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Prediction of hemodialysis sorbent cartridge urea nitrogen capacity and sodium release from in vitro tests

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Abstract

In sorbent-based hemodialysis, factors limiting a treatment session are urea conversion capacity and sodium release from the cartridge. In vitro experiments were performed to model typical treatment scenarios using various dialyzers and 4 types of SORB^{TM} sorbent cartridges. The experiments were continued to the point of column saturation with ammonium. The urea nitrogen removed and amount of sodium released in each trial were analyzed in a multi-variable regression against several variables: amount of zirconium phosphate (ZrP), dialysate flow rate (DFR), simulated blood flow rate (BFR), simulated patient whole-body fluid volume (V), initial simulated patient urea concentration (BUN_i), dialyzer area permeability (KoA) product, initial dialysate sodium and bicarbonate (HCO_{3i}) concentrations, initial simulated patient sodium (Na_i), pH of ZrP, creatinine, breakthrough time, and average urea nitrogen concentration in dialysate. The urea nitrogen capacity (UNC) of various new SORB^{TM} columns is positively related to ZrP, BFR, V, BUN_i, and ZrP pH and negatively to DFR with an $R^2_{adjusted}$=0.990. Two models are described for sodium release. The first model is related positively to DFR and V and negatively to ZrP, KoA product, and dialysate HCO_{3i} with an $R^2_{adjusted}$=0.584. The second model incorporates knowledge of initial simulated patient sodium (negative relationship) and urea levels (negative relationship) in addition to the parameters in the first model with an $R^2_{adjusted}$=0.786. These mathematical models should allow for prediction of patient sodium profiles and the time of column urea saturation based on simple inputs relating to patient chemistries and the dialysis treatment.

Key words: Sorbent, urea, sodium, hemodialysis, cartridge, capacity

INTRODUCTION

In current sorbent-based hemodialysis therapy using sorbent columns, predictive formulas for sorbent cartridge urea nitrogen capacity (UNC) and sodium release during a session are based on clinical experience and estimations of the amount of urea to be removed. The sodium and bicarbonate concentration of the starting bath is adjusted in order to maintain a relatively stable sodium concentration and to increase the bicarbonate level in the patient. The formulas used are empirical and observation of the chemical changes in the patient is recommended for the first few treatments. The variables affecting UNC and sodium release are known, but the exact relationship between these variables and the chemical changes is not easily predicted. Knowledge of UNC and affecting variables would allow anticipation of ammonium breakthrough time. Anticipated breakthrough would allow a

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dialysis treatment design to assure that a column would last through the prescribed treatment, avoiding premature end of even very long treatments (such as 8 hr). Though newer sorbent-based dialysis systems such as the Allient® (Renal Solutions Inc., Warrendale, PA) contain an ammonium monitor, avoiding column saturation decreases the risk of patient exposure to ammonium. Prediction of the amount of sodium released during a complete dialysis session would allow the user to accurately and programmatically calculate the sodium load imposed upon the patient and adjust the starting bath composition appropriately.

This research was conducted to determine the UNC and the amount of sodium released from SORB™ columns during simulated full-length hemodialysis sessions. Two existing columns, SORB™ and HISORB™, were tested. Two new columns designed for higher ammonium capacity, SORB+™ and HISORB+™ were also tested (Renal Solutions Inc., Warrendale, PA, and Oklahoma City, OK). The exact composition in each column is found in Table 1. The column tests in this research were also reported in part in previous publications describing the correlation between dialysate sodium concentration and conductivity measurements.[1] Knowing the sodium concentration of dialysate would allow operative methods to control the sodium load to which a patient is exposed; however, this would add to the complexity of the sorbent dialysis system.

Sorbent-based systems have been a part of hemodialysis technology for a number of years.[2–5] In a sorbent column (Figure 1), urea is catalyzed to ammonium and carbonate. The ammonium exchanges in the zirconium phosphate (ZrP) cation exchange layer for hydrogen and sodium, as do calcium, magnesium, and potassium. In the older SORB™ columns, phosphate is exchanged for acetate in a layer of acetate-loaded zirconium oxide (ZO). In the new series of SORB™ columns, phosphate exchanges for this ZO and also a sodium carbonate-loaded zirconium.[6] A reinfusate pump administers calcium, magnesium, and potassium acetate to the dialysate after it passes through the column, replacing these cations after they are removed by the sorbent column. As these cations exchange with the sorbent column, sodium is released. Besides the cation exchange there is also some direct adsorption of ammonium to the ZrP portion of the sorbent column. Stoichiometric analysis indicates that for every mole of NH_4^+ removed by the column there is generation of 0.1–0.2 M sodium and 0.4–0.5 M of hydrogen (removing this amount of bicarbonate). This adsorption is due to hydrogen bonds forming between NH_4^+ and phosphate, and NH_3 and hydrogen.

