Once upon a time in dialysis: the last days of Kt/*V*?

Raymond Vanholder[1], Griet Glorieux[1] and Sunny Eloot[1]

[1]*Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium*

After its proposal as a marker of dialysis adequacy in the eighties of last century, Kt/V_{urea} helped to improve dialysis efficiency and to standardize the procedure. However, the concept was developed when dialysis was almost uniformly short and was applied thrice weekly with small pore cellulosic dialyzers. Since then dialysis evolved in the direction of many strategic alternatives, such as extended or daily dialysis, large pore high-flux dialysis, and convective strategies. Although still a useful baseline marker, Kt/V_{urea} no longer properly covers up for most of these modifications so that urea kinetics are hardly if at all representative for those of other solutes with a deleterious effect on morbidity and mortality of uremic patients. This is corroborated in several clinical studies showing a dissociation between removal of urea and that of other uremic toxins. In addition, randomized controlled trials showed no benefit of increasing Kt/V_{urea}. Finally, this parameter also hardly is evocative for metabolic or intestinal generation of toxins, for their removal by residual renal function and for the complex interaction of dialysis length with removal pattern and patient outcomes. We conclude that apart from being a baseline parameter of dialysis adequacy, Kt/V_{urea} insufficiently represents all novel strategic changes of modern dialysis. Kt/V_{urea} is too simple a concept for the complexities of uremia and of today's dialysis.

Kidney International advance online publication, 10 June 2015; doi:10.1038/ki.2015.155

KEYWORDS: hemodialysis; urea; uremia; uremic toxins

Correspondence: *Raymond Vanholder, Nephrology Section, Department of Internal Medicine, 0K12, University Hospital Ghent, De Pintelaan 185, Gent B9000, Belgium. E-mail: Raymond.vanholder@ugent.be*

Received 29 August 2014; accepted 4 September 2014

Kt/V_{urea} (clearance of urea multiplied by dialysis duration and normalized for urea distribution volume) was first proposed as a parameter of dialysis adequacy in a period of worrisome mortality on dialysis in the USA. After the randomized National Cooperative Dialysis Study had demonstrated that a higher time averaged urea concentration was related to higher hospitalization,[1] Kt/V_{urea} emanated from a post hoc mechanistic study on the same data.[2] The threshold of this absolute value was originally set at 0.8 but soon was increased to 1.2 or higher. With the introduction of Kt/V_{urea}, adequacy of dialysis was no longer assessed by a single static pre-dialysis value, of which the low concentration could be due to negative confounders such as low protein intake for urea or low muscle mass for creatinine. Kt/V_{urea} instead is a dynamic parameter that assesses removal by dialysis as a whole (Kt), including not only clearance but also dialysis length and above all a correction for body mass (V). For the first time not only the therapy but also the patient was taken into account by acknowledging that a voluminous person needs more dialysis compared with a tiny one. This led to a more standardized dialysis approach and was translated into a better survival with higher Kt/V_{urea} in essentially observational studies.[3,4]

However, Kt/V_{urea} quite soon appeared to be far from the only determinant of outcomes of dialysis. A study by Owen *et al.*[5] demonstrated a relation between urea reduction ratio (as surrogate for Kt/V_{urea}) and outcomes, but a much stronger consistent relationship was found for hypoalbuminemia, as an index of malnutrition and fluid overload. In an analysis of the Dialysis Outcomes Practice Pattern Study, dialysis length appeared an important determinant of survival, even in patients stratified for Kt /V_{urea}.[4]

When different thresholds of Kt/V_{urea} were compared in controlled trials, increasing its value above standard did not impact survival,[6,7] suggesting that the upper limit of improving outcomes based on this parameter had been reached. This raised the question whether Kt/V_{urea} can grasp all effects of modern dialysis in all its variants and also which potential pitfalls skew its interpretation.

THE CONCEPT OF KT/V_{UREA} IS BASED ON A TYPE OF DIALYSIS THAT IS OFTEN NO LONGER APPLIED

Urea kinetic modeling was developed when hemodialysis was applied almost systematically three times weekly with small pore cellulosic dialyzers causing substantial inflammatory reaction. Moreover, the session length of this dialysis was usually short, and as Kt/V_{urea} was conceived in the US

even shorter (mostly 2.5–3 h) than what was standard elsewhere (4 h).

Since then the dialysis concept has changed markedly, with many alternatives to standard, by the introduction of large pore high-flux dialyzers, convective strategies such as hemodiafiltration, extended dialysis, and frequent dialysis,[8] which all have been shown to better remove molecules with proven biological impact and/or result in better outcomes.[9] The question arises whether Kt/V_{urea} is still representative for the kinetics of solutes preferentially removed by these alternative strategies, which usually have no added value for the removal of urea in contrast to their impact on the elimination of many other solutes.

