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An evaluation of twelve nested models of transperitoneal transport of urea: the one-compartment assumption is valid

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Models of transperitoneal urea transport are generally based on the one-compartment assumption, i.e. that the plasma water urea concentration in the peritoneal capillary bed is equal to the plasma water urea concentration in the peripheral veins. The aim of this study was to investigate the mechanism(s) of transperitoneal urea transport and to test the one-compartment assumption for urea. A total of 12 nested models were formulated and validated on the basis of experimental results obtained from 23 non-diabetic patients undergoing peritoneal dialysis. The validation procedure demonstrated that transperitoneal transport of urea probably involves diffusion, non-lymphatic convection and lymphatic convection. It was furthermore demonstrated that the inclusion of lymphatic convection changes the mass transfer area coefficient considerably. Finally, no deviation from the one-compartment assumption was demonstrated by our results.

Key words: diffusive mass transfer area coefficient; kinetic modelling; lymphatic convective solute transport; peritoneal dialysis; ultrafiltration sieving coefficient

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INTRODUCTION

A large number of different mathematical models have been used to investigate the mechanisms of transperitoneal solute transport and to provide estimates of the transport parameters. In early modelling studies the transperitoneal solute transport was described in terms of diffusion only [1–6], whereas later models include convective solute transport [7–15] or both lymphatic and non-lymphatic convective solute transport [16–19]. These models are based on the one-compartment assumption, i.e. the peritoneal capillary plasma water solute concentration is identical to the peripheral vein plasma water solute concentration. One-compartment models have been used for many years to describe haemodialysis urea kinetics [20–24]. However, there has been growing criticism of this approach, because the use of one-compartment models resulted in unphysiological estimates of urea generation rate [25] and distribution volume [26, 27]. The solute flux during peritoneal dialysis is only a fraction of the haemodialysis solute flux. Although it seems justified to apply one-compartment models to describe urea

kinetics in peritoneal dialysis, the validity of this approach has never been tested experimentally.

The aim of the present study was: (1) to study the mechanism of transperitoneal urea transport by validation of 12 nested mathematical models [28], and (2) to test the validity of the one-compartment assumption.

METHODS

Clinical studies

Patients. A total of 23 non-diabetic patients (14 men and nine women) undergoing peritoneal dialysis therapy were included. Of these, 12 had chronic renal failure of unknown aetiology, six had chronic glomerulonephritis, two had chronic pyelonephritis, two had polycystic kidney disease and one had nephrosclerosis. The median age was 62 years (range 23–75), median daily urine output was 500 ml (range 0–2500) and median body weight was 74 kg (range 41–87). Of the patients, 20 had been treated with continuous ambulatory peritoneal dialysis (CAPD) and three with continuous cycling peritoneal dialysis (CCPD) for 2 weeks to 78 months prior to the study.

Ethics. Written informed consent was obtained from all the patients. 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 [29, 30]. A 2-l volume of preheated (37–38°C) dialysis fluid, with a glucose concentration of 22.7 g l^{-1} (Dianeal, Baxter Healthcare Corporation) or 23.0 g l^{-1} (Lockolys-Glucos, Fresenius AG) was used. The patients were recumbent in an armchair throughout the 6-h investigation period. Dialysate samples were collected every half-hour from 0 to 360 min. Blood samples were drawn at 0, 120, 240 and 360 min.

Dialysate volumes. These were measured using haemoglobin as a volume marker. This is a modification of the method of Brouard *et al.* [31], first described by Canaud *et al.* [32]. For details of the volume measurements see Graff *et al.* [30].

Analytical methods

Urea concentrations in serum and dialysate were measured with a SMAC 3 (Technicon, Tarrytown, New York, USA). Plasma urea was assumed to equal serum urea [33]. Dialysate haemoglobin concentrations were measured by the cyan-methaemoglobin method, after centrifugation of the dialysate.

Model formulation

A family of 12 models was formulated.

Models 1A and 1B were purely diffusive, i.e. non-lymphatic convective transport and lymphatic convective transport were ignored. These models resemble the previous models of Kallen [1], Miller *et al.* [2], Henderson & Nolph [3], Popovich *et al.* [4], Bomar *et al.* [5] and Goldsmidt *et al.* [6].

Models 2A and 2B included diffusive transport, non-lymphatic convective transport (constant ultrafiltration sieving coefficient = 1), and lymphatic convective transport. These models resemble the model of Leypoldt *et al.* [17].

