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Real-time *Kt/V* determination by ultraviolet absorbance in spent dialysate: technique validation

Alex Castellarnau[1], Michael Werner[2], Roman Günthner[3] and Marten Jakob[1]

[1]*B Braun Avitum AG, Melsungen, Germany;* [2]*Nieren- and Hochdruckzentrum Bad Wildungen, Bad Wildungen, Germany and* [3]*PHV Dialysezentrum Melsungen, Melsungen, Germany*

Real-time determination of *Kt/V* can be provided by monitoring ultraviolet absorbance of solutes in spent dialysate. This not only overcomes dependency on error-prone pre- and post-dialysis blood sampling; it circumvents inaccuracies associated with estimating the urea distribution volume and its high measurement frequency tightly reflects the course of the dialysis. Our study compared the ultraviolet-based sp*Kt/V* and e*Kt/V* with the commonly used blood-based counterparts. A first study of 16 patients compared ultraviolet *Kt/V*s against blood *Kt/V*s obtained by using the 'gold standard' of serial blood samples. A second study included 18 patients and compared the ultraviolet and blood values under routine conditions. Both studies showed mean blood-based sp*Kt/V* and e*Kt/V* values statistically indistinguishable from their ultraviolet-based counterparts. Hence, on-line monitoring of ultraviolet absorption of spent dialysate is applicable in routine hemodialysis allowing continuous measure of removed solutes from spent dialysate without disturbing the patient or treatment session.

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KEYWORDS: absorption; dialysis adequacy; *Kt/V*; online *Kt/V* monitoring; spectrophotometry; spent dialysate; ultraviolet (UV)

Correspondence: *Alex Castellarnau, B Braun Avitum AG, Thüringer Street 30, 34212 Melsungen, Germany. E-mail: alex.castellarnau@gmail.com*

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Patient outcome in terms of mortality and morbidity is strongly correlated with hemodialysis adequacy.[1,2] A minimum dose of 1.2 sp*Kt/V* is recommended for patients undergoing chronic hemodialysis therapy three times a week.[3] Although recent works[4] raise doubts regarding the validity of the *Kt/V* to express or prescribe dialysis dosage, it is still one of the most widely used adequacy parameters in clinical practice.

The standard procedure for calculating *Kt/V* requires blood samples before and after treatment. The major drawbacks of the method are (i) the sampling time of the post-dialysis blood sample, together with laboratory errors, impairs the accuracy of the method; (ii) it is not possible to know whether the treatment is adequate or not before it finishes, it is therefore not possible to take corrective measures during treatment; and (iii) the obtained *Kt/V* value is a single-pool *Kt/V*, which does not account for the urea rebound effect. Ideally, an equilibrated blood sample taken 30 min after the end of therapy would deliver the actual or equilibrated *Kt/V*. However, the impracticability of such an approach requires estimation of the equilibrated sample by using (in most cases) the rate-adjustment method, which leads to further inaccuracies.[5,6]

During recent years, different methods and devices to measure the *Kt/V* on-line have been developed. All deliver *Kt/V* measurements before the treatment's end, overcoming the drawback of the blood-sampling method. These measurement systems can be classified in three groups according to the technical principle: conductivity-based methods, urea sensors, and spectrophotometric methods.

Urea sensors[7,8] are measuring cells that continually monitor urea concentration in effluent dialysate. The exponential factor of the time decay of concentration matches the *Kt/V* value. These systems offer a high measurement rate, which tightly reflects the course of dialysis and eliminates the need for *V* estimation.[9] However, because of the problems related with calibration, maintenance, and costs, urea sensors have not been used widely.

