ABOUT DRUG DIALYZABILITY

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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 hemodialysis[1]. 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 membrane[2].

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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 binding[3]. 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, digitoxin, 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 drugs[4]. 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 bind[5]. These basic drugs may bind still more avidly to these nonalbumin proteins during catastrophic illnesses[6]. 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 effect[7]. 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 cefoxitin[8]. Golper showed the addition of free fatty acids to increase the free fraction of phenytoin, a highly protein bound drug[9]. 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 clearance[10]. 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 cells[11]. 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 states[12]. 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 phenomenon[13]. 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 closely[14].

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 clearance, 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 important[4].

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 significant[5].

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 overload[15]. 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. H_2-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 dialysis[4].

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 apper 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 conditions[16].

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 *at 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 diffusable species[17]. 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 membranes[18]. Drug membrane binding has also been demonstrated in the absence of proteins in experimental conditions of continuous methods of hemofiltration[19].

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 membrane[20]. 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 removal[21]. 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 account[22].

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 membrane[23].

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 membrane[24]. 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 hemodialysis[25]. 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 patients[25]. 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 CRRT[30].

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 regimens[31-34].

Table 1. Drug dialyzability

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

Drug	Hemodialysis		Peritoneal
	Conventional	High-permeability	dialysis
Bumetanide	NO	ND	U
Busulfan	ND	ND	ND
Butorphanol	U	ND	U
Cadmium	NO	NO	–
Caffeine	ND	ND	ND
Calcitriol	NO	NO	U
Camphor	NO	NO	–
Captopril	YES	L	NO
Carbamates	YES	YES	–
Carbamazepine	NO	ND	NO
Carbencillin	YES	L	NO
Carbidopa/Levodopa	ND	ND	ND
Carboplatin	YES	L	ND
Carboprost	ND	ND	ND
Carmustine	NO	ND	ND
Carnitine	YES	L	ND
Carvedilol	NO	ND	ND
Cefaclor	YES	L	YES
Cefadroxil	YES	L	NO
Cefamandole	YES	L	NO
Cefazolin	YES	L	NO
Cefepime	YES	L	YES
Cefixime	NO	ND	NO
Cefodizime	NO	ND	NO
Cefoperazone	NO	ND	NO
Cefotaxime	YES	L	NO
Cefpirome	YES	YES	NO
Ceftazidime	YES	L	YES
Ceftibuten	YES	L	ND
Ceftriaxone	NO	ND	NO
Cefuroxime	YES	L	NO
Celecoxib	U	ND	U
Cephalexin	YES	L	NO
Cephalothin	YES	L	NO
Cephapirin	YES	L	NO
Cerivastatin	U	ND	U
Cetirizine	NO	ND	U
Chloral hydrate	YES	L	ND
Chlorambucil	NO	ND	NO
Chloramphenicol	YES	L	NO
Chloroquine	NO	ND	NO
Chloropheniramine	YES	L	NO
Chloropromazine	NO	ND	NO
Chlorpropamide	NO	ND	NO
Chlortetracycline	YES	YES	-
Chlorthalidone	NO	ND	U
Cidofovir	ND	YES	NO
Cilastatin	YES	L	ND
Cimetidine	NO	ND	NO
Ciprofloxacin	NO	ND	NO
Cisapride	NO	ND	U
Cisplatin	NO	ND	ND
Cladribine	ND	ND	ND
Clarithromycin	ND	ND	ND
Clavulanic acid	YES	ND	YES
Clindamycin	NO	ND	NO
Clobazam	?	?	–
Clodronate	YES	ND	NO

Drug	Hemodialysis		Peritoneal
	Conventional	High-permeability	dialysis
Clofazimine	NO	ND	NO
Clofibrate	NO	ND	NO
Clomipramine	U	ND	U
Clonazepam	NO	ND	U
Clonidine	NO	ND	NO
Clopidogrel	U	ND	U
Clorazepate	NO	ND	U
Cloxacillin	NO	ND	NO
Clozapine	U	ND	U
Cocaine	YES	YES	–
Codeine	NO	ND	U
Colchicine	NO	ND	NO
Colistine	YES	YES	–
Contrast media	YES	YES	–
Copper	YES	YES	–
Cortisone	NO	ND	NO
Cyanide	YES	YES	–
Cyclophosphamide	YES	L	ND
Cycloserine	YES	L	ND
Cyclosporine	NO	ND	NO
Cysteamine	ND	ND	NO
Cytarabine	NO	ND	NO
Dacarbazine	ND	ND	ND
Dalteparin	U	ND	U
Dapsone	YES	L	ND
Daunorubicin	ND	ND	ND
Deferoxamine	YES	L	ND
Desmopressin	ND	ND	ND
Dexamethasone	NO	ND	NO
Dexfenfluramine	ND	ND	ND
Diazepam	NO	ND	U
Diazoxide	YES	L	YES
Diclofenac	U	ND	U
Dicloxacillin	NO	ND	NO
Didanosine	NO	ND	NO
Diethylpropion	ND	ND	ND
Digitoxin/digoxin/ medigoxin	NO	ND	NO
Dihydroergotamine	ND	ND	ND
Diltiazem	NO	ND	NO
Diphenhydramine	U	ND	U
Dipyridamole	U	ND	ND
Disopyramide	YES	L	ND
Dobutamine	NO	ND	NO
Docetaxel	U	ND	U
Dolasetron	ND	ND	ND
Donepezil	U	ND	U
Dopamine	NO	ND	U
Doxazosin	NO	ND	NO
Doxercalciferol	NO	ND	U
Doxorubicin	NO	ND	ND
Doxycycline	NO	ND	NO
EDTA calcium	YES	L	YES
Enalapril/enalaprilat	YES	L	YES
Enoxaparin	NO	ND	U
Epinephrine	ND	ND	ND
Epoetin alfa	NO	ND	NO
Eprosartan	U	NO	U

