; Dasta, J.F.; Armstrong, D.K.; Crist, K.D.; Ellison, C. Tobramycin disposition into ascitic fluid. *Clin. Pharm.*, **1984**, *3*(2), 203-205.

[53] Barry, M.; Keeling, P.W.; Weir, D.; Feely, J. Severity of cirrhosis and the relationship of alpha1-acid glycoprotein concentration to plasma protein binding of lidocaine. *Clin. Pharmacol. Ther.*, **1990**, *47*(3), 366-370.

[54] Pedersen, L.E.; Bonde, J.; Graudal, N.A.; Backer, N.V.; Hansen, J.E.; Kampmann, J.P. Quantitative and qualitative binding characteristics of disopyramide in serum from patients with decreased renal and hepatic function. *Br. J. Clin. Pharmacol.*, **1987**, *23*(1), 41-46.

[55] Pacifici, G.M.; Viani, A.; Taddeucci-Brunelli, G.; Rizzo, G.; Carrai, M.; Schulz, H.U. Effects of development, aging, and renal and hepatic insufficiency as well as hemodialysis on the plasma concentrations of albumin and alpha 1-acid glycoprotein: implications for binding of drugs. *Ther. Drug Monit.*, **1986**, *8*(3), 259-263.

[56] Bower, S.; Sear, J.W.; Roy, R.C.; Carter, R.F. Effects of different hepatic pathologies on disposition of alfentanil in anaesthetized patients. *Br. J. Anaesth.*, **1992**, *68*(5), 462-465.

[57] Thiessen, J.J.; Sellers, E.M.; Denbeigh, P.; Dolman, L. Plasma protein binding of diazepam and tolbutamide in chronic alcoholics. *J. Clin. Pharmacol.*, **1976**, *16*(7), 345-351.

[58] Williams, R.L.; Blaschke, T.F.; Meffin, P.J.; Melmon, K.L.; Rowland, M. Influence of acute viral hepatitis on disposition and plasma binding of tolbutamide. *Clin. Pharmacol. Ther.*, **1977**, *21*(3), 301-309.

[59] Klotz, U.; Avant, G.R.; Hoyumpa, A.; Schenker, S.; Wilkinson, G.R. The effect of age and liver disease on the disposition and elimination of diazepam in adult man. *J. Clin. Invest.*, **1975**, *55*(2), 347-359.

[60] Olsen, G.D.; Bennett, W.M.; Porter, G.A. Morphine and phenytoin binding to plasma proteins in renal and hepatic failure. *Clin. Pharmacol. Ther.*, **1975**, *17*(6), 677-684.

[61] Leithe, M.E.; Margorien, R.D.; Hermiller, J.B.; Unverferth, D.V.; Leier, C.V. Relationship between central hemodynamics and regional blood flow in normal subjects and in patients with congestive heart failure. *Circulation*, **1984,** *69*(1), 57-64.

[62] Benowitz, N.; Forsyth, F.P.; Melmon, K.L.; Rowland, M. Lidocaine disposition kinetics in monkey and man. I. Prediction by a perfusion model. *Clin. Pharmacol. Ther.*, **1974**, *16*(1), 87-98.

[63] Benowitz, N.; Forsyth, R.P.; Melmon, K.L.; Rowland, M. Lidocaine disposition kinetics in monkey and man: II. Effects of hemorrhage and sympathomimetic drug administration. *Clin. Pharmacol. Ther.*, **1974**, *16*(1), 99-109.

[64] Benowitz, N.L.; Meister, W. Clinical pharmacokinetics of lignocaine. *Clin. Pharmacokinet.*, **1978**, *3*(3), 177-201.

[65] Race, G.A.; Scheifley, C.H.; Edwards, J.E. Albuminuria in congestive heart failure. *Circulation*, **1956**, *13*(3), 329-333.

[66] Gerstein, H.C.; Mann, J.F.; Yi, Q.; Zinman, B.; Dinneen, S.F.; Hoogwerf, B.; Hallé, J.P.; Young, J.; Rashkow, A.; Joyce, C.; Nawaz, S.; Yusuf, S. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*, **2001**, *286*(4), 421-426.

[67] van de Wal, R.M.; Asselbergs, F.W.; Plokker, H.W.; Smilde, T.D.; Lok, D.; van Veldhuisen, D.J.; van Gilst, W.H.;Voors, A.A. High prevalence of microalbuminuria in chronic heart failure patients. *J. Card. Fail.*, **2005**, *11*(8), 602-606.

[68] Deckert, T.; Feldt-Rasmussen, B.; Borch-Johnsen, K,; Jensen, T.; Kofoed-Enevoldsen, A. Albuminuria reflects widespread vascular damage. The steno hypothesis. *Diabetologia,* **1989**, *32*(4), 219-226.

[69] Lima, J.J.; Binkley, P.F.; Johnson, J.; Leier, C.V. Dose- and time-dependent binding and kinetics of pindolol in patients with congestive heart failure. *J. Clin. Pharmacol.*, **1986**, *26*(4), 253-257.

[70] Nomura, A.; Yasuda, H.; Kobayashi, T.; Kishino, S.; Kohri, N.; Iseki, K.; Miyazaki, K. Serum alpha-1-acid glycoprotein and protein binding of disopyramide in patients with congestive heart failure. *Eur. J. Clin. Pharmacol.*, **1992**, *42*(1), 115-116.

[71] Bone, R.C.; Balk R.A.; Cerra, F.B.; Dellinger, R.P.; Fein, A.M.; Knaus, W.A.; Schein, R.M.; Sibbald, W.J. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*, **1992**, *101*(6), 1644-1655.