Conductivity methods are based on the observation that sodium and urea clearance are almost equal. It is possible to measure sodium transfer from dialysate to blood or vice versa, and by extension the urea clearance *K* of the dialyzer.[10] In addition, an anthropometric estimation,

or a bioimpedance measurement of the urea distribution volume of the patient V, is required for a final Kt/V calculation. Although conductivity methods offer a good measurement of the sodium clearance;[11,12] (i) the estimation of V introduces a major uncertainty;[13] (ii) the measurement requires changes of the conductivity level of the dialysis fluid (which might influence the plasma composition of the patient);[14] (iii) the obtained K represents the membrane performance, but does not give information regarding the patient's hemodynamic idiosyncrasies; and (iv) the measurement frequency does not suffice to monitor the course of the dialysis treatment.

High-performance liquid chromatography studies reported that many substances present in the uremic serum are active in the ultraviolet (UV) range of the light spectra.[15] These studies led to the development of spectrophotometric sensors. Monitoring UV-absorbing compounds in spent dialysate not only offers enough data to tightly monitor a dialysis treatment, but also eliminates the need for V, by directly obtaining the ratio K/V from the decaying absorbance curve. This technique was first reported by Gál *et al.*;[16] the investigators measured at 254 nm wavelength. Recently, Uhlin *et al.*[17] have shown good agreement between the traditional blood eKt/V values (1.30 ± 0.20) and the eKt/V obtained with UV absorbance at 280 nm (1.19 ± 0.23). In this work, the UV-Kt/V was calculated by (i) applying the natural logarithm to the measured absorbance decay, and (ii) by fitting the resulting line using a linear fitting procedure. This algorithm, however, has a drawback: if the clearance is impaired during the treatment, for example, because of secondary membrane formation or access recirculation, less urea diffuses to the dialysate side, resulting in a higher slope and a higher Kt/V, suggesting better dialysis, when in fact, it is worse.

This work compares traditional blood eKt/V with UV-eKt/V, which has been measured by a UV measuring cell totally integrated in the dialysis machine. An enhanced calculation algorithm that can overcome the Kt/V overestimation problem described above has been used. Two clinical studies are presented here: S1, which compares the 'gold standard' of serial blood urea measurements to tightly monitor the blood urea concentration decay with the UV-Kt/V method; and S2, which compares the UV-based eKt/V with the most-commonly used blood-based 'Daugirdas' eKt/V under routine hemodialysis condition.

RESULTS

Figure 1 shows the blood urea concentration curve, together with the UV curve, of 4-h hemodialysis therapy, superimposed. UV absorption values have been normalized to blood urea concentration values to render a visual comparison.

Figure 2 shows the linear relation between the UV absorbance and urea concentration of spent dialysate. The s.d. between the actual measurements and the modeled line was $\pm 2\%$, which was considered to be the accuracy of the UV sensor.

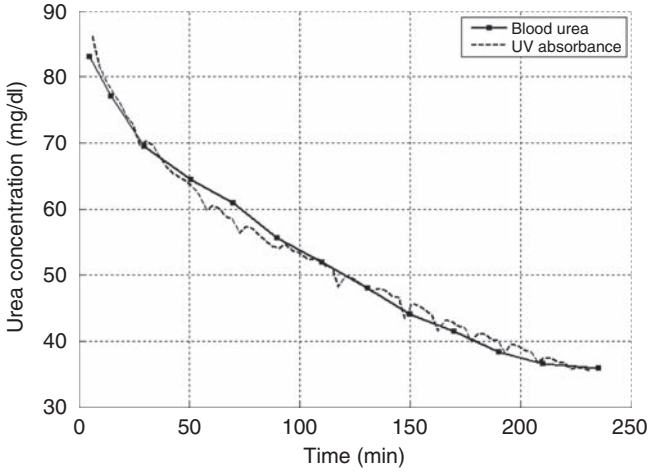

Figure 1 | Blood urea concentration vs ultraviolet (UV) absorbance. Both curves are superimposed based on blood urea concentration. UV absorbance has been normalized to the blood concentration values to render a visual comparison. Normalization resulted from multiplying the UV absorbance values by a constant factor, that is, 115.02.