The dialysate volume is 6 L. Most of the volume resides in a bag (in the Allient® machine) or an open reservoir (in the REDY® 2000 machine).[3,7] The dialysate begins as a solution of sodium bicarbonate and sodium chloride in tap water, which is passed through the sorbent column for purification before passing through the dialyzer during prime. The dialysate solution after prime typically starts out hypotonic to allow a sodium space to absorb some of the sodium generated by the sorbent cartridge during removal of ammonium throughout the dialysis session. The desired degree of hypotonicity depends upon the patient's starting sodium and the urea nitrogen load expected to be removed by the column. The bicarbonate concentration is adjusted to increase the patient's bicarbonate level, which is also dependent upon the amount of urea nitrogen exchanged for hydrogen. Throughout a treatment, the dialysate sodium concentration begins lower than the patient's serum level and increases to a level higher than the patient sodium. The range in sodium concentration is a result of mass transfer between the dialysate, the sorbent column, and the patient. The changes are greater than with standard dialysate because the 6 L of dialysate is only about one-fifth of the patient's whole-body fluid volume. Extremes in concentration are also prevented because of the small volume of dialysate.

MATERIALS AND METHODS

Experimental setup

The apparatus used to acquire the in vitro data consisted of: peristaltic pumps (dialysate, blood side solution, infusate), a dialyzer, a sorbent cartridge, a covered stirred

Table 1 Characteristics of SORB™ columns used in experiments

Cartridge	ZrP (~g)	ZrP pH	mEq of Na+ per gram of ZrP	Hydrous ZO (~g)	Anion loaded	Activated carbon (~g)
SORB™	800–1100	6.25–6.35	3.1	105	Acetate	235
HISORB™	1100–1300	6.25–6.35	3.1	105	Acetate	235
SORB+™	1300	5.95–6.05	2.5	205	Acetate and Bicarbonate	405
HISORB+™	1600	5.70–5.80	2.3	205	Acetate and Bicarbonate	405

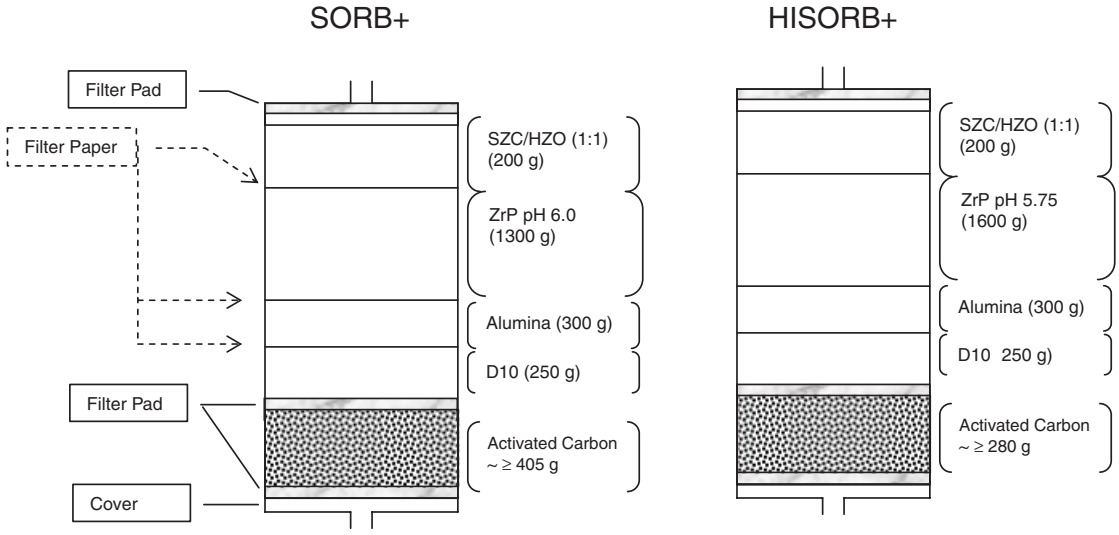

Figure 1 Schematic of SORB+™ and HISORB+™ cartridges.

