**Kt/V urea does not tell it all**

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**Keywords:** dialysis adequacy; haemodialysis; Kt/V urea; protein-bound solutes; uraemic toxin

**Introduction**

In this issue of *Nephrology Dialysis and Transplantation*, Sirich et al. provide evidence that 8-h treatments with large dialysers and higher dialysate flows greatly increase the clearances of protein-bound compounds p-cresol sulphate and indoxyl sulphate without altering Kt/V urea [1]. Thus, this paper is a further striking example of the limitations of urea-based dialysis ‘dosing’ and allows us to confirm that Kt/V urea does not tell it all.

In order to quantify the removal of uraemic toxins and the treatment time, some decades ago, Sargent and Gotch proposed a mathematical model based on the dialytic removal of urea, introducing the concept of Kt/V urea, i.e. a clearance that is expressed as the product of the dialyser clearance (K) multiplied by the duration of treatment (t) and divided by the estimated volume of distribution (V) of urea [2]. Urea seemed ideal as a marker because it is the end product of protein catabolism, is a small water-soluble molecule (60 Da), easily measured in blood and dialysate and with V equal to the water body volume.

**The triumph of Kt/V urea**

The main issue which justifies the fact that Kt/V urea be considered the key of the adequacy of dialysis is that it is related to mortality. The evidence is given by retrospective observational studies [3, 4] and by a single interventional trial that had a great impact on the global dialysis community [5]. Although the National Cooperative Dialysis Study (NCDS) was not designed to test the usefulness of Kt/V urea, two post hoc analyses were made using this parameter. In their post hoc ‘mechanistic analysis’, Gotch and Sargent recommended a target Kt/V urea of ~1.0, above which the dialysis ‘is of no apparent clinical value’ [5]. In a subsequent post hoc analysis of the NCDS data, Keshaviah [6] suggested that a further benefit could be achieved by raising the target Kt/V urea to 1.2. The positive effects of the worldwide acceptance of the ‘dogma’ of Kt/V urea are that dialysis treatment is tailored to the characteristics (V) of the patient and that the efficiency of the dialyser (urea clearance) assumes a role of particular importance: actually, this led to the development of even more efficient dialysers.

Thus, it can be said that the development of Kt/V urea ranks easily as the most important theoretical development in the history of dialysis [7]. It constituted a major evidence-based step forward from prescribing treatment based on achieving target blood urea levels. It also allowed treatment to be standardized based on the readily available urea nitrogen assay while the identity of toxic uraemic solutes remained unknown [7].

**The sunset of Kt/V urea**

However, there are also negative consequences of the acceptance of the dogma of Kt/V urea: (i) Kt/V urea can
change by adapting $K$, $t$ or $V$: as a consequence, for example, the time of dialysis can be reduced simply by increasing the clearance of the dialyser; (ii) the removal of higher molecular weight solutes (e.g. the middle molecules) is not taken into account; (iii) furthermore, doubts have arisen from the fact of considering urea as a true marker of ‘uraemia’, as, in the classification of the European Uremic Toxin Work Group (EUTox), urea is defined as a ‘not necessarily toxic’ solute [1]. In addition, concerns arise from the fact that even within the group of small water-soluble molecules (<500 Da), some solutes, such as the guanidino compounds, show completely different kinetic behaviours compared to urea [8].