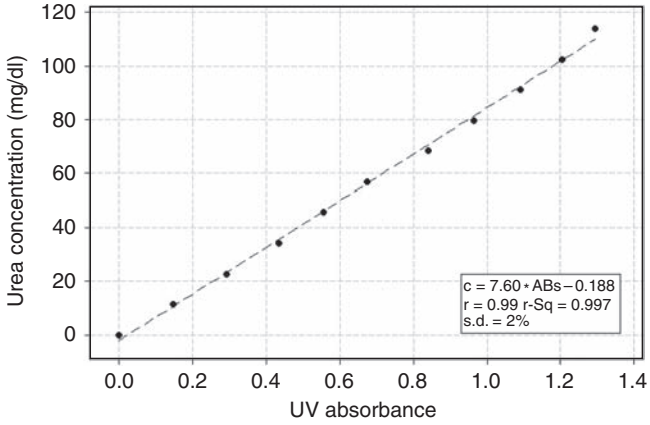

Figure 2 | Linear relation between ultraviolet (UV) absorbance and urea concentration. The s.d. between the actual measured points and the modeled line is $\pm 2\%$, which was considered to be the accuracy of the UV sensor.

Study S1

Mean blood spKt/V was 1.36 ± 0.25, and the mean blood eKt/V was 1.20 ± 0.23; whereas the mean UV-spKt/V was 1.41 ± 0.27, and the mean UV-eKt/V was 1.24 ± 0.24. Mean absolute error between blood spKt/V and UV-spKt/V was 0.09 ± 0.06, while the mean absolute error between blood eKt/V and UV-eKt/V was 0.08 ± 0.05. No significant difference (Mann–Whitney U-test (confidence interval (CI): 95%)) was found between blood values and UV values, either in terms of spKt/V ($P = 0.33$) or in terms of eKt/V ($P = 0.39$). A Pearson product moment correlation analysis was 0.93 for spKt/V and eKt/V; concordance was 0.92 for spKt/V and eKt/V. (Figure 3 shows a scatter plot of the blood-based eKt/V against the UV-based eKt/V. Figure 4 shows the difference between both variables in a Bland–Altman plot.)

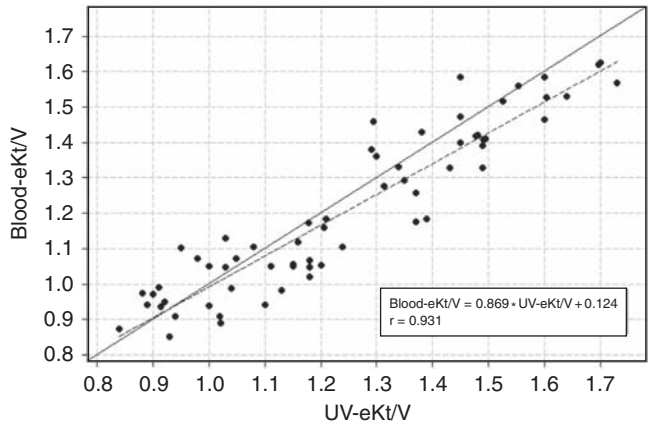

Figure 3 | Study S1: blood e*Kt/V* plotted against ultraviolet (UV) e*Kt/V*. $r = 0.93$; intraclass correlation coefficient (ICC) = 0.92; $n = 64$; solid line: identity line; dashed line: least squares linear correlation line.

