

ABOUT DRUG DIALYZABILITY

Siniša Šefer¹ and Vesna Degoricija²

¹Department of Nephrology and Dialysis and ²University Department of Medicine, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Drug dialyzability is determined by complex interaction of many factors, including the characteristics of the drug and the technical aspects of the dialysis system. Numerous aspects of dialysis prescription, including some elaborated in this article, have the potential to influence drug removal by dialysis. Care must be exercised when applying information from published reports of drug dialyzability to the individual patient. In order to provide the best information for individual patients, healthcare professionals should become familiar with the dialysis membranes utilized at their healthcare facility, and interpret literature information in that light. This article includes a table on dialyzability of drugs during conventional and high-permeability dialysis, and during peritoneal dialysis.

Key words: *Peritoneal dialysis; Kidney failure, therapy; Dialysis solutions, pharmacokinetics; Renal dialysis, trends; Renal replacement therapy, methods; Pharmaceutical preparations, administration and dosage*

Introduction

The extent to which a drug is affected by dialysis is determined primarily by several physicochemical characteristics of the drug. These include molecular size, protein binding, volume of distribution, water solubility, and plasma clearance. In addition to these properties of the drug, technical aspects of the dialysis procedure may also determine the extent to which a drug is removed by dialysis.

What Determines Drug Dialyzability?

Drug Properties That Affect Dialyzability

Molecular weight

One of the most reliable predictors of the dialyzability of a drug is its molecular weight. Dialysis is dependent on the dialytic membrane used, i.e. either a synthetic membrane with fixed pore size, as in hemodialysis, or a naturally occurring peritoneal membrane, as in peritoneal dialysis. The movement of drugs or other solutes is largely determined by the size of these molecules in relation to

the pore size of the membrane. As a general rule, smaller molecular weight substances will pass through the membrane more easily than larger molecular weight substances. Drugs of molecular weight above 1,000 daltons depend less on diffusion and more on conventional dialytic clearance. Hemodiafiltration does not differ from conventional dialysis with respect to clearance of small solutes with molecular weights <500 daltons. However, the hemodiafiltration clearance of middle molecular weight molecules (500 to 5,000 daltons) exceeds that in conventional dialysis by 10%, and large molecular clearance (>5,000 daltons) in hemodiafiltration is increased by 24% over that in conventional hemodialysis¹. Molecular volume is determined by the weight, shape and charge of the species in question. If a drug cannot fit through a dialysis membrane pore because of its geometric proportions, it is reflected and cannot be cleared by the dialyzer. The term 'molecular size' is used to indicate the relationship of molecular weight, volume, shape, charge and steric hindrance to the ability of a molecular species to permeate a membrane pore. A common assumption is that pore size of the peritoneal membrane is somewhat larger than that of the hemodialysis membrane; this would explain the observation that larger molecular weight substances appear to cross the peritoneal membrane to a greater extent than they cross the hemodialysis membrane².

Correspondence to: *Siniša Šefer, M.D.*, Department of Nephrology and Dialysis, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia

E-mail: sinisa.sefer@zg.htnet.hr

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Protein binding

Another important factor determining drug dialyzability is the concentration gradient of unbound (free) drug across the dialysis membrane. The bound and unbound fractions of the total drug are in constant equilibrium. If the drug is tightly protein-bound, then the flux between bound and unbound drug occurs more slowly. Unbound drug is the pharmacologically active form, for it can be freely distributed to targeted tissue receptor sites, metabolic inactivating sites (e.g., the liver), or excretory sites (e.g., the kidneys or dialyzer). Certain conditions of uremia may inhibit or enhance protein binding³. Malnutrition and proteinuria lower serum protein levels, thereby increasing the free fraction of a drug due to saturation of a reduced number of protein binding sites available. Consequently, dialyzer clearance increases and the possibility of drug toxicity is enhanced, particularly if the drug has a narrow therapeutic window. Accumulation of uremic toxins decreases the affinity of albumin for drugs such as penicillins, digoxin, phenobarbital, phenytoin, warfarin, morphine, primidone, salicylates, theophylline, and sulfonamides. Acid drugs (e.g., cephalosporins, imipenem, vancomycin, and ciprofloxacin) have a higher free fraction than do basic drugs such as tobramycin because of the chronic organic acidemia that accompanies renal failure. Organic acids compete with acid drugs for certain protein binding sites. On the other hand, uncomplicated uremia causes few alterations in the protein binding of basic drugs⁴. Basic drugs bind more avidly to nonalbumin serum proteins than to albumin. The protein binding of basic drugs is often increased owing to elevated levels of the acute-phase reactant α_1 acid glycoprotein, to which these drugs readily bind⁵. These basic drugs may bind still more avidly to these nonalbumin proteins during catastrophic illnesses⁶. As the result, less unbound drug is available for dialytic clearance or for pharmacologic activity. However, since metabolism is slowed by the enhanced protein binding, drug presence may also be prolonged. Heparin use during hemodialysis stimulates the activity of lipoprotein lipases, which break down triglycerides into free fatty acids. Elevated levels of plasma free fatty acids compete with drugs such as tryptophan, sulfonamides, salicylates, phenylbutazone, phenytoin, thiopentone and valproic acid for protein binding sites, causing an increase in the free fraction during and after the action of heparin effect⁷. To illustrate the complexity of drug-protein interactions, free fatty acids may displace cefamandole but may enhance the binding of other cephalosporins such as cephalothin or cefoxitin⁸.

