

Original Article

Dialysis dose (Kt/V) and clearance variation sensitivity using measurement of ultraviolet-absorbance (on-line), blood urea, dialysate urea and ionic dialysance

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Abstract

Background. An on-line monitoring system for dialysis dose calculations could make it possible to provide an adequate dialysis dose that is consistently given to haemodialysis (HD) patients. The aim of this study was to compare dialysis dose (Kt/V) using four different methods and their sensitiveness to a reduction in clearance.

Methods. Six patients were monitored on-line with ultraviolet (UV)-absorbance at a wavelength of 297 nm in three consecutive dialysis sessions during 1 week. During the last treatment, the clearance was reduced by ~25% by decreasing the blood flow. For the determination of UV-absorbance, a spectrophotometer was connected to the fluid outlet of the dialysis machine with all spent dialysate passing through a flow cuvette. The equilibrated Kt/V (eKt/V) estimated by UV-absorbance was compared with eKt/V from the ionic dialysance method using the on-line clearance monitor (OCM) and the appurtenant software dose-calculation tool DCTool (Fresenius Medical Care, Germany), eKt/V calculated from the dialysate-urea slope and with eKt/V from pre- and post-dialysis blood-urea samples as reference.

Results. The study demonstrates that the sensitiveness to clearance reduction is similar in the four methods compared for eKt/V. When the different methods were compared, the mean eKt/V of UV-absorbance was 1.21 ± 0.20 , blood 1.30 ± 0.21 , dialysate 1.32 ± 0.21 and OCM (using the DCTool) 1.31 ± 0.21 . The standard deviation was of the same magnitude.

Conclusion. The UV-method gives a similar response to clearance reduction compared with the other methods when comparing dialysis dose. The high sampling

rate by continuous monitoring of UV-absorbance allows evaluation of the clearance process during dialysis and gives immediate feedback to on-line adjustments.

Keywords: clearance; haemodialysis monitoring; ionic dialysance; Kt/V; ultra violet absorption; urea

Introduction

It has been recommended, by NKF-DOQI guidelines [1], that at least a monthly control of dialysis dose should be performed using blood samples. Inpatient variations occur in dialysis adequacy [2]. Evaluation of every haemodialysis (HD) treatment by an on-line monitoring system makes it possible to provide an adequate dialysis dose consistently given to the HD patients [3].

On-line urea monitors based on direct measurement of urea loss, e.g. an ammonium ion sensor [4], offering dialysis parameters such as dialysis dose (Kt/V), TRU (total removed urea), and PCR (protein catabolic rate) have not found wide utilization in clinical practice. Possible reasons could be high initial and running costs, need for disposals and extra work for the staff.

Kt/V determined from the ionic dialysance method is a tool easily integrated into the dialysis machine at a relatively low cost. This method is based on the assumption that sodium clearance is equal to urea clearance, K, which can be calculated from the conductivity difference between dialysate inlet and outlet of the dialyser after inducing changes in conductivity [5].

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Table 1. Data of the study patients

Patient no.	Time in HD (months)	Kidney disease	Residual renal function, creatinine clearance (ml/min/1.73)	Qb/Qb-reduced (last-in-week session)	Dialyser	Age (years)	Gender
1	15	Kidney cancer	0	310/210	Polyflux 17L	68	Female
2	25	UNS	0	325/200	Nephral 300	49	Male
3	50	Polycystic	3	325/205	Polyflux 17L	69	Female
4	50	Diab nephropathy	6	330/220	Tricea 150G	76	Female
5	41	Reflux nephropathy	0	300/200	Polyflux 17L	33	Male
6	20	Polycystic	8	325/220	Polyflux 17L	70	Male

Residual renal function was measured several months prior to the study period.

Quite recently, optical-based monitoring of urea concentration during dialysis using a Fourier-transform infrared spectrometer (FTIR) has been clinically tested [6].

