Supplementary Table 1. Characteristics of Hemodialysis Patients and Normal Subjects

	Hemodialysis Patients (n=25)	Hemodialysis Patients: Clearance Studies (n=8)	Normal Subjects (n=16)	Normal Subjects: Clearance Studies (n=9)
Age (yrs)	58 ± 12	69 ± 14	47 ± 13	40 ± 10
Gender (f/m)	5/20	0/8	5 / 16	3 / 9
Diabetes (yes/no)	14/11	4/4	0 /16	0/9
Dialysis Vintage (yrs)	3 ± 2	3 ± 2		
Treatment Durations (hrs)	3.2 ± 0.5	3.2 ± 0.5		
Blood Flow Rate (ml/min)	420 ± 35	394 ± 18		
Dialysate Flow Rate (ml/min)	783 ± 37	796 ± 7		
Monthly $spKt/V_{urea}$	1.52 ± 0.39	1.59 ± 0.30		

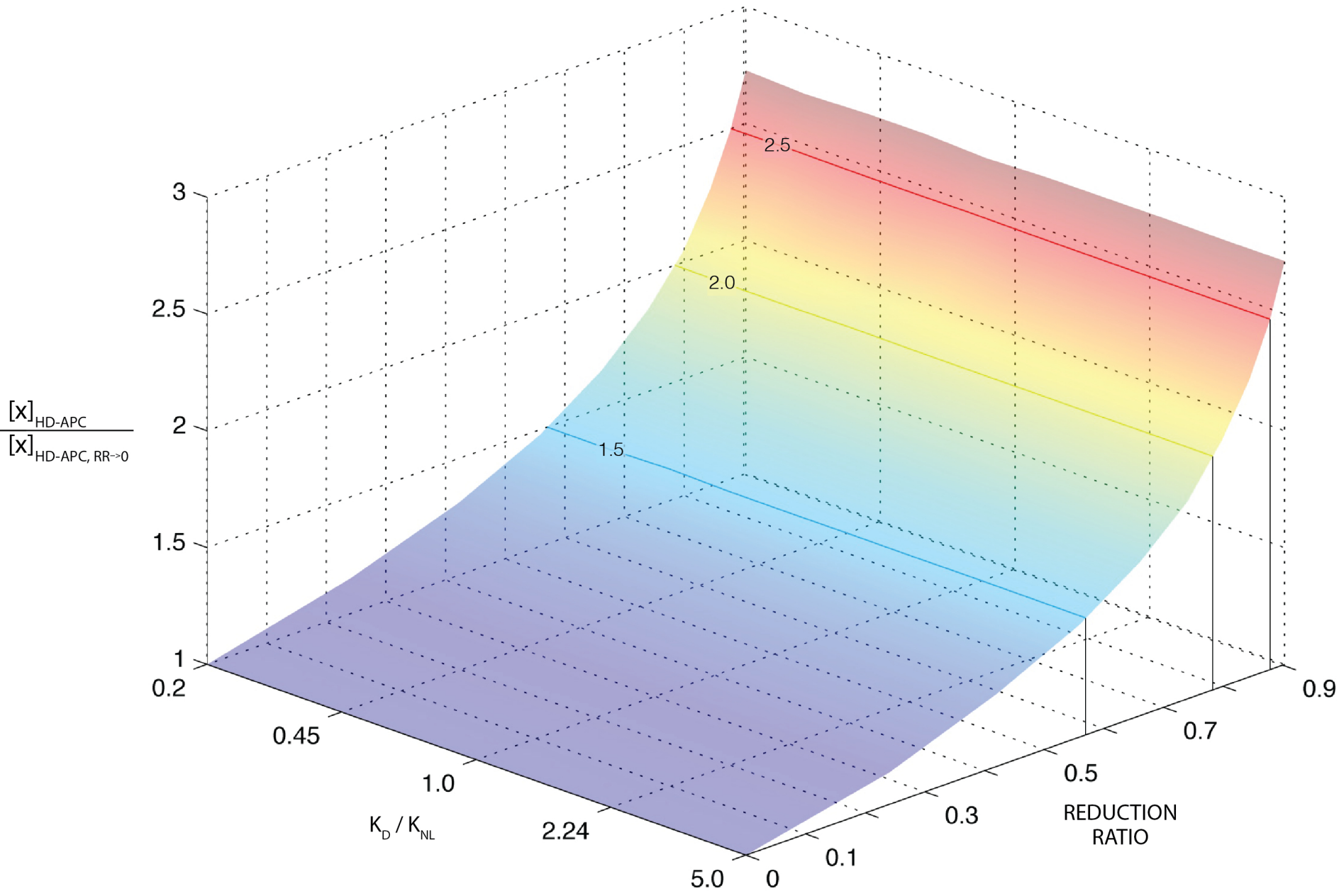
Values are mean ± sd. Dialyzers used in the n=25 hemodialysis patients were Revaclear (n=6), Revaclear Max (n=4), F160NR (n=3), F160A (n=1), F180NR (n=8), F200NR (n=2), and Rexeed 25 (n=1). Dialyzers used in the n=8 hemodialysis patients undergoing clearance studies were Reveclear (n=5) and Revaclear Max (n=3).

