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The removal of uremic toxins

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The removal of uremic toxins. Three major groups of uremic solutes can be characterized: the small water-soluble compounds, the middle molecules, and the protein-bound compounds. Whereas small water-soluble compounds are quite easily removed by conventional hemodialysis, this is not the case for many other molecules with different physicochemical characteristics. Continuous ambulatory peritoneal dialysis (CAPD) is often characterized by better removal of those compounds. Urea and creatinine are small water-soluble compounds and the most current markers of retention and removal, but they do not exert much toxicity. This is also the case for many other small water-soluble compounds. Removal pattern by dialysis of urea and creatinine is markedly different from that of many other uremic solutes with proven toxicity. Whereas middle molecules are removed better by dialyzers containing membranes with a larger pore size, it is not clear whether this removal is sufficient to prevent the related complications. Larger pore size has virtually no effect on the removal of protein-bound toxins. Therefore, at present, the current dialytic methods do not offer many possibilities to remove protein-bound compounds. Nutritional and environmental factors as well as the residual renal function may influence the concentration of uremic toxins in the body fluids.

Uremic syndrome can be defined as the deterioration of many biochemical and physiological functions, in parallel with the progression of renal failure [1]. This article summarizes the present state of knowledge of the biochemical, physiologic, and/or clinical impact of the most prevalent uremic retention solutes, divided according to their physicochemical characteristics: small water-soluble compounds, larger (middle) molecules, and protein-bound compounds. This analysis is followed by remarks about their specific intradialytic behavior, as summarized in Table 1. For each item, groups of solutes are first discussed, followed by a discussion of individual substances. Finally, the dialytic removal of these compounds, the ways to optimize this effort, and alternative options that could lead to a decrease of their serum levels will be examined.

Key words: hemodialysis, peritoneal dialysis, CAPD, dialysis efficiency, body fluid toxicity, renal disease.

SMALL WATER-SOLUBLE COMPOUNDS

Guanidines

The guanidines are structural metabolites of arginine and urea. They cause several pathophysiologic alterations, such as inhibition of neutrophil superoxide production (abstract; Hiravama et al, *J Am Soc Nephrol* 8:238A, 1997), induction of seizures [2, 3], and suppression of natural killer cell response to interleukin-2 [4].

Arginine is the substrate of nitric oxide (NO) production. Some of the other guanidines, as arginine analogues, are strong competitive inhibitors of NO synthase, resulting in vasoconstriction [5, 6], hypertension [7], ischemic glomerular injury [8], immune dysfunction [9], and neurological changes [10].

Dialytic removal of the individual guanidino compounds is characterized by a substantial variability that cannot be explained by their molecular weight or isoelectric point [11]. Protein binding, or more probably multicompartmental distribution, plays a role in this kinetic behavior. Despite their approximately similar molecular weight as urea, the dialytic kinetics may be quite different for some of the guanidines.

Because of their specific characteristics, some guanidines (creatinine and asymmetric N^GN^G dimethylarginine) are discussed separately.

Asymmetric dimethylarginine

Asymmetric dimethylarginine (ADMA) is significantly increased in end-stage renal disease (ESRD) [12] and has been implicated in the development of hypertension [13–15]. In hemodialysis (HD) patients, predialysis plasma ADMA concentrations are sixfold higher than those in control subjects, whereas in peritoneal dialysis (PD)-treated patients, plasma ADMA levels are similar to those in control subjects [16]. The increase in symmetric dimethylarginine (SDMA) is, however, more pronounced, but this compound is biologically less active. ADMA is the most specific guanidine with inhibitory effects on NO synthesis. In the brain, ADMA causes vasoconstriction and inhibits acetylcholine-induced vasorelaxation [17].

In spite of its low molecular weight, removal by HD is only in the range of 20 to 30% [12].

Table 1. Uremic toxins: Characteristics and dialytic removal

Type	Hydrophobic	Protein bound	Dialytic removal parallel with urea
Small water-soluble molecules			
Guanidines	−	−	−
Purines	−	−	±
Oxalate	−	−	+
Phosphorus	−	−	−
Urea	−	−	
Middle molecules			
Cystatin C, Clara cell protein, leptin	−	−	−
Advanced glycosylation end products	±	±	−
Oxidation products	±	±	−
Peptides (β-endorphin, methionine-enkephalin, β-lipotropin, GIP I, GIP II, DIP, adrenomedullin)	−	−	−
β_2-microglobulin	−	−	−
Parathyroid hormone	−	−	−
Protein bound compounds			
Indoles (indoxyl sulfate)	+	+	−
Carboxy-methyl-propyl-furanpropionic acid (CMPF)	+	+	−
Hippuric acid	±	+	−
P-cresol	+	+	−
Polyamines (spermine, spermidine, putrescine, cadaverine)	+	+	−

Creatinine

Creatinine, an end-product of muscle breakdown, is retained during the progression of renal failure and has been held responsible for only a few side effects, such as chloride channel blocking [2, 3] and the reduction of the contractility of cultured myocardial cells [18]. It is a precursor of methylguanidine [19]. Creatinine diffuses from red blood cells to plasma during transit of the blood through the dialyzer, hence, creatinine is mainly extracted from the plasma during dialysis [20].

