Review Article

The Role of Diuretics in the Management of Fluid Balance in Peritoneal Dialysis Patients

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Abstract

Diuretics have an important role in fluid management in peritoneal dialysis patients. Appropriate use of diuretics can increase urine volume and sodium excretion, results in better volume control and possibly patient outcome. This article discusses about the role of diuretic drugs to control sodium and water balance in peritoneal dialysis patients and how to apply to clinical practice.

Key words: diuretics, fluid balance, peritoneal dialysis

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Introduction

To maintain the body fluid and sodium balance are extremely important in end-stage renal disease patients who on renal replacement therapy (RRT). Although RRT is now widespread, it also found that the death rate of patients with end-stage renal disease (ESRD) is 10 - 20 times higher than the general population. The cause of death is a mainly cardiovascular disease[1]. This article will discuss about the role of diuretic drugs to control sodium and water balance in peritoneal dialysis (PD) patients and how to apply to clinical practice, including the opportunity to develop further clinical trial in the future.

Clinical Problems

The data from the United States Renal Dada Survey (USRDS) from 1996 to 2000 showed at the beginning of RRT, the incidence of heart failure in ESRD patients was 30 - 45 percent and increased with increasing age. In ESRD patients undergoing hemodialysis were hospitalized for heart failure more often than peritoneal dialysis patients in the first RRT year[2]. However, over-hydration often happens in peritoneal dialysis patients, as shown in the retrospective data from Tazamaloukas et al, 25 percent of 262 PD patients had signs and symptoms of excess water, all of the participants were edematous, 80 percent had pulmonary congestion, 76 percent had pleural effusion, 76 percent had systolic hypertension and 66 percent had diastolic hypertension. The hospitalization rate in PD patients with hypervolemia was 4.1 ± 5.8 days per patient-year higher than general PD patients. The factors that affect over-hydrated state were lack of control of dietary salt and water, inappropriate PD prescription, high or high average transporter peritoneal membrane (from the peritoneal equilibration test)[3].

The incidence of hypertension in PD patients in the United States (BP ≥ 150/90 mmHg) and Italy (BP ≥ 140/90 mmHg) was higher than the general population in both studies (30 and 88 percent respectively)[4, 5]. It was also found that more than 50 percent of patients had no nocturnal BP dipping that associated with increased cardiovascular disease. Over-hydration and high blood pressure affect survival rate of PD patients, thus good control of water balance and achievement of normo-tension are major goal for treatment.

The principle of management to control water and salt balance in peritoneal dialysis is restriction of salt intake and adjusting treatment to get rid of salt and water from their bodies. There are three important keys:

1. Adjust the prescription of PD regimen to increase ultrafiltration volume.

2. If residual urine remained, consider to adjust the dose and type of diuretic regimens properly to increase urine volume.

3. Preserve residual renal function, which helps to remove excessive water and electrolyte, by using ACEI / ARB and avoiding nephrotoxic agents such as NSAIDS and aminoglycoside.

The mechanism of action of diuretics

1. Loop diuretics include furosemide, bumetanide, and ethacrynic. They inhibit Na^+-K^+-$2Cl^-$ co-transporter at the thick ascending limb of the loop of Henle that enhanced excretion of water, sodium, potassium and chloride (Figure 1A). Loop diuretics are the main drug used in patients with end-stage renal disease because they are effective even in patients with reduced renal function. However, the decrease in the filtration rate of the kidneys effects on reducing transport diuretic to the site of action. In the case of the glomerular filtration rate (GFR) less than 15 milliliters per minute, the drug was secreted into the tubular lumen only 10 - 20 percent of patients with normal renal function[6]. The effect of this drug is minimal in patients with GFR of less than 10 milliliters per minute and less than 100 milliliters of urine[7].