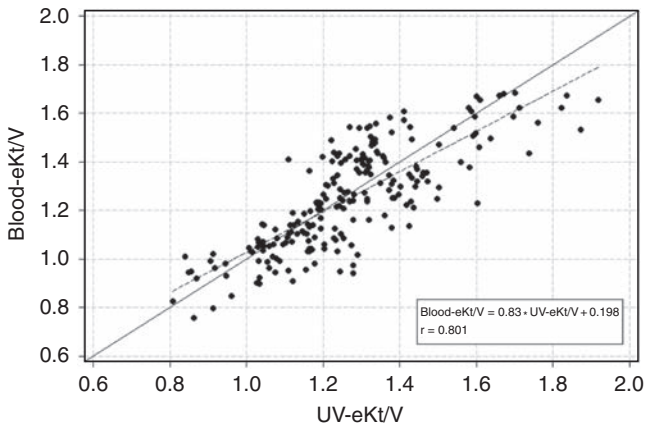

Figure 5 | Study S2: Blood e*Kt/V* plotted against ultraviolet (UV) e*Kt/V*. $r = 0.801$; intraclass correlation coefficient (ICC) = 0.8; $n = 217$; solid line: identity line; dashed line: least squares linear correlation line.

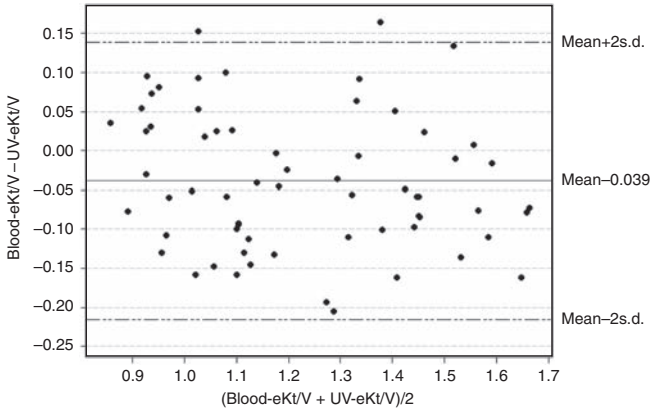

Figure 4 | Study S1: Bland–Altman blood e*Kt/V* against ultraviolet (UV) e*Kt/V*. $r = 0.93$; intraclass correlation coefficient (ICC) = 0.92; $n = 64$.

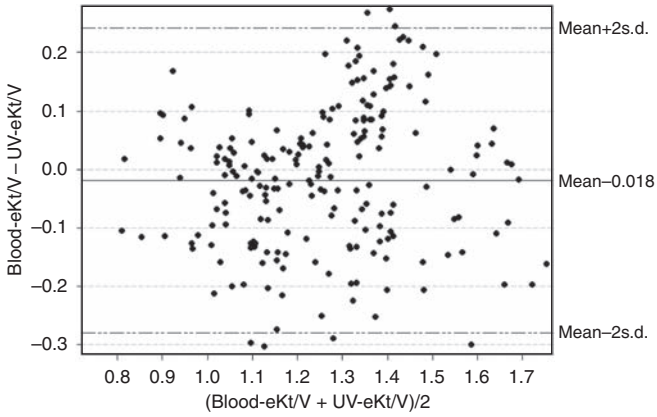

Figure 6 | Study S2: Bland–Altman blood e*Kt/V* against ultraviolet (UV) e*Kt/V*. $r = 0.801$; intraclass correlation coefficient (ICC) = 0.8; $n = 217$.

Study S2

Mean blood sp*Kt/V* was 1.42 ± 0.24, and mean blood e*Kt/V* was 1.25 ± 0.21; whereas mean UV-sp*Kt/V* was 1.44 ± 0.22, and mean UV-e*Kt/V* was 1.27 ± 0.2. Mean absolute error between blood sp*Kt/V* and UV-sp*Kt/V* was 0.12 ± 0.09, while the mean absolute error between blood e*Kt/V* and UV-e*Kt/V* was 0.10 ± 0.08. No significant differences (Mann–Whitney *U*-test (CI: 95%)) were found between blood values and UV values, either in terms of sp*Kt/V* ($P = 0.47$) or in terms of e*Kt/V* ($P = 0.49$). The Pearson product moment correlation analysis was 0.80 for e*Kt/V*; concordance was 0.80 for e*Kt/V*. (Figure 5 shows a scatter plot of the blood-based e*Kt/V* against the UV-based e*Kt/V*. Figure 6 shows the difference between both variables in a Bland–Altman plot. Figure 7 and Table 1 summarize the results of both studies.)

