Comparison of methods to estimate haemodialysis urea clearance

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Abstract
Introduction

Dialysis adequacy is traditionally measured by monthly blood urea sampling and calculating sessional Kt/Vurea. Modern dialysis machines can estimate clearances each session, so we wished to compare on-line measurements with standard Kt/Vurea.

Methods

Urea clearance was estimated by intermittent changes in effective ionic dialysance (EID) and by continuous ultra violet (UV) light absorption of spent during the mid-week dialysis session. Total body water was calculated by the Watson equation and measured by multifrequency bioimpedance.

Results

We compared Kt/Vurea measurements in 162 patients with on-line assessments; 38 by UV absorption, 124 by EID (50 Fresenius 4008, and 74 Fresenius 5008). All on-line measurements over estimated single pool Kt/Vurea (UV absorption mean bias 0.25 ±0.24, EID 4008H 0.25 ±0.21 and 5008H 0.20±0.25), $p < 0.001$. However, there was no difference between dual pool Kt/V and UV absorbance (1.28±0.26 vs 1.29 ±0.27), or by EID with the 4008 (1.40±0.26 vs 1.46±0.33), although the EID 5008 over estimated clearance (1.39 ±0.27 vs 1.31 ±0.22), $p < 0.01$. Similarly, with dual pool Kt/Vurea the mean bias for UV absorption was 0.08 ±0.35, IED 4008 0.13 ±0.55, and IED 5008 -0.2 ±0.36. Hence the mean bias was greater with the IED 5008 compared to UV absorption (0.08±0.35 vs -0.2 ±0.36 vs $p < 0.01$),

Conclusions

On-line measurements allow dialysis adequacy to be measured every session. We found that although on-line clearances over estimated single pool Kt/Vurea measurements, there were no significant differences between the continuous UV light absorbance method, and intermittent EID.

Introduction

Dialysis dose is an important determinant of clinical outcomes for patients with End Stage Renal Disease (ESRD) treated by maintenance dialysis. The European Best Practice Clinical Guidelines recommend a minimum treatment dose, based on serum urea clearance, measured by equilibrated Kt/Vurea of 1.2 (K – urea dialyzer clearance, t sessional time, V volume of urea distribution) [1]. However, in routine clinical practice this value may not be achieved for every haemodialysis session in all patients [2,3]. Clinical guidelines, recommend that the dialysis dose should be measured by a validated method [1]. Apart from blood sample-based methods, alternative methods determining dialysis dose have been developed, mostly based on measurements of dialysate conductivity [4,5] or urea [6], and more recently using ultraviolet absorbance in the spent dialysate [7].These methods potentially allow quantitative assessment of dialysis clearance with every dialysis session.

The dose of dialysis is traditionally defined as the amount of urea cleared/session. Current methods include the Urea Reduction Ratio (URR) which is a simple comparison of the pre- and post-dialytic serum urea concentrations. In contrast to other methods, the URR method does not take into account that urea is additionally removed from the blood by ultrafiltration. As such the greater the ultrafiltration volume removed during dialysis, the more inaccurate the results of dialysis dose calculation become based on URR [8,9]. As such most centres use Kt/Vurea, which incorporates ultrafiltrate urea losses [10-12]. There are several variations of the Kt/Vurea formula, depending upon whether urea distribution in the body is modelled as a single or dual pool, and whether Kt/Vurea reflects a single mid-week session, or is equilibrated, or averaged over a week to allow for comparison of less or more frequent dialysis treatment schedules [13].

Advances in dialysis machine technology have introduced automatic non-invasive online measurements designed as alternatives to the conventional blood sampling method, laboratory analysis, and calculation. These include intermittent assessments of clearance by measuring the effective ionic dialysance (EID) of dialysate sodium (Na+)