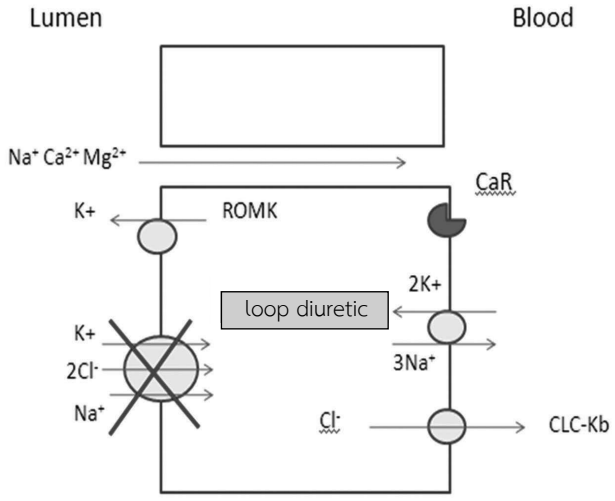

Figure 1A shows the effect of loop diuretic drugs inhibit Na^+-K^+-$2Cl^-$ co-transporter at the thick ascending limb of the loop of Henle.

2. Thiazide diuretics include hydrochlorothiazide, metolazone, indapamide and chlorthalidone. They inhibit Na^+ - Cl^- co-transporter at the distal tubule (Figure 1B). Patients whose renal function impairment should be given high enough doses to deliver thiazide diuretics to the distal tubular lumen. For example, patients with decreased renal function, mild to moderate level, should use hydrochlorothiazide 50 - 100 mg per day and 100 - 200 mg per day in patients with severe kidney function decline[8]. However, patients with glomerular filtration rate (GFR) of less than 30 milliliters per minute, hydrochlorothiazide may perform poorly. It is often used in combination with the loop diuretics[9]. Metolazone is a drug that has a long half-life and it is the main thiazide drug that is usually used with loop diuretics in patients with end-stage renal disease. The thiazide has effects on decreasing peripheral vascular resistance independent of natriuresis, thus the drug can be used to treat hypertension in patients with chronic kidney disease[10].

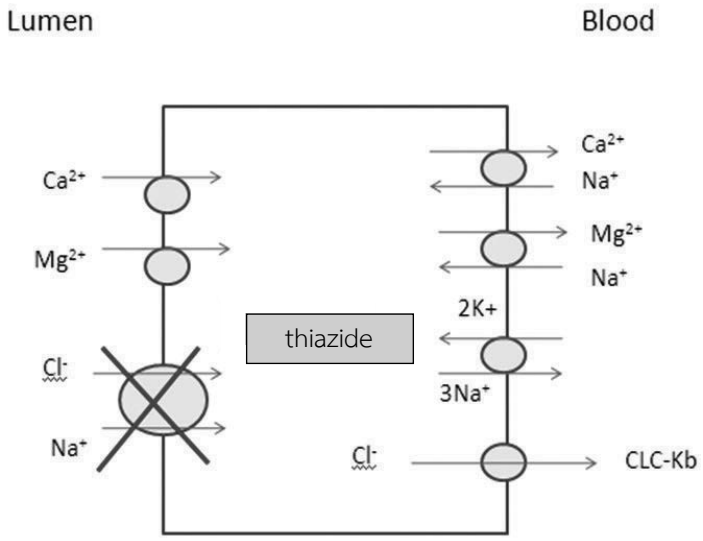

Figure 1B shows the effect of thiazide drugs inhibit Na^+- Cl^- co-transporter at the distal tubule.

3. Potassium-sparing diuretics include spironolactone, amiloride and triamterene. They are active at cortical collecting tubule. Spironolactone competes for aldosterone binding to aldosterone receptor to increase excretion of sodium, water and chloride but increase potassium reabsorption. Amiloride and triamterene restrain epithelial sodium channels to inhibit the reabsorption of sodium, and to minimize loss of potassium in urine (Figure 1C). The caution in the use of these drugs in chronic renal failure patients is hyperkalemia.