Models 3A and 3B included diffusive and non-lymphatic convective transport (fitted ultrafiltration sieving coefficient), but no lymphatic convective transport. These models resemble the Pyle–Popovich model [11].

Models 4A and 4B included diffusive and lymphatic convective transport, but no non-lymphatic convective transport.

Models 5A and 5B included diffusive transport and non-lymphatic convective transport (constant ultrafiltration sieving coefficient = 1), while lymphatic convective transport was not included. These models resemble the models of Babb *et al.* [8], Randerson & Farrell [10], Garred *et al.* [12] and Krediet *et al.* [13].

Models 6A and 6B (the global models) included all three mechanisms of transport: diffusion, non-lymphatic convective transport (fitted ultrafiltration sieving coefficient) and lymphatic convective transport.

The models in this study were based on the following assumptions:

(1) The peritoneal membrane is a barrier separating a well-mixed dialysate compartment of variable volume and composition from the well-mixed peritoneal capillary plasma water. In models 1A–6A the one-compartment assumption was abandoned to allow for urea concen-

tration differences between peritoneal capillary plasma water and peripheral vein plasma water. As an approximation it was assumed that the peritoneal capillary plasma water urea concentration is a linear function of the peripheral vein plasma water urea concentration. Thus, in the calculations the measured peripheral vein plasma water urea concentrations were replaced by the peritoneal capillary plasma water urea concentrations, expressed as the product of a fitted time-independent phenomenological factor (fct) and the measured peripheral vein plasma water urea concentrations (Cpw). (See Appendix for further explanation of abbreviated terms.) In this way a deviation from the one-compartment assumption would reveal itself as an estimate of fct different from one. In models 1B–6B it was assumed that the patient was a well-mixed compartment, i.e. that the peripheral vein plasma water urea concentration (Cpw) was identical to the peritoneal capillary plasma water urea concentration.

(2) Measured net changes of peritoneal volume (dVol/dt) can be partitioned into:

(i) water transport, characterized by concomitant urea transport subject to molecular sieving, henceforward referred to as ultrafiltration, and

(ii) water transport characterized by concomitant urea transport not subject to molecular sieving, henceforward referred to as lymphatic flow.

It is recognized that water transport is defined in terms of the resulting urea transport, and the definition of lymphatic flow includes a number of water transport mechanisms, e.g. dialysate sampling, direct lymphatic entry, interstitial lymphatic entry, and direct blood entry [34].

Net volume change was experimentally determined, and no attempt was made to investigate the mechanisms of water transport.

(3) Urea moves across the peritoneum by one, two or three of the following transport mechanisms.

(i) Diffusive transport is defined as a passive process whose transport rate is proportional to the driving concentration difference between dialysate and plasma.

(ii) Non-lymphatic convective transport is defined as a process whose transport rate is proportional to the ultrafiltration rate and the average intramembrane solute concentration.

(iii) Lymphatic convective transport is defined as a solute size-independent process, whose transport rate is proportional to the solute concentration of the plasma water or the dialysate, depending on the direction of flow.

(4) The transport parameters (diffusive mass transfer area coefficient, ultrafiltration sieving coefficient and lymphatic flow rate) are constant during the experiment.

(5) The haemoglobin disappearance rate from the peritoneal cavity is proportional to the intraperitoneal mass of haemoglobin.

(6) The mechanisms of urea transport are identical in all patients, whereas the magnitude of the individual transport parameters varies between individuals.

Calculations

1. Parameter estimation. The 12 models were mathematically formulated in two differential equations:

$$dVol/dt = QU - QL, \quad (1)$$

where dVol/dt is the rate of peritoneal net volume change, QU is the ultrafiltration rate, and QL is the lymphatic flow rate.

$$dM/dt = MTAC \times ((fct \times Cpw) - CD) + (SiCo \times QU \times MC) - (QL \times CL), \quad (2)$$

where dM/dt is the net transperitoneal urea mass transport rate; MTAC is the mass transfer area coefficient; fct is a fitted time-independent phenomenological factor; Cpw is the peripheral vein plasma water urea concentration; CD is the dialysate urea concentration; SiCo is the ultrafiltration sieving coefficient; MC is the average intramembrane urea concentration, and CL is the urea concentration in plasma water or in the dialysate, depending on the direction of flow (QL).