DISCUSSION

The obtained results show the ability of the UV method to accurately estimate the dialysis dosage in terms of *Kt/V* even under routine hemodialysis conditions. The outstanding correlation and concordance found during the study S1 are attributed to the tight control of the blood urea concentration, which was achieved by sampling the patient's blood every 20 min over the treatment time (see Materials and Methods). The lower correlation and concordance found during study S2 are explained rather by the inherent inaccuracies associated with the traditional blood-based approach.

The course of UV absorbance closely follows urea concentration, which shows that UV-absorbing compounds follow a urea-like kinetic model, and validates the presented UV approach as a reliable method to measure the *Kt/V* parameter (Figure 1).

Uhlin *et al.*[17] found that UV-based values were systematically 10% lower than the blood-based values. The investigators attribute the deviation to the higher molecular weight of the UV-absorbing compounds, and by extension to its lower clearance. However, in 1991, Garred *et al.*[9] found

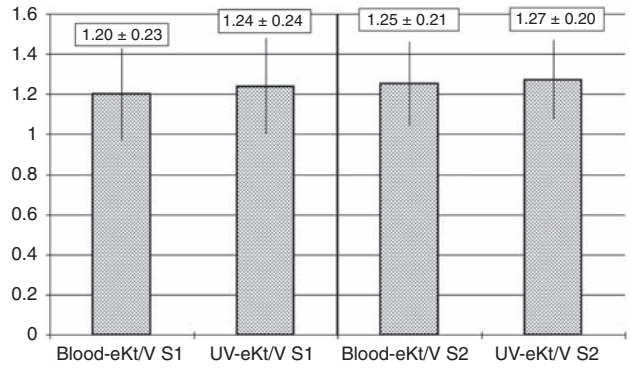

Figure 7 | Blood-based e*Kt/V* vs ultraviolet (UV)-based e*Kt/V*. Study S1: the mean blood e*Kt/V* was 1.20 ± 0.23, whereas the mean UV-e*Kt/V* was 1.24 ± 0.24. Study S2: the mean blood e*Kt/V* was 1.25 ± 0.21, whereas the mean UV-e*Kt/V* was 1.27 ± 0.2.

Table 1 | Results summary

	Blood	UV	*n*	Error[a]	MW	*r*	ICC
Study S1							
sp*Kt/V*	1.36 ± 0.25	1.41 ± 0.27	64	0.09 ± 0.06	*P*=0.33	0.93	0.92
e*Kt/V*	1.20 ± 0.23	1.24 ± 0.24	64	0.08 ± 0.05	*P*=0.39	0.93	0.92
Study S2							
sp*Kt/V*	1.42 ± 0.24	1.44 ± 0.22	217	0.12 ± 0.09	*P*=0.47	0.79	0.79
e*Kt/V*	1.25 ± 0.21	1.27 ± 0.2	217	0.10 ± 0.08	*P*=0.49	0.80	0.80

Abbreviations: ICC, intraclass correlation coefficient; MW, Mann–Whitney *U*-test; *r*: Pearson product moment correlation analysis; UV, ultraviolet.
[a]Mean absolute error.