Purines

The best known purines retained in uremia are uric acid, xanthine, hypoxanthine, and guanosine. Both xanthine and hypoxanthine induce vasocontraction, inhibit platelet-induced vasorelaxation [21], and disturb the endothelial barrier [22]. The purines are involved in disturbances of calcitriol production and metabolism [23–25], and possibly could take part in the calcitriol resistance that has been observed in experimental renal failure and in the presence of uremic biological fluids [26, 27]. The immune response to calcitriol, as illustrated by the expression of the lipopolysaccharide receptor CD14 on the monocyte membrane, is blunted in the presence of uric acid, xanthine, and hypoxanthine [28].

In spite of a markedly diminished urinary secretion of uric acid in renal failure, the rise in plasma uric acid levels is only moderate, because of intestinal secretion [29]. Uric acid is a small water-soluble compound that is removed from the plasma by HD in a similar way as urea [30]. However, its removal from the intracellular compartment is less efficient [31]. Dialytic removal of xanthine and hypoxanthine shows no correlation with the removal of urea and creatinine [30].

Oxalate

Secondary oxalosis in ESRD patients not suffering from primary hyperoxaluria is characterized by deposition of calcium oxalate in myocardium, bone, articulations, skin, and blood vessels [32]. Nowadays, this occurs less frequently, provided there is no excessive intake of oxalate precursors (ascorbic acid) [33] or no inflammatory bowel disease [34].

Oxalate clearance by PD is only 8% of the normal renal clearance. As a result, plasma oxalate levels are higher in PD patients than in controls [35]. Since oxalate is a small water-soluble compound, removal by efficient modern HD is usually adequate enough to prevent intratissular deposition.

Phosphorus

A high level of organic phosphates is related to pruritus and hyperparathyroidism [36]. Phosphorus excess inhibits the production of calcitriol by 1α-hydroxylase [37]. At least in animals, phosphate restriction has an attenuating effect on the progression of renal failure. The results are less compelling in humans [38].

The blood phosphorus concentration is the result of protein catabolism and intake of protein or other phosphorus-rich dietary sources. Restriction of oral protein intake increases the risk of protein malnutrition [36], which can be avoided by the administration of oral phosphate binders [39]. Their effect, however, is often insufficient, especially in subjects with high phosphorus intake. New phosphate binders (for example, lanthanumcarbonate, polynuclear iron hydroxide, cross-linked poly-allylamine-hydrochloride, calcium hydroxy-methylbutyrate), which presumably will be more efficient, have recently been

developed. However, the results of large scale control trials should be awaited before a definite opinion can be proposed. Phosphate is easily removed by HD, but the clearance from the intracellular component is considerably less substantial [40]. Consequently, dialytic removal is not always predictable, and substantial postdialytic rebound may annihilate much of the intradialytic removal.

Urea

Despite extensive study, the number of reports in which an adverse impact of urea has been reported is low. Johnson et al demonstrated that dialysis against high urea dialysate worsens clinical symptoms, but globally, the differences were not impressive and not consistent in every patient [41]. This study was not controlled. Lim, Gasson, and Kaji have shown that urea inhibits NaK_2Cl cotransport [42], which is an ubiquitous process that maintains cell volume and influences extrarenal potassium regulation. The presence of urea in blood has been held responsible for a decreased affinity of oxygen for hemoglobin [43]. Urea inhibits macrophage inducible NO synthesis at the post-transcriptional level (abstract; Prabhakar et al, *J Am Soc Nephrol* 8:24A, 1997).

Urea is one of the only solutes that has been correlated with clinical outcome of HD [44]. Low reduction rates rather than high serum concentrations are related to increased mortality [45]. In this way, urea can be conceived as a marker of uremic toxin removal, rather than being a toxin itself.

However, one might question the validity and representativity of urea as a marker for the retention and even for the removal of other solutes. Even if dialytic removal from the plasma is identical, the shift from the intracellular compartment to the plasma might be different, as is the case for creatinine and uric acid [30, 31]. For various other solutes, for example, the protein-bound compounds [46] or the larger molecules in case of conventional low-flux dialysis, no or only a weak correlation between urea and these molecules can be expected.

LARGE (MIDDLE) MOLECULES

Middle molecules (molecular weight range of 300 to 12,000 D) have been held responsible for at least some aspects of the uremic syndrome: Chromatographic fractions between 1 and 5 kD extracted from human uremic ultrafiltrate inhibit appetite and suppress food intake in animals [47]. This effect was obtained only after concentration of the samples by a factor of 25. A 500 to 2000 D subfraction of uremic serum inhibits apolipoprotein (apo) A-I secretion [48]. Andress, Howard, and Birnbaum described an inhibitor of osteoblast mitogenesis originating from uremic plasma, with a molecular weight in the range between 750 and 900 D [49].