Then, the need to correlate the dialysis clearance with mortality in a large prospective trial arose [9]: in other words, the nephrology community wondered whether a further increase in the $Kt/V$ urea could lead to a reduction in mortality and morbidity [9]. Patients were divided into four groups depending on the dose ($Kt/V$ urea 1.65 or 1.25) and membrane permeability (clearance of β₂-microglobulin > or <20 mL/min). The results showed that there was no difference in terms of mortality and morbidity, either as far as dose of dialysis or membrane permeability are concerned [9]. The results of the HEMO Study marked the beginning of the decline of $Kt/V$ urea. Lowrie et al. had already pointed out the limits of $Kt/V$ urea in defining adequate dialysis, as they had shown that $V$ of the patient, when calculated as total body water, body weight, body mass index (BMI) and body surface area, was an independent variable of outcomes of the patients. Therefore, they proposed to use only $K$ as an index of adequacy [10]. The same authors also warned about the risk that the choice of a dialysis treatment time sufficient to obtain a value of $Kt/V$ urea equal to 1.2 could determine underdialysis especially in patients with low BMI [11]. In addition, the group of Salahudeen [12] analysed the ‘paradox of $Kt/V$ urea’ (why some patients with $Kt/V$ urea >1.4 have a higher mortality than patients with $Kt/V$ urea 1.2?) in a prospective study of 9 months on 1151 patients. The authors concluded that the ‘paradox of $Kt/V$ urea’ was more frequent in patients with body weight <70 kg and low levels of pre-albumin; furthermore, they pointed out that the duration of dialysis session of 180 min contributed to this paradox [12]. Other studies confirmed that scaling for $V$ could be a confounding factor and that in patients on dialysis, sex and BMI directly affect the mortality and morbidity of the patient and even the amount of dialysis dose [13, 14]. Then, alternative methods of normalization of $K$ were proposed with the aim of identifying a normalizing factor that best reflects a metabolic activity: they are body weight$^{1/67}$ [15], body surface area [16], resting energy expenditure [17], high metabolic rate organ mass [18], liver mass [19] and bioelectrical resistance [20].

The clinical illogicality of $Kt/V$ urea

Currently, >93% of the US patients reach the recommended target $Kt/V$ urea [21]; however, the survival of dialysis patients remain unsatisfactory: the mortality of patients on maintenance haemodialysis (HD) is four times higher than that of the general population aged >65 years [21]. This suggests that there may be factors that influence survival and that dialysis, as quantified by $Kt/V$ urea, does not correct. On the other hand, it is important to underline that many observational studies have suggested that longer treatment times and/or more frequent dialyses may lead to better outcomes and improved laboratory results [22–28].

These studies suggest that it is more important to dialyse longer and/or more frequently to increase survival rather than increasing the removal of urea through more efficient dialysis. This raises the hypothesis that the duration and/or frequency of the treatment involve other factors affecting survival on dialysis. While this may simply reflect a better clearance of toxins mainly with features of time-dependent clearance [29, 30], it is also logical to assume that these factors may include parameters known to influence mortality: nutrition, serum albumin, mineral metabolism, inflammatory markers, volume control, blood pressure, left ventricular hypertrophy and haemodynamic stability [31, 32]. Regarding the latter, it must be underlined that dialysis hypotension is a significant and independent factor influencing the mortality in HD patients [33]. Moreover, the importance of the cardiac damage induced by dialysis has been underlined recently by Burton et al. [34]: hypoperfusion and myocardial ‘stunning’ during the dialysis session are clearly associated with a decrease in intradialytic systolic blood pressure. On the other hand, the importance that a high ultrafiltration rate during the dialysis session may have on outcomes is well known [22, 35, 36]. However, $Kt/V$ urea, duration and frequency of dialysis sessions almost always inevitably overlap, and only randomized controlled trials may clarify the true effect of the duration and frequency of treatment on outcomes [37]. The US National Institute of Health and the Centers for Medicare and Medical Services have funded two parallel randomized controlled trials, giving rise to the Frequent Hemodialysis Network Trial Group [38]. The first trial, that of daily dialysis, enrolled 125 patients in the daily dialysis arm and 120 patients in the thrice-weekly conventional HD arm [39]. At the end of 12 months, the daily HD was associated with favourable results as far as the composite outcomes of death or change in left ventricular mass and death or physical symptoms that affect quality of life are concerned. A better control of hypertension and hyperphosphataemia was observed but also a greater number of vascular access interventions [39]. The second trial, that of nocturnal dialysis, enrolled only 45 patients in the frequent nocturnal HD arm and 42 in the thrice-weekly conventional HD arm [40]. No positive effect of the frequent nocturnal HD was found for any composite outcomes of death or change in left ventricular mass and death or physical symptoms that affect quality of life [40]. The simplest and most logical explanation for the lack of any statistical significance in these composite outcomes lies in the very low statistical power of the study.

