Improved clearance of iohexol with longer haemodialysis despite similar $Kt/V$ for urea

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Abstract

Background. The efforts to improve the quality of haemodialysis (HD) has renewed the interest in the consequences of blood-flow distribution for removal of solutes.

Methods. To test the effects of HD time per se, 10 patients were studied in a cross-over fashion with HD for 3 h and 1 week later for 6 h, with similar blood urea $Kt/V$, achieved by adjusting the blood flow rate to 290 and 120 ml/min respectively. Injections of iohexol (MW 821 Dalton) were given 2 days prior to the dialysis sessions. Blood samples were taken before, during (6 h), 1 and 24 h after the HD and analysed for concentrations of urea and iohexol. A urea on-line monitor (Gambro) was used for continuous recordings and sampling of dialysate.

Results. According to the study design the blood $Kt/V$ for urea (Daugirdas II) was similar for 3 and 6 h HD, close to 1.0 (n.s), while the removed mass of urea showed that $Kt/V$ was slightly and significantly higher for the 6 h HD. The ‘apparent’ mass of iohexol, defined as plasma concentration times estimated distribution volume, fell to 29% and 21% of pre-dialysis levels after 3 h and 6 h HD, respectively ($P<0.01$), but increased after HD, and more so after the short dialysis, reaching 46% of the predialysis mass 24 h after 3 h HD vs 36% after 6 h HD ($P<0.05$). The removed mass of iohexol was 920 ± 110 mg with 6 h HD and 700 ± 81 mg with 3 h HD, ($P<0.01$). Thus, the longer dialysis removed 32% more iohexol despite similar blood $Kt/V$ for urea.

Conclusion. The treatment time per se affects solute removal despite similar blood $Kt/V$ for urea. This is particularly true for an intermediate-size molecule like iohexol.

Key words: adequacy; distribution; haemodialysis; iohexol; time; urea kinetics

Introduction

All dialytic therapies have the same objective: to give adequate renal replacement therapy (RRT). The averaged clearance obtained with haemodialysis (HD) is, however, still much less than the normal renal function. For larger solutes, the dialysis clearance represents an even smaller fraction of the normal values since the clearance of the dialyser decreases dramatically with increasing molecular weight. Accordingly, some of the basic questions that remain to be answered are: What is adequate therapy? How should it be performed? A contributing fact is also that the substances or toxins causing the uraemic state not yet have been clearly identified [1]. The urea blood concentration indicates the degree of uraemic toxicity but it is also dependent on protein intake. Therefore a low blood urea value may equally well reflect malnutrition as efficient dialysis. Moreover, molecules in the larger size range have been identified as possible uraemic toxins and the removal of intermediate sized molecules in addition to small solutes has been suggested to be important for the clinical effects of dialytic treatment [2].

Urea kinetics was introduced in the early 1980s and it has remained one of the major laboratory parameters upon which adequacy of dialysis is evaluated. For quantitation of HD the term $Kt/V$ for urea ($K=\text{total urea clearance}, t=\text{treatment time and } V=\text{total body water}; \text{which is the volume of distribution for urea}$) has been found to be a useful measure. The original $Kt/V$ calculations are based on the assumption that the human body is a well-mixed single-compartment model. However, the human body is not. Since the body fluid is distributed in several different compartments with variable blood flows, multi-compartment models that were actually developed for dialysis decades ago have lately been reintroduced. These models seem to be more accurate for describing the effects of dialysis including the post-dialytic urea rebound phenomenon [3–6]. Hence, the blood flow distribution models imply that the treatment time per se is important and that $Kt/V$ must be further increased to assure adequate dialysis if time is reduced [4].
The aim of this study was to evaluate the effects of treatment time on removal of small and intermediate size solutes during a single dialysis session as well as in the 24-h post-dialytic period.

