What has balANZ taught us about balancing ultrafiltration with membrane preservation?

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It has been difficult to show clinically meaningful benefits of the biocompatible peritoneal dialysis solutions. The balANZ trial is the most important attempt to do this so far, showing delayed time to anuria, less frequent and severe peritonitis and in this edition of NDT differential effects on membrane function. In the short term, the biocompatible, normal pH, low glucose degradation product (GDPs) containing the fluid 'Balance' increased solute transport and reduced ultrafiltration (UF) capacity, whereas no progressive changes in membrane function were seen over two years in contrast to the conventional solution. How these short- and long-term differences interact with the preservation of residual renal function and protection of membrane function undoubtedly shed light on how we should manage patients on PD.

The balANZ trial is the most significant trial yet undertaken to evaluate the clinical benefits of a biocompatible peritoneal dialysis solution. An investigator led study, it evaluates relevant endpoints including preservation of residual renal function [1], peritonitis [2] and membrane function [3]; in this edition of NDT, the authors present their analysis of the differing effects on membrane function [3]—both solute transport and ultrafiltration (UF) capacity—thus, completing the picture of what turns out to be a relatively complex and interesting ‘balance’ between achieved UF, residual renal function and the changing effects on membrane function over time.

The investigators used the well-established peritoneal equilibration test to quantify membrane function and it is important to recognize that the first test was done 1 month after commencing peritoneal dialysis (randomization occurred at the start of treatment in this incident cohort). Excellent equivalence of the patient characteristics was achieved at baseline with equal drop-out between the groups, so the observed differences in the membrane function when first measured as well as at subsequent time points can reasonably be assumed to be due to the different effects of the two solutions on the membrane. The biocompatible Balance solution caused solute transport to be modestly increased when compared with the Stay-Safe solution, and this was associated with a reduced UF capacity that was rather more than could be explained by the differences in solute transport alone (see Figure1). This seems to imply that there are two effects of the Balance solution: the modest increase in solute transport which could be explained by an increase in peritoneal blood flow, and in fact we know from the 'Euro-Balance' trial [4], in which an identical increase in solute transport was observed, that this is reversible (there was an equal and opposite effect of the two solutions in

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this cross-over design study). The disproportionate reduction in UF capacity is less easy to explain, and it implies a change in the osmotic conductance and is again likely reversible as shown in ‘Euro-Balance’. This reversibility is important as it makes it more likely that these changes are functional rather than structural.

The ‘balANZ’ study also confirms much more clearly the ‘Euro-Balance’ observation that this reduction in UF capacity was associated with a lower overall achieved daily UF. This is more significant than might at first be appreciated—partly because the authors have expressed the data as the overall ‘ultrafiltration’ volume rather than the net UF following adjustment for overfill [5]. The vast majority of patients enrolled into the trial were treated with continuous ambulatory peritoneal dialysis and the average overfill for both solutions (fortunately the same) was 100 mL per exchange—which means that for a typical CAPD prescription using four exchanges per day that UF is over-estimated on average by 400 mL per day (confirmed with David Johnson, personal communication). This in effect means that the Balance group achieved ∼50% of the UF compared with the Stay-Safe group during the first 9 months of the study with an initial daily net removal of just 300 mLs—little more than fluid balance neutral—compared with 600 mL in the Stay-Safe patients. It is clear that the investigators were not aware of this discrepancy as the glucose prescription did not differ between the groups significantly throughout the study (additional evidence that there was a true difference in the UF capacity associated with these two solutions). However, despite what might seem a potential problem—significantly less UF associated with the biocompatible solution—it would appear that, if anything, this is associated with a clinical advantage: better preservation of residual renal function and less peritonitis.

In contrast to these initial differences in membrane function, the longitudinal changes tell a quite different story. The biocompatible Balance solution had no further impact on membrane function over 2 years, whereas the Stay-Safe solution was associated with a steady rise in solute transport and a fall-off in the UF capacity—which was of a magnitude expected from the change in the small-solute transport rate (see Figure 1), reflecting the previously described changes in membrane function seen with non-biocompatible dialysis solutions [6]. This difference could not be explained by differing glucose prescriptions, so it must therefore be attributed to the different properties of the biocompatible solution, i.e. a normal pH and the ultra-low concentrations of glucose degradation products (GDPs). Not all biocompatible solutions are the same in this regard, so care is needed in interpreting the mechanism of action of these solutions on membrane and kidney function.