Diascan™, Baxter Health Care, Deerfield, USA, and Online Clearance Monitoring (OCM™) and Online Clearance (OLC™) Fresenius Medical Care, Bad Homberg, Germany), and continuous methods based on ultraviolet light (UV) optical sensors measuring absorbance, using C band: 280 nm -100 nm light emitting diodes, in spent dialysate (Adimea™ B. Braun, Hessen, Germany, and Dialysis Dose Monitor™, Nikkiso, Tokyo, Japan). Although, UV absorbance of the spent dialysate is not specific for urea [14]. Castellarnau and colleagues reported a correlation of 0.93 between blood based Kt/Vurea and Adimea™ measured clearance in a study of 64 subjects [7]. Sodium ions represent the largest proportion of freely mobile charged electrolytes in the dialysate and their concentration predominantly determines the total conductivity. Although the smaller, positively-charged sodium ions differ from the larger non-charged urea molecule, both particles exhibit comparable in-vitro and in-vivo diffusion characteristics across synthetic dialysis membranes, as their specific diffusion coefficient is almost identical at 37°C (Na+: $1.94 \times 10 - 5$ cm^2/s, Urea: $2.20 \times 10 - 5$ cm^2/s [15,16]. Under real dialysis conditions, the difference in clearance is even smaller than the difference of diffusion coefficients, as the clearance is limited by blood and dialysate flow rates and not by the diffusion process across the dialyser membrane. By means of indirect determination of ion concentrations in the dialysate (measurement of conductivity at the inflow and outflow of the dialyser) it is technically possible to determine the diffusion profile of sodium ions across the dialysis membrane and thus estimate the dialysance or ionic clearance (D). On the basis of the dialysance of sodium ions, the "diffusibility" of urea through the membrane (permeability) and thus urea clearance can be estimated [16,17]. In order to achieve a detectable diffusion of sodium ions across the membrane, then the diffusion gradient of sodium between the blood and dialysate fluid must be temporarily increased. For this purpose, the dialysis machine induces a short term pulse to increase (or decrease) the sodium concentration in the dialysate, thereby resulting in an increase in diffusion of sodium ions into the blood compartment or in the reverse direction [18]. Assuming that the conductivity pulse does not exceed the specified conductivity limits, alternate pulses increase and decrease conductivity to ensure that the sodium balance remains as neutral as possible [19].

It has been suggested that with the advances in dialysis machine technology then on-line clearance could replace traditional pre- and post-dialysis blood sampling to estimate dialyzer urea clearance. As there have been no studies comparing traditional blood based Kt/Vurea measurements of dialysis clearance and both the continuous UV absorbance method and intermittent EID methods we evaluated our own data.

Materials and Methods

We retrospectively audited measurements of dialysis session urea clearance measured by traditional blood based methods in adult haemodialysis patients attending for routine mid-week assessments of outpatient dialysis treatments. To be included in the audit patients had to have contemperaneous pre- and post-dialysis session bioimpedance measurements and on-line clearance, in addition to pre- and post-sessional serum sampling. 162 patients fulfilled all of these criteria. The audit reviewed dialysis sessions in separate dialysis centres in July and November 2016.

Serum urea, other biochemistries were measured in a UK accredited laboratory (External Quality Assurance (EQA) ISO/IEC 17043) using an automated analyser (Roche Cobas, Roche Diagnostics, Maidenhead, UK), with the post-dialysis samples taken using the slow-flow method [1,10]. Sessional Kt/Vurea was calculated by both single and dual pool methods (appendix) [1,10]. We also recorded assessments of on-line clearance either using continuous UV absorbance method (BBraun Dialogue[R+], (BBraun Avitum AG, Melsungen, Germany) or by the intermittent EID method (Fresenius 4008H and 5008H, Fresenius Medical company AG, Bad Homberg, Germany). All patients used high flux dialysers (Elisio series, Nipro, Osaka, Japan) [20], and were anticoagulated with a single bolus dose of tinzaparin (Leo Laboratories, Prices Risborough, UK), median dose 2500 (2500-2500) IU [21]. Dialysate water met ultrapure standards and temperature was cooled to 35-35.5°C. Dialysate biochemistry; sodium 138 (136-138), potassium 2.0 (1.0-2.0) mmol/L, calcium 1.25 (1.0-1.35) mmol/L, bicarbonate, acetate and magnesium concentrations were set at 32, 3.0 and 0.5 mmol/L, respectively, Patients were allowed one drink (180 mL) during dialysis and actively discouraged from eating during dialysis sessions. We excluded any patient who became

symptomatically hypotensive during the dialysis session requiring a reduction in ultrafiltration rate or given intra-venous fluids.

Patients had standing height measured and weighed pre-and post-dialysis. Urea volume was estimated using the Watson formula (appendix) [18], and by multifrequency bio-impedance (InBody S10, Seoul, South Korea) [22,23]. Patients with amputations, paralysed limbs, pacemakers or other implantable cardiac devices were excluded.

Statistical analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. We used standard statistical analysis D'Agostino & Pearson normality test, t test, Mann Whitney U test, anova or Kruskal Wallis were used for parametric and nonparametric data respectively, with appropriate correction for multiple analyses where appropriate, and Chi square testing with correction for small numbers, with Spearman correlation used for non-parametric data. Statistical analysis was performed using Graph Pad Prism (version 7.0, Graph Pad, San Diego, CA, USA) and Statistical Package for Social Science version 24.0 (IBM Corporation, Armonk, New York, USA) and Analyse-It (Analyse IT 4.0, Leeds, UK) for Bland Altman analysis. Statistical significance was taken at or below the 5% level.