[72] Keel, M.; Trentz, O. Pathophysiology of polytrauma. *Injury*, **2005**, *36*(6), 691-709.

[73] Anderson, G.D.; Gidal, B.E.; Hendryx, R.J.; Awan, A.B.; Temkin, N.R.; Wilensky, A.J.; Winn, H.R. Decreased plasma protein binding of valproate in patients with acute head trauma. *Br. J. Clin. Pharmacol.*, **1994**, *37*(6), 559-562.

[74] Conil, J.M.; Georges, B.; Fourcade, O.; Seguin, T.; Houin, G.; Saivin, S. Intermittent administration of ceftazidime to burns patients: influence of glomerular filtration. *Int. J. Clin. Pharmacol. Ther.*, **2007**, *45*(3), 133-142.

[75] Conil, J.M.; Georges, B.; Lavit, M.; Laguerre, J.; Samii, K.; Houin, G.; Saivin, S. A population pharmacokinetic approach to ceftazidime use in burn patients: influence of glomerular filtration, gender and mechanical ventilation. *Br. J. Clin. Pharmacol.*, **2007**, *64*(1), 27-35.

[76] Walstad, R.A.; Aanderud, L.; Thurmann-Nielsen, E. Pharmacokinetics and tissue concentrations of ceftazidime in burn patients. *Eur. J. Clin. Pharmacol.*, **1988**, *35*(5), 543-549.

[77] Zaske, D.E.; Sawchuk, R.J.; Gerding, D.N.; Strate, R.G. Increased dosage requirements of gentamicin in burn patients. *J. Trauma.*, **1976**, *16*(10), 824-828.

[78] Loirat, P.; Rohan, J.; Baillet, A.; Beaufils, F.; David, R.; Chapman, A. Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. *N. Engl. J. Med.*, **1978**, *299*(17), 915-919.

[79] Kopcha, R.G.; Fant, W.K.; Warden, G.D. Increased dosing requirements for amikacin in burned children. *J. Antimicrob. Chemother.*, **1991**, *28*(5), 747-752.

[80] Macfie, A.G.; Magides, A.D.; Reilly, C.S. Disposition of alfentanil in burns patients. *Br. J. Anaesth.*, **1992**, *69*(5), 447-450.

[81] Niemiec, P.W.; Allo, M.D.; Miller, C.F. Effect of altered volume of distribution on aminoglycoside levels in patients in surgical intensive care. *Arch. Surg.*, **1987**, *122*(2), 207-212.

[82] Beckhouse, M.J.; Whyte, I. M.; Byth, P.L.; Napier, J.C.; Smith, A.J. Altered aminoglycoside pharmacokinetics in the critically ill. *Anaesth. Intensive Care*, **1988**, *16*(4), 418-422.

[83] Triginer, C.; Izquierdo, I.; Fernández, R.; Rello, J.; Torrent, J.; Benito, S.; Net, A. Gentamicin volume of distribution in critically ill septic patients. *Intensive Care Med.*, **1990**, *16*(5), 303-306.

[84] Marik, P.E. Aminoglycoside volume of distribution and illness severity in critically ill septic patients. *Anaesth. Intensive Care*, **1993**, *21*(2), 172-173.

[85] Oparaoji, E.C.; Cornwell, E.E.; Hekmat, E.; Lum-Cheong, R.; Adir, J.S.; Siram, S. Aminoglycoside volume of distribution in postoperative patients with septic shock. *Clin. Pharm.*, **1993**, *12*(2), 131-134.

[86] Lugo, G.; Castaneda-Hernandez, G. Relationship between hemodynamic and vital support measures and pharmacokinetic variability of amikacin in critically ill patients with sepsis. *Crit. Care Med.*, **1997**, *25*(5), 806-811.

[87] Tang, G.J.; Tang, J.J.; Lin, B.S.; Kong, C.W.; Lee, T.Y. Factors affecting gentamicin pharmacokinetics in septic patients. *Acta Anaesthesiol. Scand*, **1999**, *43*(7), 726-730.

[88] Lipman, J.; Wallis, S.C.; Rickard, C.M.; Fraenkel, D. Low cefpirome levels during twice daily dosing in critically ill septic patients: pharmacokinetic modelling calls for more frequent dosing. *Intensive Care Med.*, **2001**, *27*(2), 363-370.

[89] Joynt, G.M.; Lipman, J.; Gomersall, C.D.; Young, R.J.; Wong, E.L.; Gin, T. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. *J. Antimicrob. Chemother.*, **2001**, *47*(4), 421-429.

[90] Brunner, M.; Pernerstorfer, T.; Mayer, B.X.; Eichler, H.G.; Muller, M. Surgery and intensive care procedures affect the target site distribution of piperacillin. *Crit. Care Med.,* **2000**, *28*(6), 1754-1759.

[91] Botha, F.J.; van der Bijl, P.; Seifart, H.I.; Parkin, D.P. Fluctuation of the volume of distribution of amikacin and its effect on once-daily dosage and clearance in a seriously ill patient. *Intensive Care Med.*, **1996**, *22*(5), 443-446.

[92] Gous, A.G.; Dance, M.D.; Lipman, J.; Luyt, D.K.; Mathivha, R.; Scribante, J. Changes in vancomycin pharmacokinetics in critically ill infants. *Anaesth. Intensive Care*, **1995**, *23*(6), 678-682.

Received: April 07, 2010 **Accepted: April 28, 2010**