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Transperitoneal transport of sodium during hypertonic peritoneal dialysis

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Summary. The mechanisms of transperitoneal sodium transport during hypertonic peritoneal dialysis were evaluated by kinetic modelling. A total of six nested mathematical models were designed to elucidate the presence or absence of diffusive, non-lymphatic convective and lymphatic convective solute transport. Experimental results were obtained from 26 non-diabetic patients undergoing peritoneal dialysis. The model validation procedure demonstrated that only diffusive and non-lymphatic convective transport mechanisms were identifiable in the transperitoneal transport of sodium. Non-lymphatic convective sodium transport was the most important quantitative transport mechanism during the first 90 min of the dwell. Significant sodium sieving was demonstrated and explains the observation of hypernatremia in dialysis with hypertonic dialysis fluid.

Key words: Donnan potential, diffusive mass transfer area coefficient, kinetic modeling, lymphatic convective solute transport, sodium transport, ultra-filtration sieving coefficient.

Introduction

In peritoneal dialysis sodium overload is common and dietary salt restriction alone is usually inefficient. The patients therefore rely on the dialysis procedure for sodium removal, but only a few investigations of transperitoneal sodium transport have been published (Nolph *et al.*, 1969; Rubin *et al.*, 1982; Waniewski *et al.*, 1991a, b, 1992a, b; Heimbürger *et al.*, 1992).

The aim of the present study was to investigate the mechanism of transperitoneal sodium transport by kinetic modeling. A family of six nested models was mathematically formulated and validated.

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Methods

CLINICAL STUDIES

Patients. A total of 26 non-diabetic patients (16 men and 10 women) undergoing peritoneal dialysis for chronic renal failure were included in the study. Median age was 63 years (range 23–75 years), median daily urine output was 500 ml (range 0–2500 ml) and median body weight was 73 kg (range 41–90 kg).

Ethics. Written informed consent was obtained from all patients and the study protocol was approved by the local medical ethics committee.

Dialysis procedure. Each patient participated in a 6 h dwell study as described in detail previously (Fugleberg *et al.*, 1994; Graff *et al.*, 1994). Two litres of preheated (37–38°C) dialysis fluid containing 22.7–23.0 g glucose l^{-1} (Dianeal, Baxter Healthcare Corporation, Ireland or Lockolys-Glucos, Fresenius AG, Bad Homburg, Germany) were used. Dialysate samples were collected at 0, 30 and 60 min, then every 30 min up to 360 min. Blood samples were drawn at 0, 120, 240, and 360 min.

ANALYTICAL METHODS

Sodium concentrations in serum and dialysate were measured with a SMAC 3 multichannel analyser (Technicon, Tarrytown, NY, USA). Plasma sodium was assumed to equal serum sodium (Ladenson *et al.*, 1974). Dialysate haemoglobin concentrations were measured using the cyanmethaemoglobin method, after centrifugation (4000 *g*) of the dialysate.

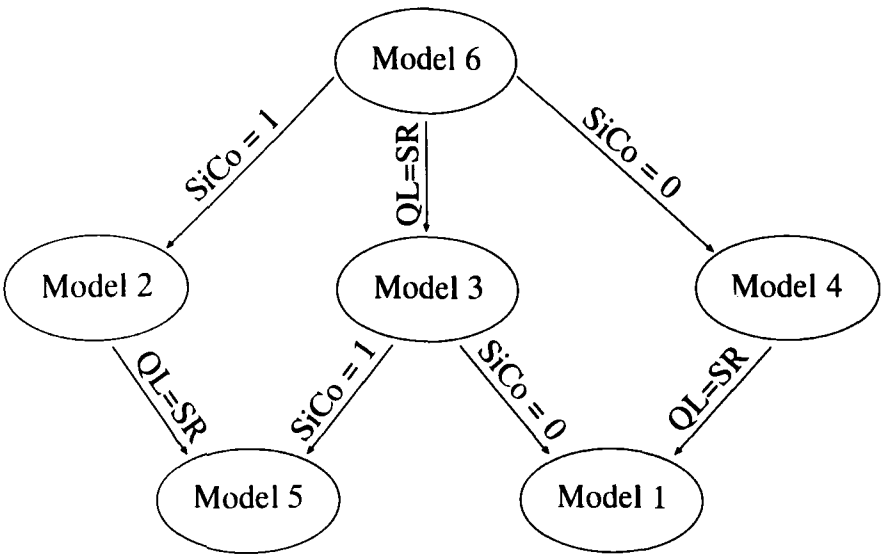

Fig. 1. The connection between the nested models. SiCo: ultrafiltration sieving coefficient, QL: lymphatic flow rate, SR: sampling rate.

