Peritoneal Dialysis: Nanoparticles Have Entered the Game

Dialysate fluids are essential to drive water and solute transport across the peritoneal membrane in patients treated by peritoneal dialysis (PD). Water transport is driven by crystalloid (glucose-based) or colloid (icodextrin) dialysates, whereas solutes move across the peritoneal membrane by convective and diffusive transport (1). Despite its advantages, the use of PD may be hampered by the relatively low clearance for specific solutes, a situation that can be limiting in critical circumstances such as congenital metabolic disorders or drug intoxications. A recent study, based on the physiology of solute transport combined with the latest technological advances in nanomedicine, supports the potential benefit of adding liposomes to the dialysate, in an effort to improve the extraction of ionizable drugs and ammonia (2).

Liposomes are nanometric particles formed by a phospholipid bilayer membrane surrounding an aqueous core. The technology is established for sustained or targeted drug delivery, with several formulations already on the market (3). The possibility of creating liposomes with a transmembrane pH gradient offers the opportunity to trap uncharged molecules (such as ammonia or drug metabolites) which diffuse from the blood into the acidic core of the liposome, become protonated and then retained in the vesicle due to the low diffusion of charged molecules across lipid membranes. Proof-of-principle studies have shown that intravenously injected nanosized acidic liposomes can trap the calcium channel blocker verapamil in the blood in case of intoxication (4). However a limitation of the intravenous injection is that it does not allow efficient removal of the drug from the body.

In their novel study, published in *Science Translational Medicine*, J.-C. Leroux and colleagues extended the paradigm by showing that liposome-supported peritoneal dialysis (LSPD) is able to extract endogenous ammonia as well as verapamil in rat models (2). To perform LSPD, acidic liposomes were added to standard, 7.5% (w/v) icodextrin dialysate. Relatively large (850 nm) liposomes of a given bilayer composition were shown to be stable in the dialysate and minimally reabsorbed from the peritoneal cavity into the blood (0.2% of the total injected dose after 4 h of PD). *In vivo* experiments showed that the acidic liposomes (initial internal pH, 3.2) were able to extract endogenous ammonia from the blood in a fast and efficient manner (7.5-fold and 20-fold enrichment in PD fluid vs plasma after 30 min and 3 h of LSPD, respectively).

Liposome-supported peritoneal dialysis was also tested in a rat model of verapamil intoxication. After 3 hours of LSPD, the drug was removed from circulation much more effectively (30-fold increase) than with the dialysate (icodextrin) alone. Furthermore, 3 hours of LSPD was able to significantly decrease the hemodynamic effects induced by a high dose of verapamil in this model. Of note, some liposomes containing verapamil diffused into the blood after 6 hours of LSPD. As the drug is trapped in the liposome core, it should remain pharmacologically inactive.

Besides verapamil, LSPD was able to extract different basic and acidic drugs often associated with intoxications, including propranolol, amitriptyline, haloperidol, phenobarbital, and salbutamol, with a plateau reached after 2 to 4 hours of PD. Furthermore, basic liposomes obtained using a calcium acetate buffer (internal pH, 10.0) were shown to be able to extract propionic and isovaleric acids *in vitro*, opening perspectives for treatment of congenital metabolic disorders.

These data show that supplementing icodextrin dialysate with acidic or basic liposomes efficiently increases the extraction of a wide range of small metabolic compounds or drugs associated with common intoxications. The characteristics of LSPD, including simple access, biocompatibility, high extraction capacity, and very limited diffusion into the circulation (at least for short dwells), make this technique particularly attractive for the treatment of neonates with metabolic diseases leading to hyperammonemia. The use of LSPD would offer a fast and therefore neuro-protective detoxication with a minimized risk of hemodynamic instability often faced in HD. The fact that the dialysate is drained at the end of the dwell also means a more efficient detoxification of any toxic compound. Of note, LSPD does not work for neutral molecules such as urea, high molecular weight compounds such as heparin, or charged molecules like phosphate ions.

The promising features of LSPD will need to be supported by further studies addressing the manufacturing and long-term stability of liposomes, the feasibility of using glucose-based dialysates instead of icodextrin, and transport kinetics and metabolic clearance in appropriate animal models.

DISCLOSURES

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