Our group has earlier demonstrated the possibility of estimating Kt/V [7], TRU and PCR [8] by ultraviolet (UV) light-absorbance measurement on the spent dialysate using a spectrophotometer with a specially designed flow cuvette for on-line single-wavelength measurements [9]. Good correlation between UV-absorbance and concentrations of several small removed waste solutes, such as urea, creatinine and uric acid has been found [9]. Urea itself is not detected by UV-absorbance measurement, instead a total absorbance is measured, reflecting the overall retention of accumulated UV-absorbing solutes. The mean UV-absorbance contribution from every compound in the spent dialysate varies at different wavelengths [10]. The wavelengths of 280–320 nm have been found to be suitable for on-line dialysis monitoring of small solutes like urea [10]. In the present study, the wavelength of 297 nm was chosen due to practical reasons: available UV-lamps.

The aim of this study was to compare Kt/V and sensitiveness to clearance variation using the slope of the on-line UV-absorbance measurements, the ionic dialysance method, the slope of dialysate urea and finally, pre- and post-dialysis blood-urea concentration (reference).

Materials and methods

Subjects

Six patients, three females and three males, mean age 61 ± 16 years, on chronic thrice-weekly haemodialysis at the Department of Nephrology, University Hospital of Linköping, Sweden, were included in the study.

Each patient was monitored during three dialysis treatments each for a duration of 240–270 min ($n = 18$). The treatments were serially consecutive, from the first session of the week. During the last treatment of the week for each patient, the clearance was reduced by ~25% by decreasing the blood flow. Four patients, i.e. 12 treatments, were dialysed by a low-flux membrane (Polyflux 17L, Gambro, Sweden) with an ultra-filtration coefficient (UF_{coeff}) of 12.5 ml/h mmHg and

an effective membrane area of 1.7 m² and two patients, i.e. six treatments, with high-flux membranes (Nephral 300, HOSPAL Industrie, Meyzieu, France and Tricea 150, Baxter Healthcare Corp., IL, USA) with UF_{coeff} 40 and 29 ml/h mmHg, and effective membrane area 1.30 m² and 1.50 m², respectively. The dialysate flow (Q_d) was 500 ml/min and effective blood flow ($Q_{b,\text{eff}}$) was 300–320 ml/min in the first-in-week and mid-week sessions according to the patient records. During the last-in-week session, the $Q_{b,\text{eff}}$ varied between 200–220 ml/min, corresponding to a clearance reduction of ~25%. All patients were dialysed via arteriovenous fistulas using a two-needle system. Additional data about the study patients are shown in Table 1.

The dialysis machine used in the study of sensitivity was Fresenius 4008H (Fresenius Medical Care, Germany) ($n = 18$). During the clinical examples of alarms and manipulations, a Gambro dialysis machine was used (Gambro Lundia AB, Sweden).

The Ethics Committee approved the study protocol and informed consent was obtained from all patients.

On-line clearance monitor, OCM

The dialysis machine was equipped with an on-line clearance monitor (OCM, Fresenius Medical Care, Germany) for the measurement of single-pool Kt/V ($spKt/V_{\text{OCM}}$) named as 'endKt/V' by the machine. Patient parameters were dry weight, height, age, gender and haematocrit (used for the sodium calculation), and the measurement interval was set to 25 min.

Sampling and laboratory analysis

Blood samples were drawn before the start of the dialysis treatment (C_0) and at the end of dialysis (C_t) using the slow flow/stop pump sampling technique [1].

Dialysate samples were taken from the drain tube at 5, 60, 120 and 180 min, and at the end of the treatment (240 or 270 min). The samples were sent to the laboratory and the analysis of urea concentration was performed within 1–4 h.

The concentration of urea was determined at the Clinical Chemistry Laboratory at Linköping University Hospital using a standardized method. The accuracy of the method for the determination of urea in blood and dialysate was $\pm 5\%$.