Golper showed the addition of free fatty acids to increase the free fraction of phenytoin, a highly protein bound drug⁹. Thus, any perturbation in the serum free fatty acid concentration may alter drug-protein binding and ultimately drug clearance. Drugs with a high degree of protein binding will have a small plasma concentration of unbound drug available for dialysis. Uremia may have an effect on protein binding for some drugs. Through the mechanisms not yet completely understood, protein binding may decrease in uremic serum. Should this change in binding be substantial, increased dialyzability of free drug may occur. Because the primary binding proteins for most drugs (albumin, α_1 -acid glycoprotein) are of large molecular size, the drug-protein complex is often too large to cross the dialysis membrane, especially in case of hemodialysis membrane. Since peritoneal membrane does permit the passage of some proteins, there may be some limited drug-protein removal with this technique. Increased protein concentrations have been noted in peritoneal effluent during episodes of peritonitis.

Red blood cell binding

Related to tissue compartmentalization is the phenomenon of drug partitioning into red blood cells. Marbury *et al.* first raised this concern because ultrafiltration during dialysis raises hematocrit and complicates the determination of intradialytic drug clearance¹⁰. The question is whether the whole blood concentration or the plasma concentration is the proper reference value; this is particularly relevant to the clearance of ethambutol, a drug known to partition into red blood cells¹¹. Drugs that have a partition coefficient (whole blood to plasma concentration ratio) exceeding unity (e.g., procainamide, glutethimide and acetaminophen) may have decreased clearance due to hemoconcentration at the end of dialysis. Thus, for drugs that partition into red blood cells, total dialytic clearance may be reduced in these hemoconcentrated states¹². Furthermore, the issue of rapid re-equilibration between red blood cell drug and plasma drug becomes more important. These observations were made before they had been in the pre-erythropoietin era. Higher predialysis hematocrits will result in greater red blood cell partitioning and in less free drug, with the potential consequences described above. Even for a drug with low red blood cell partitioning, clearance may be decreased in a setting of higher hematocrit because, as with all plasma solutes, dialytic clearance is dependent on plasma delivery to the dialyzer. With higher hematocrits more red cell mass and less plasma are delivered to the dialyzer.

Volume of distribution

The volume of distribution (Vd) is a mathematically determined volume representing the extent of drug distribution into body tissues. A drug with a large Vd (e.g., digoxin) is distributed widely throughout tissues and is present in relatively small amounts in the blood. Factors that contribute to a drug having a large Vd include a high degree of lipid solubility and low plasma protein binding. Drugs with a large Vd are likely to be minimally dialyzed. Despite rapid extracellular clearance with any type of short-time dialysis, intracellular equilibration with extracellular fluid can be slow, especially with middle to large molecular weight solutes. This is probably related to the lipid solubility of the drug and tissue compartmentalization. Quantitatively, postdialysis intracellular concentrations may vary by only 1% to 2%, and as the result there is a drug concentration gradient between intracellular and extracellular fluid. There may be a posthemodialysis rebound of 10%-25% with intercompartmental equilibration. Higher ultrafiltration rates, as with short-time high-flux hemodiafiltration, can aggravate this rebound phenomenon¹³. Matzke et al. found that for vancomycin the rebound level was by 50% higher than the initial postdialysis drug concentration. The maximum posthemodiafiltration rebound time, defined as the time at which the maximum drug plasma concentration occurred postdialysis, was highly variable for vancomycin, ranging from 2.8 to 45.8 hours. Therefore it would be difficult to predict this phenomenon for a specific patient, and it is advised to follow drug levels closely¹⁴.

Water solubility

The dialysate used for either hemodialysis or peritoneal dialysis is an aqueous solution. In general, drugs with high water solubility will be dialyzed to a greater extent than those with high lipid solubility. Highly lipid-soluble drugs tend to be distributed throughout tissues, and therefore only a small fraction of the drug is present in plasma and accessible for dialysis.

Plasma clearance

The inherent metabolic clearance – the sum of renal and nonrenal clearance – of a drug is often termed the ‘plasma clearance’ of a drug. In dialysis patients, renal clearance is largely replaced by dialysate clearance. If for a particular drug nonrenal clearance is large compared to renal clear-

ance, the contribution that dialysis may make to total drug removal is low. However, if renal (dialysis) clearance increases plasma clearance by 30% or more, dialysis clearance is considered to be clinically important⁴.