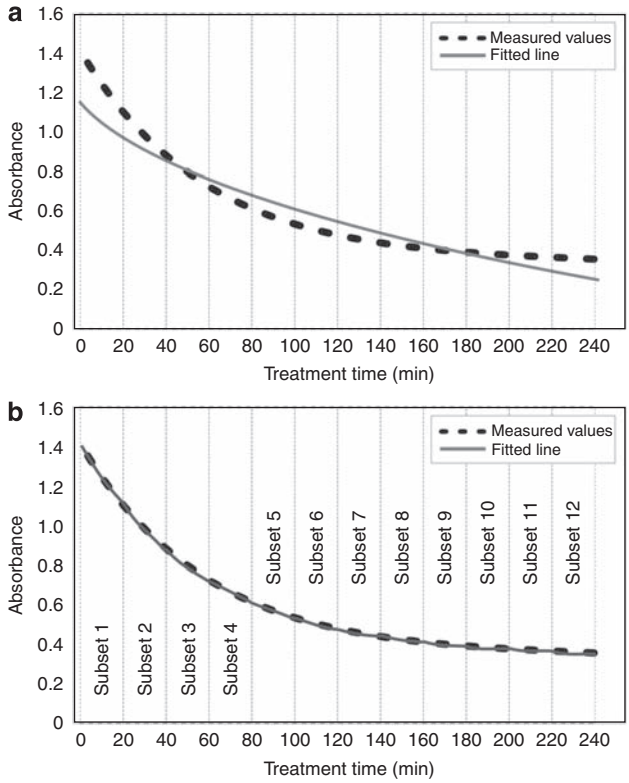

Figure 8 | Effect of the calculation algorithm on fit goodness. A single exponential fit to the whole absorbance curve shows underestimation during the first hour, overestimation in the middle, and again underestimation at the end of treatment (**a**); whereas multiple single exponential fits to subsets of the absorbance curve closely follow the real measured data (**b**).

exactly the same systematic deviation when fitting urea concentration data in spent dialysate. Both research groups neglected the double-pool nature of the human body and assumed single-pool kinetics, in which the UV absorbance (A) or urea concentration (C) over the therapy time can be described as follows:

$$A_t = A_0 \times e^{-K/V \times t} \text{ or } C_t = C_0 \times e^{-K/V \times t} \qquad (1)$$

where K is the clearance of the dialysis procedure, V is the urea distribution volume, and t is the treatment time in minutes.

In both cases, the same calculation algorithm was used: first, linearization of the exponential decay by applying the natural logarithm to the measured values $-A_t$ or C_t–; and second, a subsequent linear fit of the data pairs $-\ln(A_t)$-time or $\ln(C_t)$-time–. Output of the fitting procedure was the ratio K/V, which, when multiplied by the treatment time, resulted in the Kt/V value.

Figure 8a shows the result of fitting a single exponential function (equation (1)) to double-pool absorbance data in spent dialysate. The lack of agreement between both curves may be the reason for the reported deviations.

In our approach, the absorbance curve is split into fixed-time intervals; each of these intervals is individually fit, and yields a partial Kt/V value; finally, the overall Kt/V is obtained by adding each partial Kt/V value (Figure 8b). In contrast to the linearization approach (described by previous investigators), we improved the fit quality by using an iteration-based algorithm, that is, Levenberg–Marquardt, which directly fits the exponential curve (data not shown).

With these algorithm enhancements, we could considerably reduce the systematic difference between blood and UV, and minimize the effects of Kt/V overestimation in case of sudden clearance impairment during the treatment. The remaining error, UV-eKt/V is 3.3% higher than blood-eKt/V, may indeed be introduced by using blood urea concentration as a reference.

The UV-eKt/V showed a 7% nonsystematic error for full eKt/V, contrasting with up to 18% attributed to conductivity-based methods.[18] This higher error is because of the need for an anthropometric estimation of V, that is, Watson formulae. In the UV method, the ratio K/V is directly obtained by fitting the decaying absorbance curve, and then multiplying it by the treatment time to get a final Kt/V value. This is carried out without the need of either an estimation or an independent measurement of the urea distribution volume V.[19]

The presented UV method is less-sensitive to measurement errors than the blood-sampling-based procedure. Overestimation risk of the Kt/V value in case of dialyzer clotting can be controlled by proper calculation algorithm, monitoring the pressure difference between dialyzer inlet and outlet, and monitoring deviations of the expected absorbance

decay. The measuring principle, together with the high sampling rate, tightly reflects the course of the dialysis from the patient point of view, instead of merely assessing the dialyzer clearance.