THE EVIDENCE OF THE TOXICITY OF UREA IS LIMITED

To the best of our knowledge, only a few experimental studies point to a toxic effect of urea at concentrations currently observed in uremia. D'Apolito *et al.*[10] found that urea induced the generation of Radical Oxygen Species (ROS) and insulin resistance *in vitro* and in mice. In an *in vitro* study, *V*aziri *et al.*[11] showed disruption of the intestinal epithelial barrier function by derangement of tight junctions. Trécherel *et al.*[12] explored regulatory proteins of apoptosis and showed an upregulation of Bcl2-associated death promoter, a pro-apoptotic protein.

The clinical equivalent to these experimental suggestions is, however, scanty. Adding urea to the dialysate up to concentrations two to three times higher than usual in dialysis patients induced no consistent changes in uremic symptoms.[13] Increasing urea removal in controlled trials had no impact on hard clinical outcomes.[6,7] An observational study by Koeth *et al.*[14] found an association with mortality of homocitrulline, a marker of carbamylation to which also urea is supposed to contribute. However, the concentration of urea was only modestly correlated to that of homocitrulline, with an R^2 of 0.14, suggesting that other factors than urea were more important for homocitrulline generation and its association to death. In addition, urea by itself was not related to mortality.[14]

Thus, urea, in spite of its everyday application as marker of dialysis adequacy, has rarely been assessed for its toxicity and up till now has not been proven in clinical studies to affect outcomes. Its choice as a marker cannot really be supported by robust biochemical or clinical arguments. However, even if urea would be a recognized toxin, there remain questions about the representativeness of Kt/V_{urea} for the removal of other uremic retention solutes.

THE KINETICS OF UREA ARE NOT REPRESENTATIVE FOR OTHER SOLUTES, OF WHICH TOXICITY IS BETTER DOCUMENTED

Basic principles of kinetic modeling

(Figures 1 and 2) The concept of dialysis kinetic analysis lays at the origin of urea kinetic modeling.[15] The basic principle is the mirror image of pharmacokinetics, where the distribution pattern of a drug throughout the body to reach the most remote compartments is studied after the plasma concentration rises

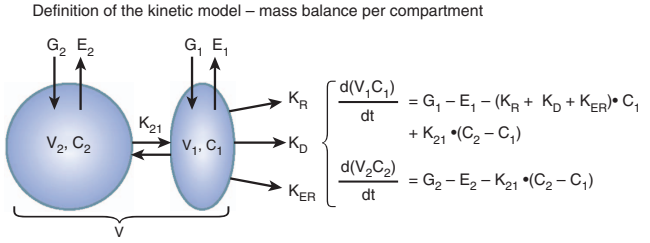

Figure 1 | Basic principles of kinetic modeling. Uremic solute is primarily removed from the plasmatic compartment by dialysis causing a fast decrease in its concentration. Only once this plasmatic concentration starts to decrease sufficiently, concentration in the extra-plasmatic compartment can also decrease, based on a diffusive concentration gradient. C_1 and C_2, solute concentration in V_1 and V_2; E_1 and E_2, elimination rate in V_1 and V_2; G_1 and G_2, generation rate in V_1 and V_2; K_D, dialyzer clearance; K_{ER}, extra-renal clearance; K_R, renal clearance; K_{21}, inter-compartmental clearance; V, distribution volume; V_1, plasmatic volume; V_2, extra-plasmatic volume.

following administration. In dialysis kinetics, the disappearance of solutes out of these remote compartments is studied during their removal by dialysis. Although a large number of different compartments are possible, in theory two compartments are critical: (1) the plasma compartment, from which solute removal by dialysis is relatively easy if dialyzer pores are large enough, and (2) the (sum of) extra-plasmatic compartment(s) where solute concentration tends to lag behind on plasma concentration, as inter-compartmental shifts largely depend on diffusion from high to low concentration, which is hindered by a variable resistance from the compartmental boundaries. The more important this resistance, the more dialysis adequacy will be reduced. Also post-dialytic rebound, creating a quick increase in uremic solute concentration immediately after dialysis due to the backlog of extra-plasmatic concentration, is an epiphenomenon of this process (Figure 2).

Resistance to shifts between compartments is minimal for urea compared with other solutes,[16] which, as a consequence, are more difficult to remove. Hence, the question should be raised whether urea kinetics are representative for uremic toxins at large.

In the next sections, we will describe discrepancies between solute kinetics of urea and that of other uremic toxins, based on the classical subdivision of uremic toxins in small water soluble compounds, protein-bound solutes, and middle molecules.[17]

Small water soluble compounds

The question has been raised whether urea as one of the small water soluble compounds would have similar kinetics as other solutes with the same characteristics, such as the guanidino compounds, which have a well-documented biologic (toxic) impact.[18] However, when their kinetics were compared, distribution volume was definitely different and mostly larger for the guanidino compounds as compared with urea, giving rise to less efficient removal.[19] Those mathematical findings were corroborated by assessing *in vivo* concentrations of guanidino compounds in erythrocytes, the most easily