MODEL FORMULATION

The six models used in the present study were mathematically formulated from the differential equation:

$$dM/dt = MTAC \times (0.94 \times Cpw - CD) + SiCo \times QU \times MC - QL \times CL$$

This equation partitions net solute mass transport per unit time (dM/dt) into diffusive transport, non-lymphatic convective transport and a remainder term (lymphatic convective transport).

The first term on the right-hand side of the equation describes diffusive mass transport rate as the product of clearance (MTAC) and the electrochemical gradient. The electrochemical gradient is defined as the difference between 0.94×Cpw and CD, where 0.94 is the equilibrium distribution ratio for monovalent cations (Fogh-Andersen *et al.*, 1993; Graff *et al.*, 1995), Cpw is the peripheral vein plasma water sodium concentration, and CD is the dialysate sodium concentration. Cpw=U×plasma sodium concentration; U=1/(0.984–0.000718×Cprot); Cprot=plasma total protein concentration (g l^{-1}); plasma sodium concentration=serum sodium concentration (mmol l^{-1}).

The second term describes non-lymphatic convective mass transport rate as the product of the ultrafiltration sieving coefficient (SiCo), the ultrafiltration rate (QU) and the average intramembrane sodium concentration (MC) (Graff *et al.*, 1995).

The third term describes the remainder transport rate (lymphatic convective transport) as the product of the lymphatic flow rate (QL) and the sodium concentration (CL). QL was defined by the equation dVol/dt=QU-QL. CL=CD or Cpw, depending on the direction of the lymphatic flow.

The six models were mathematically nested (Fig. 1). Model 1 was purely diffusive (SiCo=0 and QL=sampling rate). Model 2 included diffusive transport, non-lymphatic convective transport, and lymphatic convective transport (SiCo=1, QL was searched). Model 3 included diffusive and non-lymphatic convective transport without lymphatic convective transport (SiCo was searched, QL=sampling rate). Model 4 included diffusive and lymphatic convective transport without non-lymphatic convective transport (SiCo=0, QL was searched). Model 5 included diffusive transport and non-lymphatic convective transport without lymphatic convective transport (SiCo=1, QL=sampling rate). Model 6 (the global model) included all 3 mechanisms of transport: diffusion, non-lymphatic convective transport and lymphatic convective transport (both SiCo and QL were searched. For a detailed discussion of the assumptions of the six models, see Fugleberg *et al.* (1994).

CALCULATIONS

In each model M(t=0) (the intraperitoneal sodium mass at zero time) and MTAC were searched for in the set of real numbers, whereas SiCo and QL were searched for in the set of real numbers or kept constant, as indicated in Table 1. The searched values of

Table 1. Median (95% confidence interval) of the transport parameter estimates (constants in boldface text), and median ranks (95% confidence interval) of the Akaike information criterion (AIC) of models 1–6. The values of MTAC and QL in ml min^{-1}

	MTAC	SiCo	QL	AIC	R	F
1	13.3 (7.2–16.7)	0	SR	6 (6–6)	3	—
2	0.4 (0.1–0.8)	1	−0.3 (−1.3–2.1)	4 (3–4)	3	—
3	4.2 (1.7–6.1)	0.70 (0.64–0.87)	SR	1 (1–2)	5	NO
4	257 (71–980)	0	17.3 (5.6–63.7)	4 (3–5)	6	—
5	1.1 (0.6–2.8)	1	SR	4 (4–5)	3	—
6	5.4 (2.2–8.6)	0.74 (0.67–0.80)	1.7 (0.3–4.4)	2 (1–2)	5	YES

SR: sampling rate; R: number of runs (analysis of residual errors, runs test); F: excluded by the *F*-test.

M(t=0), MTAC, SiCo and QL were calculated by numerical integration (fourth order Runge-Kutta's method) using the simplex method for function minimization. The ultrafiltration rate was calculated from the estimated dialysate volumes (using haemoglobin as a volume marker) and the lymphatic flow rate. Details can be found in Fugleberg *et al.* (1994) and Graff *et al.* (1994).

To compare the goodness of fit in two competing models with an unequal number of estimated parameters, the Akaike criterion (AIC) (Akaike, 1974) and the *F*-test (Bates & Watts, 1988) were used.