The results show a close concordance between the blood-based and UV-based e*Kt/V*-values. On-line monitoring of UV absorption of spent dialysate is thus applicable in routine hemodialysis to allow continuous measurement of removed solutes from spent dialysate and direct surveillance of the dialysis course without disturbing either the patient or the treatment session.

MATERIALS AND METHODS

Dialysis centers

Study S1 was an anonymous monocentric study, conducted in the Nieren- and Hochdruckzentrum Bad Wildungen. Study S2 was conducted in two centers, the PHV Dialysezentrum Melsungen and the Nieren- and Hochdruckzentrum Bad Wildungen.

Patients

The study protocol was reviewed by the Freiburger Ethik-Komission GmbH International in Freiburg, Germany, which declared the study as non-interventional. A contract was signed with the medical direction of each center, in which the nephrologist in charge assumed the responsibility of informing the included patients and getting their consents.

In total, 15 uremic patients (4 women, 11 men; mean age, 65.5 years; range, 45–85 years) with either an arteriovenous fistula or an arteriovenous graft on chronic hemodialysis therapy three times a week were included in study S1. Blood flow ranged from 230 to 370 ml/min, and dialysate flow was 500 ml/min. In all, 82 sessions were recorded.

In total, 18 uremic patients (8 women, 10 men; mean age, 64.4 years; range, 22–86 years) with either an arteriovenous fistula or an arteriovenous graft on chronic hemodialysis therapy three times a week were included in study S2. Blood flow ranged from 200 to 400 ml/min, and dialysate flow was 500 ml/min. In all, 251 sessions were recorded.

Three different types of dialyzers were used: high-flux polysulfone, with an effective membrane area of 1.5 m^2; high-flux polysulfone, with an effective membrane area of 1.8 m^2; and low-flux polysulfone with an effective membrane area of 1.5 m^2 (Diacap HI PS 15, HI PS 18 and LO PS 15, B Braun Avitum AG, Melsungen, Germany). The dialysis machine Dialog$^+$ (B Braun AG) with a built in UV-Spectrophotometer (Option Adimea, B Braun AG) was used in all recording sessions.

Blood sampling and laboratory analysis

Study S1 was aimed at avoiding the inaccuracies owing to post-dialysis blood-sampling time. Blood samples were taken from the arterial port of the extracorporeal tube system at 5 and 15 min after the therapy start; every 20 min during the therapy; and 5 min before the end of the therapy. The intratherapy blood urea concentration data (C_t) was fit to the equation (2), using an iteration-based algorithm, that is, Levenberg–Marquardt. Output of the fitting procedure was the ratio *K/V*, which, when multiplied by the therapy time, resulted on a first *Kt/V* value.

$$C_t = C_0 \times e^{-K/V \times t} \quad (2)$$

The Daugirdas formulae[20] were further used to express the obtained *Kt/V* in terms of sp*Kt/V*, to account for urea generation and ultrafiltration; and in terms of e*Kt/V*, to account for the double-pool nature of the human body. The blood-based sp*Kt/V* and e*Kt/V* were compared against their respective UV counterparts.

During the S2 study, blood samples were drawn before and after the dialysis treatment. The error owing to access and cardiopulmonary recirculation was minimized by taking the post-dialysis blood sample after the standard procedure described in the Kidney Disease Outcomes Quality Initiative guidelines.[21] The blood urea concentration values, together with treatment time, ultrafiltration, and patient dry weight, were used to calculate sp*Kt/V* and e*Kt/V* values by applying the Daugirdas formulae. These blood-based values were taken as reference, and compared with their respective UV-based values.

Urea concentrations were determined at the MVZ Laborzentrum Kassel GmbH using the UV kinetic test on a Hitachi/Roche (Basel, Switzerland) modular device. The variation coefficient of the urea determination procedure was ± 2%.