UV-absorbance monitoring

The UV-instrumentation has been described earlier [7] (see also Appendix and Figure 1). The wavelength used in this

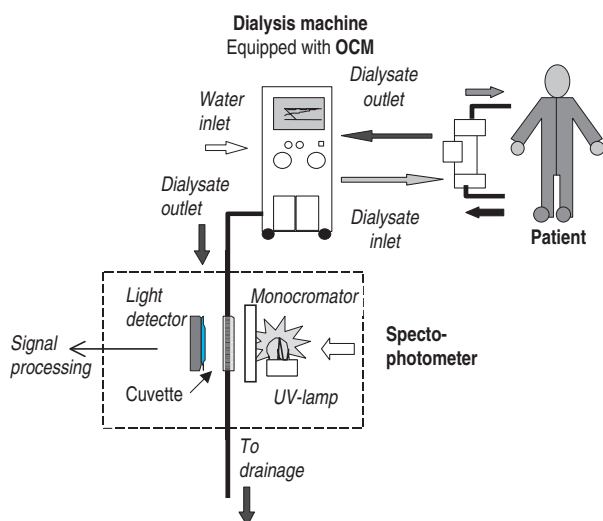


Fig. 1. The clinical experimental set-up.

study was 297 nm ($n=18$), except in the clinical examples where 280 and 285 nm were used. The sampling frequency was set at two samples per minute.

The baseline was measured a few minutes before the start of each dialysis treatment on the flowing pure dialysate (reference solution) when the temperature and conductivity had been stabilized and the sodium and bicarbonate level had been preset according to the patient records.

The obtained UV-absorbance values were processed and presented on a computer screen by a PC incorporated into the spectrophotometer using Kontron software (UVIKON 943, version 7.0 for Windows; Kontron Instruments, Italy). Data were then transformed to an EXCEL file at the end of the treatment.

Estimation of dialysis dose

Dialysis dose from blood (spKt/V_b) was calculated according to the Daugirdas second-generation formula [11] using the pre- and post-dialysis urea concentration (C_0 and C_t), which is equivalent to the slope between C_0 and C_t . For the determination of the dialysis dose from UV-absorbance (spKt/V_a) and dialysate urea (spKt/V_d), the slope was used [7] (see Appendix). For the calculation of equilibrated Kt/V (eKt/V) from blood (eKt/V_b), from dialysate (eKt/V_d) and from UV-absorbance (eKt/V_a), the rate-adjustment equation was used [11].

The software Dose Calculation Tool (DCTool, Fresenius Medical Care, Germany) was used to calculate the urea distribution volume (V) based on readings of spKt/V from OCM and blood samples according to the single-pool variable volume (spVV) calculation. This V was then used when the $\text{eKt/V}_{\text{OCM}}$ was calculated.

All values of eKt/V from the four methods were finally compared.

Statistical analysis

The results were presented as mean \pm SD. A two-way ANOVA analysis, adjusted by Tukeys method, was performed to compare the means of the four methods.

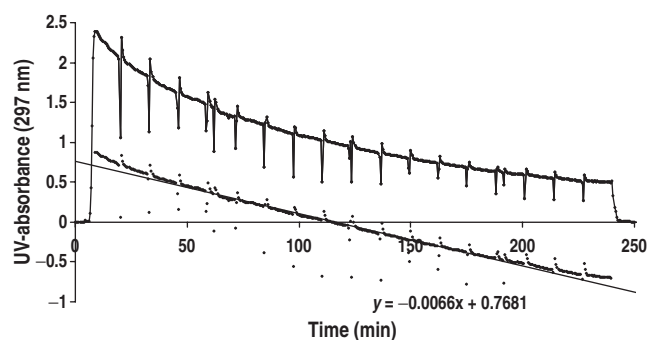


Fig. 2. A typical on-line absorbance curve during a single haemodialysis treatment where UV-absorbance at the wavelength 297 nm is plotted against time. The corresponding natural logarithmic (\ln) fitting line is also shown.

The significance level was set to $P < 0.05$. The statistical analysis was performed in SPSS version 11. In one session, the pre-dialysis blood sample was extrapolated (due to a laboratory measurement error), using intradialytic 60, 120, 180 min and post-dialysis samples.