Supplementary Table 2. Coefficients of Variation and Limits of Detection

	Normal Persons			Dialysis Patients		
	Plasma	UF	Urine	Plasma	UF	Dialysate
Intrassay Coefficient of Variation						
Phenylacetylglutamine	0.04±0.02	0.05±0.05	0.03±0.02	0.03±0.02	0.02±0.01	0.02±0.01
Hippurate	0.03±0.02	0.03±0.01	0.04±0.03	0.06±0.07	0.03±0.02	0.05±0.03
Indoxyl sulfate	0.06±0.02	0.14±0.07	0.05±0.01	0.05±0.02	0.06±0.03	0.04±0.03
p-Cresol Sulfate	0.03±0.02	0.05±0.03	0.04±0.03	0.04±0.02	0.03±0.01	0.03±0.02
Interassay Coefficient of Variation						
Phenylacetylglutamine	0.08±0.03	0.08±0.07	0.04±0.01	0.06±0.03	0.02±0.01	0.02±0.01
Hippurate	0.05±0.02	0.04±0.02	0.04±0.02	0.07±0.07	0.03±0.01	0.04±0.04
Indoxyl sulfate	0.10±0.04	0.34±0.20	0.04±0.03	0.06±0.04	0.11±0.09	0.04±0.04
p-Cresol Sulfate	0.03±0.02	0.09±0.05	0.05±0.04	0.06±0.04	0.08±0.05	0.03±0.03
Limit of Detection	µg/dl	µg/dl	µg/min	µg/dl	µg/dl	µg/dl
Phenylacetylglutamine	0.4	0.1	0.001	4	1	1
Hippurate	3.8	0.4	0.005	38	5	5
Indoxyl sulfate	0.5	0.1	0.001	5	1	1
p-Cresol Sulfate	0.1	0.1	0.001	2	1	1

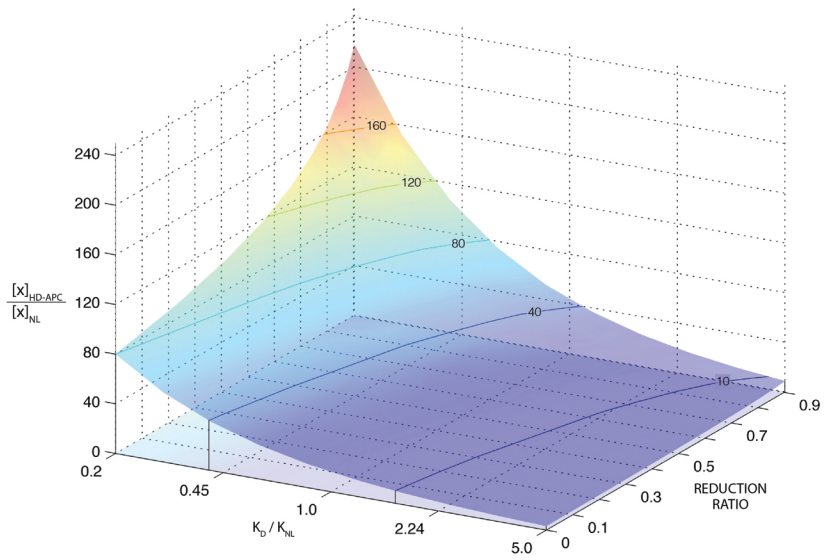
UF, plasma ultrafiltrate. Coefficients of variation (CVs) were determined on samples from normal persons and dialysis patients prepared individually using the same methods and dilutions as employed with study samples. For assays in normal persons, intrassay CV values were calculated as mean values for three samples run three times in each of three different assays and interassay values were calculated as means values for nine samples run in three different assays. The relatively large CV for indoxyl sulfate in UF may have been caused by the high salt concentraitons in samples which were concentrated 10 fold prior to assay but this has not been confirmed. For assays in HD patients, intrassay CV values were calculated as mean values for three samples run three times in each of two different assays and interassay values were calculated as means values for nine samples run in two different assays. Values for the limit of detection were obtained by assay of n=20 replicates of very low concentrations of the analytes in aqueous solution and then calculating the limit of detection as 3.14 fold the standard deviations of these measurements and adjusting for the dilutions at which study samples were assayed. The limit of detection in urine is presented in units of ug/min because urine samples were diluted in inverse proportion to the urine flow rate. It is noted that limits of detection in the experimental matrices (plasma, ultrafiltrate, urine, and dialysate) cannot be measured because matrix samples known to contain the analytes at zero concentration cannot be obtained. The limits of detection in aqueous solution are however orders of magnitude lower than the values measured in study samples.