tank to simulate patient whole-body water volume, and tubing (Figure 2). The dialysate bath was contained in a 12-L bag and held at 37 °C. Premix consisted of 6 L of tap water and various salts, sent in single-pass through the column and into the bag during a purification step before starting dialysis. The premix chemical makeup varied and was: $NaHCO_3$ 20–60 mEq/L, NaCl 40–120 mEq/L, dextrose 4 g/L, $CaAc_2$ monohydrate 3 mEq/L, $MgAc_2$

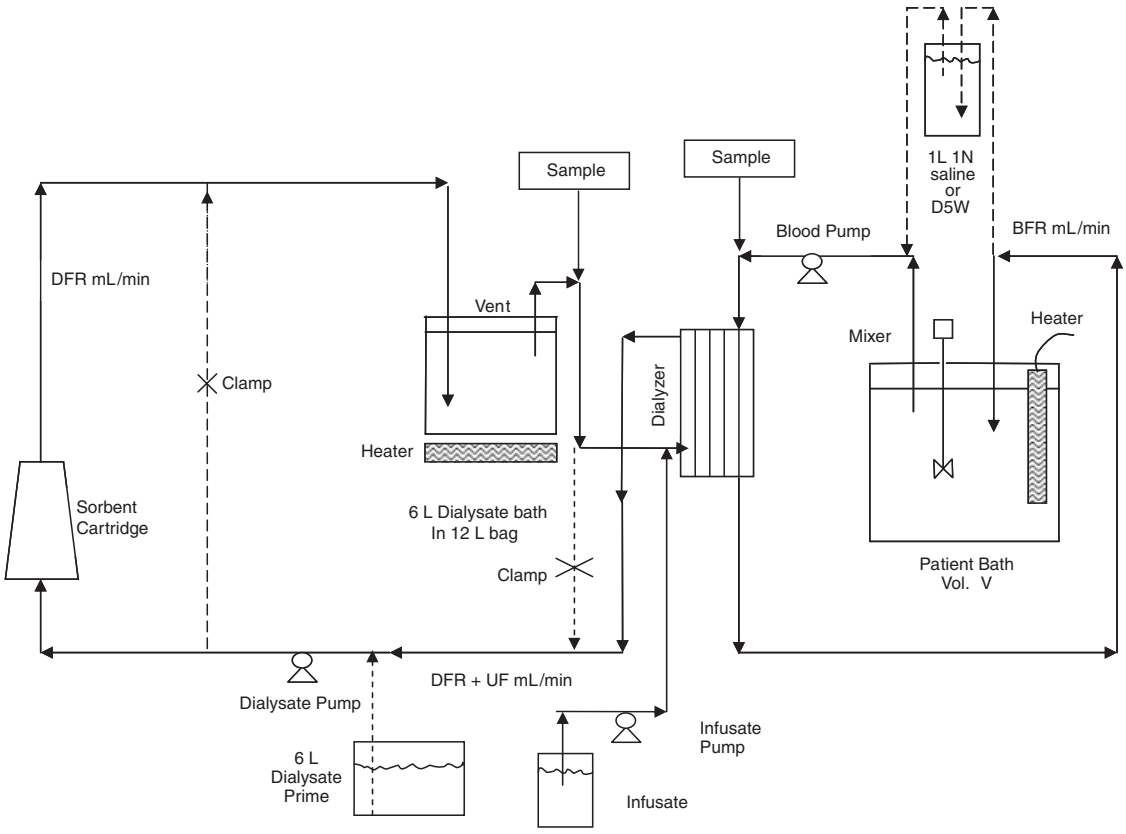

Figure 2 Schematic of experimental apparatus used.

tetrahydrate 1 mEq/L, potassium acetate (Ac) anhydrous 2 mEq/L, 1 N HCl as necessary to adjust pH to 7–7.4. The blood side priming solution was 1 L 1 N saline or 1 L 5% w/v dextrose in water. The resulting postprime starting bath had varying concentration of sodium and bicarbonate. Compared with the blood side, the postprime starting bath was hypotonic in sodium and hypertonic in bicarbonate. The infusate was an acetate-based solution consisting of 3 mEq/L $CaAc_2$ monohydrate, 1 mEq/L $MgAc_2$ tetrahydrate, and 2 mEq/L KAc anhydrous. The infusate was fed into the dialysate to maintain those concentrations throughout each trial. The simulated blood side solution consisted of variable volume (24–61 L), 25 mEq/L $NaHCO_3$, 115 mEq/L NaCl, 100 mg% dextrose, pH 7.4, and varying physiologic amounts of urea, creatinine, phosphate, sodium, chloride, and bicarbonate.