Results

The upper curve in Figure 2 shows an on-line UV-absorbance at the wavelength of 297 nm during a single haemodialysis treatment where UV-absorbance is plotted against time. UV-absorbance drops and peaks, which normally occurred at predestined intervals during the dialysis, correspond to the self-tests of the dialysis machine. Kt/V was determined as a linear fitting curve of the natural logarithmic slope (\ln) of the UV-absorbance values = S_a , i.e. the unbroken line in Figure 2. In this example $y = -0.0066x + 0.7681$, where S_a corresponds to 0.0066. S_a was then inserted into Equation 3 (see Appendix) to obtain spKt/V_a .

Besides the self-tests, Figure 3A and B present examples of response in UV-absorbance during clinical alarm situations that occurred during the dialysis treatment. Figure 3A shows some lower-limit artery-pressure alarms resulting in blood pump stop for a few seconds. Figure 3B visualizes the result of restricted blood flow in the artery needle. From ~ 50 – 145 min, a decrease in clearance appeared as a decrease in the UV-absorbance curve due to the low artery pressure, below -200 mmHg. The blood flow was preset at a constant flow of 300 ml/min during the whole treatment.

Figure 4A and B shows UV-absorbance during manual manipulations of blood flow and dialysate flow, respectively. Decreased blood flow corresponded to a decrease in UV-absorbance and decrease in dialysate flow corresponded to an increase in UV-absorbance. The increase in UV-absorbance when decreasing the dialysate flow is the result of lower fluid volume in the dialysate inlet which gives a higher concentration of solutes in the dialysate outlet.

Figure 5 presents eKt/V (mean \pm SD) in all 18 treatments. The eKt/V_b was 1.30 ± 0.21 ($n=18$),

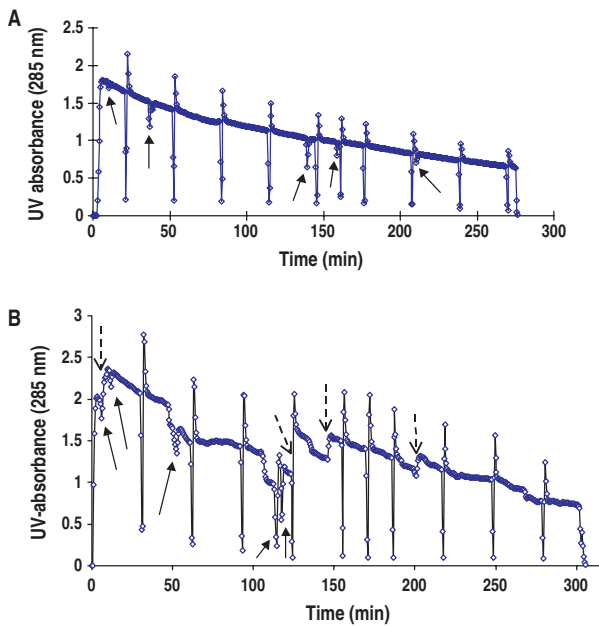


Fig. 3. Two clinical alarm situations are demonstrated. (A) UV-absorbance curve during a dialysis treatment with a few seconds of blood pump stops due to alarms of low artery pressure. (B) A problematic treatment, where the main problem was bad flow in the artery needle. Blood pump stop. Interventions by needle correction.