Elimination

The primary organs of drug elimination are the liver and kidneys, with the skin, gastrointestinal tract and the lungs also involved to an appreciable degree. Dialysis may play a significant role in drug elimination for the individual with end-stage renal failure. If alternative routes of elimination are not available for drug clearance, the parent drug and its metabolites accumulate. Thus, the quantity of drug administered and/or the frequency of dosing must be considered. Metabolic biotransformation is the chemical conversion of a drug to another form. This process, occurring mainly in the liver, results in a more polar, less lipid-soluble and more extractable metabolite, which often differs from the parent drug in its pharmacologic effects. Most metabolites are pharmacologically inert, although some may possess pharmacologic activity and/or toxicity (e.g., N-acetylprocainamide). Hepatic metabolism of most drugs is usually normal or accelerated with uremia. This may be related to an increased availability of free drug because of decreased protein binding. Cytochrome P450 metabolism of phenytoin is accelerated in uremia, probably as the result of enzyme induction due to the increased free fraction. The metabolism of peptides (e.g., insulin) and procaine is reduced secondary to the inhibition of ester hydrolysis, while hepatic acetylation (e.g., isoniazide) and glucuronide (e.g., acetaminophen) and sulfate conjugate hydrolysis (e.g., sulfa compounds) are usually normal. Drugs and metabolites that have a small molecular size, small volume of distribution, and high water solubility are more likely to be eliminated by dialysis. A dialytic clearance that increases plasma clearance by more than 30% is considered significant⁵.

Bioavailability

Bioavailability is defined as the fraction of administered drug that reaches the bloodstream. It is dependent on the completeness and rate of absorption. The technique of administration will determine how much drug is bioavailable. A drug's absorption is affected by the character of the membranes it must cross to reach the circulation, the blood flow at the site of absorption, the absorptive surface area, and the contact time between the drug and the absorp-

tive area. In addition, physicochemical drug properties such as molecular size and lipid solubility affect drug absorption, particularly after oral administration. The routes of drug administration include the gastrointestinal tract and injection into subcutaneous tissue, muscle and bloodstream. Since maximum absorption is obtained with intravenous administration, this is the standard with which all other forms of administration are compared. Interstitial edema can retard absorption after subcutaneous or intramuscular injection. If a dialysis patient has large interdialytic fluid gains, one would expect erratic or delayed absorption of drugs administered by either of these conditions of volume overload¹⁵. However, there is the potential for increase in either pharmacologic or toxic effect when the patient approaches dry weight and absorbs the drug properly. In the uremic patient three factors affect gastric absorption: gastric pH, gastric motility, and mucosal integrity. An increase in gastric pH as the result of urea breakdown to ammonia greatly reduces absorption. Aluminum hydroxide, used as a phosphate binder, further raises gastric pH, delays gastric emptying, and forms poorly absorbed complexes with drugs. Drugs such as digoxin, tetracycline and probably ciprofloxacin may form nonabsorbable chelation products with aluminum hydroxide. H₂-blockers and proton inhibitors may also rise gastric pH without concomitant motility effects. Mucosal edema delays absorption in the same manner as interstitial edema delays absorption after intramuscular and subcutaneous injection. Bioavailability is closely related to hepatic metabolism owing to the first-pass effect of the enterohepatic circulation, which the drug enters following enteral absorption. The liver can metabolize and inactivate drugs before they reach the systemic circulation. Drugs may never reach their intended site of action due to this first-pass effect. One cannot consistently predict how uremia will affect hepatic metabolism. Hemodialysis can indirectly alter absorption or bioavailability. It can reduce edema in the bowel, muscles and skin, as described above. Dialysis can lower urea levels and can slightly reduce the need of phosphate binders, which may improve absorption of some drugs. On the other hand, hypotension associated with dialysis can impair mesenteric blood flow and may contribute to malabsorption. Removal of uremic toxins may result in more available protein binding sites, thus increasing the drug fraction bound to protein, and this in turn may affect drug metabolism or removal by dialysis⁴.

Dialysis Properties That Affect Drug Clearance

Hemodialyzer properties

Dialysis membrane characteristics that affect drug clearance can be divided into five categories: membrane materials, surface area, drug-membrane charge interaction, drug-membrane binding, and dialyzer reuse.

Membrane materials

Dialyzer membranes are fabricated from a variety of natural and synthetic polymers: cellulose, cellulose acetate, polysulfone, polyamide, polyacrylonitrile, and polymethylmethacrylate. Concern over the possible importance of higher molecular weight toxins has led to the development of membranes with a wide range of solute permeabilities. This development has accelerated in recent years with the availability of dialysis equipment capable of controlling fluid removal. With polysulfone membranes, trace quantities of albumin can appear in the dialysate. Clearance of vancomycin vary with different membranes. AN69 and polysulfone membranes have the greatest clearance, while cuprophane has minimal clearance of this drug under similar hemodialysis conditions¹⁶.

Surface area

The removal of small solutes is dependent upon the concentration gradient between blood and dialysate. This gradient can be maximized by increasing flow rates and/or by increasing surface area, thus dispersing the undialyzed blood to areas of fresh dialysate. Both these principles apply to either high-flux or high-efficiency dialysis. As molecular size increases and diffusivity is increasingly limited by membrane pore size, molecular clearance becomes more dependent upon convection. The hydraulic permeability of high-flux membranes exceeds that of conventional membranes, thus enhancing convective clearance of these larger molecules. When hydraulic permeability limits are achieved, larger surface area becomes the factor most influencing the total rate of convective clearance. Jindal *et al.* have shown that for PAN, PMMA and polysulfone dialyzers, surface area and ultrafiltration have great effect on the clearance of β_2 -microglobulin and phosphate, two poorly diffusible species¹⁷. As mentioned previously, the characteristics of the dialysis membrane determine to a large extent the dialysis of drugs. Pore size, surface area and geometry are the primary determinants of the performance of a given membrane. The technology of hemodialysis continues to evolve, and new membranes continue to be

introduced for clinical use. Interpretation of published literature should be tempered with the understanding that newer membranes may have different drug dialysis characteristics. On the other hand, because the peritoneal membrane is natural, little can be done to alter its characteristics.