In each model, $M_{t=0}$, MTAC and fct 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 below:

1A and 1B: SiCo = 0
QL = 0.00065 l min^{-1} (sampling rate)
2A and 2B: SiCo = 1
QL = searched

3A and 3B: SiCo = searched
QL = 0.00065 l min^{-1} (sampling rate)
4A and 4B: SiCo = 0
QL = searched
5A and 5B: SiCo = 1
QL = 0.00065 l min^{-1} (sampling rate)
6A and 6B: SiCo = searched
QL = searched.

The search for the best fit values of $M_{t=0}$, MTAC, fct and SiCo was not constrained to positive values, since unphysiological (negative) estimates effectively invalidate the model(s) in question. The best fit lymphatic flow rate was searched for in the set of real numbers, i.e. among positive as well as negative numbers. The a priori inclusion of negative numbers is justified since it is a common clinical experience that some peritoneal dialysis patients accumulate fluid intraperitoneally, in the absence of dialysate, by a process not related to osmosis. The calculated lymphatic flow rate is time-independent and should be regarded as the net lymphatic flow rate during the 6-h dwell.

2. Dialysate volume calculation. The dialysate volumes were calculated as described previously [29, 30].

3. The ultrafiltration rate. This rate at time t, QU_t, was calculated from the estimated dialysate volumes at time t min, Vol_t, and at time t + 1 min, Vol_{t+1}, and the lymphatic flow rate:

$$Vol_{t+1} - Vol_t = QU_t - QL;$$

$$QU_t = Vol_{t+1} - Vol_t + QL.$$

4. The average intramembrane solute concentration (MC). MC was calculated as described by Villaroel *et al.* [35]. The average intramembrane urea concentration was, in models 1A–6A, calculated as:

$$MC = (fct \times Cpw) - f((fct \times Cpw) - CD);$$

and in models 1B–6B as

$$MC = Cpw - f(Cpw - CD).$$

In all 12 models:

$$f = (1/\beta) - 1/(\exp(\beta) - 1),$$

where

$$\beta = \text{Peclet number} = (QU \times SiCo)/MTAC.$$

5. Calculation of dialysate solute concentration–time curve from $M_{t=0}$, MTAC, fct, SiCo, and QL. The relationship between time (t, min, independent variable) and dialysate solute concentration (CD, mmol l^{-1}, dependent variable) for given values of $M_{t=0}$, MTAC, fct, SiCo, and QL was calculated by numerical integration (4th order, Runge–Kutta's method). The calculation was performed from t = 0 to t = 360 min in steps of 1.0 min, in order to keep the relative errors of the calculated dialysate solute concentrations below 0.25%, i.e. below 1/10 of the estimated within-series measurement error of the dialysate solute concentrations. When measured values of Cpw were not available, concentrations were estimated by linear interpolation.

6. Curve fitting procedure. For each dialysate solute concentration–time curve the sum of squared residuals (SSQ) was calculated as:

$$SSQ = \frac{\Sigma\,(CD_{calculated} - CD_{measured})^2}{\text{var}\,(CD_{measured})}.$$

The vector ($M_{t=0}$, MTAC, fct, SiCo, QL) giving the smallest sum of squared residuals was found by the Simplex method [36]. To avoid local (i.e. non-global) minima, iteration was started from 10 or more randomly chosen vectors. Iteration was continued until the error of approximation was less than 1% of the estimated values of $M_{t=0}$, MTAC, fct, SiCo and QL. Residual errors (RE) were calculated as:

$$RE = \frac{(CD_{calculated} - CD_{measured})}{SD(CD_{measured})}.$$

7. Goodness of fit. This describes in quantitative terms the agreement between raw data and model prediction; in this case measured and calculated dialysate urea concentrations.

When models with an equal number of estimated parameters are compared, goodness of fit can be estimated solely from the sum of squared residuals. When two or more models with different numbers of estimated parameters are compared, a comparison of the sums of squared residuals is not appropriate, since the addition of parameters to a model always lowers the sum of squared residuals. Therefore the improvement in fit obtained by adding parameters to any given model should not be evaluated from the uncorrected sum of squared residuals: the sums of squared residuals should be corrected for the

difference in the number of parameters. The Akaike criterion (AIC) [37] and the *F*-test [38, 39] are available for this purpose.

AIC is calculated as

$$AIC = (N \times \ln(SSQ)) + 2P,$$

where N is the number of points in the CD *vs.* t plot (N = 13); ln is the natural logarithm; P is the number of estimated parameters. For models 1B and 5B, P = 2; for models 1A, 5A, 2B, 3B and 4B, P = 3; for models 2A, 3A, 4A and 6B, P = 4, and for model 6A, P = 5.