Experimental approach

The experimental approach was to acquire data from in vitro trials in a variety of sorbent and dialyzing configurations that were representative of typical sorbent-based hemodialysis conditions. The variables independently varied in each trial were dialysate flow rate (DFR), simulated blood side solution flow rate (BFR), simulated patient whole-body fluid volume (V), simulated blood side initial urea nitrogen concentration (BUN_i), dialysate initial sodium concentration, dialysate initial sodium bicarbonate concentration, dialyzer type quantified by area permeability product (KoA), sorbent cartridge content of zirconium phosphate (ZrP), and sorbent cartridge pH. Additional dependent variables that were considered in the correlations were: time to ammonium breakthrough, and average urea nitrogen concentration in dialysate (C_d average). Each trial progressed until ammonium breakthrough occurred as measured by ammonium electrode on the effluent of the column. Column saturation was considered complete when the effluent ammonium concentration was 2 mg/dL.

Sample collection and analysis

The following samples were collected throughout each trial:

- 20 mL samples from the cartridge effluent at 0, 15, and 30 min, and then at 30-min intervals until NH_4 breakthrough time to check concentrations of urea nitrogen (BUN), PO_4, creatinine, Ca^{2+}, Mg^{2+}, K^+, and leakage of NH_4^+.
- 25 mL samples from the cartridge effluent every 15 min close to the end to determine the NH_4^+ breakthrough time as accurately as possible.
- 5 mL sample from the dialysate at sorbent cartridge inlet at 0 min and every 30 min.
- 10 mL sample from the simulated patient fluid at 0 min and every 30 min to determine the removal of urea, creatinine, and PO_4.

In all above samples, BUN, PO_4, creatinine, Na^+, K^+, and bicarbonate were determined using a Cobas Mira Plus Analyzer (Roche Applied Science, Indianapolis, IN); NH_4^+ by using an ammonia electrode; bicarbonate by using pH titration; Ca^{2+} and Mg^{2+} by using direct current plasma spectrometry. NH_4^+, pH, and bicarbonate were tested as quickly as possible to avoid change upon storage.

Calculating cartridge UNC and sodium release

The data captured during the trials included the urea nitrogen and sodium levels of the initial patient tank, the dialysate effluent, and patient tank in 15- or 30-min intervals to 3 significant figures.

The column urea capacity was calculated from the time average urea nitrogen concentration in the dialysate and checked against the drop in BUN on the patient side. The amount of sodium released during a time interval was assumed to be any part of the time interval where the dialysate cartridge effluent sodium concentration was greater than the patient's initial sodium level assuming a linear trend during the interval. The amount released during each interval was summed to estimate the total sodium release for the entire trial. The summed value was used in the regression analysis.

The UNC and amount of sodium released from the sorbent cartridge were analyzed against a number of independent and dependent variables as previously mentioned. The regression models assume knowledge of the patient's whole-body fluid volume (an independent variable in the trials—tank volume, assuming single compartment). Whole-body volume can be estimated through correlations based on age, gender, weight, and height. The Watson method may be used for adults and the Mellits–Cheek method may be used for children.[8,9]

Model development—multiple regression

The method of multiple regression was used to analyze the data. The models were established using JMP statistical software multi-variable linear regression (SAS Institute, Cary, NC). The data were screened such that questionable or inconsistent data were not used in the

Table 2 Dependent and independent variable definitions with units

Variable	Description	Units
BFR	Simulated blood flow rate	mL/min
BUN_i or BUN	(Initial) simulated patient urea nitrogen concentration	mg/dL
Cartridge Na Released	Calculated sodium released from sorbent cartridge	mEq
Cd Avg#	Average urea nitrogen concentration in dialysate	mg/dL
DFR	Dialysate flow rate	mL/min
Dialysate HCO_{3i}	Initial dialysate bicarbonate concentration	mEq/L
Dialysate Na_i	Initial dialysate sodium concentration	mEq/L
KoA Product	Dialyzer area permeability	Dimensionless
Patient Cr_i	Initial simulated patient creatinine concentration	mg/dL
Patient Na_i	Initial simulated patient sodium concentration	mEq/L
T_b	Breakthrough time	min
UNC	Calculated UNC by sorbent cartridge	mg
V	Simulated patient whole-body fluid volume, pretreatment	mL
ZrP	Amount of zirconium phosphate in sorbent cartridge	~g
ZrP pH	pH of zirconium phosphate layer in sorbent cartridge	Dimensionless

BFR = blood side solution flow rate; BUN = blood side initial urea nitrogen concentration; Cd Avg # = average urea nitrogen concentration in dialysate; DFR = dialysate flow rate; KoA = dialyzer area permeability; UNC = urea nitrogen capacity; V = volume; ZrP = Zirconium phosphate.

regression. The first step in performing the multiple regression was to identify the variables upon which UNC and sodium release could be dependent (Table 2). The variables selected were required to be variables obtainable or determined before the beginning of treatment. By producing a model of UNC and sodium release based on different combinations of possible significant variables, it was possible to examine the statistical significance of potential model parameters. The analysis was performed in a stepwise manner—terms were added or removed to determine their significance. Individual variable significance was determined by a p value < 0.06.