Drug-membrane charge interaction and membrane binding

The negative charge of the PAN membrane repels anionic solutes such as doxycycline and gentamicin. The negative charge of the membrane retarded gentamicin clearance. Other possibilities for decreased gentamicin clearance could involve drug adsorption on the dialysis membranes¹⁸. Drug membrane binding has also been demonstrated in the absence of proteins in experimental conditions of continuous methods of hemofiltration¹⁹.

Dialyzer reuse

Reuse may affect clearance by reduction of fiber bundle volume (loss of surface area), by alteration in the diffusive property of the membrane, or by the loss of hydraulic permeability. Observations recorded during continuous hemodiafiltration suggest a predictable decline in ultrafiltration with time due to either fibrin or protein adherence to the membrane²⁰. Despite these observations, the role of reuse in membrane deposition of protein has not been fully elucidated and its effect on drug clearance remains uncertain.

Blood and dialysate flow rates

The hemodialysis prescription contains determination of blood and dialysate flow rates. As drugs normally move from blood to dialysate, the flow rates of these two substances may have a pronounced effect on dialyzability. In general, increased blood flow rates during hemodialysis will enable greater amounts of drug to be delivered to the dialysis membrane. As drug concentrations increase in the dialysate, the flow rate of the dialysis solution also becomes important in overall drug removal²¹. Greater dialysis can be achieved with faster dialysate flow rates that keep dialysate drug concentrations at a minimum. Therefore, when interpreting studies of drug dialyzability, these flow rates should be taken into account²².

During peritoneal dialysis, little can be done to alter blood flow rates to the peritoneum. However, dialysate flow rates are determined by the volume and frequency of dialysate exchange in the peritoneum. At low exchange rates,

drug concentrations in the dialysate will increase during the period of time in which the dialysate resides in the peritoneal cavity, thus slowing additional movement of drug across the membrane. More frequent exchanges will favor increased drug dialyzability, provided the drug's physicochemical characteristics permit its movement across the peritoneal membrane²³.

Special considerations

High-permeability dialysis

Most of the information contained in this guide have been obtained from studies conducted under conditions of standard hemodialysis that employed conventional dialysis membranes. Recent changes in dialysis technology have led to more permeable dialysis membranes and the opportunity to employ higher blood and dialysate flow rates. These new technologies are often referred to as 'high-permeability', 'high-efficiency' and 'high-flux' dialysis. The Food and Drug Administration has proposed that high-permeability dialysis membranes be defined as those with *in vitro* ultrafiltration coefficient (CUf) above 12 mL/mm Hg *per* hour (Federal Register, March 15, 1999, p. 12776). Commonly included in this group of dialysis membranes are polysulfone, polyacrylonitrile, and high-efficiency cuprammonium rayon dialyzers. Changes in dialysis membranes, and changes in blood and dialysis flow rates may have clinically important effects on drug removal through the membrane²⁴. There are increasing numbers of studies to examine the effects of high-permeability dialysis on drug dialyzability. Results of these studies have confirmed predictions that drug removal from plasma is often enhanced as compared with more traditional dialysis membranes. Studies with high-permeability dialysis have also demonstrated that removal of drug from plasma often exceeds the transfer of drug from tissues to plasma. As a result, there is often a rebound of plasma drug concentrations following the conclusion of dialysis as blood-tissue drug equilibration occurs. Patients receiving high-permeability dialysis may require more drug compared with those receiving standard hemodialysis²⁵. Due to the many technical and physiologic variables, individualized therapeutic drug monitoring may be necessary. The reader is referred to the primary literature for more details.

Continuous renal replacement therapy

Another therapeutic development that will affect drug dialyzability is continuous renal replacement therapy

(CRRT), known in its various forms as continuous arteriovenous hemofiltration (CAVH), continuous venovenous hemofiltration (CVVH), continuous arteriovenous hemodialysis (CAVHD), continuous venovenous hemodialysis (CVVHD), continuous venovenous hemodiafiltration (CVVHDF), continuous arteriovenous hemodiafiltration (CAVHDF), slow continuous ultrafiltration (SCUF), continuous arteriovenous high-flux hemodialysis (CAVHFD) and continuous venovenous high-flux hemodialysis (CVVHFD). These various techniques are used in the management of acute renal failure in critically ill patients²⁵. CRRTs differ considerably from intermittent hemodialysis. Relying heavily upon continuous ultrafiltration of plasma water, CRRT has a potential for the removal of large quantities of ultrafilterable drugs contained in the plasma. Unfortunately, few *in vivo* studies have been published, and very few drugs have been studied pharmacokinetically in intensive care patients^{9,26,27}. Therefore, many guidelines for drug dosing during CRRT have been extrapolated from experiences with chronic hemodialysis or from theoretical

considerations based upon general principles of drug removal derived from the physicochemical characteristics of the drug and the CRRT technique employed^{28,29}. Once again, the reader is referred to the primary literature for assistance with the dosing of specific drugs under conditions of CRRT³⁰.

