

Development of an optical monitoring technology for urea rebound assessment

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Abstract. The aim of the study was to explore the possibility of utilizing UV-absorbance measurements of spent dialysate to assess urea rebound. Ten patients on chronic three-times-a-week hemodialysis were included in the study. On-line UV-absorbance of spent dialysate was monitored. Urea rebound was calculated based on urea concentration in blood (R_b) and UV-absorbance in spent dialysate (R_a). R_b and R_a were not statistically different. In summary, the results show that it is possible to assess post-dialysis urea rebound in blood based on UV-absorbance in spent dialysate, which may offer a more personalized approach to the dialysis treatment.

Keywords: hemodialysis monitoring; urea; rebound; UV-absorption

1. Introduction

Urea is a low-molecular-weight metabolic end-product of the catabolism of proteins. For the range of low-molecular weight solutes, it is considered to be the most suitable marker [EBPG]. Urea Kt/V, which is viewed as a sensitive measure of the overall dialysis dose to characterize dialysis adequacy, is traditionally derived from formal urea kinetic modeling (UKM) [NKF KDOQI]. UKM is based on blood samples at the start and end of dialysis [EBPG].

Kt/V can be significantly overestimated if the immediate post-dialysis urea concentrations are used for the calculation. The reason for this is urea rebound – an increase in blood urea concentration, which occurs after completion of the dialysis session. This process is complete within 30-60 min after the cessation of dialysis. Thus, waiting up to 60 min after the completion of the treatment before drawing the post-dialysis sample would be the most accurate way for the calculation of Kt/V. However, this approach is not practical for the patients and dialysis facilities.

Algorithms for anticipating post-dialysis rebound of urea have been developed [Smye et al., 1992, Daugirdas and Schneditz, 1995] with the purpose of avoiding the delay of waiting for the equilibrated post-dialysis blood sample. The percentage value of rebound relative to concentration at the end of dialysis could be used to estimate the true dialysis dose, as it approximates the percentage difference between single-pool Kt/V (spKt/V) and equilibrated Kt/V (eKt/V) [Alloatti et al., 1998].

The Smye algorithm [Smye et al., 1992] estimates the post-dialysis equilibrated urea concentration in blood based on conventional pre- and post-dialysis blood samples and an additional intradialytic blood sample. However, it suffers from the effects of small urea concentration measurement errors [Gotch and Keen, 2005], which is the drawback of the Smye algorithm. Also, additional intradialytic blood sampling is time-consuming, requires experienced nurses, and could be problematic due to the anemia risk of the dialysis patients in long term. Because of these drawbacks, this approach cannot be applied on a regular basis for every patient. The algorithm has been modified for the use together with a continuous urea sensor [Garred et al., 1997] and the results show good agreement between the estimated equilibrated urea concentration and urea concentration 25-40 min following termination of dialysis.

There is a need for an instrument capable of directly and easily assessing post-dialysis urea rebound without the need to have the patient wait 30-60 min after the treatment and without repeated blood samples. As a good linear relationship between UV-absorbance and dialysate urea concentration in the wavelength range 210-330 nm [Fridolin and Lindberg, 2003] has been found, an optical method has

been proposed for the monitoring of dialysis adequacy [Fridolin et al., 2002, Castellarnau et al., 2010]. The method enables to follow a single hemodialysis session continuously and monitoring deviations in dialysis efficiency. It has been shown that due to the good correlation between UV-absorbance and urea concentration in dialysate, the latter can be estimated from UV-absorbance measurements even if the UV-technique does not measure urea itself [Uhlen et al., 2005]. Moreover, urea concentration in spent dialysate is a fixed fraction of arterial urea concentration as long as dialysate flow rate, dialyser clearance and recirculation rate remain unchanged [Garred et al., 1997].

It has been previously shown that the possibility of assessing post-dialysis urea rebound in blood based on UV-absorbance measurements in spent dialysate exists [Tomson et al., 2014], with a very good estimate of the urea rebound achieved using on-line UV-absorbance. This study was undertaken to explore the effect of varying dialysate flow, blood flow and treatment modality when utilizing UV-absorbance measurements of spent dialysate to assess urea rebound.