For each patient models 1 through 6 were given ranks from 1 (lowest AIC) to 6 (highest AIC). For presentation in tables only, the median rank was calculated for each model.

The *F*-test is an alternative method for comparing goodness of fit in two competing models with unequal numbers of estimated parameters.

$$Q_{j,k} = \frac{(SSQ_j - SSQ_k) \times (N - p_k)}{(p_k - p_j) \times SSQ_k},$$

where p_j is the number of parameters in model j; p_k is the number of parameters in model k ($p_k > p_j$); SSQ_j is the sum of squared residuals in model j; SSQ_k is the sum of squared residuals in model k, and N is the number of data points.

The statistic $Q_{j,k}$ is *F*-distributed with ($p_k - p_j$, $N - p_k$) degrees of freedom. Model k is adopted if $Q_{j,k}$ exceeds the *F*-value, otherwise model j is preferred.

Statistical analysis

Since the parameter estimates are skewed, the results are presented as medians (95% confidence interval). Differences in goodness of fit (AIC and *F*-test) between two models were analysed using the sign test. Residual errors were tested for randomness by the runs test. Differences of location of paired observations and sample data were compared with Wilcoxon's distribution-free signed rank test. The level of significance was 0.05.

RESULTS

Model validation

Theoretical identifiability. The global models (models 6A and 6B) are linear equations in five and four unknowns, respectively. All parameters ($M_{t=0}$, MTAC, fct, SiCo and QL) are theoretically identifiable if the dialysate volume–time profile and five or more (model 6A) or four or more (model 6B) experimental points (time, dialysate urea concentrations) are provided. All models (1A–6A and 1B–6B) are therefore theoretically identifiable.

The 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 models 3A, 3B, 6A and 6B were randomly distributed, whereas the residual errors of the other models were non-random (Tables I and II). Models 1A, 1B, 2A, 2B, 4A, 4B, 5A, 5B were rejected and excluded from the goodness-of-fit analysis.

Parameter plausibility. Model 2B was rejected on the basis of the unphysiologically high median QL (Table II).

Goodness of fit. Models 3A, 6A, 3B and 6B were analysed for goodness of fit with the Akaike information criterion (Tables I and II) and with the *F*-test.

When models 3A and 6A were compared with the Akaike information criterion, model 3A was preferred for all patients ($p < 0.001$, sign test). When models 3A and 6A were compared with the *F*-test, model 3A was preferred for all patients ($p < 0.001$, sign test), and model 6A was rejected.

When models 3B and 6B were compared, using the Akaike information criterion, model 3B was preferred for four patients and model 6B for 19 patients ($p = 0.0026$, sign test). When models 3B and 6B were compared using the *F*-test, model 3B was preferred for 11 patients and model 6B for 12 patients ($p = 1$, sign test).

When models 3A and 6B were compared using the Akaike information criterion, model 3A was preferred for 11 patients and model 6B for 12 patients ($p = 1$, sign test). It was not possible to compare models 3A and 6B with the *F*-test, since both models are special cases of model 6A, but neither model is a special case of its competitor.

In summary, models 3A and 6B were superior to the remaining 10 models, but our data do not allow further conclusions concerning model evaluation.

TABLE I. Median (95% confidence interval) of the transport parameter estimates (constants in boldface), and median ranks (95% confidence interval) of the Akaike information criterion (AIC), of models 1A–6A. (See Appendix for explanation of abbreviations.)

Model	MTAC, ml min^{-1}	SiCo	QL, ml min^{-1}	AIC	fct	R
1A	35.1 (28.7–40.8)	**0**	**SR**	5 (5–5)	0.93 (0.92–0.97)	3
2A	25.7 (19.9–29.4)	**1**	1.9 (0.0–6.9)	4 (3–4)	0.96 (0.95–0.98)	4
3A	21.7 (16.1–29.9)	1.39 (0.76–2.04)	**SR**	1 (1–2)	0.98 (0.94–1.01)	7
4A	34.9 (28.0–40.4)	**0**	1.0 (0.7–1.1)	6 (6–6)	0.94 (0.92–0.97)	3
5A	29.1 (21.7–33.6)	**1**	**SR**	3 (2–3)	0.96 (0.95–0.98)	4
6A	19.3 (15.9–27.2)	1.39 (0.84–2.09)	0.7 (0.4–0.9)	2 (2–4)	0.99 (0.95–1.03)	7

Parameter estimates and the validity of the one-compartment assumption

The peripheral vein plasma water urea concentrations measured at 0, 120, 240 and 360 min demonstrated a statistically significant difference in location (Friedmann's test, corrected for ties, N=23, K=4, p=0.0002) (Fig. 1).