Automated peritoneal dialysis

Automated peritoneal dialysis (APD) is the fastest growing renal replacement therapy by percentage in the US, and provides dialysis exchanges *via* a machine while the patient is sleeping, thereby improving patient convenience, peritoneal dialysis compliance rates, and decreasing peritonitis rates. Well-designed pharmacokinetic studies involving APD have not been conducted. Consequently, no formal drug dosing recommendations are available for APD, and pharmacists must rely on established dosing guidelines for continuous ambulatory peritoneal dialysis when recommending dosing regimens³¹⁻³⁴.

Table 1. Drug dialyzability

Drug	Hemodialysis		Peritoneal dialysis	Drug	Hemodialysis		Peritoneal dialysis
	Conventional	High-permeability			Conventional	High-permeability	
Abciximab	U	ND	ND	Amphetamines	NO	-	-
Acarbose	ND	ND	ND	Aprotinin	U	ND	U
Acetaminophen	YES	L	NO	Arsenic	YES	YES	-
Acetazolamide	U	ND	NO	Ascorbic acid	YES	YES	-
Acetic acid	YES	YES	-	Asparaginase	U	ND	U
Acetilsalicylic acid	YES	YES	-	Atenolol	YES	L	NO
Acitretin	U	ND	U	Atorvastatin	U	ND	U
Acyclovir	YES	L	NO	Atracurium	U	ND	U
Albendazole	NO	ND	U	Atropine	NO	ND	ND
Albumin	U	ND	U	Auranofin	NO	ND	ND
Alendronate	NO	ND	ND	Azathioprine	YES	L	ND
Allopurinol	YES	L	ND	Azithromycin	ND	ND	ND
Alprazolam	NO	ND	U	Azlocillin	YES	L	NO
Alprostadil	NO	ND	ND	Aztreonam	YES	L	NO
Alteplase	U	ND	U	Bacitracin	YES	YES	-
Amantadine	NO	ND	NO	Baclofen	ND	ND	ND
Amifostine	ND	ND	ND	Barbital	YES	YES	-
Amikacin	YES	L	YES	Barium	YES	YES	-
Amiloride	ND	ND	ND	Basiliximab	U	ND	U
Aminocaproic acid	YES	ND	YES	Betamethasone	ND	ND	ND
Aminoglutethimide	YES	L	ND	Betaxolol	NO	ND	NO
Aminosalicic acid	YES	L	ND	Bicalutamide	U	ND	U
Amiodarone	NO	ND	NO	Bismuth	YES	YES	-
Amitriptyline	NO	ND	NO	Bisoprolol	NO	ND	ND
Amlodipine	NO	ND	NO	Boric acid	YES	YES	-
Amoxicillin	YES	L	NO	Bretylium	YES	L	ND
Amphotericin B	NO	ND	NO	Bromazepam	?	?	-
Ampicillin	YES	L	NO	Bromfenac	NO	ND	U
Anastrozole	ND	ND	ND	Bromocriptine	U	ND	U
Antithymocyte globulin	U	ND	U	Buflomedil	NO	NO	U