Subjects and methods

Subjects

Ten patients, five women and five men (age 61 ± 6 years, body weight 68 ± 4 kg) with end-stage renal disease and maintenance HD three times a week participated in the study. It was approved by the ethical committee of the University of Göteborg. All patients were recruited from the Sahlgrenska University Hospital and they gave their written informed consent before entering the study. Only patients who were regarded to be in a stable clinical condition, with respect to their underlying renal disease, standard laboratory variables and blood pressure were selected for the study. Three patients had no residual renal function (RRF) whereas the RRF of the other seven patients ranged between 0.1 and 1.4 ml/min/1.73 m², which was corrected for in the subsequent calculations by assuming free filtration of iohexol.

Methods

Experimental protocol

The study period was 2 weeks. The ordinary dialysis schedule was followed with the exception of the midweek dialysis session. The first week the midweek dialysis had a 3-h duration and the following week 6 h. During the short (3-h) dialysis treatment session the blood flow was kept as high as possible in this patient group (250–300 ml/min). Based on the calculated urea $K_t/V$ value (Daugirdas II [5]) obtained from this session, the blood flow was adjusted to reach a similar urea $K_t/V$ for the 6-h treatment (approximately 100 ml/min).

Blood samples for analyses of urea and iohexol were repeatedly collected, immediately before the start of dialysis, during the treatment, and in the first post-dialytic hour. All together 10 samples were collected from each session. Moreover, the plasma concentrations of urea and iohexol were determined after 24 h. All samples were collected by venepuncture in the contralateral arm to the vascular access in order to avoid influences of recirculation.

Urea measurements

An on-line urea monitor for repetitive measurements of dialysate urea concentrations was used during the study sessions (Urea monitor, Gambro, Sweden). This device was connected to the HD machine, but had no contact with the blood of the patient. It recorded the urea concentration in the dialysate outflow as well as enabling representative sampling of dialysate. The urea monitor allows for determinations of the removed amount of urea with high precision and based on these values $K_t/V$ (according to Daugirdas II) and urea removal rate (URR) are continuously calculated and presented on a screen during the dialysis.

In parallel with measurements by the urea monitor, urea concentrations in plasma were analysed by an enzymatic colorimetric test using double samples. This was done at the department of Clinical Chemistry at this hospital.

Iohexol measurements

Iohexol is a non-ionic, low-osmolar, X-ray contrast medium with a molecular weight of 821 Daltons and it is mainly eliminated from plasma in its intact form by glomerular filtration (extrarenal clearance $\approx 2$ ml/min) and it is often stated to be effectively removed by HD [7,8]. Iohexol (300 mg/ml, 10 ml, Omnipaque®, Nycomed) was administered approximately 44 h before each study session. During this time it is effectively equilibrated in the extracellular fluid volume (ECV) and can serve as a marker of this compartment [7]. Iohexol concentrations in plasma, dialysate and urine were determined by high-performance liquid chromatography (HPLC). The intra-assay coefficient of variance was 5.12%.

The iohexol analysis performed by HPLC technique is advantageous, since it requires only small volumes of plasma.

Calculations

$K_t/V$ values were calculated in the following ways:

(i) $K_t/V$ for urea in blood was calculated according to the Daugirdas II formula [5], (eq. 1)

$$K_t/V = -LN\left(\frac{C_t}{C_0} - 0.008t + \left(4 - 3.5 \frac{C_t}{C_0}\right)Uf/t/W\right)$$

where $K$ is clearance (ml/min), $t$ is treatment time (min), $V$ denotes the volume of distribution (1), $C$ the concentration of solute (mg/ml) at time $t$ and at start 0, $Uf$ the ultrafiltration (ml/min) and $W$ the body weight (kg).

The $K_t/V$ values for urea provided by the urea on-line monitor are based on the same expression (eq. 1).