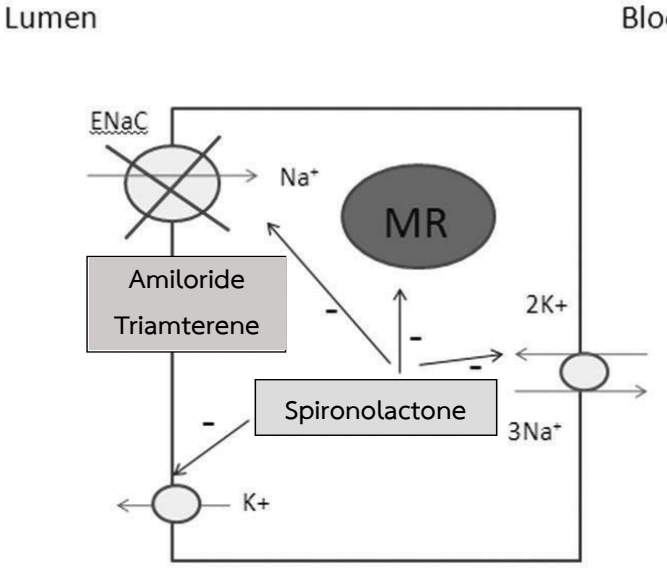

Figure 1C shows the effect of diuretic drugs at principal cell of collecting tubule; triamterene and amiloride inhibit epithelium sodium channels in the luminal membrane. Spironolactone binds to the aldosterone receptor in the cytoplasm to inhibit epithelium sodium channels, reduce of sodium-potassium ATPase function, enhances Na^+ excretion and reduces K^+ wasting.

4. Vasopressor V2-receptor antagonists are a new group of diuretic drugs. They produce aquaresis by interfering the action of vasopressin type 2 receptors in the collecting ducts, thus increasing the excretion of solute free water. Vasopressin type 2 receptor is the main receptor for maintaining water balance which increase water transport passes water channel that called aquaporin 2 channels. Vasopressor V2-receptor antagonists include tolvaptan, lixivaptan, conivaptan, mozavaptan and satavaptan.

The major side effects of diuretics in dialysis patients

1. The loop diuretics

The most common side effects of these drugs are ototoxicity, especially in patients receiving high doses intravenous injection. Ototoxicity often occurs temporary and reversible when the drug is stopped. The risk is higher in patients who receive furosemide than bumetanide and ethacrynic acid[6]. One study found that when gave an intravenous furosemide rate 25 mg per minute, the hearing disorder was 2/3 of the patients while dose 15 mg per minute found only minimal hearing disorders. The researchers suggest that the rate of furosemide in intravenous injection should be less than 4 mg per minute to avoid adverse effects on the ear[11]. Rastogi et al studied on an oral dose of furosemide in patients with kidney disease. They showed no hearing impairment in patients who received furosemide less than 2 grams per day[12]. However, there was a

case report of permanent hearing loss in patients taking low-dose furosemide[13]. Furosemide should be carefully used especially in the high dose.

2. Aldosterone antagonists

Hyperkalemia is a major side effect of aldosterone antagonist in patients with chronic kidney disease. The incidence reported up to 10 percent and increased when used with other drugs, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, trimethoprim, non-steroidal anti-inflammatory drugs and the antifungal azole.

Baker et al reviewed the literature regarding the safety of using mineralocorticoid antagonists in hemodialysis patients, spironolactone dose was varied from 12.5 mg three times per week to 300 mg per day. It showed that the drug was safe in hemodialysis patients. The occurrence of severe hyperkalemia was rare. However, data from these studies was a small study without control group and patients were followed by a short period[14]. Taheri et al studied a prospective randomized double-blind placebo controlled trial to check the safety and efficacy of spironolactone which was given 25 mg every other day to 25 PD patients who had heart failure with New York Heart Association class III or IV. Patients in both groups had non-significance increased potassium level. There was only 1 patient who had hyperkalemia (≥ 5.7 mmol per liter)[15].

In conclusion, aldosterone antagonists can be used safely in end-stage renal failure patients who receiving renal replacement therapy. The benefits of these diuretics are improved cardiac function and reduce left ventricular mass in moderate to severe heart failure patients. However, the potassium level of patients should be closely followed, especially in patients who received the combined drugs that cause high potassium.