$Kt/V$ urea and the protein-bound uraemic solutes

Most of the uraemic toxins defined as protein-bound compounds have a low molecular weight, but some have characteristics of middle molecules, such as leptin and retinol-binding protein. The most important among them
are p-cresol, homocysteine, indoles and phenols. Some studies suggest a correlation between the concentration of uraemic retention protein-bound solutes and some clinical outcomes [41–45]. Focussing our attention on the cardiovascular system, the EUTox Work Group concluded that most of the molecules involved in the vascular damage were protein-bound and/or middle molecules [46]. These compounds are difficult to remove by most of the dialysis techniques currently available. No interventional studies are available today, showing the effect of an improvement in the removal of protein-bound compounds on the outcome, simply because the largest part of the alternatives dialysis strategies proposed so far is not superior to standard dialysis in removing protein-bound compounds. The high-flux HD does not have a significant impact on the concentration of protein-bound solutes compared to standard HD [47]. One study that compared the removal of protein-bound compounds in HD and post-dilutional haemodiafiltration showed that the removal of these substances is governed mainly by diffusion [48]. These data confirm previous in vitro studies suggesting that the increase in protein-bound toxin removal through increased convective transport is negligible [49]. In addition, another recent study showed that increasing the area of mass transfer coefficient (KwA) of the dialyser and the dialysate flow (Qd) had a positive effect on clearances of protein-bound solutes [50].

In this issue of Nephrology Dialysis and Transplantation, the same group provides evidence that 8-h treatments with large dialysers and higher dialysate flows greatly increase the clearances of p-cresol sulphate and indoxyl sulphate without altering Kt/V urea [1]. In other words, Sirich et al. [1] show that it is possible to increase the clearances of protein-bound solutes by increasing KwA and Qd and by keeping blood flows (Qb) virtually unchanged. This maneuver does not significantly increase the clearance of small solutes, which depends mainly on Qb. Thus, it gives the possibility of producing two different levels of clearances of protein-bound solutes in the presence of unchanged levels of clearances of small solutes: this could allow to test the clinical usefulness of selectively increasing the clearance of protein-bound uraemic solutes. The hypothesis made by Sirich et al. [1] is that increasing the Qd maintains the transmembrane concentration gradient by keeping the dialysate solute concentration below the free solute concentration in the plasma. Furthermore, increasing KwA increases transmembrane solute diffusion while the free solute concentration in the plasma limits the transmembrane concentration gradient. In conclusion, Sirich et al. claim that these measures can increase clearance for bound solutes like p-cresol sulphate and indoxyl sulphate because as free solute diffuses across the membrane, solute is released from albumin to maintain equilibrium between the free and bound portion as governed by the association constant. This tends to maintain the free solute level and allows the solute clearance to rise to values which are much higher than the product of the plasma flow and the free solute concentration at the dialyser blood inlet [1]. If this hypothesis made by Sirich et al. is true, it would imply that the dissociation constant for these protein-bound solutes to albumin or other carrier proteins is very high and if this is the case, why then is the removal of these protein-bound solutes so cumbersome, as it would be simply governed by free concentration that is governed on its term by the disappearance rate to the dialysate? The paper by Sirich et al. does not address these questions, and this is a potential flaw of the paper.

Conclusions

Uraemic syndrome is a complex clinical picture that involves a large number of retention solutes much wider than the small water-soluble molecules. However, an assessment of the amount of dialysis delivered is vital. Kt/V urea, although not perfect, is a useful marker of adequacy. This urea-based standard provides a useful tool to avoid grossly inadequate dialysis. Dialysis dosing, however, based on measurement of a single relatively non-toxic solute can provide only a very limited guide towards improved treatment [7]. New dialysis strategies should aim to remove not only urea mainly because middle and protein-bound molecules appear to be correlated more frequently with deleterious biological, biochemical and clinical effects. Thus, the most logical approach in order to diminish the mortality on dialysis must be an individualized prescription of the duration and/or of the frequency of the dialysis treatment, developed through a global assessment of the proven predictors of morbidity and mortality. These parameters include nutrition, albuminemia, mineral metabolism, inflammatory markers, volume control, blood pressure, left ventricular hypertrophy and haemodynamic stability. Each of these variables seems to be associated with the duration and/or the frequency of the dialysis treatments. Even though several observational studies and preliminary randomized controlled trials seem to confirm these associations, time has come that interventional studies confirm these complex relationships.

Conflict of interest statement. The authors have no conflict of interest. This was a fully internally funded study without company involvement.

(See related article by Sirich et al. Selectively increasing the clearance of protein-bound uremic solutes. Nephrol Dial Transplant 2012; 27: 1574–1579.)

References


Received for publication: 20.11.11; Accepted in revised form: 14.12.11

*Nephrol Dial Transplant* (2012); Editorial Comments 1287