Supplementary Figure 1

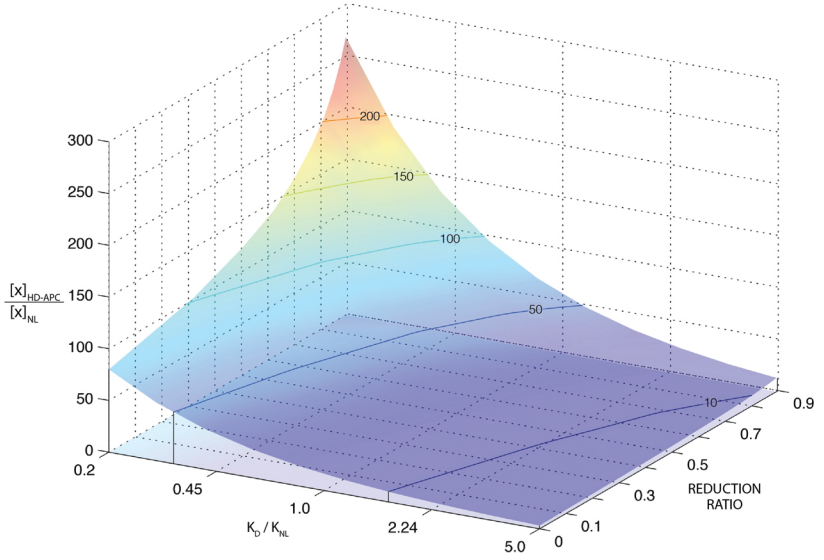


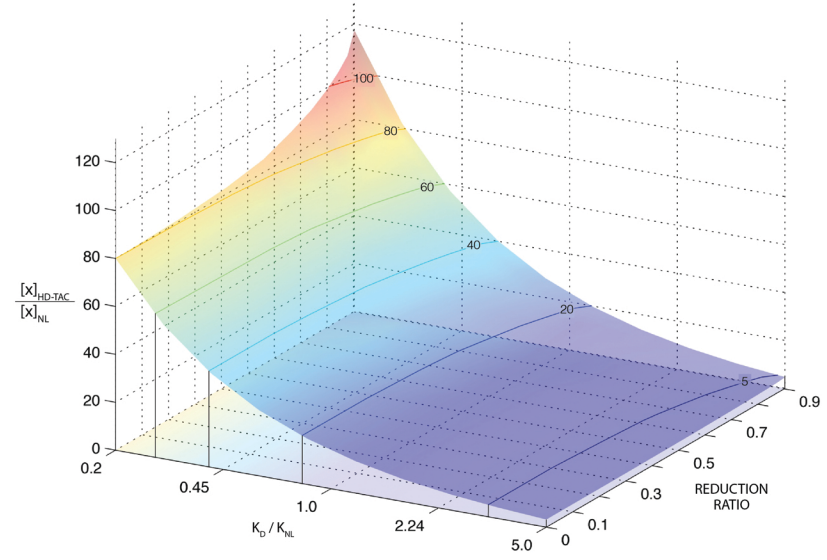
Supplementary Figure 2

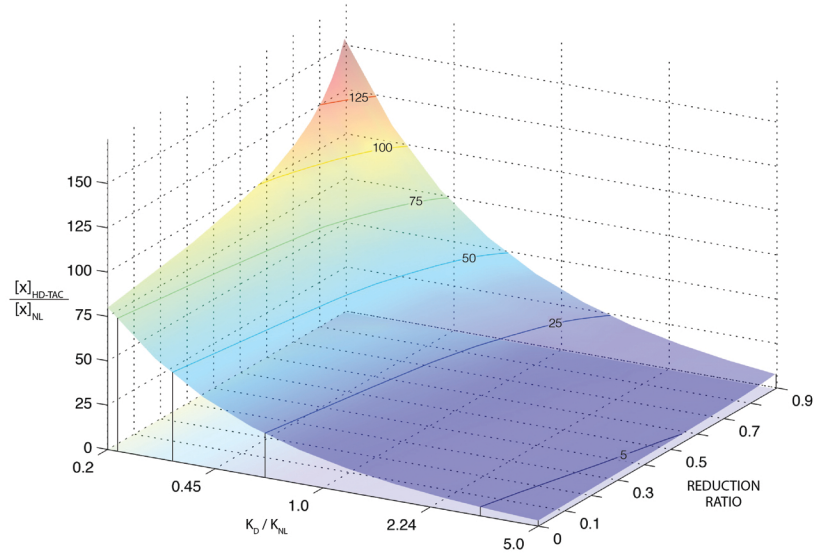
ONE COMPARTMENT



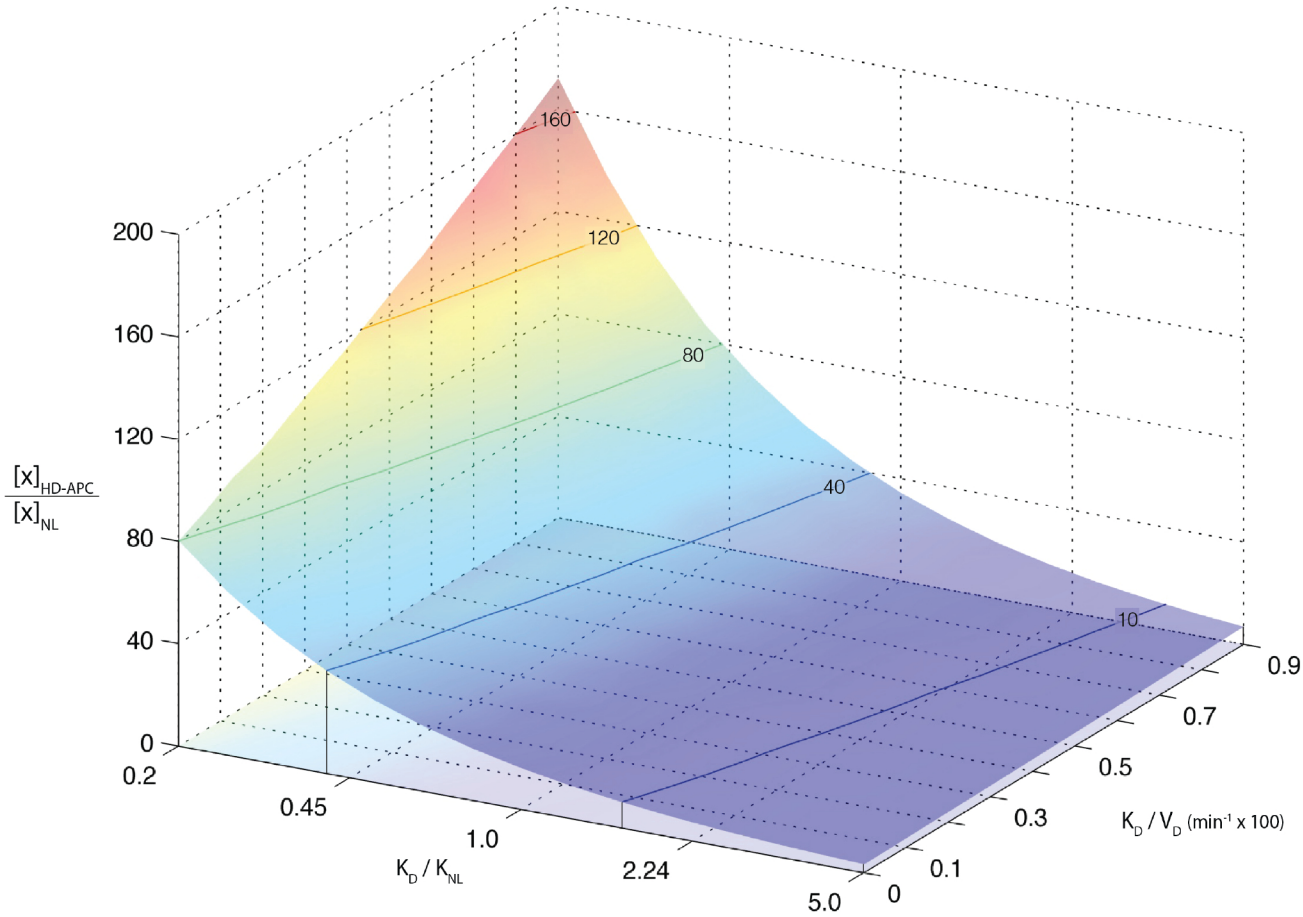
TWO COMPARTMENT







Supplementary Figure 3



Legends for Supplementary Figures

Supplementary Figure 1. In addition to the ratio of the dialytic clearance K_D to the native kidney clearance K_{NL}, the elevation of a solute's concentration relative to normal in hemodialysis patients depends heavily on the extent to which the solute's concentration is reduced during intermittent dialysis treatment. If the reduction ratio is high, as will be the case when the dialytic clearance is large relative to the volume of distribution, intermittent dialysis will be relatively ineffective in controlling the solute level. As illustrated by this figure, the dependence of the elevation in concentration on the reduction ratio is the same for all values of K_D/K_{NL}.

Supplementary Figure 2. Predicted pretreatment and time-averaged solute concentrations relative to normal in patients maintained on conventional hemodialysis. Values are plotted on the vertical axis as a function of the ratio of the dialytic clearance to normal kidney clearance (K_D/K_{NL}) and the concentration reduction ratio during treatment. The left panel depicts values