(ii) For determinations of blood $K_t/V$ of iohexol a slightly modified version of the Daugirdas II formula was applied, where the generation term was omitted:

$$K_t/V = -LN\left(\frac{C_t}{C_0} + \left(4 - 3.5 \frac{C_t}{C_0}\right)Uf/t/W\right)$$

(iii) Estimates of $K_t/V$ can also be based on the removed mass, where $K$ is obtained from:

$$K = \frac{m}{\int_0^T C_p(t)dt}$$

Moreover, $V$ equals total body water for urea and creatinine and the extracellular volume for iohexol. The formulas of Watson et al. [9] were applied for determinations of $V$ and the extracellular fluid volume was assumed to constitute one-third of $V$. The predialysis oedema removed by ultrafiltration was assumed to be distributed mainly in the extracellular compartment.

Dialysate volume and removed mass. The total volume of
dialysate ($V_i$) used during each HD session was provided by the product of dialysate flow rate recorded by the urea monitor (500 ml/min ± 1%) and time. A precise sampling of dialysate was done giving average concentrations of urea and iohexol and the removed mass was subsequently obtained by multiplying with $V_i$.

The ‘apparent’ mass. This is calculated as the plasma concentration times the volume of distribution and equals the ‘true’ mass of the extracellular solute at steady state when the interstitial concentration ($C_i$) equals that of plasma ($C_p$). The ‘apparent’ mass will more or less underestimate the ‘true’ mass if $C_p < C_i$, i.e. immediately after a dialysis session. Prior to dialysis and 24 h after HD, the distribution of iohexol should be close to equilibrium, i.e. $C_p \approx C_i$. Moreover, mass balance analysis is simplified for iohexol since there is no generation in the body. Thus, the iohexol mass prior to dialysis equals the sum of that removed by HD ($m_{HD}$), the amount remaining at 24 h and the iohexol excreted in the urine:

$$C_p(0) \cdot V_{i,0} = C_p(24) \cdot V_{i,24} + RRF \cdot \hat{C} + m_{HD}$$  \hspace{1cm} (4)

Where $C_p$ denotes the plasma concentration at time $t$ or the average plasma concentration, $V_{i,t}$ denotes the extracellular volume at time $t$, $RRF$ denotes the residual renal function and $m_{HD}$ is the mass removed by dialysis. Possible extrarenal elimination was not included in this equation.

### Statistical methods

Results are presented as means ± SE. Statistical significance of differences was tested with Student’s two-tailed $t$-test for paired data. Differences with a $P$ value <0.05 were considered as statistically significant.

### Results

The first 3-h HD session was performed with an average blood flow of 293 ± 5.3 ml/min and the second 6-h HD with an average blood flow of 118 ± 2.0 ml/min. No adverse events occurred during or between the HD sessions.

#### Effects of treatment time on clearance and removed mass of urea and iohexol

**Urea**

The blood urea $K_t/V$ (Daugirdas II formula) was similar for the 3- and the 6-h HD, reaching 0.87 ± 0.06 and 0.92 ± 0.07 respectively (n.s.). The corresponding $K_t/V$ values achieved by the on-line urea-monitor were higher 1.10 ± 0.08 for 3-h HD and 1.28 ± 0.14 for 6-h HD, ($P<0.05$, Table 1). Also the $K_t/V$ based on calculations of removed mass were slightly higher compared to the blood $K_t/V$ urea values, and differed significantly between the two treatment times: 0.95 ± 0.04 for the short and 1.03 ± 0.04 for the longer HD ($P<0.05$). The removed mass of urea based on dialysate concentration analyses were more variable and the differences did not reach statistical significance, see Table 1 and Figure 1a.

**Iohexol**

$K_t/V$ for iohexol based on the analysis of blood samples was significantly lower for the 3-h HD, 1.18 ± 0.10, compared to 1.51 ± 0.15, for the 6-h HD ($P<0.05$). Also the removed mass of iohexol calculated using...
mass balance differed significantly between the two treatment regimens, reaching 700 ± 81 mg and 120 ± 110 mg for the 3- and 6-h HD respectively (P < 0.01, Table 1, Figure 1b).