2. Material and Methods

2.1. Subjects

After approval of the protocol by the Tallinn Medical Research Ethics Committee at the National Institute for Health Development, Estonia, ten patients, 5 male and 5 female, were studied at the Centre of Nephrology, North-Estonian Medical Centre during 21 dialysis sessions. An informed consent was obtained from all participating patients. The mean age of the patients was 62.0±10.8 years.

Hemodialysis (n=18), and hemodiafiltration (n=3) sessions were followed. Two types of membranes were used: a) a low-flux membrane (FX8, Fresenius Medical Care, Germany), with an effective membrane area of 1.4 m²; b) a high flux membrane (FX1000, Fresenius Medical Care, Germany), with an effective membrane area of 2.2 m². Treatment duration was for all followed sessions 240 minutes. Dialysate flow was fixed for an individual session at 500 ml/min or 800 ml/min. The blood flow varied between 300 ml/min to 350 ml/min. The type of dialysis machine used was Fresenius 5008 (Fresenius Medical Care, Germany).

2.2. Sampling and laboratory analysis

Blood samples were taken before the start of the dialysis, at the end of the treatment and 30 minutes after the end of the treatment. The blood samples were sent to the laboratory for analysis within 2-4 h. Laboratory's standard sampling procedures were followed without any additional preparation. The concentration of urea was determined at Quattromed HTI clinical laboratory using a standardized method. The accuracy of the method for the determination of urea in blood and dialysate was ±5%.

2.3. UV-absorbance monitoring

The UV-instrumentation setup for the determination of UV-absorbance on-line has been described earlier [Uhlen et al., 2003]. The spectrophotometer HR2000 (Ocean Optics Inc.) was used. The wavelength 297 nm was used. The sampling frequency was set at two samples per minute.

A few minutes before the start of each dialysis treatment the baseline was measured 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 computer screen by a PC incorporated into the spectrophotometer using Ocean Optics' software (OOI-Base32, version 2.0.2.2 for Windows). Data were then transformed to an Excel file at the end of the treatment. The absorbance A of a solution, obtained by the spectrophotometer using pure as the reference solution, was determined as

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

where I_r is the intensity of the light transmitted through the reference solution (pure dialysate) and I_{r+s} is the summated intensity of light transmitted through the reference solution containing solutions under study (pure dialysate + waste products from the blood). In Fig. 1 an example of an on-line UV-absorbance curve at the wavelength 297 nm is presented.

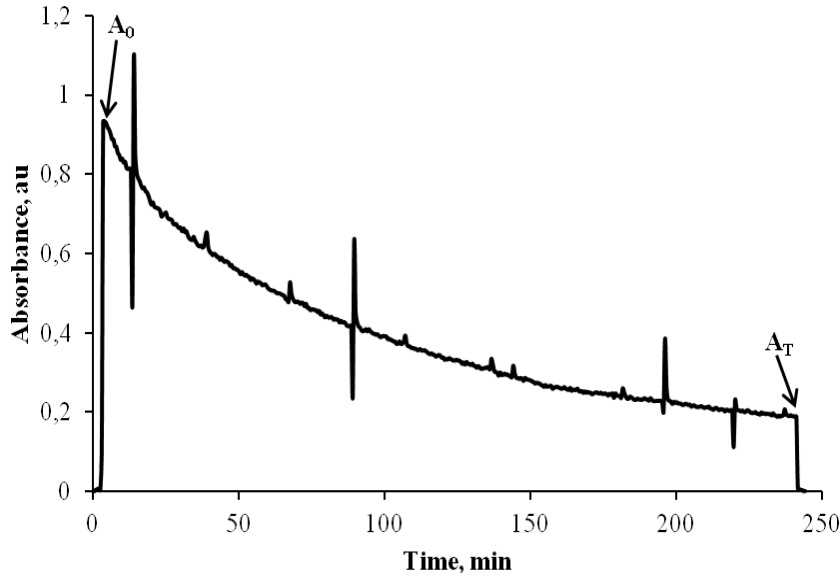


Figure 1. An example of the UV-absorbance curve for a single hemodialysis treatment.