Drug	Hemodialysis		Peritoneal dialysis	Drug	Hemodialysis		Peritoneal dialysis
	Conventional	High-permeability			Conventional	High-permeability	
Bumetanide	NO	ND	U	Clofazimine	NO	ND	NO
Busulfan	ND	ND	ND	Clofibrate	NO	ND	NO
Butorphanol	U	ND	U	Clomipramine	U	ND	U
Cadmium	NO	NO	-	Clonazepam	NO	ND	U
Caffeine	ND	ND	ND	Clonidine	NO	ND	NO
Calcitriol	NO	NO	U	Clopidogrel	U	ND	U
Camphor	NO	NO	-	Clorazepate	NO	ND	U
Captopril	YES	L	NO	Cloxacillin	NO	ND	NO
Carbamates	YES	YES	-	Clozapine	U	ND	U
Carbamazepine	NO	ND	NO	Cocaine	YES	YES	-
Carbencillin	YES	L	NO	Codeine	NO	ND	U
Carbidopa/Levodopa	ND	ND	ND	Colchicine	NO	ND	NO
Carboplatin	YES	L	ND	Colistine	YES	YES	-
Carboprost	ND	ND	ND	Contrast media	YES	YES	-
Carmustine	NO	ND	ND	Copper	YES	YES	-
Carnitine	YES	L	ND	Cortisone	NO	ND	NO
Carvedilol	NO	ND	ND	Cyanide	YES	YES	-
Cefaclor	YES	L	YES	Cyclophosphamide	YES	L	ND
Cefadroxil	YES	L	NO	Cycloserine	YES	L	ND
Cefamandole	YES	L	NO	Cyclosporine	NO	ND	NO
Cefazolin	YES	L	NO	Cysteamine	ND	ND	NO
Cefepime	YES	L	YES	Cytarabine	NO	ND	NO
Cefixime	NO	ND	NO	Dacarbazine	ND	ND	ND
Cefodizime	NO	ND	NO	Dalteparin	U	ND	U
Cefoperazone	NO	ND	NO	Dapsone	YES	L	ND
Cefotaxime	YES	L	NO	Daunorubicin	ND	ND	ND
Cefpirome	YES	YES	NO	Deferoxamine	YES	L	ND
Ceftazidime	YES	L	YES	Desmopressin	ND	ND	ND
Ceftibuten	YES	L	ND	Dexamethasone	NO	ND	NO
Ceftriaxone	NO	ND	NO	Dexfenfluramine	ND	ND	ND
Cefuroxime	YES	L	NO	Diazepam	NO	ND	U
Celecoxib	U	ND	U	Diazoxide	YES	L	YES
Cephalexin	YES	L	NO	Diclofenac	U	ND	U
Cephalothin	YES	L	NO	Dicloxacillin	NO	ND	NO
Cephapirin	YES	L	NO	Didanosine	NO	ND	NO
Cerivastatin	U	ND	U	Diethylpropion	ND	ND	ND
Cetirizine	NO	ND	U	Digitoxin/digoxin/ medigoxin	NO	ND	NO
Chloral hydrate	YES	L	ND	Dihydroergotamine	ND	ND	ND
Chlorambucil	NO	ND	NO	Diltiazem	NO	ND	NO
Chloramphenicol	YES	L	NO	Diphenhydramine	U	ND	U
Chloroquine	NO	ND	NO	Dipyridamole	U	ND	ND
Chloropheniramine	YES	L	NO	Disopyramide	YES	L	ND
Chlorpromazine	NO	ND	NO	Dobutamine	NO	ND	NO
Chlorpropamide	NO	ND	NO	Docetaxel	U	ND	U
Chlortetracycline	YES	YES	-	Dolasetron	ND	ND	ND
Chlorthalidone	NO	ND	U	Donepezil	U	ND	U
Cidofovir	ND	YES	NO	Dopamine	NO	ND	U
Cilastatin	YES	L	ND	Doxazosin	NO	ND	NO
Cimetidine	NO	ND	NO	Doxercalciferol	NO	ND	U
Ciprofloxacin	NO	ND	NO	Doxorubicin	NO	ND	ND
Cisapride	NO	ND	U	Doxycycline	NO	ND	NO
Cisplatin	NO	ND	ND	EDTA calcium	YES	L	YES
Cladribine	ND	ND	ND	Enalapril/enalaprilat	YES	L	YES
Clarithromycin	ND	ND	ND	Enoxaparin	NO	ND	U
Clavulanic acid	YES	ND	YES	Epinephrine	ND	ND	ND
Clindamycin	NO	ND	NO	Epoetin alfa	NO	ND	NO
Clobazam	?	?	-	Eprosartan	U	NO	U
Clodronate	YES	ND	NO				

Drug	Hemodialysis		Peritoneal dialysis	Drug	Hemodialysis		Peritoneal dialysis
	Conventional	High-permeability			Conventional	High-permeability	
Eprifibatide	ND	ND	ND	Idarubicin	U	ND	U
Ergocalciferol	ND	ND	ND	Ifosfamide	YES	L	ND
Erythromycin	NO	ND	NO	Imipenem	YES	L	YES
Ethacrynic acid	NO	ND	U	Imipramine	NO	ND	NO
Ethambutol	NO	NO	U	Immune globulin	U	N	U
Ethinyl estradiol	ND	ND	NO	Indapamide	NO	ND	U
Ethosuximide	YES	L	ND	Indinavir	ND	ND	ND
Etoposide	NO	ND	NO	Indomethacin	NO	ND	U
Famciclovir/penciclovir	YES	L	ND	Insulin	NO	ND	NO
Famotidine	NO	ND	NO	Interferons	NO	ND	NO
Fenofibrate	NO	ND	U	Iodoxanol	YES	L	ND
Fentanyl	ND	ND	ND	Iopromide	YES	YES	ND
Ferric gluconate	NO	ND	U	Irinotecan	U	ND	U
Ferrous (iron) salts	U	ND	U	Isoniazid	NO	NO	U
Fexofenadine	NO	ND	U	Isosorbide dinitrate	NO	ND	NO
Filgrastim	NO	ND	U	Isosorbide mononitrate	YES	L	NO
Finasteride	U	ND	U	Itraconazole	NO	ND	U
Fluconazole	YES	L	YES	Ketoconazole	NO	ND	NO
Fludarabine	ND	ND	ND	Ketoprofen	U	ND	U
Flumazenil	ND	ND	ND	Lamivudine	NO	ND	U
Fluorouracil	YES	L	ND	Lamotrigine	NO	ND	U
Fluoxetine	NO	ND	NO	Lansoprazole	NO	ND	U
Fluphenazine	U	ND	U	Leflunomide	NO	ND	NO
Flurazepam	NO	ND	U	Letrozole	ND	ND	ND
Flurbiprofen	ND	ND	NO	Leuprolide	ND	ND	ND
Flutamide	NO	ND	U	Levamisole	ND	ND	ND
Fluvastatin	U	ND	U	Levobupivacaine	U	ND	U
Fluvoxamine	U	ND	U	Levonorgestrel	U	N	U
Foscarnet	YES	YES	ND	Levothyroxine	U	ND	U
Fosfomycin	YES	L	ND	Lidocaine	NO	ND	U
Fosinopril/fosinoprilat	NO	ND	NO	Lincomycin	NO	ND	NO
Fosphenytoin	U	ND	U	Lisinopril	YES	L	ND
Furosemide	NO	ND	U	Lithium	YES	L	YES
Fusidic acid	NO	ND	NO	Loperamide	ND	ND	ND
Gabapentin	YES	L	ND	Loratadine	NO	ND	NO
Gadodiamide	YES	L	NO	Lorazepam	NO	ND	U
Gadoversetamide	YES	L	NO	Losartan	NO	ND	NO
Gallium	ND	ND	ND	Lovastatin	U	ND	U
Ganciclovir	YES	L	ND	Mannitol	YES	L	YES
Gemcitabine	ND	ND	ND	Maprotiline	NO	ND	U
Gemfibrozil	NO	ND	NO	Melphalan	NO	ND	ND
Gentamicin	YES	YES	YES	Meprobamate	YES	L	YES
Glatiramer	ND	ND	ND	Mercaptopurine	YES	L	ND
Glimepiride	ND	ND	ND	Meropenem	YES	L	ND
Glipizide	U	ND	U	Mesalamine	U	ND	U
Glucagon	U	ND	U	Mesna	ND	ND	ND
Glutethimide	NO	ND	NO	Metformin	YES	L	ND
Gold sodium thiomalate	NO	ND	U	Methadone	NO	ND	NO
Granisetron	ND	ND	ND	Methenamine	ND	ND	ND
Haloperidol	NO	ND	NO	Methylphenobarbitone	YES	YES	-
Heparin	NO	ND	NO	Methimazole	NO	ND	NO
Hirudin	NO	NO	ND	Methotrexate	YES	YES	NO
Hydralazine	NO	ND	NO	Methyldopa	YES	L	YES
Hydrochlorothiazide	NO	ND	U	Methylprednisolone	YES	L	ND
Hydrocodone	ND	ND	ND	Metoclopramide	NO	ND	NO
Hydrocortisone	U	ND	U	Metoprolol	YES	L	ND
Hydroxychloroquine	ND	ND	ND	Metronidazole	YES	L	NO
Ibuprofen	NO	ND	U	Mexiletine	YES	L	NO