UV-absorbance monitoring

A double-beam, UV spectrophotometer, measuring at 280-nm wavelength (Option Adimea, B Braun Avitum AG) coupled with the out flowing water system of the dialysis machine (Dialog$^+$, B Braun Avitum AG) was used to monitor continuously the spent dialysate. The UV-absorbance *A* was calculated as follows:

$$A_t = \log_{10} \frac{I_0}{I_t} \quad (3)$$

where I_0 is the transmission of light when measuring fresh dialysate during preparation, and I_t is the transmission of light when monitoring spent dialysate during therapy.

Accuracy of the UV sensor was assessed by measuring UV absorbance on a battery of spent dialysate dilutions with different urea concentrations. The linear relation between absorbance and concentration was found. The s.d. between measured concentrations and modeled line was considered the accuracy of the UV sensor.

During treatment, UV absorption was measured every 3 min, which allows approximately 80 measurements in a standard 4-h dialysis. The investigators found that using higher sampling rates does not further improve accuracy (data not shown). An algorithm integrated in the software of the dialysis machine processed the UV absorbance readings, calculated the accumulated *Kt/V* for every new absorbance value, and showed the *Kt/V* and urea reduction ratio trends in the machine's display.

UV-*Kt/V* calculation algorithm

The calculation algorithm differed from the one used in previous works.[9,17] Instead of using the absorbance curve as a whole, it was divided in intervals of 20 min. A standard 4-h hemodialysis therapy had 12 intervals with approximately 7 absorbance readings in each. The investigators found that using 12 intervals optimizes accuracy of the method (data not shown). An iterative procedure, that is, the Levenberg–Marquardt algorithm, was used to fit each collection of absorbance readings to equation (1). The fit output was the ratio *K/V*, which, when multiplied by the interval time, resulted in the *Kt/V* achieved during the considered interval. The whole therapy *Kt/V* was calculated by adding up each of the obtained partial *Kt/V*s (Figure 8b).

The calculation algorithm also accounted for changes in the treatment parameters having an effect on the *K/V* ratio: blood and

dialysate flow. A change in these parameters triggered a new interval, regardless of whether the defined 20 min were over. This approach assured that all the absorbance measurements belonging to the same collection were recorded under constant treatment conditions.

The Daugirdas formulae[19] were used to further express the obtained UV-*Kt*/*V* in terms of UV-sp*Kt*/*V*, to account for urea generation and ultrafiltration, and in terms of UV-e*Kt*/*V* to account for the double-pool nature of the human body.

Statistical analyses

During study S1, dialyzer second membrane effects were controlled by monitoring the pressure difference between blood-side dialyzer inlet and outlet. Sessions showing a change on the pressure drop along the dialyzer >30 mm Hg during the treatment were excluded because of blood clotting. In all, 18 out of 82 sessions were excluded from the statistical analysis: 1 because of UV-sensor failure; 4 because of blood-sampling or laboratory errors; 1 because of dialyzer clotting; (patient 4 (6 sessions) was totally excluded because of dialyzer clotting, which was reported by the nurses and detected by the pressure monitoring, and patient 10 (6 sessions) was totally excluded because the medical direction reported unstable *Kt*/*V* during the last quarter of 2008).

During the study S2, 34 out of 251 recorded sessions were excluded: 24 because of UV-sensor failure, 4 because of lack of either pre-dialysis or post-dialysis blood sample, and 6 because of implausible blood values (most likely because of typos when transcribing the data).

The results are expressed as mean ± s.d. Blood values were always taken as reference; hence, a positive deviation means higher blood values, and a negative deviation means higher UV values. Each obtained variable was tested for normality (Anderson–Darling test, CI: 95%). Significant differences between variables were tested using the Mann–Whitney *U*-test (no significant difference, CI: 95%). Pearson product moment correlation analysis and intraclass correlation coefficient or concordance was calculated for each pair of corresponding variables (CI: 95%). Minitab Statistical Software (version 15.1; Minitab; State College, PA, USA) was used for all statistical calculations.

DISCLOSURE

This work was performed by employees of B Braun Avitum AG. Both the UV sensor and the used dialysis machines (Dialog$^+$) are products manufactured by B Braun Avitum AG.

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