**Post-dialytic concentrations of iohexol and urea**

The blood concentration of iohexol increased after HD without any generation or additional injections (Table 2). Thus, the ‘apparent’ mass of iohexol came down to 29 ± 2.2% and 21 ± 3.0% of predialysis values after 3- and 6-h HD respectively (P < 0.05). After 24 h the iohexol level was 46 ± 4.0% for the 3-h HD and 36 ± 3.5% for 6-h HD compared to predialytic levels (P < 0.05, Figure 2).

There was no significant difference in post-dialytic concentrations of urea between 3- and 6-h HD, either immediately after the dialysis or during the subsequent 24 h (Table 2).

**Discussion**

The results of the present study demonstrate that the duration of the HD session per se affects the removal of solutes. Hence, the Ki/V-values based on the removed mass of urea and iohexol were significantly increased after long dialysis sessions despite similar blood Ki/V values for urea. This effect was most pronounced for the intermediate-size molecule iohexol, which emphasizes the imbalances between body compartments during dialysis. Attempts to correct for the effects of treatment time using equilibrated (e)Ki/V [10] did indeed reveal a significant difference, eKi/V being 0.92 ± 0.07 and 1.20 ± 0.12 for 3 h and 6 h of HD respectively (P < 0.01). A similar pattern was observed with the Ki/V data obtained using equation 3, see Results.

The post-dialytic increase of the ‘apparent’ mass of iohexol was significantly higher after the shorter dialysis session, while no such effects were observed for urea. Moreover, the rebound is far greater for iohexol than generally appreciated from urea kinetics. Since there is no endogenous generation of iohexol, the continuous increase of the post-dialytic plasma iohexol concentration is interpreted as a rebound effect attributable to variations in blood flow distribution between body compartments.

The initial protocol of this study included determinations of Ki/V for urea and iohexol based on blood samples and analyses of removed mass of solutes in the dialysate. However, the low concentrations of iohexol in the dialysate were influenced by background activity. The interpretation of the dialysate concentrations therefore became somewhat ambiguous and the data presented in Table 1 were obtained from mass balance analysis from the plasma concentrations of iohexol, see Methods eq. 4. Thus, the patient was considered to be in steady state with respect to iohexol before dialysis and 24 h after dialysis. Since there is no generation of iohexol, the total amount of the substance in the body can easily be estimated. The iohexol mass removed by dialysis and the residual renal function (if any) equals the difference of the two estimates of body iohexol, see eq.4. Significantly more iohexol was removed by the longer dialysis, +32% see Figure 1b and Table 1. The obtained results were qualitatively similar to those obtained by analysis of the dialysate but those measurements had a higher variability. This was also the case for urea where the removed mass determined from the dialysate urea monitor showed considerable variation and did not reach statistical significance see Table 1. In contrast, the Ki/V values for urea determined by the urea monitor were significantly higher for the longer dialysis, see Results.

The Ki/V values obtained from calculations of removed mass of urea as well as by the on-line urea monitor were higher than the corresponding blood Ki/Vs. This could be explained by consequences of compartment disequilibrium induced by the dialysis. In order to avoid influence of recirculation the opposite arm to the vascular access site was used for venepuncture and for collection of blood samples. However, this precaution was probably counteracted by the fact that this opposite arm instead can behave as a compartment with high resistance to urea diffusion [11]. This may result in a delayed fall in venous blood urea concentration and consequently in underestimated
blood urea $Kt/V$'s. The conclusions drawn from the results of the present study are, however, not influenced by this effect.

To compensate for the reduced dialysis treatment times with increased blood flows may accentuate the impact of the uneven blood flow distribution. Thus, for a given $Kt/V$, a decreased dialysis duration implies an increased ultrafiltration rate resulting in a relative hypovolaemia in the cardiopulmonary region. As a consequence, volume- and baroreceptors may be activated and increase the sympathetic vasoconstrictor activity, mainly to the skeletal muscles. The total peripheral resistance will subsequently increase and urea removal from that compartment may be reduced in parallel to the altered blood flow distribution [12].