STATISTICAL ANALYSIS

As the parameter estimates were skewed, the results were presented as medians (95% confidence interval). Differences in the goodness of fit (AIC and *F*-test) between two models were analysed with the sign test. Residual errors were tested for randomness by the runs test. A *P* value of less than 0.05 was considered significant.

Results

The peripheral vein plasma water sodium concentrations (Cpw), measured at 0, 120, 240 and 360 min, demonstrated a statistically significant difference in location (Friedman's test (corrected for ties), $n=26$, K=4, $P=0.00005$). The dialysate sodium concentrations (CD) measured at 0, 30, 60 ... 360 min, demonstrated a statistically significant difference in location (Friedman's test (corrected for ties), $n=26$, K=13, $P<0.00001$).

Median transport parameter estimates (95% confidence interval), the median ranks of AIC and the number of runs from the analysis of residual errors are given in Table 1. Fig. 1 depicts the connection between the six nested models. Fig. 2 shows mean dialysate and mean peripheral vein plasma water sodium concentrations vs. time, whereas Fig. 3 depicts the calculated diffusive and non-lymphatic convective sodium mass transport rates during the 6 h of dwell.

Theoretical identifiability. The global model (model 6) is a linear equation in four unknowns. All parameters (M(t=0), MTAC, SiCo and QL) are theoretically identifi-

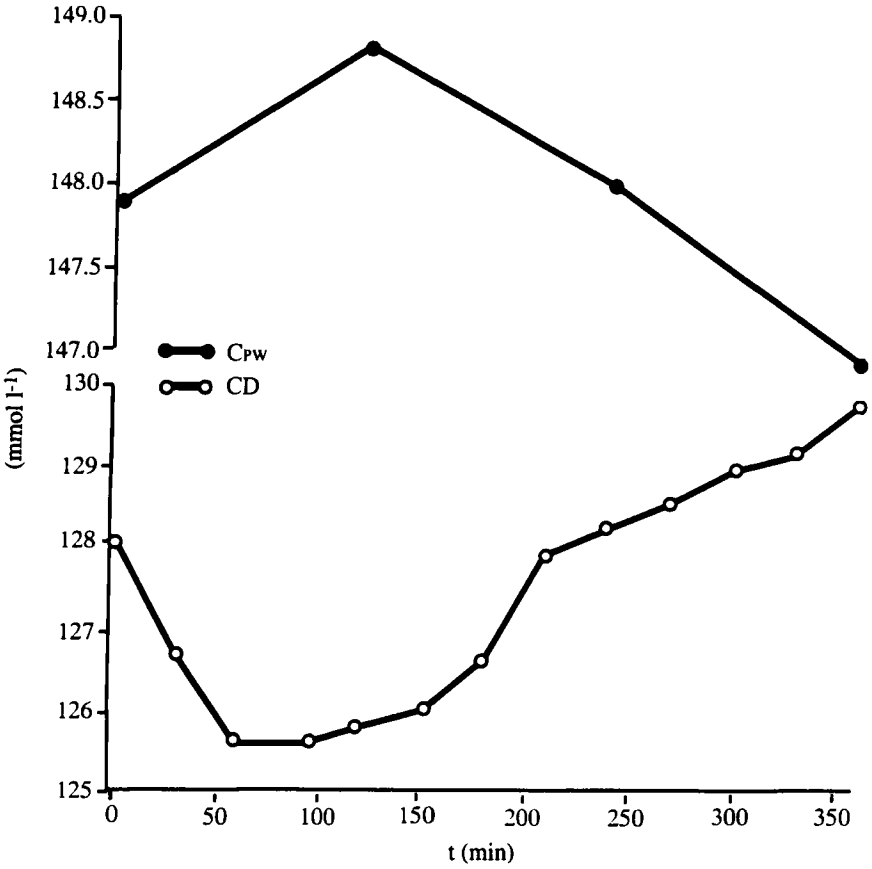

Fig. 2. The mean dialysate (CD) and mean plasma water (Cpw) sodium concentrations vs. time (t).

able, if the dialysate volume-time profile and four or more experimental points (time, dialysate sodium concentrations) are provided. All models are therefore theoretical identifiable.

Residual errors. The expected number of runs for $n=13$ was 7.5 (approximate 95% confidence interval: 5–10). The runs test demonstrated that the residual errors of model 3, 4 and 6 were randomly distributed, whereas the residual errors of the other models were non-random. Models 1, 2 and 5 were rejected and excluded from the quality-of-fit analysis.