calculated assuming that solute is removed from a single compartment. The upper figure depicts values for the average pretreatment concentration relative to normal (it is the same as Figure 1 in the manuscript and is reproduced here for comparison). The lower figures depicts values for the time-averaged solute concentration. These values have the same overall pattern as those for pretreatment concentration but the time averaged concentration rises less as the reduction ratio increases. The right panel depicts values calculated if it is assumed that dialysis removes solute from a first, accessible compartment with solute moving by diffusion between this compartment and a second compartment. The relative elevation of solute concentration for any given values of K_D/K_{NL} and the reduction ratio cannot be predicted without specifying the relation among

the volumes of the two compartments and the intercompartmental coefficient governing diffusion between them. The values depicted here were calculated using the proportions among these parameters found for guanidinoacetic acid in the description by Eloot et al.[1] of the complex compartmental behavior of guanidines during hemodialysis. As illustrated in the figure, the general effect of this compartmental behavior is to make dialysis less efficient. The average pretreatment and time-averaged solute concentrations are higher than they would be if solute were removed from a single compartment. The overall pattern of concentration dependence on the ratio of dialytic to native kidney clearance and the reduction ratio during treatment, however, remains the same. Values for both the one compartment and two compartment models were calculated assuming that treatment is performed thrice weekly for 3.5 hours, that solute production is the same in dialysis patients and normal subjects, that dialysis patients have no residual function, and that there is no non-renal, non-dialytic solute clearance.

Supplementary Figure 3. If a solute is modeled as being removed from a single compartment, the reduction ratio is determined by the ratio of the dialytic clearance to the volume of distribution, K_D/V_D. This figure is similar to Figure 1 in our article, but illustrates the elevation of a solute's concentration relative to normal as a function of K_D/V_D in place of the reduction ratio. When K_D is small compared to V_D, the reduction ratio approaches zero, and intermittency does not diminish the efficiency of treatment.

1. Eloot, S, Torremans, A, De Smet, R, Marescau, B, De Wachter, D, De Deyn, PP, Lameire, N, Verdonck, P, Vanholder, R: Kinetic behavior of urea is different from that of other water-soluble compounds: the case of the guanidino compounds. Kidney Int, 67: 1566-1575, 2005