The median MTAC values in models 3A and 6B were significantly different (two-tailed Wilcoxon's signed rank test for pairs, N=23, p<0.00005).

The median ultrafiltration sieving coefficients in models 3A and 6B were not significantly different (two-tailed Wilcoxon's signed rank test for pairs, N=23, p=0.31) and not significantly different from unity (two-tailed Wilcoxon's signed rank test, N=23, p=0.12 (3A) and p=0.34 (6B)). The 95% confidence intervals are relatively wide, reflecting the difficulty in estimating this parameter in the face of low ultrafiltration rates (Figs. 2 and 3).

The median lymphatic flow rate in model 6B was not significantly different from the dialysate sampling rate (two-tailed Wilcoxon's signed rank test, N=23, p=0.19) but was significantly different from zero (two-tailed Wilcoxon's signed rank test, N=23, p=0.035).

The median fct in model 3A was not significantly different from unity (two-tailed Wilcoxon's signed rank test, N=23, p=0.34), i.e., no difference between peritoneal capillary plasma water urea concentration and peripheral

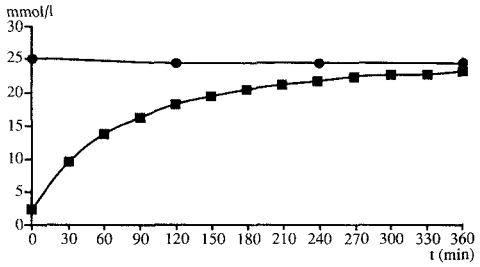

FIG. 1. The mean dialysate (CD) and mean plasma water (Cpw) urea concentrations in 23 patients during a 6-h dwell. ■ = CD, ● = Cpw.

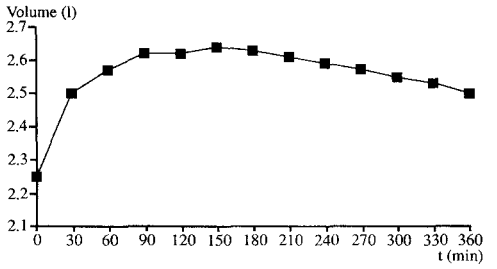

FIG. 2. The mean intraperitoneal dialysate volume in 23 patients during a 6-h dwell. The volume was calculated with autologous haemoglobin as a volume marker.

TABLE II. Median (95% confidence interval) of the transport parameter estimates (constants in boldface), and median ranks (95% confidence interval) of the Akaike information criterion (AIC), of models 1B–6B.

Model	MTAC, ml min^{-1}	SiCo	QL, ml min^{-1}	AIC	R
1B	30.8 (24.8–33.7)	**0**	**SR**	6 (6–6)	4
2B	0.86 (0.65–3.45)	**1**	17.0 (9.2–24.7)	3 (3–4)	2
3B	21.9 (16.7–28.0)	1.33 (0.93–1.98)	**SR**	2 (2–3)	5
4B	33.2 (28.0–38.1)	**0**	3.3 (1.7–3.8)	4 (4–5)	3
5B	26.2 (20.1–29.1)	**1**	**SR**	4 (3–5)	2
6B	16.7 (11.1–27.2)	1.02 (0.84–1.78)	1.5 (0.3–3.5)	1 (1–2)	7

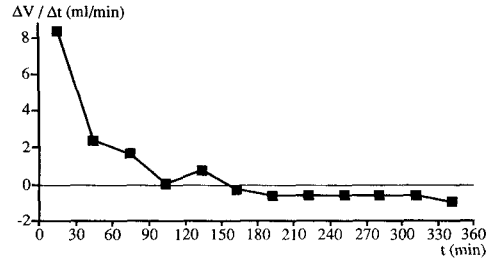

FIG. 3. The mean volume change rate, $\Delta V/\Delta t$, *vs.* time, calculated from the volume data in Figure 2 (n = 23).

vein plasma water urea concentration was demonstrated.