Dialysis membranes with a capacity to remove middle molecules (high-flux membranes) have been related to lower morbidity and mortality of dialysis patients [50–53]; however, these highly efficient membranes at the same time are often less complement activating than their counterpart in many studies, which is usually unmodified cellulose. This might as well have an impact on clinical outcome.

Molecules with a molecular weight of more than 12 kD might display a comparable kinetic behavior. Serum concentrations of cystatin C (13.3 kD, a cystein-proteinase inhibitor) and Clara cell protein (CC16; 15.8 kD, an immunosuppressive α-microprotein) [54] are elevated in renal failure. High-flux membranes remove up to 50% of cystatin C, whereas Clara cell protein is not eliminated by HD [54].

Leptin, a 16 kD plasma protein suppressing appetite [55], and inducing weight reduction in mice [56], is retained in renal failure [57]. Leptin levels in uremia are positively correlated to body fat [58]. Therefore, the biochemical role of leptin in renal failure remains inadequately defined.

Leptin is not removed by conventional HD with modified cellulose [57]. In contrast, dialysis with high-flux membranes lowers leptin levels [59].

Several other uremic solutes conform with the definition of middle molecules [parathyroid hormone (PTH), β_2-microglobulin (β_2m), peptides, advanced glycosylation end product (AGEs)] and are discussed separately in what follows.

Advanced glycosylation end products

Glucose and other reducing sugars react nonenzymatically with free amino groups to form stable Amadori products. Through a series of chemical rearrangements, some Amadori products are converted to AGEs [60]. Several of the AGEs in ESRD are peptide-linked degradation products (molecular weight, 2000 to 6000 D) [61], which show strong cross-linking activity with long-living body proteins.

Advanced glycosylation end products are involved in modification of tissue structures and in functional alterations of enzymes. AGEs induce inflammatory reaction by monocytes [62]. AGE-modified β_2m may play a role in the formation of dialysis-associated amyloidosis [63]. Protein-bound AGEs can react with and chemically inactivate NO [64], a potent endothelium-derived vasodilator, antiaggregant, and antiproliferative factor. AGEs may also be related to oxidative protein modification [65]. Their accumulation was recently attributed to increased plasma concentrations of small reactive carbonyl precursors resulting from increased oxidation of carbohydrates and lipids or inadequate inactivation of these compounds [66].

Removal of AGEs by conventional HD is ineffective. Elimination is significantly higher with high-flux dialysis [67]; however, despite this more efficient removal, levels remain still far above normal [67].

Oxidation products

Enhanced oxidative capacity in uremia results in structural modification and irreparable damage, with albumin and low-density lipoprotein (LDL) being its major targets [65, 68, 69]. Oxidized LDL is claimed to play a role in atherogenesis [70]. Several smaller molecular compounds might also result from oxidation [71]. Organic chloramines originate from the chemical binding of hypochlorite moieties, produced after leukocyte activation, to retained organic compounds [65]. They increase endothelial permeability [72] and affect liver function and hepatic perfusion pressure [73].

Peptides

The opioid peptides β-endorphin, methionine-enkephalin, and β-lipotropin are elevated in dialyzed patients [74], and opioids influence the endocrine function and vasopressor response. Granulocyte-inhibiting protein I (GIP I) affects various functions of the polymorphonuclear cell and shows structural analogies with the κ light chains [75]. Another peptide with granulocyte-inhibitory effect (GIP II) has partial homology with β_2m [76]. A degranulation-inhibiting protein (DIP), identical to angiogenin, was isolated from plasma ultrafiltrate [77]. A variant of ubiquitin inhibits polymorphonuclear chemotaxis [78]. Adrenomedullin, a 52-amino acid hypotensive peptide, activates inducible NO synthase [79].

Most peptides are larger molecules that are supposed to have multicompartmental behavior during dialysis. They are only removed by dialyzers with a large pore size or are not removed at all. Even if removal is present, plasma levels far above normal are reached.

β_2-microglobulin

β_2-microglobulin (molecular weight of about 12,000 D) is a component of the major histocompatibility antigen. Dialysis-related amyloid, as found in amyloid bone disease and carpal tunnel syndrome after long-term dialysis, is to a large extent composed of β_2m. This amyloidosis sometimes develops as early as one to two years following the start of dialysis [80, 81].

Advanced glycosylation end products (discussed previously in this article) and β_2m are closely connected. AGE-modified β_2m has been identified in amyloid of hemodialyzed patients [82]. AGE-modified β_2m enhances monocytic migration and cytokine secretion [63], suggesting that foci containing AGE-β_2m may initiate an inflammatory reaction, leading to bone/joint destruction. On the other hand, AGE modification is not essential for β_2m-related tissue destruction (abstract; Bailey and Moe, *J Am Soc Nephrol* 8:227A, 1997). β_2m amyloidosis is not more prevalent in diabetic renal failure patients, although AGE modification in these patients should be substantial [83].