The periodical drops and peaks in the UV-absorbance signal correspond to the self-tests in the dialysis machine during the dialysis when the dialyser is in the bypass mode. Various noises of different origin can also cause deviations in the UV-signal.

2.4. Data analysis

Urea rebound (R) was expressed relative to urea concentration at the end of dialysis (C_T):

$$R1 = ((C_{eq} - C_T) / C_T) 100\% \quad (2)$$

and relative to the decrease in urea concentration during the dialysis session:

$$R2 = ((C_{eq} - C_T) / (C_0 - C_T)) 100\% \quad (3)$$

where C_0 is the concentration of urea before dialysis and C_{eq} is the equilibrium concentration of urea at the end of the rebound phase. Rebound was calculated based on urea concentration in blood samples ($R1_b$, $R2_b$) and UV-absorbance in spent dialysate ($R1_a$, $R2_a$). In case of $R1_a$ and $R2_a$ urea concentrations were substituted by UV-absorbance values. Also, A_T (the substitute value for C_T) was the average value of the last 5 min of the on-line UV-absorbance signal in the end of the dialysis treatment (Fig 1).

In order to estimate urea rebound based on UV-absorbance in spent dialysate a substitute value for C_{eq} (A_{eq}) was calculated according to the Smye algorithm [Smye et al., 1992] where urea concentrations were substituted by UV-absorbance values

$$A_{eq} = A_0 e^{-\lambda t} \quad (4)$$

so that A_0 is the average value of 2 to 6 min from the beginning of dialysis and t is the duration of the treatment in minutes. λ was obtained by line fitting on the on-line UV-signal from 60 min to the end of the dialysis session.

Student's t-test for dependent samples was used to compare means for the estimated parameters and $p < 0.05$ was considered significant. Individual differences in $R1_a$ and $R2_a$ compared to $R1_b$ and $R2_b$, respectively, were also examined using Bland and Altman analysis [Bland and Altman, 1986].

For the analysis Excel (version 2007 for Windows) was used.

3. Results

Average $R1_b$ was $17.40 \pm 9.16\%$. Average $R1_a$ was $18.20 \pm 10.30\%$ and it was not statistically different from $R1_b$ ($p=0.78$). Fig. 2 shows the Bland-Altman plot of the differences between $R1_b$ and $R1_a$. The mean difference between $R1_b$ and $R1_a$ was $-0.81 \pm 13.26\%$.

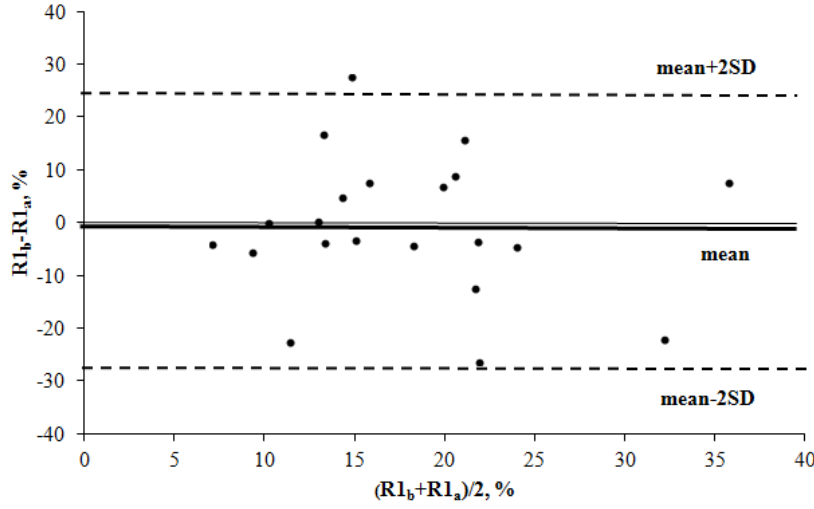


Figure 2. Bland-Altman plot of the differences between $R1_b$ and $R1_a$ ($N=21$)

Average $R2_b$ was $6.24 \pm 3.21\%$. Average $R2_a$ was $6.20 \pm 3.55\%$ and it was not statistically different from $R2_b$ ($p=0.97$). Fig. 3 shows the Bland-Altman plot of the differences between $R2_b$ and $R2_a$. The mean difference between $R2_b$ and $R2_a$ was $0.04 \pm 4.67\%$.