DISCUSSION

The estimates of the diffusive mass transfer area coefficient for urea (models 3A and 6B) were considerably smaller than results reported by others [12, 15, 40–45]. Probably, the reason for this is the use of plasma water urea concentrations instead of plasma urea concentrations in parameter calculations. As demonstrated by Waniewski *et al.* the plasma concentrations of small uncharged solutes should be adjusted for plasma proteins [46]. The average MTAC of Waniewski *et al.* [46] is identical to the median MTAC of model 6B.

Interestingly, the inclusion of a lymphatic convective transport mechanism changed the MTAC considerably but did not improve goodness of fit (compare models 3A and 6B). Thus in models 3A the estimated diffusive mass transfer area coefficient for urea was considerably larger than the estimate in model 6B (21.7 *vs.* 16.7 ml min^{-1}).

The ultrafiltration sieving coefficient depends on the properties of both membrane and solute. The relative size of the solute molecule, the charge of the solute and the charge of the membrane, steric hindrance and solubility in the membrane may influence the ultrafiltration sieving coefficient. The ultrafiltration sieving coefficient can never become negative, and should not exceed unity in the case of an uncharged molecule.

The model validation procedure clearly demonstrated the existence of non-lymphatic convective urea transport and the median of the parameter estimates is physiologically plausible. The median ultrafiltration sieving coefficients in models 3A and 6B are considerably larger than results reported by others [3, 11, 41, 45], but in good agreement with results reported by those who have used plasma water urea concentrations [46].

Also, the existence of lymphatic convective urea transport was confirmed, and the net direction and magnitude of the lymphatic flow rate is in good agreement with the results of others who have estimated the lymphatic flow rate from the disappearance rate of intraperitoneal colloids [47].

We therefore conclude that transperitoneal transport of urea probably involves three mechanisms: diffusion, non-lymphatic convection and lymphatic convection.

In transperitoneal kinetic modelling it is generally assumed that no concentration gradient exists between peritoneal capillary and peripheral vein plasma and therefore calculations can be based on the concentration difference between dialysate and peripheral vein plasma. To investigate the validity of this one-compartment assumption, the peritoneal capillary plasma water urea concentration (models 1A–6A) was expressed as fct × Cpw. If the one-compartment assumption were valid, the calculated estimate of fct would be expected to be 1. In model 3A, median fct was 0.98. This finding corroborates the one-compartment assumption for urea, i.e. the plasma water urea concentration at the blood sampling site (a peripheral vein) is equal to the peritoneal capillary plasma water urea concentration.

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APPENDIX: ABBREVIATIONS

AIC	Akaike information criterion.
CAPD	Continuous ambulatory peritoneal dialysis.
CCPD	Continuous cycling peritoneal dialysis.

CD	Dialysate urea concentration (mmol l^{-1}).
CL	If $QL \geqslant 0$ then $CL = CD$, otherwise $CL = fct \times Cpw$ (models 1A–6A) or $CL = Cpw$ (models 1B–6B).
Cpw	Peripheral vein plasma water urea concentration (mmol l^{-1}), (time-dependent); $Cpw = U \times$ plasma urea concentration; $U = 1/(0.984 - [0.000718 \times C_{prot}])$; C_{prot} = plasma total protein concentration (g l^{-1}).
dM/dt	Net transperitoneal urea mass transport rate (mmol min^{-1}).
dVol/dt	Rate of peritoneal net volume change.
exp(x)	The base of the natural logarithm raised to the power of x.
fct	The fitted time-independent phenomenological factor.
ln(x)	The natural logarithm of x.
M	Intraperitoneal urea mass (mmol).
MC	Average intramembrane urea concentration (mmol l^{-1}).
MTAC	Diffusive urea mass transfer area coefficient (l min^{-1}).
QL	Defined by the equation $dVol/dt = QU - QL$ (l min^{-1}). The following sign convention was adopted: $QL \geqslant 0$ if the direction of flow was from the peritoneal cavity into the plasma, otherwise $QL < 0$.
QU	The ultrafiltration rate (l min^{-1}). The following sign convention was adopted: $QU \geqslant 0$ if the direction of ultrafiltration was from plasma into the peritoneal cavity, otherwise $QU < 0$.
R	Number of runs (analysis of residual errors, runs test).
RE	Residual errors.
SiCo	Ultrafiltration sieving coefficient.
SR	Sampling rate = 0.00065 l min^{-1} (233 ml 360 min^{-1}).
SSQ	Sum of squared residuals.
Vol	Peritoneal volume.

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