Cuprophane membranes do not remove β_2m, whereas large-pore membranes do. Some of the large-pore dialyzer membranes, such as polyacrilonitrile, adsorb substantial amounts of β_2m [84]. It has been suggested that the use of these high permeability membranes lessens the likelihood for development of dialysis amyloidosis [85].

Complement factor D

Complement factor D accumulates because of a decrease in its renal removal [86–88]. Its protease activity is highly specific for its natural substrate, complement factor B. An increased level of complement factor D activates the alternative pathway of complement [89], which could, in part, be responsible for the inflammatory status in chronic renal disease. Some dialysis membranes (for example, AN69) adsorb complement factor D [86].

Parathyroid hormone

Parathyroid hormone (PTH), a middle molecule with a molecular weight of ±9000 D, is generally recognized as a major uremic toxin, although its increased level during ESRD is merely attributable to enhanced glandular secretion, rather than to decreased removal by the kidneys. Excess PTH gives rise to an increase in intracellular calcium, resulting in disturbances in the function of virtually every organ system [90–94]. Hyperparathyroidism is also related to uremic pruritus.

The increased PTH concentration in uremia is the consequence of a number of compensatory homeostatic reactions in response to phosphate retention, decreased production of calcitriol [1,25$(OH)_2$vitamin D_3] and/or hypocalcemia.

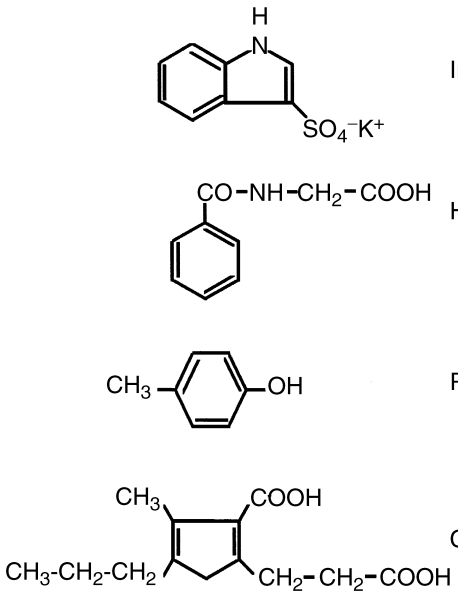
During HD, PTH concentrations are mainly dependent on intradialytic changes of ionized calcium; in addition, dialysis membranes with a large pore size remove PTH. Differences in plasma concentrations at the end of the dialysis session are subtle, however, and can be expected to be compensated by homeostatic adaptations in glandular secretion [95].

PROTEIN-BOUND COMPOUNDS

The molecular structure of some of the most important protein-bound uremic toxins are illustrated in Figure 1, together with their molecular weight and protein binding. Figure 2 illustrates their specific elution pattern during high-performance liquid chromatography (HPLC), with a gradient from hydrophilic to lipophilic. As they all elute in the lipophilic range, there seems to be a relationship between protein binding and lipophilicity.

Indoles

Indoles are found in various plants and are produced by the intestinal flora. Indoxyl sulfate (discussed later in this article), tryptophan, melatonin, and indole-3-acetic



	Molecular weight	Percent protein binding
Indoxyl sulfate	251	89
Hippuric acid	179	41
P-cresol	108	88
CMPF	240	100

Fig. 1. Protein-bound uremic toxins: Chemical formula, molecular weight, and percent protein binding.

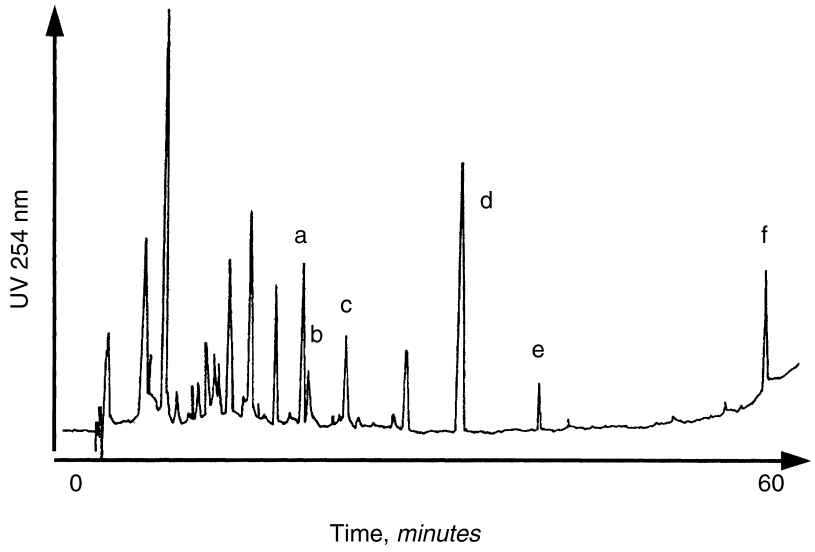


Fig. 2. Elution pattern of uremic ultrafiltrate with HPLC. The elution pattern is such that the gradient goes from hydrophilic (left on the chromatogram) to hydrophobic (right). Identified protein-bound uremic solutes: a, indoxyl sulfate; b, tryptophan; c, hippuric acid; d, indole-3-acetic acid, e, CMPF; f, internal standard.

acid all are indoles; however, the concentrations of tryptophan and melatonin are not increased in uremia. Some indoles are carcinogens [96], whereas others are tumor growth inhibitors [97]. As a protein-bound compound, indole-3-acetic acid enhances drug toxicity by competition for drug protein binding and inhibition of tubular secretion [98].