Drug	Hemodialysis		Peritoneal dialysis	Drug	Hemodialysis		Peritoneal dialysis
	Conventional	High-permeability			Conventional	High-permeability	
Mezlocillin	YES	L	NO	Pindolol	ND	ND	ND
Miacalcin	ND	ND	ND	Piperacillin	YES	L	NO
Miconazole	NO	ND	NO	Piroxicam	U	ND	U
Midazolam	NO	ND	U	Pralidoxime	ND	ND	ND
Midodrine	YES	ND	NA	Pravastatin	NO	ND	ND
Milrinone	ND	ND	ND	Prazosin	NO	ND	NO
Minoxidil	YES	L	YES	Prednisone	NO	ND	NO
Misoprostol	U	ND	U	Primidone	YES	L	ND
Mitomycin	ND	ND	ND	Probucof	NO	ND	NO
Mitoxantrone	NO	ND	NO	Procainamide	YES	L	NO
Montelukast	U	ND	U	Procarbazine	ND	ND	ND
Morphine	YES	ND	NO	Promazine	U	ND	U
Muromonab-CD3	U	ND	U	Promethazine	NO	ND	ND
Naloxone	ND	ND	ND	Propafenone	NO	ND	NO
Naproxen	NO	ND	U	Propofol	U	ND	U
Naratriptan	ND	ND	ND	Propranolol	NO	ND	NO
Nelfinavir	U	ND	U	Pyrazinamide	YES	YES	NO
Netilmicin	YES	L	YES	Pyrimethamine	ND	ND	ND
Nevirapine	ND	ND	ND	Quinidine	NO/HP YES	ND	NO
Nicardipine	NO	ND	U	Quinine	NO	ND	NO
Nicotine	ND	ND	ND	Raloxifene	U	ND	U
Nicotinic acid	ND	Nd	ND	Ramipril/ramiprilat	NO	ND	ND
Nifedipine	NO	ND	NO	Ranitidine	NO	ND	NO
Nilutamide	ND	ND	ND	Repaglinide	U	ND	U
Nimodipine	NO	ND	NO	Reserpine	NO	ND	NO
Nitrofurantoin	YES	L	ND	Reviparin	NO	ND	U
Nitroglycerin	NO	ND	NO	Rifampin	NO	NO	NO
Nitroprusside	YES	L	YES	Risperidone	ND	ND	ND
Nizatidine	NO	ND	NO	Ritodrine	YES	L	YES
Norethindrone	ND	ND	NO	Ritonavir	U	ND	U
Norfloxacin	NO	ND	U	Rizatriptan	ND	ND	ND
Nortriptyline	NO	ND	NO	Rocuronium	ND	ND	ND
Octreotide	YES	L	ND	Rofecoxib	NO	ND	U
Ofloxacin	YES	ND	NO	Ropinirole	U	ND	U
Olanzapine	NO	ND	NO	Rosiglitazone	NO	ND	U
Olsalazine	U	ND	U	Saquinavir	U	ND	U
Omeprazole	U	ND	U	Selegiline	ND	ND	ND
Ondansetron	U	ND	U	Sertraline	NO	ND	U
Orlistat	U	ND	U	Sibutramine	U	ND	U
Oxazepam	NO	ND	U	Sildenafil	U	ND	U
Paclitaxel	NO	ND	U	Silver	NO	ND	U
Pamidronate	ND	ND	ND	Simvastatin	U	ND	U
Pancuronium	ND	ND	ND	Somatropin	U	ND	U
Pantoprazole	NO	ND	ND	Sotalol	YES	L	ND
Paricalcitol	NO	ND	ND	Spectinomycin	YES	L	YES
Paroxetine	NO	ND	U	Spironolactone	U	ND	U
Pefloxacin	NO	ND	NO	Stavudine	ND	ND	ND
Penicillamine	YES	L	ND	Streptomycin	YES	L	YES
Penicillin G	YES	L	NO	Streptozocin	ND	ND	ND
Pentazocine	YES	L	ND	Sucralfate	NO	ND	NO
Pentobarbital	NO	ND	U	Sulbactam	YES	L	NO
Pentoxifylline	U	ND	ND	Sulfamethoxazole	YES	L	NO
Perindopril/perindoprilat	YES	L	ND	Sulfisoxazole	YES	L	YES
Perphenazine	U	ND	U	Sulindac	NO	ND	U
Phenobarbital	YES	L	YES	Sumatriptan	ND	ND	ND
Phentolamine	ND	ND	ND	Tamoxifen	ND	ND	ND
Phenylbutazone	NO	ND	U	Tazobactam	YES	L	NO
Phenytoin	NO	YES	NO	Teicoplanin	NO	ND	NO