So what has balANZ taught us? It is easy to jump to the conclusion that just because in the past patients with rapid solute transport at the commencement of CAPD had worse outcomes, we should be concerned that this is an unwanted effect of this more biocompatible solution. This would be a mistake; however, the increase in solute transport is very modest, did not lead to excessive fluid reabsorption and in general the worse outcomes associated with a high transport status have now all but disappeared with recognition and modification of prescription practice [7, 8]. Does it mean that Balance causes more intra-peritoneal inflammation? Several studies have now shown that local intra-peritoneal interleukin (IL)-6 production is the best determinant of transport status [9–11], but it is far from certain that this is necessarily a bad thing. It may reflect better viability of those cells responsible for making IL-6, as might be expected in a more normal pH environment. This improvement in cell viability, demonstrated in ex vivo and animal studies [12], could translate into better preservation of the intra-peritoneal host defence mechanisms which is reflected in the reduced peritonitis observed in this study, adding to the biological plausibility of this observation. It is also important to put this finding in the context of other studies evaluating biocompatible solutions. In general, previous studies, in which either isolated comparisons of standard glucose-containing solutions with their biocompatible counterparts or in combination with other ‘low’ GDP solutions were undertaken (e.g. icodextrin and nutrineal), have observed similar increases in solute transport, especially in patients new to PD. Interpretation is difficult as the studies are confounded by differences in pH, lactate versus bicarbonate buffer and the unknown isolated effects of icodextrin and amino acids, but it does appear to be a feature of more biocompatible regimes [13–17]. Increased IL-6 production is observed in some combinations [16] and not others [14, 15]; furthermore, vascular endothelial growth factor rather than IL-6 may be the downstream mediator in the pathway determining peritoneal blood flow. Analysis of dialysate biomarkers in balANZ is eagerly awaited.

The absence of longitudinal changes in membrane function is more clearly a benefit of peritoneal membrane exposure to
Balance. Given that cohort studies have consistently shown that increasing solute transport is the first sign of acquired membrane injury [6], then a lack or delay of this process is a very positive study finding. Whether this will translate into protection against the longer term, more serious membrane injury seen in a relatively small proportion of PD patients which is associated with acquired reduction of osmotic conductance (reduced membrane efficiency for a given osmotic gradient) would not be expected to be answered by a study of this duration. The main problem that has bedevilled clinical studies of the biocompatible solutions exploring important clinical endpoints, such as UF failure, is that they are impossible to do without recruiting vast numbers of patients and extending follow-up to at least 5 years. Hopefully, the authors will continue to follow up this cohort (although they had a high level of drop-outs so this may not be meaningful) but it is likely that other types of study design will need to be undertaken to link practice patterns to these less common endpoints.

The most controversial aspect of this study is the mechanism by which the Balance solution delayed the onset of anuria. Publication of the membrane function data certainly sheds further light on this issue. Three main hypotheses have been entertained: first, reduced systemic levels of GDPs and their resultant advanced glycation endproducts (AGEs) might lead to reduced nephrotoxicity in the Balance group. The circulating AGEs imidazolone and carboxymethyllysine were reduced (≤20–30%) in the ‘Euro-Balance’ trial [4] when the patients were on the low GDP solution, a pattern of reduction that differs from other ‘low GDP’ regimes [18], so this is plausible, although determining cause and effect is difficult given their inter-dependency on kidney function for removal and the fact that the levels remain high on either solution [19]. Second, given that the Balance patients had less frequent and less severe peritonitis [2] and the potential for inter-current illnesses to accelerate loss of residual kidney function due to hypovolaemia, this is a theoretical possibility but not in fact a known association. Third, the reduced UF observed in the Balance group protected against the loss of residual diuresis. Given the wealth of observational data [20] and clear association between changes in the extracellular volume status and urine volume in interventional trials [21–23], this is an attractive explanation. What the present analysis [3] adds is a clear explanation as to why the Balance group has less UF—at least during the first year of the study which is when the main differences in the residual urine volume were observed: by whatever mechanism, compared with Stay-Safe the Balance solution does cause membrane changes in a short term which reduce the UF capacity. The consequent fall in the daily UF volume was almost exactly matched by the preserved urine volume. It is the big picture, however, that is important here [13]. Looked at from another perspective, the balANZ group has done an even more important study than they set out to do. Observational studies in PD and haemodialysis patients have convinced us that preservation of residual renal function is a worthy goal, but it does not necessarily follow that a treatment strategy aimed at minimizing UF to preserve urine volume will be a safe one. Indeed one of the main criticisms levelled at PD in general is that it can cause harmful overhydration [24]. If we now consider balANZ as a trial comparing a low versus high UF target during the first year of treatment, it would appear that avoiding excess UF can preserve renal function without compromising patient outcomes or other surrogate markers of inadequate volume control [1]. Although there remains a lot to learn about how we should balance UF with the preservation of residual function, balANZ seems to tell us that this line of research enquiry is worth pursuing. Given the problems alluded to above in undertaking randomized trials of sufficient size and duration, the PD community will have to work together to achieve this. The UK-wide Peritoneal Dialysis Competitive Risk Analysis For long-Term outcomes study, which will marry prescription and clinical phenotype with a comprehensive biorepository, and the forthcoming international Peritoneal Dialysis Outcomes and Practice Patterns Study provide the best opportunity to achieve this goal.

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CONFLICT OF INTEREST STATEMENT

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