The design of the study implies that each patient serves as its own control, participating in two HD sessions for 3- and 6-h duration respectively. $Kt/V$ for urea was calculated for the 3-h HD, with blood flows kept as high as the vascular access allowed. The flow of the subsequent 6-h HD was adjusted with the purpose to reach a similar $Kt/V$ value. In this patient population it was, however, not possible to reach higher blood flows than 250–300 ml/min. The magnitude of urea rebound shortly after dialysis has previously been correlated to the efficiency of the dialysis expressed as urea removal [13] or urea $Kt/V$ [6] where the dialysis dose was altered by varying the blood flow. If anything, the effects of treatment time per se reported in the present investigation would be even more pronounced with higher blood flows.

A complementary approach to kinetic analyses is to determine the clearance of exogenous markers like iohexol. Such intermediate-size molecules should exclusively be extracellularly distributed and thereby serve as a marker of the extracellular compartment [7]. Other factors that influence the kinetic estimates are minimized, since there is no endogenous production [7]. Other factors that influence the kinetic estimates are minimized, since there is no endogenous production of this substance. The elimination of iohexol during the dialysis sessions in the present study is of the same order of magnitude as previously reported [8]. The post-dialytic increase of plasma iohexol concentration that was found for as long a time-period as 24 h does, however, not seem to have been studied before. This indicates that the post-dialytic rebound is a more prolonged process than the generally appreciated 1–2 h [6]. Alternative explanations to the post-dialytic increase of the iohexol concentration could include an overcompensation of the extrarenal component in the calculations of iohexol clearance. However, recalculation of data without compensation for the extrarenal clearance did not significantly influence the results. Furthermore, more iohexol was removed with the longer treatment time, while the rebound of urea was similar for the two HD treatments and in agreement with previous data [6]. This is probably because of the small molecular size of urea in combination with the relatively low blood flows used.

The concept of a relationship between the dose of dialysis and mortality has gradually gained general acceptance [14-16]. However, it is still not clear what the most adequate or rather sufficient dialytic treatment is for a patient with ESRD. Since its introduction the $Kt/V$ concept based on urea kinetic modelling has remained a key variable for the assessment of the dose of dialysis [17]. Nevertheless, the $Kt/V$ must be interpreted with caution, since the estimated $Kt/V$ tends to overestimate the delivered dialysis dose. The various models that compensate for uneven flow-distributions to different organs provide better reflections of urea removal and rebound after HD than the single-compartment model [18,19]. The results of the present study further stress that a reduced duration of the HD session must be compensated for by a relatively higher $Kt/V$ in order to reach the same delivered dose of dialysis in terms of solute removal [4]. Moreover, this effect of time seems to be pronounced for intermediate-size molecules. It is plausible that it therefore should be significant for the uraemic toxins in this size range.

An alternative way to quantify dialytic therapy is to measure the actual removed mass of solutes. This is now possible by the urea monitoring sensors. For clinical practice, urea monitoring is simple, practical and reliable. The urea monitor used in the present study represents a ‘second generation' with very high precision [20]. The device is connected to the dialysate outflow of the HD machine, which facilitates repetitive analyses of the removed mass of urea without interference with the patient. These recordings make it possible to present ‘on-line' $Kt/V$ values. In addition, the present urea monitor allows for representative dialysate sampling which makes it possible to determine the content of other solutes than urea, for instance of iohexol.

In summary, the results of this study suggest that longer dialysis treatment times may provide beneficial effects since intermediate sized solutes are more effectively removed despite the same blood $Kt/V$ for urea.

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References
6. Pedrini LA, Zereik S, Rasmy S. Causes, kinetics and clinical

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