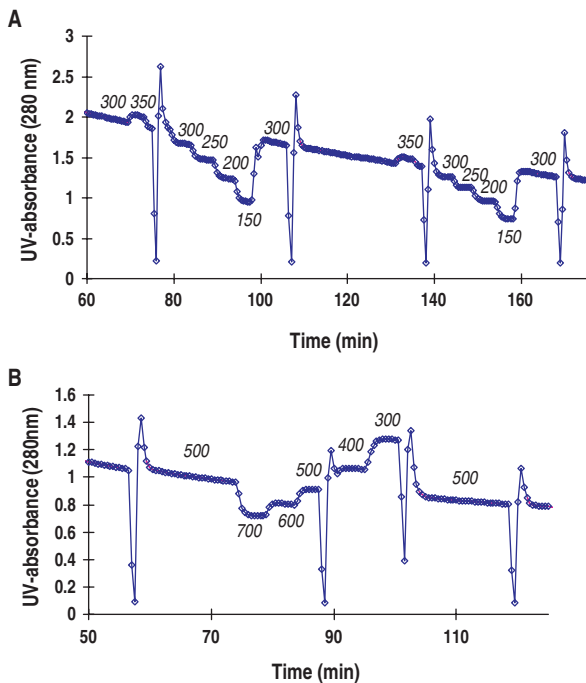


Fig. 4. Response to the manipulations during two dialysis treatments. (A) Changes in Q_b . The blood flow rate in ml/min is presented in the figure. (B) Changes in Q_d . The dialysate flow rate in ml/min is presented in the figure.

eKt/V_d 1.32 ± 0.21 ($n=18$), eKt/V_a 1.21 ± 0.20 ($n=18$) and eKt/V_{OCM} 1.31 ± 0.21 ($n=18$). Statistically significant lower values for eKt/V_a were obtained compared with eKt/V_b , eKt/V_d and eKt/V_{OCM} ($P < 0.05$).

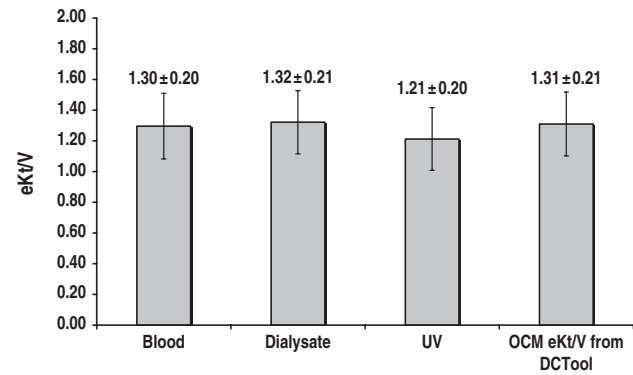


Fig. 5. eKt/V in mean \pm SD from pre- and post-dialysis blood urea (number of HD sessions, $n=18$), dialysate-urea from the natural logarithmic slope of five measuring points ($n=18$), UV-absorbance from the natural logarithmic slope based on 480–540 measuring points ($n=18$) and from OCM using the software DCTool ($n=18$).

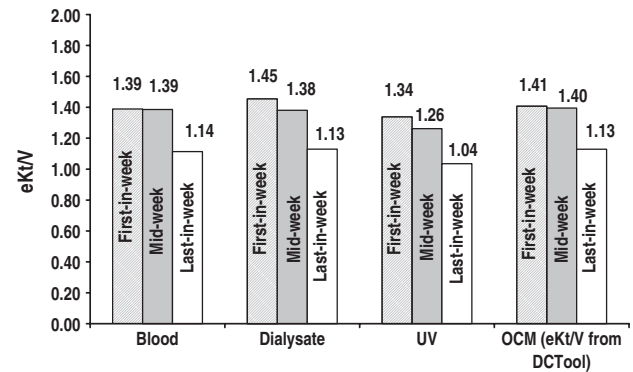


Fig. 6. The response of clearance reduction in $spKt/V$ during the last session in the week, in comparison with first- and mid-week session. The number of treatments and patients was six for each day.

Figure 6 shows the result in eKt/V when the four methods were separated into groups of dialysis days, first-in-week ($n=6$), mid-week ($n=6$) and last-in-week ($n=6$). The difference in mean eKt/V between mid-week session and last-in-week session was as follows: blood 0.25 (18%), dialysate 0.25 (18%), UV-absorbance 0.26 (17%) and OCM 0.27 (19%).

Discussion

All four methods showed a similar sensitivity to a clearance reduction that was manually performed in the last dialysis session of the three in subsequent serial-study treatments (Figure 6). The lowest eKt/V mean value was obtained from UV-absorbance compared with blood- and dialysate-urea and OCM. The results also showed advantages by monitoring the dialysis treatment with a high sampling rate as for the optical method. This study stresses the importance of evaluating the UV-absorbance curve when estimating the dialysis dose calculated from the slope.