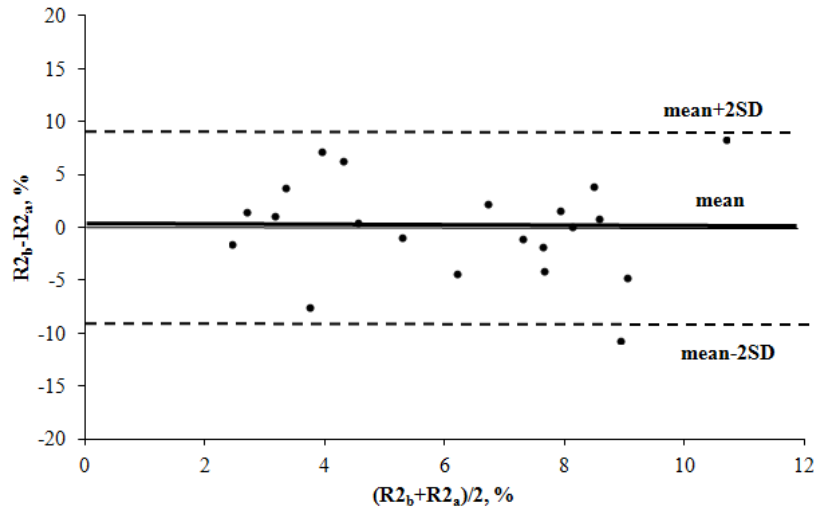


Figure 3. Bland-Altman plot of the differences between $R2_b$ and $R2_a$ ($N=21$)

4. Discussion

The present study investigated further the possibility of utilizing UV-absorbance measurements of spent dialysate to assess urea rebound. This process is relevant because it affects the post-dialysis blood urea concentration and through that also Kt/V [5].

The results indicated that it is possible to assess post-dialysis urea rebound in blood based on UV-absorbance measurements in spent dialysate, as has also been suggested previously [Tomson et al., 2014].

The optical method using UV-absorbance, proposed for the monitoring of dialysis adequacy [Fridolin et al., 2002, Castellarnau et al., 2010], offers the possibility to continuously follow the urea elimination profile without the need for disposables or chemicals. Taking full advantage of the

possibilities offered by the UV-technique, it is also possible to derive the slope of the urea log concentration curve for the calculation of A_{eq} , a substitute value for C_{eq} . $R1_a$ and $R2_a$, calculated based on A_{eq} , were not statistically different from $R1_b$ ($p=0.78$) and $R2_b$ ($p=0.97$), respectively. Thus, the outcome coincides with the results of the previous study [Tomson et al., 2014].

The Bland-Altman plots (Fig. 2, Fig. 3) show a considerable dispersion in the results. The reasons for this are yet unclear. One of the reasons could be multi-compartmental behavior of the patients [Fernandez et al., 2007] instead of the bicompartimental behavior assumed by the Smye algorithm [Smye et al., 1992]. However, this issue is too comprehensive for this paper and will be explored in further studies.

The estimation of urea rebound based on on-line UV-absorbance could also be affected by the disturbances in the on-line UV-signal of the individual dialysis sessions (Fig. 1). To overcome this problem, signal processing can be utilized to remove disturbances [Fridolin et al., 2013]. Exploration of the effects of signal processing on the estimates of urea rebound based on on-line UV-absorbance will be an issue of next studies.

The merits of the described method are that it does not need blood samples or the patient to wait 30-60 min after the completion of HD before drawing the post-dialysis blood sample. Also, the high sampling frequency of the UV-signal reduces the effect of measurement errors that could occur with the analysis of blood samples in the laboratory.

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