Ethics

This retrospective audit complied with NHS guidelines (UK NHS guidelines for clinical audit and service development). In keeping with the Hospital Trust policy no patient identifiable data was used.

Results

We reviewed the results from 162 patients, who had paired sessional Kt/Vurea and on-line clearance measurements. Their mean age was 68.0±14.1 years, 58% were male (94); 75 (46.3%) diabetic, white ethnicity 78 (48%), black: 31 (19%), asian 47 (29.3%) and other races 6 (3.7%). There were no differences in patient demographics,

percentage of diabetics or body composition between the groups (Table 1). Similarly, there were no differences in standard pre-dialysis blood testing. On-line clearance was greatest with EID with the 4008 dialysis machine and least with UV light absorbance with the BBraun Dialogue $^{R+}$ (table 1).

There was a correlation between single pool Kt/Vurea using the Watson equation and on-line clearance for all machines; BBraun Dialogue $^{R+}$ r^2=0.40, Fresenius 4008H r^2=0.62, and Fresenius 5008H r^2=0.31, all p<0.001. For all machines the single pool Kt/Vurea using the Watson formula was greater than on-line clearance (all p<0.001). The mean bias between Kt/Vurea and on-line clearance was similar for all three dialysis machines; BBraun Dialogue $^{R+}$ 0.25 ±0.24, and Fresenius 4008H 0.25 ±0.21 and the Fresenius 5008H 0.20±0.25 (Figures 1-3).

Total body water was also measured by bioimpedance, and single pool Kt/Vurea, using bioimpedance measured total body water, was greater for all dialysis machines when compared to the on-line clearance (Table 1). We noted that the difference in single pool Kt/Vurea between bioimpedance and Watson formula was greater for smaller patients and less for larger patients (Figure 4). There was a correlation between single pool Kt/Vurea using bioimpedance total body water and on-line clearance for all machines; BBraun Dialogue $^{R+}$ r^2=0.21, p=0.003; Fresenius 4008H r^2=0.34, p=0.001; and Fresenius 5008H r^2=0.12, all p=0.002.

We then calculated dual pool Kt/Vurea, and using the Adimea™ the UV absorbance method was not different to Kt/Vurea clearance, mean bias 0.014 ±0.237, p>0.05, r^2 =0.36, nor was the EID method when using the 4008 dialysis machine, mean bias 0.055 ±0.677, p>0.05, r^2 =0.60, but mean bias was significantly greater with the EID and the 5008 dialysis machine, 0.08 ±0.23, p <0.01. In addition, bias appeared to increase with increasing clearance. For all machines single pool Kt/Vurea was greater compared to dual pool calculated Kt/Vurea using the Watson formula, (all p<0.001). When using a dual pool Kt/Vurea model then the mean bias for UV absorption was 0.08 ±0.35, IED 4008 0.13 ±0.55, and IED 5008 -0.2 ±0.36. As such, the mean bias was greater with the IED 5008 compared to Adimea™ (0.08±0.35 vs -0.2 ±0.36 vs p<0.01),

but not with 4008 machines. As with total body water measured by Watson formula, the degree of bias increased with the 5008 with increasing total body water.

Although there was no difference in the pre-dialysis serum sodium, when we compared the relative change in pre minus post serum sodium, the difference was significantly different using the BBraun DialogueR+ machines compared to the Fresenius 4008 and 5008 machines, -2 (-4 to 0) vs 0 (-2 to 2) and 1.0 (-1.8 to 3.0) mmol/L, p<0.001, respectively,despite similar changes in pre- to post-dialyhsis weight.

Discussion

The National Co-operative study (NCDS) established the importance of urea clearance by haemodialysis in determining patient outcomes [24], and Frank Gotch subsequently suggested a sessional Kt/Vurea cut off to determine dialysis adequacy [25]. The NCDS measured urea post-dialysis and then pre- and post-the following dialysis session to establish a time averaged urea concentration. Gotch simplified this to two blood samples, pre- and post-the midweek dialysis session. Errors in calculating Kt/Vurea can be introduced by not compensating for the rebound in serum urea post-dialysis [8], and as such clinical guidelines advise on standardised methods to take the post-dialysis sample [1,10]. Advances in dialysis machine technology have led to the development of on-line clearance monitors. Indeed, in some countries, the practice has changed from measuring Kt/Vurea by monthly blood testing to using the on-line clearance for each dialysis session, and dispensing with blood testing [26].