Table 2. eKt/V values ($n = 18$) when different number of measuring points are used in the slope and Equation (3)

	First and last point (value) ^a	Slope of five points	Slope of 480–540 points
eKt/Vb (mean \pm SD)	1.30 \pm 0.21	1.29 \pm 0.20	
eKt/Vd (mean \pm SD)	1.33 \pm 0.21	1.32 \pm 0.21	
eKt/Va (mean \pm SD)	1.27 \pm 0.21		1.21 \pm 0.20

^aEquivalent to slope of two points.

In this study, the dialysis dose estimated from UV-absorbance, eKt/Va, was in mean 7% lower compared with the corresponding blood value, eKt/Vb (Figure 5). This is in accordance with the difference, 8%, seen in an earlier study when eKt/V was considered [7]. However, in both the studies the SD of eKt/Va was similar to that of blood.

This difference in eKt/V between UV-absorbance and blood urea may indicate that other molecules with a somewhat lower elimination rate (clearance) compared with urea are measured by the UV-method. The different number of measuring points, which the determinations of Kt/V are based on, may also explain the difference. When using only the maximum and minimum of UV-values for the calculation of the slope and eKt/Va, the eKt/Va value was approaching that of eKt/Vb (Table 2). The mean difference between eKt/Vb and eKt/Va using the slope of max/min values ($n = 18$), decreased from 7% (using the slope value 480–540 measuring points) to 2.5%, which indicates that the difference is affected by the number of measures. This may in turn be interpreted as the linear fitting curve of the natural logarithmic slope (ln) of the UV-absorbance values better mirror the clearance process when compared with a slope based on only two samples. This may also mean that the UV-absorbance reflects variations in clearance coming from compartment effects [12]. In other words, a Kt/V from two blood samples probably overestimates the actual Kt/V. Even five samples instead of two to some extent enhanced the Kt/Vd in the case of dialysate urea (Table 2).

When eKt/V from different dialysis days in the week was separated (Figure 6), all four methods showed a notable and similar response to the reduced clearance that was performed in the last treatment of the week (Figure 6). This may indicate that on-line deviations in UV-absorbance could be a reliable approximation for deviations in urea clearance during day-to-day dialysis.

The UV-curve drops when the dialyser is in a bypass mode. The peak, seen immediately at the end of the bypass, is the result of a few seconds of stationary fluid in the dialyser (during the bypass mode), where the on-going diffusion has built-up a higher concentration of solutes.

The occurrence rate of by-pass differs between manufacturers. In an earlier study, the self-tests were excluded to reduce the risk of interfering with the slope [7], but in the present study the self-tests were included. The difference between eKt/Va calculated using slopes

with self-tests included was 0.14% lower compared with the eKt/Va with self-tests excluded, which indicates that the self-tests do not affect the slope, and thereby the eKt/Va value, substantially.

Incorrectness in V is a well-known problem resulting in errors when calculating Kt/V and PCR [13,14]. Anthropometry-based equations, e.g. the Watson formula, overestimate V in haemodialysis patients [15], which may give an underestimation of the Kt/V value. The OCM utilizes the Watson formula for the V calculation, which could explain the lower values obtained with OCM in case of readings of spKt/V, compared with spKt/V from blood. The computer program DCTool was used for the calculation of V based on the effective *in vivo* clearance as measured by the OCM (sodium clearance \approx urea clearance) and two blood-urea samples (pre- and post dialysis). In this study, the DCTool corrected the spKt/V value from OCM from 1.21 \pm 0.21 to 1.52 \pm 0.22 (mean \pm SD), and the SD of the difference between spKt/Vb and spKt/V_{OCM} was substantially improved, showing a value of -0.02 ± 0.03 (mean \pm SD). This again shows the importance of having a correct V in the dialysis dose calculations [15].