Removal of the protein-bound compounds during HD is only limited and is not enhanced during treatment with high-flux membranes (Fig. 3) [46].

3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid

3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF) is a strongly lipophilic uremic solute and one of the major inhibitors of drug protein binding [98]. It causes a decrease in renal excretion of various compounds, which are removed via the para-aminohippuric acid (PAH) pathway. CMPF inhibits hepatic glutathione-S-transferase [99], deiodination of T4 by cultured hepatocytes [100], and ADP-stimulated oxidation of NADH-linked substrates in isolated mitochondria [101]. Because CMPF is strongly bound to albumin, its removability during HD is hampered. Even high-flux dialysis removes no CMPF [46, 101]. This is illustrated in Figure 3. In contrast, predialysis plasma concentrations of CMPF decrease significantly when albumin-permeable membranes are used [102, 103]. Also, in continuous ambulatory PD (CAPD), a significant amount of albumin is

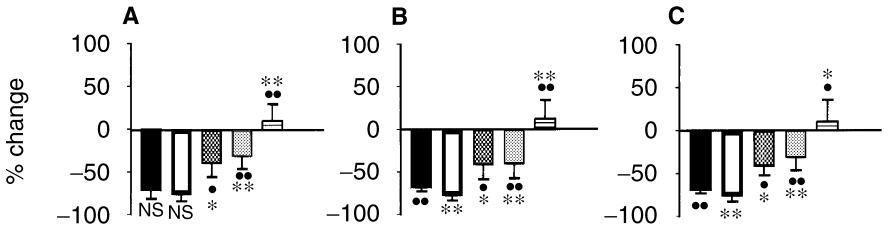


Fig. 3. Percentage change in serum concentrations of uremic toxins after correction for hemoconcentration during dialysis with low-flux polysulfone (*A*), high-flux polysulfone (*B*), and high-flux cellulose triacetate (*C*). Symbols are: ■, creatinine; □, urea; ▩, indoxyl sulfate; ▨, p-cresol; ▤, CMPF. High flux polysulfone or high-flux cellulose tri-acetate vs. low-flux polysulfone. Symbols are: NS, not significant; •, $P < 0.05$ vs. urea; ••, $P < 0.01$ vs. urea; *, $P < 0.05$ vs. creatinine; **, $P < 0.01$ vs. creatinine.

lost into the dialysate. Hence, in CAPD patients, CMPF levels are more than three times lower than in HD patients, pointing to a better removal by CAPD [104]; however, this may also be the consequence of a higher residual renal function than in HD.

Hippuric acid

Environmental or toxicologic contact with toluene is a source of hippuric acid [105]. Toluene is transformed to benzyl alcohol, benzoic acid, and after glycination, to hippuric acid. Benzoic acid is also widely used as a food preservative and is a product of phenylalanine metabolism.

Hippuric acid, as a protein-bound compound, may enhance toxicity of protein-bound drugs and uremic solutes by competition for protein binding [106, 107] and interference with tubular organic acid secretion [98]. Hippuric acid has been related to insulin resistance and glucose intolerance [108]. Hippuric acid is easily removed by HD, with a 60% decrease of the free fraction [109]. However, because of its protein binding, during HD hippuric acid behaves like a larger molecule [110]. The removal of hippuric acid is more pronounced by hemodiafiltration compared with HD [31].

Homocysteine

Homocysteine (Hcy) is a sulfur-containing amino acid that is produced by the demethylation of methionine. Its retention results in the cellular accumulation of S-adenosyl Hcy (AdoHcy), an extremely toxic compound that inhibits methyltransferases [111]. Moderate hyperhomocysteinemia is an independent risk factor for cardiovascular disease [112, 113].

Patients with chronic renal failure have total serum Hcy levels that are twofold to fourfold above normal. The serum concentration depends not only on the degree of kidney failure, but also on nutritional intake (methionine), vitamin status (folate), genetic factors, and renal metabolism [114–117].

Hcy increases the proliferation of vascular smooth muscle cells, one of the most prominent hallmarks of atherosclerosis [118]. Hcy also disrupts several vessel wall-related anticoagulant functions, resulting in enhanced thrombogenicity [119].

Hcy levels can be reduced by folic acid, vitamin B_6, and/or vitamin B_{12} administration [120, 121]. The ESRD population may require higher quantities of vitamins than the nonuremic population [122]. To our knowledge, direct clinical proof of the benefit of such a treatment in uremia is not available.

Homocysteine is partly bound to albumin so that removal by HD is hindered [123].

