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Clearance dose in acute kidney injury

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In the last decade substantial efforts have been made towards defining the dose threshold for renal replacement therapy in acute kidney injury (AKI), which would enable to reduce the high mortality associated with this common complication in hospitals.

The first problem we came up against was how to measure the actual dose we applied reliably. The second was to find a dose range which would prove as beneficial as possible in terms of patient survival and recovery from AKI.

We have the option of treating our patients with severe AKI by means of intermittent haemodialysis (IHD) or continuous renal replacements therapies (CRRT). Our choice of the technique is conditioned by two factors: the first and most important of these is the severity of the patient's illness; thus, patients with haemodynamic instability are usually treated with CRRT and more stable patients are with IHD. The second factor is determined by where the patient is to receive treatment or by logistic criteria. In cases in which patients have been admitted to hospital wards or acute nephrology units, they are treated using IHD and patients admitted to critical care units are subjected to CRRT. This was demonstrated in the large-scale epidemiological study by Uchino et al.[1] However, it is not the aim of this "Editorial comment" to opt in favour of one or other of these therapeutic alternatives. Recent studies, such as the multi-centre French study,[2] have shown that, if they are carefully applied, either of the two variants can produce equivalent results in terms of survival, and properly conducted meta-analyses have not resulted clearly in favour of one or other modality.[3] The IHD used three decades ago shows no resemblance whatsoever to the technique applied today. Nowadays the generalized use of bicarbonate concentrates in the dialysis fluid, together with better water treatment and the control of conductivity, pH and the temperature of the monitors used, as well as the fact that the membranes are becoming increasingly biocompatible and permeable, have made IHD a highly effective tool, even in the haemodynamically unstable patient.

Generally speaking, in order to measure the dose in the case of IHD, extrapolating the knowledge acquired from patients with end-stage or stage 5 CRF, the calculation of the urea Kt/V value has been used (where K is clearance, t effective dialysis time and V the urea distribution volume). The Daugirdas mathematical formula has become widely used for such calculations.[4]

In the Schiffl et al's study,[5] daily IHD, compared to classic HD schedules applied every 2 days, improved the 2-week survival, which was 72 as opposed to 54% respectively. In the former treatment schedule, the clearance dose adjusted for time and urea volume distribution (Kt/V) virtually duplicated its conventional regime counterpart, although in both groups the results were distinctly lower than the expected.

Another major problem, apart from not being able to achieve the proposed dose, lies in the fact that the total proportion of body water (urea distribution volume) varies much more widely in the acute than in the chronic patient, a phenomenon which is especially important in the critical patient. Furthermore, methods designed to determine body water (e.g. vectorial bioimpedance), which are used more and more frequently in the patient with end-stage CRF, are rarely applied in the critical patient. This is why, and with the primary aim of not introducing inaccurate factors, the calculation of Kt is being recommended, in other words the absolute "clearance over time" value which has not been adjusted to the volume of body water. Reference values, which only show differences for sex, are then established. In the latest models of monitors the implementation of the calculation of ionic dialysance allows the dialysis dose to be constantly measured, as well as the accumulated dose for each IHD session, reliably and in real time. In the current issue of the journal NEFROLOGÍA two studies, which show us the results and its reliability compared with other

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calculations, have been published.[6,7] Beforehand[8,9] another two studies of excellent design had laid the groundwork for these two studies. The first study[6] includes an evaluation of Kt by ionic dialysance and demonstrates an optimal correlation without significant differences in the values obtained with respect to the reference methods. In this study an evaluation of the difference in the dose obtained in relation to the prescribed dose was not included, but the authors obtained a Kt value which was lower than values which are taken as standard in patients with end-stage CRF.

The second study[7] reaches the conclusion that the measurement of dialysis dose by means of Kt identified a greater number of inadequate sessions than the standard Kt/V_{UREA} method, these accounting for a total of 71 compared to 31% of those detected using the classical method.

It is true that when we introduce weight and urea distribution volume (nearly always unknown in patients who are critical), we may apply an inaccurate value, but it is also evident that, when we establish absolute values for males (45-50L) and females (40-45L), we are making a simplification which is very likely to be exaggerated. A patient weighing 50kg is in no way comparable to one who weighs 120kg so, in our opinion, it would be more sensible to establish scales or intervals which could correct these discrepancies.

The calculation of clearance values in CRRT is simpler. If we concentrate exclusively on measuring the elimination of small molecules (the simplest example of which is urea), we can adjust clearance to the volume of effluent, albeit plasma ultrafiltrate (haemofiltration), dialysis fluid (haemodialysis) or a mixture of both (continuous haemodiafiltration). The flows permitted for the dialysis liquid by CRRT monitors virtually manage to equate the concentration of the effluent output with that of the patient, so that clearance (K_D) will be the same as the dialysis flow (Q_D). The same is true regarding the ultrafiltrate volume ($K_F = Q_F$), where the sieving coefficient (S) will be the unit for small molecules and will gradually decrease as the Einstein's molecular radius increase. The *cut off* point will depend very much on how the membrane is designed and on how its pore sizes are distributed. However, we need to remember that continuous techniques are not entirely so, given that their application involves interruptions,[10] owing to problems with blood clots in the circuit or times when the treatment is not effective (*bypass)* because of the need for intervention on the part of nursing personnel (e.g. the changing of bags, emptying of effluent), as well as times in which the patient is disconnected from the circuit in order to perform surgical interventions or radiological explorations. Occasions when the dialysis machine demands the attention of nursing personnel with alarms, which can sometimes be quite irritating, are relatively frequent (figure 1). Consequently, we need to programme a longer regime than we really think will be needed.