Parameter plausibility. In model 4, the estimates of the mass transfer area coefficient and the lymphatic flow rate were unphysiologically high and this model was excluded from the goodness-of-fit analysis.

Goodness of fit. The remaining two models (3 and 6) were analysed for goodness of fit. When models 3 and 6 were compared by the Akaike information criterion, model 3 was preferred for 15 patients and model 6 for 11 patients ($P=0.56$, sign test). When

models 3 and 6 were compared by the *F*-test, model 3 was preferred for 21 patients, model 6 for five patients (P=0.003, sign test).

In summary, model 3 was superior to the remaining five models.

Discussion

Previous studies on the mechanisms of transperitoneal solute transport have concentrated on model formulation. The general question of model validity has never received adequate attention. In many cases the validation problem has been reduced to one of fitting test data to curves. Crucial problems, such as examining whether or not specific parameters can be estimated from a given set of experimental data, have not been carefully examined. In this study we used the criteria of model validation, as suggested by Carson *et al.* (1983), in order to investigate whether the best model of transperitoneal sodium transport during a hypertonic exchange is purely diffusive, or whether non-lymphatic convective and/or lymphatic convective transport mechanisms are identifiable as well. Six nested mathematical models were formulated and tested for theoretical identifiability, goodness of fit, random residual errors and plausibility of parameter estimates. The principles of model validation have been explained elsewhere (Fugleberg *et al.*, 1994).

All models were theoretically identifiable as the amount of data was adequate to uniquely identify all parameters. Models 1, 2 and 5 were rejected on the basis of non-randomly distributed residual errors, i.e. models 1, 2 and 5 included a systematic deviation between data and model prediction. Model 4 was invalidated on the basis of unphysiological parameter estimates (MTAC and QL). The effective peritoneal capillary flow rate is near 70 ml min^{-1} (Nolph & Twardowski, 1989) and a mass transfer area coefficient exceeding this value by 300–400% invalidates the model. Likewise, a median lymphatic flow rate of 17.3 ml min^{-1}, seems unrealistic (Mactier & Khanna, 1989). Among the remaining two models (3 & 6), the model with the best goodness of fit is generally considered superior. Goodness of fit describes in quantitative terms the agreement between raw data and model prediction; in this case, measured and calculated dialysate sodium concentrations. The improvement in fit obtained by adding parameters to any given model is evaluated from the sum of squared residuals corrected for the difference in the number of parameters. The Akaike criterion (Akaike, 1974) and the *F*-test criterion (Bates & Watts, 1988) are available for this purpose. The *F*-test criterion demonstrated a significant difference in goodness of fit between models 3 and 6. However, the Akaike criterion was not able to demonstrate this difference. Thus, from the overall model validation, it must be concluded that model 3 was superior to the five other models.

The estimate of the diffusive mass transfer area coefficient for sodium (model 3) is in good agreement with results reported by others (Waniewski *et al.*, 1991a, b, 1992a, b; Heimbürger *et al.*, 1992). In calculations of the diffusive sodium transport, the plasma water sodium concentrations at equilibrium must be corrected for the actual electric

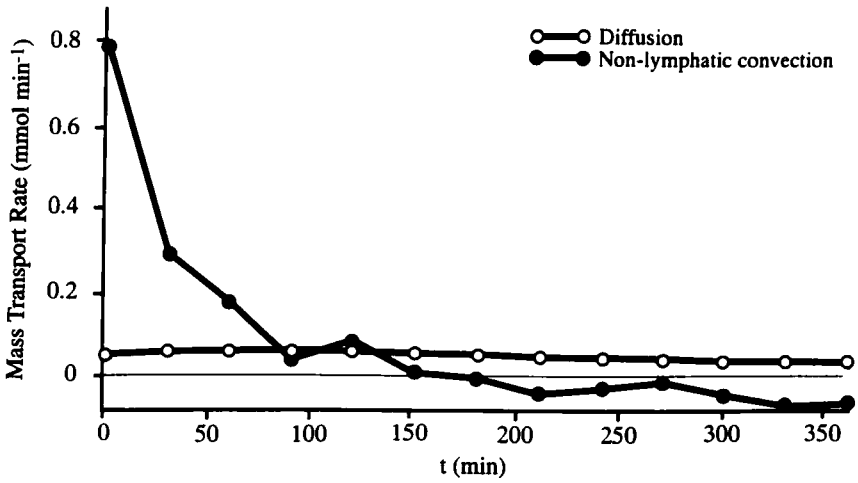

Fig. 3. The diffusive and non-lymphatic convective sodium mass transport rate vs. time (t).

potential difference. The importance of this correction has been shown by Waniewski *et al.* (1992a).