Indoxyl sulfate

Indoxyl sulfate is metabolized by the liver from indole, which is produced by the intestinal flora as a metabolite of tryptophan. As a strongly protein-bound organic compound, it enhances drug toxicity by competition with acidic drugs at the protein-binding sites [106] and inhibits the active tubular secretion of the same compounds [98]. Indoxyl sulfate inhibits deiodination of T4 [100]. The oral administration of indole or of indoxyl sulfate to uremic rats causes a progressive deterioration of renal function and an enhancement of glomerular sclerosis [124]. Removal by dialysis is reduced because of protein binding (Fig. 3). Alternative removal procedures such as intestinal adsorption or hemoperfusion should be considered.

P-cresol

P-cresol is a phenolic, volatile compound with a molecular weight of 108.1 D. It is produced by intestinal bacteria, as a result of the metabolization of tyrosine and phenylalanine [125]. Environmental sources are toluene, cigarette smoke, and menthofuran, which is present in several herbal medicines, flavoring agents, and psychedelic drugs [126].

P-cresol is strongly toxic for hepatocytes, inducing LDH leakage from rat liver slices [127], and inhibits various metabolic processes related to the production of active free radicals by phagocytic leukocytes [128]. Both hepatocyte aluminum uptake and the toxic effect of aluminum on hepatocytes are increased [129].

Prevention of the intestinal absorption of p-cresol by administration of oral sorbents decreases its serum concentration in rats [130]. Removal by HD is markedly

lower than for urea and creatinine [131] because of the lipophilicity and its protein binding (Fig. 3).

Polyamines

The best known polyamines (spermine, spermidine, putrescine, and cadaverine) have a high affinity for cells and proteins and inhibit erythroid colony growth in a dose-dependent way [132]. Several polyamines interact with the N-methyl-D-aspartate (NMDA) receptor [133], which plays a role in channel conductance and Ca^{++} permeability of brain cells. Spermine also reduces intracellular free calcium in permeabilized pancreatic islets [134] and inhibits NO synthase [135].

One of the problems with the polyamines is the relative impermeability of the cell membrane for these compounds. Their preferential intracellular storage and protein binding results in a multicompartmental behavior and a deceivingly low removal during dialysis.

OBJECTIVATION AND OPTIMALIZATION OF HEMODIALYTIC REMOVAL OF UREMIC TOXINS

Obviously, small solutes with urea as marker molecule are not the main and certainly not the only culprits of uremic toxicity. Nevertheless, urea is used as a standard to describe delivered dose of dialysis. Kt/V_{urea}, as well as urea reduction rate (URR), is generally used for that purpose. Urea can easily be determined in blood, and evidence is found in the literature that increasing Kt/V_{urea} and/or URR is associated with a better outcome both for morbidity and mortality. Held et al, for example, demonstrated that a 0.1 increase in Kt/V resulted in a 7% reduction in mortality [136].

Since the introduction of the Kt/V concept in 1985 [137], several methods have been developed to measure Kt/V, from single pool to multicompartmental, from measurements on the bloodside to measurements on spent dialysate, and from postdialysis urea values determined immediately after dialysis to urea measurements after a 30-minute equilibration time.

Multicompartment models have been introduced because of the slow movement of solutes from the tissues to the blood compartment, resulting in solute disequilibrium. This delayed equilibration is responsible for a reduced dialysis efficiency since solutes withheld in tissues are not dialysable.

Only a limited number of factors can be influenced to increase HD efficiency: time of dialysis treatment, blood flow, dialysate flow, ultrafiltration rate, membrane characteristics such as surface of dialyzer, diffusion, adsorption, and convection capacity. Increasing blood flow leads to an enhanced clearance of small solutes, but can induce hemolysis. Above a certain threshold, increases in clearance are relatively disappointing. Increasing dialysate flow above 500 mL/min is useful if high blood flows are applied. The larger the surface area of the dialyzer membrane, the larger the expected clearances will be. However, the drawback of large surface membranes is the increased bioincompatibility [138]. The duration of dialysis is one of the most problematic variables in dialysis efficiency. Increasing dialysis time asks efforts from both the dialysis center and the patient. Barriers to increase time are multiple in nature.

Organization of the dialysis center. When three sessions daily have to be performed on the same monitor, the duration of one session can hardly exceed four hours.

Organization of patient transport. Dialysis patients share common transportation, even with patients dialyzed in different centers; hence dialysis schedules need to be tailored to one another.

Lack of motivation of the patient. Most patients do not want to dialyze for more than four hours because they are not convinced that the efforts and discomfort of a longer dialysis are compensated by a better outcome. A promising alternative is overnight dialysis over six to eight hours, resulting in a better removal of toxins and water, even with lower blood and dialysate flows than conventionally applied.