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

Drug	Hemodialysis		Peritoneal
	Conventional	High-permeability	dialysis
Mezlocillin	YES	L	NO
Miacalcin	ND	ND	ND
Miconazole	NO	ND	NO
Midazolam	NO	ND	U
Midodrine	YES	ND	NA
Milrinone	ND	ND	ND
Minoxidil	YES	L	YES
Misoprostol	U	ND	U
Mitomycin	ND	ND	ND
Mitoxantrone	NO	ND	NO
Montelukast	U	ND	U
Morphine	YES	ND	NO
Muromonab-CD3	U	ND	U
Naloxone	ND	ND	ND
Naproxen	NO	ND	U
Naratriptan	ND	ND	ND
Nelfinavir	U	ND	U
Netilmicin	YES	L	YES
Nevirapine	ND	ND	ND
Nicardipine	NO	ND	U
Nicotine	ND	ND	ND
Nicotinic acid	ND	Nd	ND
Nifedipine	NO	ND	NO
Nilutamide	ND	ND	ND
Nimodipine	NO	ND	NO
Nitrofurantoin	YES	L	ND
Nitroglycerin	NO	ND	NO
Nitroprusside	YES	L	YES
Nizatidine	NO	ND	NO
Norethindrone	ND	ND	NO
Norfloxacin	NO	ND	U
Nortriptyline	NO	ND	NO
Octreotide	YES	L	ND
Ofloxacin	YES	ND	NO
Olanzapine	NO	ND	NO
Olsalazine	U	ND	U
Omeprazole	U	ND	U
Ondansetron	U	ND	U
Orlistat	U	ND	U
Oxazepam	NO	ND	U
Paclitaxel	NO	ND	U
Pamidronate	ND	ND	ND
Pancuronium	ND	ND	ND
Pantoprazole	NO	ND	ND
Paricalcitol	NO	ND	ND
Paroxetine	NO	ND	U
Pefloxacin	NO	ND	NO
Penicillamine	YES	L	ND
Penicillin G	YES	L	NO
Pentazocine	YES	L	ND
Pentobarbital	NO	ND	U
Pentoxifylline	U	ND	ND
Perindopril/perindoprilat	YES	L	ND
Perphenazine	U	ND	U
Phenobarbital	YES	L	YES
Phentolamine	ND	ND	ND
Phenylbutazone	NO	ND	U
Phenytoin	NO	YES	NO

Drug	Hemodialysis		Peritoneal
	Conventional	High-permeability	dialysis
Pindolol	ND	ND	ND
Piperacillin	YES	L	NO
Piroxicam	U	ND	U
Pralidoxime	ND	ND	ND
Pravastatin	NO	ND	ND
Prazosin	NO	ND	NO
Prednisone	NO	ND	NO
Primidone	YES	L	ND
Probucol	NO	ND	NO
Procainamide	YES	L	NO
Procarbazine	ND	ND	ND
Promazine	U	ND	U
Promethazine	NO	ND	ND
Propafenone	NO	ND	NO
Propofol	U	ND	U
Propranolol	NO	ND	NO
Pyrazinamide	YES	YES	NO
Pyrimethamine	ND	ND	ND
Quinidine	NO/HP YES	ND	NO
Quinine	NO	ND	NO
Raloxifene	U	ND	U
Ramipril/ramiprilat	NO	ND	ND
Ranitidine	NO	ND	NO
Repaglinide	U	ND	U
Reserpine	NO	ND	NO
Reviparin	NO	ND	U
Rifampin	NO	NO	NO
Risperidone	ND	ND	ND
Ritodrine	YES	L	YES
Ritonavir	U	ND	U
Rizatriptan	ND	ND	ND
Rocuronium	ND	ND	ND
Rofecoxib	NO	ND	U
Ropinirole	U	ND	U
Rosiglitazone	NO	ND	U
Saquinavir	U	ND	U
Selegiline	ND	ND	ND
Sertraline	NO	ND	U
Sibutramine	U	ND	U
Sildenafil	U	ND	U
Silver	NO	ND	U
Simvastatin	U	ND	U
Somatropin	U	ND	U
Sotalol	YES	L	ND
Spectinomycin	YES	L	YES
Spironolactone	U	ND	U
Stavudine	ND	ND	ND
Streptomycin	YES	L	YES
Streptozocin	ND	ND	ND
Sucralfate	NO	ND	NO
Sulbactam	YES	L	NO
Sulfamethoxazole	YES	L	NO
Sulfisoxazole	YES	L	YES
Sulindac	NO	ND	U
Sumatriptan	ND	ND	ND
Tamoxifen	ND	ND	ND
Tazobactam	YES	L	NO
Teicoplanin	NO	ND	NO

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