Figure 3A shows the sensitiveness of the UV-absorbance even when small disturbances caused by blood pump stops were present. In Figure 3B, the clearance was clearly affected during periods of low artery pressure, which certainly is the result of decreased $Q_{b,eff}$ through the dialyser due to difficulties in achieving the preset Q_b by the dialysis monitor. The eKt/V value, according to Figure 3B, was 1.01 from blood (pre- and post-dialysis urea concentration), 1.21 from dialysate urea (slope of 10 points) and 1.02 from UV-absorbance with the reduction in clearance included and, finally, 1.22 with the reduction excluded. This is an example of how the UV-absorbance method gives an on-line overview of the clearance process during dialysis and is perhaps a new, more reliable approach, especially when new dialysis modalities are introduced.

The response to changes in blood or dialysate flow (Figure 4A and B) shows the possibility to not only notify alarm effects but also give direct feedback after interventions resulting in clearance changes, e.g. as seen in Figure 3B. The changes in blood and dialysate flow during dialysis (Figure 4A and B) resulted in new baseline levels of the UV-absorbance. This could be a source of error when calculating dialysis dose from the slope on the dialysate-side, which must be considered.

In case of troublesome treatments as in Figure 3B, the slope will be affected differently depending on where the disturbance appears on the UV-curve. This is an issue that needs further investigation. The UV-method gives a unique opportunity to evaluate and visualize the variations in clearance during the dialysis session, due to the high sampling rate. The UV-method may be integrated into the dialysis monitor or be used as a stand-alone tool to give information separately or in combination with other machine parameters.

Blood-urea sampling for the measurement of dialysis dose is still the main performance. Hopefully, all efforts towards developing on-line monitoring equipment in the dialysate-side should be tools for routine use and not only research 'toys' [16].

In conclusion, this study demonstrates that the sensitiveness of clearance reduction is similar for all four methods regarding eKt/V . UV-absorbance showed lower eKt/V compared with blood, dialysate and OCM. The difference, first seen in the case of $spKt/V$ between blood and OCM, was eliminated when using V from DCTool.

The high sampling rate of the UV-method gives the opportunity to verify changes in clearance and perform on-line adjustments. The result of interventions in order to regulate the clearance can be confirmed directly on the screen; also, clearance and Kt/V variations from day-to-day can also be followed, estimated and adjusted.

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Conflict of interest statement. None declared.

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Appendix

A double-beam spectrophotometer (UVIKON 943, Kontron, Italy), used in earlier experiments [7], with an accuracy of $\pm 1\%$ was used for the determination of UV-absorbance. During the on-line experiments, the spectrophotometer was connected to the fluid outlet of the dialysis machine with all spent dialysate passing through a glass cuvette.

For the determination of UV-absorbance a solution, obtained by the spectrophotometer using the pure dialysate as the reference solution, was determined as:

$$A = \log \frac{I_r}{I_{r+s}} \quad (1)$$

where I_r is the intensity of transmitted light through the reference solution (pure dialysate) and I_{r+s} is the summated intensity of transmitted light through the reference solution containing the solutions under study (pure dialysate + waste products from the blood).

Estimation of dialysis dose

Kt/V may be approximated as the slope from the natural logarithmic plot of urea blood concentration (S_B) vs time [17] as well as the slopes of the UV-absorbance (S_a) or dialysate urea (S_D) vs time [7]. From that, Kt/V can be calculated according to:

$$\frac{Kt}{V} \approx -S_B * T \approx -S_D * T \approx -S_a * T \quad (2)$$

where T is the dialysis session length in minutes and V is the distribution volume of urea in the body in millilitre.

Using the UV-absorbance slope values according to Equation (2), the Daugirdas-based, monocompartmental equation can be written as [7]:

$$\frac{spKt}{V_a} = -\ln\left(\exp(S_a T) - 0.008 \frac{T}{60}\right) + (4 - 3.5 \exp(S_a T)) \frac{UF}{W} \quad (3)$$

where UF is the total ultrafiltration in kilogram and W is the patient's dry body weight in kilogram. In the case of dialysate urea, the slope can be inserted in the same way.