One of the major disadvantages of Kt/V urea is the fact that it reflects only on urea. As previously stated, uremic toxicity is not only or not at all mediated by urea accumulation. Furthermore, the removal patterns of other potential uremic solutes are different from those of urea; for example, the use of high-flux membranes increases the removal of middle molecules, AGEs or β_2m, but not of urea. Therefore, to quantitate efficiency of high-flux dialysis, a marker for middle molecules and/or protein bound should be found: The marker, whether or not with clinical relevance, should be easy to measure. For that purpose, Leypoldt et al measured the vitamin B_{12} clearance [139].

Besides the uremic toxins with large molecular weight, toxins can have an impaired removal because of pronounced protein binding. An alternative method that enables the dialyzability of protein-bound toxins from plasma is the use of a high-flux membrane in combination with an albumin-enriched dialysate [140]. For lipid-soluble toxins, even a liposome-enriched dialysate has been proposed. These are, however, labor intensive and expensive strategies. Alternatively, adsorptive systems removing protein-bound or lipophylic uremic toxins might be considered.

REMOVAL OF UREMIC TOXINS BY PERITONEAL DIALYSIS

Removal of toxins by PD differs in many aspects from that by HD, the most important difference being the CAPD and continuous cycling PD (CCPD) or nearly continuous [nightly intermittent PD (NIPD)] nature of

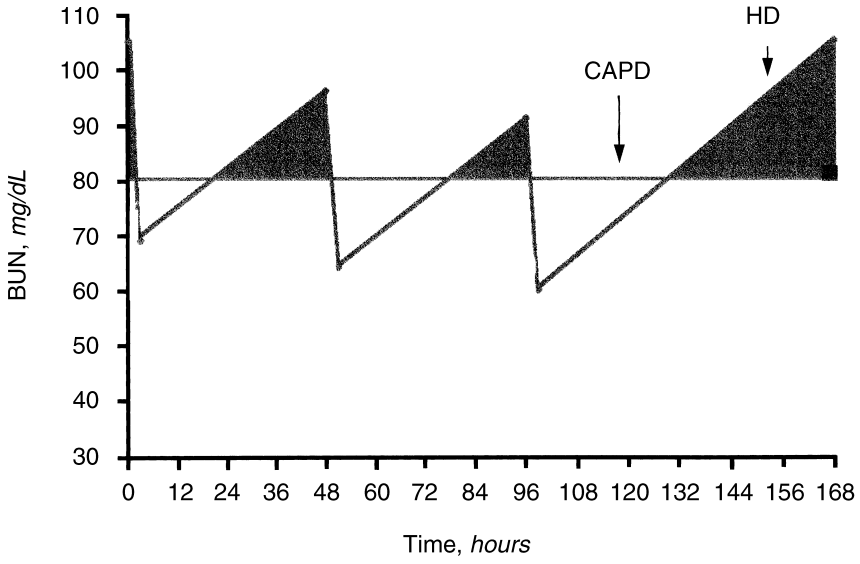


Fig. 4. Weekly BUN profiles for hemodialysis and CAPD.

the treatment, the lower efficiency per unit of time, and the use of a "personalized" membrane that is unique for every patient.

The continuous nature of the treatment results in a stable plasma concentration of uremic toxins, and this in contrast with the sawtooth pattern seen in HD, as illustrated in Figure 4. It is based on this difference that Keshaviah, Nolph, and Van Stone, using the peak concentration hypothesis, explained why CAPD patients suffer a minor degree of uremic toxicity at Kt/V values being associated with overt uremic complaints in HD patients [141]. The peak concentration hypothesis states that not the time-averaged urea, but rather the peak concentrations of urea are responsible for toxicity. When a PD and a HD patient have the same time-averaged concentration of urea during one week, the urea levels in the HD patient will, because of the intermittent nature of the treatment, be above that average for half of the week. Therefore, HD patients need lower time-averaged urea concentrations in order to maintain their urea levels at peak heights lower than those of PD patients. For the same reason, Kt/V levels in patients on NIPD must be somewhat higher than in CAPD patients.

The continuous nature of PD also makes the application of "urea kinetics" to describe the adequacy of PD not only somewhat contradictory, but also complicated. Indeed, the determination of the distribution volume "V" cannot be calculated from the urea kinetics between dialysis sessions. A more elegant approach would be to use the "urea removal index," as suggested by Chen et al [142]. These authors calculated the total mass of urea removed by dialysis. They found that this removal index was the same in HD and PD patients, and this despite differences in Kt/V.

Apart from kinetic explanations for the similar outcome between HD and PD despite a lower amount of urea removal for PD, another hypothesis could be that urea by itself is not toxic, whereas its removal is not representative for those compounds with proven toxicity, such as the middle molecules and the protein-bound compounds.

Compared with a conventional artificial membrane, it appears that an average peritoneal membrane has fewer pores, but with a greater radius [143, 144]. This implicates that the removal of middle molecules will be higher in PD compared with HD. Consequently, in patients on PD with a comparable weekly removal of small uremic toxins as HD patients, the removal of middle molecules will be superior. As the removal of middle molecules is independently associated with mortality risk [145], this higher removal may explain the better survival of patients on PD, at least in the first three to four years after start of renal replacement therapy [145, 146]. After this period, residual renal function has deteriorated in most cases, often resulting in an inadequate clearance for both small and middle molecules, explaining the increased mortality [147]. Also, protein-bound molecules are lower in the serum of PD patients, either because of better removal or higher residual renal function [148].