We therefore wished to review the results obtained with two different methods of estimating on-line clearance and standard methods of calculating Kt/Vurea. Previous validation studies have reported that the second generation Daugirdas' formula has a total error in an acceptable range of ≤ 5% for sessional Kt/Vurea between 0.7 and 2.1 [13]. The EID method measures clearance intermittently, and indirectly by inducing an increased sodium gradient between the serum and dialysate and then measuring the change in dialysate conductivity [4,5], whereas the other method used continuous monitoring of the dialysate effluent by UV light [7,14]. We found that both OCM™ and

ADMEA™ over estimated urea clearance compared to single pool Kt/Vurea. A previous study based on 10 patients using the OCM™ with a 4008 dialysis machine, reported that the OCM™ underestimated spKt/Vurea using the Watson equation but provided similar results when using bioimpedance measurements [27,28]. As with previous studies, we found that anthropomorphic estimates of total body water differed compared to bioimpedance [27], and such generally resulted in a lower Kt/Vurea value. In particular we found that total body water measured by bioimpedance was greater than that derived from the Watson formula for smaller patients, whereas total body water was greater with the Watson equation for heavier patients, in keeping with previous reports [29]. As such, depending upon the size distribution and body composition of patients, the results of studies will vary [30].

An early study on 10 patients suggested an error of around 9% between OCM™ clearance and the Daugirdas second generation spKt/Vurea [4,13], and that the main cause of error was due to estimates of body water [19]. Similarly, another small study reported a 6% difference [5], and a further small based on 10 patients reported that ionic clearance using the OCM™ reported a similar urea clearance when bioimpedance measurements of total body water were used, but not when total body water estimated by the Watson equation were used [28]. Differences between these earlier smaller studies, may be due to differences in the patient population studied and between dialysis practices, in particular whether patients were allowed to eat or drink during treatment sessions, and also potentially by differences in dialysate temperature.

Previous studies using continuous UV absorbance measurements of waste dialysate UV have reported differing results, with reports that this method underestimates urea clearance compared to spKt/Vurea [14], both over and under estimated urea clearances [7], and yet others showing similar results for both UV absorbance and EID methods [14]. We found similar bias between measured spKt/Vurea and both UV absorbance and EID methods. However, when we compared on-line clearances with dual pool Kt/Vurea, there were no significant differences with either the UV absorbance or EID on the 4008 dialysis machines, although the EID method gave higher clearances with the 5008. Previous studies have shown that differences in total body water affect

estimates of clearance with the EID method [4,5,16,17,19], and this is shown by the differences between on-line clearance estimates when using Watson and bioimpedance derived total body water.

As the EID-based methods determine on-line clearance "at predefined or programmed intervals, they could potentially over estimate clearance if blood for dialysate flows dropped during the time period between measurements. In our study we excluded patients who had symptomatic hypotension and either had a reduction in ultrafiltration rate or given intra-venous fluids, and so did not observe any major changes in patient cardiovascular stability, and as such did not note any significant difference in the bias between EID or UV absorbance methods and Kt/Vurea, although dialysis clearance was estimated to be greater by EID.

In addition, as EID relies on a change in sodium gradient, it has been estimated that for each measurement the patient receives a small net influx of sodium (1.53+/-7.62 mmol) [4]. As such, the pulsed change in sodium gradient induced between blood and dialysate should alternate to prevent any sodium loading during dialysis. We did find a difference in the change in post-dialysis serum sodium concentrations compared to pre-dialysis concentrations when using an indirect selective electrode method [31]. As we made no formal sodium balance study it is unclear whether the differences observed in pre- and post-dialysis measurements could be due to any additional sodium administered during the EID measurements. The Fresenius dialysis machines allow for different frequency of measurements, and previous studies have not specified the number of measurements made, and our centre uses the shortest time interval setting, which may have led to more measurements than previous reports. On the other hand, EID by monitoring dialysate sodium in fresh and waste dialysate, potentially offers an estimation of sodium removal during a dialysis session, and could be used to ensure no net sodium gains.

As with any study, the results must be taken in context, in that urea clearance during a dialysis session can be affected by many factors, including dialyser type, effective treatment time, blood and dialysate flows, dialysate composition both vascular access type and access recirculation, and cardiac output, and as such our

results may differ from those in other centres with different practices. In addition, our centre uses cooled dialysates, and lower dialysate sodium concentrations [32], compared to many others, and whether this may influence the IED method remains to be determined.Although, we found that both methods over-estimated clearance compared to spKt/Vurea clearances, and both under-estimated clearance compared to dual pool Kt/Vurea, on-line clearance measurements complement standard blood testing. As prospective studies have failed to demonstrate a survival benefit for achieving a higher sessional Kt/Vurea target [31], then the ability to make a relative comparison between on-line clearances and standard blood testing to assess dialysis urea clearance with each dialysis session, rather [33] han absolute values of on-line clearance measurements may be more important in clinical practice.