Each model was further analyzed as a whole to check that the overall fit to the data was appropriate. Several statistical parameters were analyzed to make this final assessment. The coefficient of determination (R^2) and adjusted coefficient of determination ($R^2_{adjusted}$) were used to judge the overall adequacy of the regression models. In order to investigate the amount of error our predictive models contained, the root mean square error (RMSE), or standard deviation of the model, was examined.

RESULTS

The resultant models are dimensional and specific units must be used for each parameter as defined in Table 2. Thirty-nine data points, each from a separate experiment, were used to generate the UNC model. Thirty-six valid data points were used to create the sodium release models.

Column UNC model

$$[\mathrm{UNC}] = 20806 + 1785[\mathrm{ZrP}] - 779[\mathrm{DFR}] + 827[\mathrm{BFR}] + 3533[\mathrm{V}] + 12457[\mathrm{BUN_i}] + 1007[\mathrm{ZrP\,pH}]$$

$R^2 = 0.991$; $R^2_{adjusted} = 0.990$; RMSE = 906 mg

Table 3 shows the significance of the variables in the model. Figure 3 shows the relative contributions of the parameters on the model.

Table 3 Urea capacity model variable significance

Variable	(p-value)
ZrP	< 0.0001
DFR	0.0001
BFR	0.0003
V	< 0.0001
BUN_i	< 0.0001
ZrP pH	0.0003

BFR = blood side solution flow rate; BUN_i = blood side initial urea nitrogen concentration; DFR = dialysate flow rate; V = volume; Zrp = Zirconium phosphate.

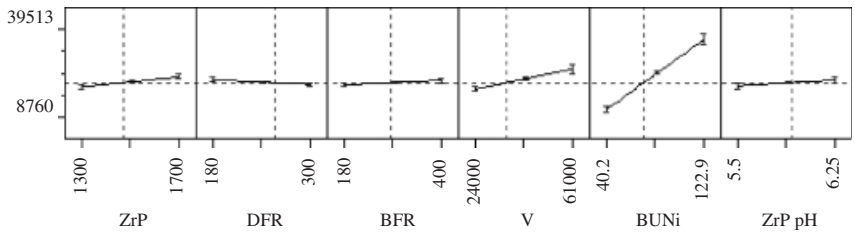

Figure 3 Relative contribution of significant variables in the urea nitrogen capacity model over the range of experimental values. Y-axis: urea nitrogen capacity in mg. X-axis labels defined in Table 2.

Sodium release model 1

This model assumes no knowledge about the patient's physiology or the dialysate bicarbonate concentration before the dialysis treatment.

$$\begin{aligned}[\text{Sorbent Cartridge Sodium Released}] &= 372.2 - 147.3[\text{ZrP}] + 113.3[\text{DFR}] + 240.9[\text{V}] \\ &\quad - 217.2[\text{KoA Product}]\end{aligned}$$

$R^2 = 0.632$; $R^2_{\text{adjusted}} = 0.584$; RMSE = 169 mEq

Table 4 shows the significance of the variables included in the model. Figure 4 shows the relative contributions of the parameters on the model.

Sodium release model 2

This model assumes knowledge about the patient's sodium and urea nitrogen physiology and the dialysate bicarbonate concentration before the commencement of the dialysis session in order to predict the sodium released from the sorbent cartridge.

$$\begin{aligned}[\text{Sorbent Cartridge SodiumReleased}] &= 372.2 - 108.2[\text{ZrP}] + 117.2[\text{DFR}] + 360.0[\text{V}] \\ &\quad - 204.4[\text{BUN}_i] - 107.5[\text{KoA Product}] \\ &\quad - 184.8[\text{Patient Na}_i] - 211.9[\text{DialysateHCO}_{3i}]\end{aligned}$$

Table 4 Sodium release model 1 variable significance

Variable	(p-value)
ZrP	0.021
DFR	0.034
V	0.0047
KoA Product	<0.0001

DFR = dialysate flow rate; KoA = dialyzer area permeability; V = volume; ZrP = Zirconium phosphate.