Considering the molecular weight of sodium (MW 23 D), the mass transfer area coefficient is smaller than expected. Thus, the mass transfer area coefficient of potassium (MW 39 D) was found to be 19.5 ml min^{-1} (Graff *et al.*, 1995). Vonesh & Rippe (1992) have proposed that sodium mass transfer was impeded by slower moving anions. It is more likely that the discrepancy is due to difficulties in the estimation of the MTAC of sodium when diffusion is responsible for only a minor part of the total solute transport. Thus, larger MTAC values have been reported in animals when sodium-free solutions were used (Knochel, 1969). Furthermore, the permeability of ions depends on their hydrated size and not on their molecular weight. Actually, hydrated sodium-ions are considerably larger (radius 0.24 nm) than hydrated potassium-ions (radius 0.17 nm) (Moore, 1972).

The estimated median ultrafiltration sieving coefficient for sodium (model 3) is considerably larger than those reported by others (Nolph *et al.*, 1969; Rubin *et al.*, 1982; Waniewski *et al.*, 1991a, 1992a, b). As the estimated ultrafiltration sieving coefficient is very sensitive to errors in the calculated ultrafiltration rate, differences in measurement and calculation of the ultrafitration rate might explain the differences between the ultrafiltration sieving coefficients in our study and those previously reported.

Models assuming the ultrafiltration sieving coefficient to be equal to unity (models 2 and 5) are invalid, probably as a result of significant sodium sieving. This was also shown by Waniewski *et al.* (1991a). They found that Garred's model (resembling model 5 in the present study) failed to describe the transperitoneal sodium transport, probably because its main assumption (SiCo=1) is not fulfilled.

As in the case of transperitoneal potassium transport (Graff *et al.*, 1995), a lymphatic convective transport mechanism was not identifiable by the best fit model, i.e. the inclusion of QL in the model did not significantly improve the goodness of fit, and did not resolve the question as to whether or not this transport mechanism existed in the system under investigation. The reason that the amount of information contained in the data was inadequate to identify this transport mechanism could be that some of the transport mechanisms included in the collective term QL (e.g. direct lymphatic, interstitial lymphatic and direct blood entry) might be influenced by the positive charge of the investigated solute. Hence, the total amount of cations transported by lymphatic convection becomes negligible compared to the amount transported by diffusion and non-lymphatic convection. Thus, anionic sites at the level of peritoneal microvasculature, interstitium and mesothelium have been shown (Leak, 1986; Gotloib *et al.*, 1987).

Although dialysis fluids are made hyponatremic to plasma, diffusive sodium transport is only moderate compared to the non-lymphatic convective sodium transport during the first 90 min of the dwell using 2.3% glucose dialysis fluid (Fig. 3). Hence, the diffusive transport becomes increasingly more important, and is the dominating transport mechanism during the rest of the dwell. The significant sodium sieving, combined with the moderate diffusive sodium transport (small MTAC), resulted in the net removal from the plasma of a fluid volume with a low sodium concentration during the first 90 min of the dwell. Thus, the plasma water sodium concentration increased and the dialysate sodium concentration decreased during this period (Fig. 2). The dialysate sodium concentration reached a minimum (of 125.6 mmol l^{-1}) at 60–90 min. This finding corroborates those of Rippe *et al.* (1991). They computer-simulated the dialysate sodium concentration as a function of dwell time, and found the minimum dialysate sodium concentration to be reached at 50 (118 mmol l^{-1}) and 90 min (132 mmol l^{-1}) for the 1.36% and 3.86% (glucose) dialysis fluid, respectively. Our results explain why the use of hypertonic peritoneal dialysis solutions for short dwell times (automated peritoneal dialysis) may result in hypernatremia (Nolph *et al.*, 1969; Ahearn & Nolph, 1972; Raja *et al.*, 1972; Heimbürger *et al.*, 1992).

CONCLUSION

Transperitoneal transport of sodium during a hypertonic exchange involves diffusive and non-lymphatic convective transports. The lymphatic convective sodium transport mechanism was not identifiable.

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