The requirement for monthly blood tests to determine HD adequacy is a compromise between cost and the utility of the measurement, but risks patients receiving reduced clearances. Whereas on-line clearance allows the delivery of the dialysis dose to be monitored during every dialysis session, and if necessary modifications can be made during the dialysis session. As such on-line clearances provide a practical instrument for regular clinical use and complement other formulas for estimating dialysis urea clearances.

Appendix

Watson formula for total body water

Men

Total body water = 2.447 - (0.09156 x age) + (0.1074 x height) + (0.3362 x weight)

Women

Total body water = -2.097 + (0.1069 x height) + (0.2466 x weight

Second generation Single pool variable volume Kt/Vurea (Daugirdas)

Kt/Vurea = - log (Post BUN/preBUN -0.3) + (4-3.5 x Post BUN/preBUN) x

ultrafiltration/post dialysis weight

Blood urea nitrogen (BUN) mg/dL

Dual pool (equilibrated) Kt/Vurea

Equilibrated Kt/Vurea = Single pool Kt/Vurea – 0.6 * (Single pool Kt/Vurea)/t + 0.03

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Figure 1. Bland Altman plot of the average dialysis session clearance and the difference between BBraun Dialogue[R+] on-line clearance and single pool Kt/Vurea using the Watson formula for total body water. Mean bias 0.25 (solid line) and 95% limits of agreement -0.13 to 0.56 (dotted lines)

Figure 2. Bland Altman plot of the average dialysis session clearance and the difference between Fresenius 4008H on-line clearance and single pool Kt/Vurea using the Watson formula for total body water. Mean bias 0.25 (solid line) and 95% limits of agreement -0.13 to 0.62 (dotted lines)

Figure 3. Bland Altman plot of the average dialysis session clearance and the difference between Fresenius 5008H on-line clearance and single pool Kt/Vurea using the Watson formula for total body water. Mean bias 0.20 (solid line) and 95% limits of agreement -0.23 to 0.65 (dotted lines)

Figure 4. Difference between bioimpedance and Watson formula derived single pool Kt/Vurea and mean bioimpedance and Watson formula total body water. Univariate analysis r= -0.19, p=0.017

Table 1. Patient demographics, body composition and pre-dialysis blood tests in patients dialysing with BBraun Dialogue[R+], Fresenius 4008H and 5008H. Results expressed as integer, percentage, mean ±standard deviation. *p<0.05,** p<0.01, **p<0.001 vs BBraun Dialogue[R+]

	BBraun Dialogue	Fresenius 4008	Fresenius 5008
Number of patients	38	50	74
Gender Male (%)	21(55.2%)	27 (54%)	46 (62%)
Age years	71.7 ±13.0	65.5 ±12.6	67.7±15.3
Diabetic (%)	22 (61)	20 (40)	41 (55.4)
Weight pre-dialysis kg	71.3 ± 20.9	72.7 ± 20.3	72.7 ± 16.9
Weight post-dialysis kg	69.4 ± 20.7	71.1± 20.0	71.1 ± 16.6
Body mass index kg/m^2	25.3 ± 6.8	26.6 ± 7.1	26.7 ± 5.9
Fat mass kg	22.8 ± 14.6	23.1 ± 12.6	21.8 ± 12.9
Pre-dialysis serum urea mmol/L	16.8 ± 6.1	19.0 ± 5.4	18.7 ± 6.4
Pre-dialysis haemoglobin g/dL	10.4 ± 1.4	11.0 ± 1.4	11.2 ± 1.1
Pre-dialysis albumin mmol/L	34.8 ± 6.7	39.8 ± 3.5	38.6 ± 4.7
Re dialysis serum sodium mmol/L	138 ±3.6	139 ±3.4	138 ±3.3

On-line clearance Kt/V	1.29 ± 0.27	1.46 ± 0..33*	1.39 ± 0.27
Single pool Kt/Vurea (Watson total body water)	1.54 ± 0.29	1.71 ± 0.30***	1.59 ± 0.26
Single pool Kt/Vurea (Bioimpedance total body water)	1.71 ± 0.27	1.99 ± 0.47***	1.75 ± 0.40
DualpoolKt/Vurea (Watson total body water)	1.28 ± 0.26	1.40 .026*	1.31 ± .022
Dual pool Kt/V (bioimpedance total body water)	1.37 ± 0.40	1.54 ±0.49	1.51 ±0.4