$R^2 = 0.829$; $R^2_{\text{adjusted}} = 0.786$; RMSE = 121 mEq

Table 5 shows the significance of the variables included in the model. Figure 5 shows the relative contributions of the parameters on the model.

Clinical results

The relationships developed in this research have been included in a computer program that is used to predict chemical effects of the Allient® treatment on patients (Therapy Calculator™; Renal Solutions Inc.). Inputs to the program include: patient age, height, gender, diabetic status, weight, desired end weight, blood rinse-back volume; pretreatment BUN, sodium, and bicarbonate concentration; dialyzer and sorbent cartridge type; blood flow rate; treatment duration; DFR; creatinine clearance, multiplied by time, divided by patient volume (Kt/V); desired posttreatment sodium and bicarbonate concentration; dialysate premix sodium, bicarbonate, and dextrose concentrations; and initial premix sodium and bicarbonate concentrations. Outputs from the program include: ultrafiltrate goal; total body water; treatment duration; DFR; Kt/V; recommended dialysate premix sodium and bicarbonate concentration; predicted patient sodium and bicarbonate change; and initial dialysate sodium and bicarbonate concentrations, and conductivity.

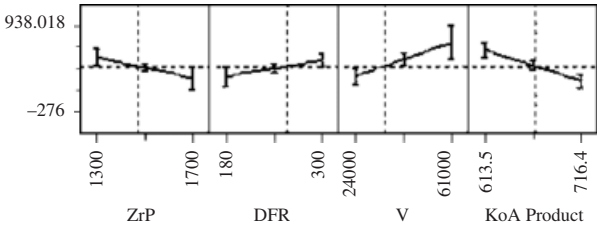

Figure 4 Relative contribution of significant variables in sodium release model 1 over the range of experimental values. Y-axis: cartridge sodium release in mEq. X-axis labels defined in Table 2.

Table 5 Sodium release model 2 variable significance

Variable	(p-value)
ZrP	0.021
DFR	0.0053
V	0.0014
BUN_i	0.054
KoA Product	0.043
Patient Na_i	0.0009
Dialysate HCO_{3i}	0.0002

BUN_i = blood side initial urea nitrogen concentration; DFR = dialysate flow rate; KoA = dialyzer area permeability; V = volume; ZrP = Zirconium phosphate.

Table 6 SORB+™ Therapy Calculator™ results from 40 experimental runs in 20 patients. Actual values were determined from pre- and postexperimental patient lab work

Variable	Predicted or entered	Actual
Pre-Run Na (mEq/L)	136 ± 4	137 ± 6
Post-Run Na (mEq/L)	140 ± 6	142 ± 5
Δ Na (mEq/L)	4 ± 2	5 ± 3
Pre-Run HCO_3 (mEq/L)	25 ± 2	23 ± 2
Post-Run HCO_3 (mEq/L)	31 ± 4	32 ± 2
Δ HCO_3 (mEq/L)	6 ± 2	10 ± 2
Kt/V	1.41 ± 0.05	1.30 ± 0.27
Percent reduction in urea concentration	68.7 ± 0.8	63.5 ± 6.5

The program has been used to determine the starting premix composition and to predict column capacity in the first treatments of many patients with the Allient system.

Table 6 demonstrates initial results with the Therapy Calculator™ from 20 patients in 40 treatment sessions using the SORB+™ cartridge. The actual values were determined from standard patient lab work drawn pre- and posttreatment. The average predicted percentage reduction in urea was 68.7 ± 0.8% and the actual reduction was 63.5 ± 6.5%. The average predicted change in sodium over the treatment session was 4 ± 2 mEq/L and the actual was 5 ± 3 mEq/L.

DISCUSSION

Urea capacity model

The UNC model provides strong evidence for the main parameters that affect the UNC of a given sorbent cartridge (Table 3). The model can potentially be used for prediction in other applications given its strong statistical significance ($R^2_{adjusted}$ = 0.990, RMSE = 906 mg).

Sodium release models

When the patient's physiology is not or cannot be known, model 1 provides a reasonable correlation of the amount of sodium expected to be released by the sorbent cartridge during the treatment. With an $R^2_{adjusted}$ = 0.584 in model 1, model 2 ($R^2_{adjusted}$ = 0.786) is preferred when patient sodium and urea levels are known before the dialysis treatment. Model 2 assumes knowledge of the patient's sodium and urea levels and the dialysate bicarbonate concentration at the beginning of the treatment. While a patient's blood chemistry is not known before each treatment, it is possible to use less frequent measures of blood electrolytes in such a model.