Figure 1. Example of how irritating the alarms of continuous technique monitors can be - Result of the reaction of a relative who decided to curtail the persistent sound of monitors by punching the screen.

In their classic study Ronco et al[11] analysed survival 14 days after finalizing haemofiltration, using a polysulfone membrane with replacement fluids in post-dilution containing lactate with 20, 35 and 45ml · kg^{-1} · h^{-1}, and a survival rate of 41, 57 and 58%, respectively, was obtained. In this way, an ultrafiltrate "magic figure" (convection) of 35ml · kg^{-1} · h^{-1} was obtained. After this level haemofiltration was defined as "high volume". However, this single centre study included a small proportion of patients with sepsis (11 to 14% in randomized groups), a percentage which was lower than that of other studies with similar characteristics, and the analysis of this subgroup of patients was not statistically or clinically significant when the *hazards ratio* was applied. The view that convection at these levels, and even at much higher levels (defended by certain influential research groups), could eliminate mediators of the inflammatory cascade and/or modulate unfavourable responses was consolidated, inclining the balance in favour of the patient.

In the study by Saudan et al[12] an increase in survival was demonstrated when diffusion (CVVHDF) was added to a normal dose of ultrafiltrate (not high volume) and it was concluded that survival improved, no longer as a result of convection but of the clearance dose for small molecules. The study was well designed and included over 100 patients in each randomized group (206 in total).

It is worth stressing that in CRRT we use highly permeable membranes, so that, although we only work in the context of dialysis (without haemofiltration), with transmembrane pressures (TMP) close to zero a convective clearance effect will be added to the diffusive clearance. The first is produced as a result of the interplay of pressures within the dialyser cartridge: when blood enters the dialyser, it does so at a pressure which is higher than that of the dialytic compartment so that internal filtration occurs and, when it is expelled from the

dialyser, the opposite takes place and retrofiltration occurs. As a result, we can obtain up to 30ml/min of convective clearance, which is not directly controlled when the treatment regime is prescribed.[13] The principle is the same as the one which is being used to eliminate light chains in the treatment of myeloma kidney.[14,15] An *in vitro* study has demonstrated that the clearance of medium-sized molecules in CRRT can be the same with haemofiltration as with dialysis and it can even be better when filters with a small surface area are employed, a phenomenon which has been partly attributed to the internal polarization of the proteins that block membrane pores during ultrafiltration, which impedes the elimination of medium-sized molecules.[16]

Two large multi-centre studies have attempted to determine with some degree of accuracy an optimal dose for the treatment of the AKI patient. The American study, known by its acronym ATN,[17] did not manage to demonstrate advantages at higher doses (20 as opposed to 35ml · kg^{-1} · h^{-1} in CRRT with haemodiafiltration or with IHD, applying 3 compared to 6 sessions per week), selecting one or other technique, depending on the haemodynamic stability of the patient. In other words, continuous techniques were used for unstable patients and intermittent techniques for more stable patients (severity score on the SOFA cardiovascular scale of 3 or 4 points for CRRT and less than 3 for IHD). This has already been refuted by different groups, including the Spanish group, which recommends a dynamic approach that constantly adjusts the dose, depending on the condition of the patient.[18]

More recently the Australian-New Zealand study, RENAL,[19] concluded. In this study 60 and 90-day survival rates were identical if a standard dose was applied (25ml · kg^{-1} · h^{-1}) rather than an intensive dose (40ml · kg^{-1} · $^{-1}$), both using haemodiafiltration in a Q_D:Q_F proportion of 1:1 and with post-dilution replacement. As well as CRRT being indicated, owing to acute kidney injury (AKI), the inclusion criteria for patients consisted of at least one of the following: oliguria (diuresis less than 100 ml during a period of 6 hours) with a lack of response to resuscitation measures using serums, serum potassium levels higher than 6.5mmol/l, significant acidaemia (pH less than 7.2), plasma urea nitrogen levels (BUN) higher than 70mg/dl (25mmol/l), serum creatinine levels higher than 3.4mg/dl (> 300μmol/l) or clinically significant oedemas (e.g. lung oedema) and over 700 patients were included in each group (total 1,464 patients). Survival was the same for both groups. The group which received highly intense treatment exhibited more cases of hypophosphataemia, which is why they insist on the idea of avoiding problems caused by excessive dosage, which ties in with the recently coined concept of "dialtrauma".[20]

In conclusion, with respect to the treatment dose in AKI patients, we believe that it is better to measure the dose than not to measure it, but that, in terms of quantity, more is not necessarily better. As we advance in our search for the ideal minimum dose, we need to concentrate on good clinical practice, using great care and common sense, and adapting ourselves to the context and the technological, human and economic resources at our disposal. Intuitively, we are led to think that during the initial phases of multi-organ failure more doses are needed than during phases of recovery or immunological paralysis. However, as we understand it, this question still remains unanswered.

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