The better removal of protein-bound molecules might also explain the slower decline in residual renal function in PD patients. Motojima et al demonstrated that in subtotally nephrectomized rats treated with PD for 12 weeks, the glomerular filtration rate was higher compared with controls, whereas the progression of glomerular sclerosis, evaluated with light microscopy, was attenuated [149]. Niwa, Ise, and Miyazaki demonstrated that this kind of glomerulosclerosis could be stimulated by

the administration to uremic rats of indole, a precursor of the uremic toxin indoxyl sulfate [150]. Intestinal binding of these compounds or their precursors by AST120 could prevent progression of renal failure. The observation of Motojima et al and the better preservation of residual renal function in PD patients could thus possibly be attributed to the removal of this kind of substances. Also, the higher hematocrits and the lower need for erythropoietin in PD patients [151, 152] could be partially attributed to the better removal of some uremic toxins. Substances like polyamines and CMPF have been identified as possible inhibitors of erythropoiesis, which are removed by PD but not by conventional HD [148, 153].

NONDIALYTIC FACTORS AFFECTING UREMIC SOLUTE CONCENTRATION

Nutritional and environmental effects

Several environmental sources in the generation of uremic toxins too often have been disregarded. These sources include: (*1*) the presence in food of conservation agents, trace elements, AGEs and other precursors, apart from the traditionally considered protein intake; (*2*) the contact with volatile compounds such as toluene; (*3*) herbal medicines, quack remedies, and psychedelic drugs; and (*4*) environmental noxes imposed by dialysis, because of the leaching from plastic devices or dialysate. An additional problem could be that the contact risks are different for each individual; if specific toxins play a role in each specific individual, they may go unrecognized in the case mix of large random populations.

Several toxins are produced from protein breakdown or from metabolization of amino acids. Therefore, protein restriction could decrease toxicity were it not that protein malnutrition might by itself increase morbidity and mortality [45].

Most solutes with toxic capacity or their precursors enter the body through the gastrointestinal tract. Some of them are produced by the intestinal flora. Inhibition of intestinal absorption and modifications in the composition of the intestinal flora could influence solute retention [130, 154, 155]. A specific oral sorbent (AST120) has been demonstrated to decrease indoxyl sulfate and p-cresol in serum of uremic rats [124, 130, 156, 157]. Other oral binders already in use today are several potassium and phosphate binders. Some of these compounds may exert their own toxicity, as is the case for the aluminum salts. In general, the possibilities to decrease intestinal delivery of uremic solutes have been insufficiently exploited.

Biological interaction between compounds

Until now, mainly the toxic action of single solutes has been emphasized, without considering the interference between compounds. Some of the uremic solutes interfere with functions that directly affect the toxic action of other solutes. The uremic milieu decreases the expression of PTH receptors and hence the cellular response to PTH [158, 159]. On the other hand, uremic solutes also blunt the response to 1,25-$(OH)_2$vitamin D_3 and hence might increase the production of PTH [27]. As a consequence of the inhibition of enzymatic actions, metabolization and breakdown of toxic solutes may be altered or hindered. The kidneys per se play an important role in the metabolization of solutes; when renal mass is lost, these metabolic processes are also restricted.

Most uremic patients are prescribed a host of drugs. The influence of drugs on uremic toxicity can be attributed to either interference of drugs with protein binding and/or tubular secretion of uremic toxins or the production of metabolites, which are not excreted by the failing kidneys, exerting their own toxicity.

Medication may also interfere at the functional level. For example, angiotensin-converting enzyme inhibitors might decrease the sensibility of erythrocyte progenitors to erythropoietin [160]. On the other hand, drugs may be of help to reduce toxin concentrations. Allopurinol decreases uric acid. Rhubarb tannins decrease the concentration of urea, creatinine, guanidino-succinic acid, and methylguanidine in rats with acute renal failure [161]. Biotin administration results in an improvement of uremic neuropathy [162]. Vitamin C increases urinary CMPF excretion but does not alter plasma concentration in hemodialyzed patients [103]. Hcy in uremic patients can be lowered by supplementation of folic acid, a compound favoring remethylation of Hcy to methionine [122, 163].

Residual renal function

The impact of residual renal function on uremic retention should not be neglected. One should realize that adding a creatinine clearance of 5 mL/min to the clearance imposed by dialysis means an increase in creatinine removal by ±50 to 100% [44]. This relative contribution is even more important for larger molecules and molecules with multicompartmental behavior, which are removed less efficiently by dialysis procedures. Therefore, the longer preservation of residual renal function with CAPD, compared with conventional HD, may be important. Uremic retention solutes have also been held responsible for deterioration of renal function, and at least one of these compounds, indoxyl sulfate, is better removed in CAPD patients [124].

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