Drug	Hemodialysis		Peritoneal dialysis	Drug	Hemodialysis		Peritoneal dialysis
	Conventional	High-permeability			Conventional	High-permeability	
Terbinafine	U	ND	U	Trapidil	ND	ND	ND
Terbutaline	ND	ND	ND	Tretinoin	ND	ND	ND
Testosterone	U	ND	U	Triamterene	ND	ND	ND
Tetracycline	NO	ND	NO	Triazolam	NO	ND	U
Thalidomide	ND	ND	ND	Trimethoprim	YES	L	NO
Theophylline	YES	L	NO	Trimipramine	U	ND	U
Thiethylperazine	ND	ND	ND	Troglitazone	U	ND	U
Thioguanine	ND	ND	ND	Tropisetron	U	ND	U
Thioridazine	U	ND	U	Valacyclovir	YES	L	ND
Ticarcillin	YES	L	NO	Valproic acid	NO	ND	NO
Ticlopidine	U	ND	U	Valsartan	U	ND	U
Timolol	NO	ND	NO	Vancomycin	NO	YES	NO
Tinidazole	YES	L	ND	Vecuronium	U	ND	U
Tirofiban	YES	L	ND	Verapamil	NO	ND	NO
Tizanidine	ND	ND	ND	Vigabatrin	YES	L	ND
Tobramycin	YES	L	YES	Vinblastine	ND	ND	ND
Tocainide	YES	L	ND	Vincristine	ND	ND	ND
Topiramate	YES	L	ND	Warfarin	NO	ND	NO
Topotecan	ND	ND	ND	Zafirlukast	U	ND	U
Torsemide	NO	ND	U	Zalcitabine	ND	ND	ND
Tramadol	NO	ND	U	Zidovudine	NO	ND	NO
Trandolapril/ trandolaprilat	YES	L	ND	Zolmitriptan	ND	ND	ND
				Zolpidem	NO	ND	U

Legend:

YES indicates supplemental dosing in conjunction with dialysis is usually required.

NO indicates supplemental dosing is not required.

U indicates significant drug removal is unlikely based on physicochemical characteristics of the drug such as protein binding, molecular size or volume of distribution.

L indicates no published data exist, but information extrapolated from studies using conventional dialysis techniques suggest significant drug removal is likely during high-permeability dialysis.

ND indicates there are no data on drug dialyzability in this type of dialysis.

NS indicates the type of high-permeability membrane was not specified.

HP removed with hemoperfusion.

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Sažetak

O DIJALIZABILNOSTI LIJEKOVA

S. Šefer i V. Degoricija

Dijalizabilnost lijekova je određena složenim međudjelovanjem mnogih čimbenika uključujući osobine lijeka i tehničke osobitosti sustava za dijalizu. Brojni čimbenici propisivanja dijalize navedeni u ovom članku imaju bitan utjecaj na odstranjivanje lijeka. Potrebna je posebna pažnja pri uporabi postojećih informacija o dijalizabilnosti lijekova iz objavljenih izvješća za svakoga bolesnika ponaosob. U cilju pronalaženja najbolje informacije za svakoga pojedinog bolesnika zdravstveni djelatnici trebaju dobro poznavati dijalizne membrane koje rabe i u tom svjetlu objasniti podatke iz literature. Ovaj članak sadrži tablicu s podacima o dijalizabilnosti lijekova tijekom konvencionalne, visokopropusne i peritonejske dijalize.

Ključne riječi: Peritonejska dijaliza; Bubrežno zatajenje, liječenje; Dijalizne otopine, farmakokinetika; Bubrežna dijaliza, trendovi; Bubrežna zamjenska terapija, metode; Farmaceutski pripravci, davanje i doziranje