Parameter contributions

While each of the model parameters is dimensional with specific units required, the relative effects of each of the parameters on the model prediction provide information on how a sorbent cartridge operates and which parameters contribute the most (Table 2).

The parameter contributions affecting the cartridge UNC are shown in Figure 3. All parameters except DFR are positively related to UNC: ZrP, BFR, V, BUN_i, and ZrP pH. The relationship between UNC and DFR is negative because higher DFRs decrease the urea concentration in dialysate, providing less driving force for ammonium sorption. The relationship between UNC and ZrP is pos-

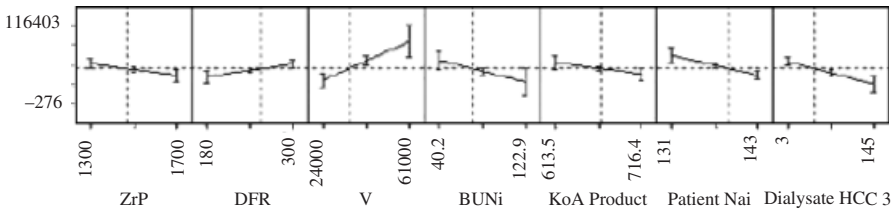

Figure 5 Relative contribution of significant variables in sodium release model 2 over the range of experimental values. Y-axis: cartridge sodium release in mEq. X-axis labels defined in Table 2.

itive because more ZrP allows for greater ammonium adsorption before breakthrough occurs. The relationship between UNC and BFR is positive because of its effect on mass transfer and the rate of urea delivery to the dialysate. The effect of ZrP pH on UNC is positive but relatively small. The depletion of H^+ from the column promotes replacement by NH_4^+ due to its high affinity on the column. Overall, ZrP affinity for cations is as follows: $NH_4 > H, K, Mg, Ca > Na$. The relationship between UNC and BUN_i is positive given that higher patient urea concentration increases dialysate urea concentration, thus increasing the mole fraction ratio of ammonium vs. all other cations. The effect of patient whole-body fluid volume (V) is somewhat positive on UNC for the reason that it also maintains dialysate urea at a higher level.

The parameters affecting the cartridge sodium release are shown in Figures 4 and 5. The following parameters have a negative effect on cartridge sodium release: ZrP, BUN_i, KoA product, patient Na_i, dialysate HCO_{3i}. The relationship between sodium release and ZrP is expectedly negative because the ZrP layer exchanges hydrogen and sodium for the ammonium generated by the conversion of urea. Because of the affinity of ZrP and the effects of carbonate in combining with hydrogen to make CO_2, hydrogen is released before sodium during dialysis. The effect of BUN_i on sodium generation is negative, explainable by the fact that higher urea concentrations results in higher generation of carbonate, and this diminishes hydrogen concentration in the fluid within the ZrP layer. The relationship between sodium release and KoA product is unexpectedly negative in its effect on sodium release. It is expected that with more dialyzer membrane area permeability, more urea can diffuse across the dialyzer and enter the column to cause sodium release. The initial patient sodium level is negative in its effect on sodium release because the higher patient sodium level results in a higher dialysate sodium level, decreasing sodium release from the column because of a smaller concentration gradient. Higher dialysate concentrations provide less space for sodium to desorb from the ZrP layer. Interestingly, the dialysate initial sodium level was not a significant model parameter. The relationship between sodium release and the dialysate initial bicarbonate concentration is negative due to diminishing hydrogen concentration within the ZrP layer fluid.

The following parameters have a positive linear effect on cartridge sodium release: DFR and V. The relationship between sodium release and DFR is expectedly positive because higher flow rates provide more mass transfer across the dialyzer and more space for sodium desorption from the ZrP layer. The relationship between sodium release and patient whole-body fluid volume is positive. Larger patients have more space for sodium released from the cartridge, which maintains a large concentration gradient in the dialysate.

Limitations

This research relies upon in vitro experiments that may not include all factors experienced in a patient treatment session: multi-compartmental effects, ultrafiltration, physiological corrections, etc. Other approaches to modeling sorbent columns based on first principles might be more informative, but the approach presented is workable from prediction to analyze the effects of the parameters presented.

Impact

The ability to predict UNC of a sorbent cartridge allows users to design a dialysis treatment that will allow the column to function through the entire treatment, reaching near capacity but not beyond. Assuming that a desired time of treatment is chosen, dialysate and blood flow rates can be varied in the models to determine rates that will bring the column to a desired level of saturation during the treatment. Avoiding column saturation decreases the number of dialysis treatments terminated early due to ammonium breakthrough. This not only increases the convenience of the dialysis treatment, but it diminishes any risk of ammonium breakthrough before the ammonium sensing system stops the treatment.

The ability to predict sodium released from sorbent cartridges allows an estimation of the increase in serum sodium occurring during a prescribed use of a column. This allows for the calculation of a sodium concentration in the premix and prime fluids that will provide space for sodium removal and diminish the overall return of sodium to the patient. This approach causes sodium removal from the patient early in the dialysis procedure and return of sodium late in the treatment. Conductivity-based measurements can also provide real-time sodium concentration measurement within dialysate in a sorbent-based system, in spite of the fact that relative concentrations of anions change significantly during a treatment.[1,10,11] In combination, several methods could be used to then modulate the sodium concentration in the dialysate. This would smooth the sodium concentration curve of the dialysate, but would add technical complexity to the sorbent-based system.

Knowledge of sodium profiles during dialysis is especially relevant in home-based therapy.[12–18] Avoiding car-

tridge saturation means that treatments can continue for the prescribed length of time, without early termination due to ammonium breakthrough. Knowledge of the sodium released from the sorbent cartridge provides information that can be used to select proper cartridges and premix sodium levels during the first treatments of a patient, during training. Analysis of postdialysis chemistries allows further minor adjustments to be made in premix makeup, to tune the chemical changes to the patient and treatment parameters. Consistency in a patient's overall chemical profile benefits clinical outcomes, especially in home dialysis.[11,19]

The models presented predict sodium release after the complete exhaustion of a sorbent cartridge, where exhaustion is defined as ammonium breakthrough. It is also possible to use the experimental data to predict sodium generation during partial saturation of a sorbent cartridge.

Finally, the models have been implemented clinically in a computer program used for prediction. Only minor modifications have been necessary in the Therapy Calculator™ program to predict accurately sodium, bicarbonate, and urea changes in patients. The column capacity predictions have appeared to be generally accurate (Table 6), though data are preliminary because very few columns proceeded to saturation.

CONCLUSION

- Multiple regression analysis can predict many column chemical functions; i.e., it shows meaningful trends to understand better the function of the column and dialyzer.
- The models provide insight into somewhat unexpected parameter effects:

1. Cartridge sodium release is decreasing with increasing dialyzer KoA product.
2. Cartridge sodium release increases with patient volume due to maintenance of higher urea levels and greater space for sodium distribution.
3. Cartridge sodium release is not related to starting and average BUN levels; higher urea levels create more carbonate, preferentially augmenting hydrogen release rather than sodium release from the column or promoting sodium exchange for hydrogen.

- The models also demonstrate several expected effects.

1. UNC is positively related to ZrP, BFR, V, BUN_i, and ZrP pH
   a. ZrP: more ZrP allows for greater ammonium adsorption before breakthrough occurs.
   b. BFR: because of its effect on mass transfer and the rate of urea delivery to the dialysate.
   c. V: maintains dialysate urea at a higher level.
   d. BUN_i: higher patient urea concentration increases dialysate urea concentration resulting in higher binding by ZrP.
   e. ZrP pH: higher pH results in depletion of hydrogen from the column, promoting replacement by ammonium, which has higher affinity.
2. UNC is negatively related to DFR
   a. DFR: higher dialysate flow rates decrease the urea concentration in dialysate, providing less driving force for ammonium sorption.
3. Cartridge sodium release is positively related to DFR
   a. DFR: higher flow rates provide more mass transfer across the dialyzer and more space for sodium desorption from the ZrP layer.
4. Cartridge sodium release is negatively related to ZrP, BUN_i, patient Na_i, and dialysate HCO_{3i}.
   a. ZrP: ZrP layer exchanges hydrogen and sodium for the ammonium generated by the conversion of urea. Because of the affinity of ZrP and the effects of carbonate in combining with hydrogen to make CO_2, hydrogen is released before sodium during dialysis.
   b. BUN_i: higher urea concentrations results in higher generation of carbonate, and this diminishes hydrogen concentration in the fluid within the ZrP layer.
   c. Patient Na_i: higher patient sodium level results in a higher dialysate sodium level, decreasing sodium release from the column because of a smaller concentration gradient. Higher dialysate concentrations provide less space for sodium to desorb from the ZrP layer.
   d. Dialysate HCO_{3i}: due to diminishing hydrogen concentration within the ZrP layer fluid.

- Although the in vitro test setup used is considerably simpler than actual patient dialysis, the results of the model have been reasonably close to the clinical results for sodium and bicarbonate change and UNC of the columns as seen in the Therapy Calculator™.

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