The clinical study data

Data from many clinical trials showed the effects of water and sodium removal on morbidity and mortality in peritoneal dialysis patients. Ates et al followed 125 patients for three years. They found that the mortality rate of PD patients could be predicted by sodium excretion. Also, the increasing of systolic blood pressure was associated with higher mortality. While the clearance of small molecules (Kt/V urea) and creatinine (total creatinine clearance) was not significantly associated with mortality of PD patients[16]. Moist et al studied the factors affecting the decline of residual renal function in ESRD patients who undergoing hemodialysis and peritoneal dialysis. They found that patients who had a history of heart failure were significantly associated with faster reduction of residual renal function. But to prevent and correct heart failure could not slow the decline of residual renal function[17].

The maintenance of water homeostasis in PD patients can reduce rates of hospitalization and death from cardiovascular disease. Euvolemic state can help to control blood pressure more effectively and reduces the use of anti-hypertensive drugs. Analysis of data from the CANUSA study found that residual renal function was more important than peritoneal clearance in predicting outcome in peritoneal dialysis patients. Every 250 ml of urine volume per day associated with 36 percent lower death rate of patients[18]. Likewise, ADEMEX study in Mexico showed that the increase in the amount of urine volume associated with an increase in survival in PD patients[19]. The above information is currently accepted that to slow deterioration of residual renal function can improve survival rate of PD patients.

In practice, control of fluid balance in PD patients is so difficult because it has many factors that affect such as the cooperation of patients in strictly limited food and water, peritoneal membrane transport status which over time lead to degenerative change of membrane thus water and solute clearance has decreased. In ESRD patients, the kidney function is progressively decreased over time, resulting in decreased urine volume. Diuretics are used to promote salt and water excretion in chronic renal

failure patients who receive renal replacement therapy.

Medcalf et al conducted a randomized control trial to compare the effect of 250 mg furosemide daily and the control group in 61 participants who starting peritoneal dialysis over one year period. The results showed that urine volume in furosemide group was more than control group at 6 months and 12 months (increase 376 ml and 354 ml at 6 months and 12 months, respectively). Similarly, urinary sodium excretion was increase in furosemide group but tend to diminish in control group at 12 month. However, the renal Kt/V urea and renal creatinine clearance between groups were not significantly difference[7].

Rudolf W et al studied the effect of high doses furosemide (2 grams per day) to urine volume and urine solute excretion in 7 PD patients who still had residual urine. The results showed that high-dose furosemide can increased urine volume about 400 ml/day and can increase the urinary sodium excretion 54 mmol/day. But it did not affect the filtration rate of the kidneys, urea clearance, creatinine clearance, and peritoneal water and solute clearance. The effect of high-dose furosemide is dependent on the residual renal function[20].

From these two studies, high doses furosemide results in increased urine volume and urinary sodium excretion in PD patients. But it cannot slow the decline of kidney function. In addition, the use of other diuretics in PD patients was also studied. Berna et al studied the effects of spironolactone on residual renal function and peritoneal function in 23 peritoneal dialysis patients. The spironolactone was given 25 mg per day for six months. The study found that spironolactone is likely to slow the deterioration of the peritoneum membrane function. It can reduce the increase in profibrotic marker and increase mesothelial cell mass, but it does not affect the deterioration of residual renal function[21].

A recent study by Yasuhiko also has similar results. The authors conducted a multicenter open-label randomized trial to study the effects of using spironolactone on left ventricular mass index in 158 peritoneal dialysis patients. They were followed for 24 months. Spironolactone can significantly decrease the change of left ventricular mass index at 6, 18 and 24 months. And left ventricular ejection fraction improved in the spironolactone group compared with the control group at 24 weeks. There were no significant differences in urine volume and renal small solute clearance between groups[22]. Yongsiri et al. studied effect of spironolactone 25 mg/day on serum potassium in PD patients over 4 week's period in a double blind placebo control, cross over study. They found that this drug was safe and did not have significance effects on serum potassium, magnesium or urinary potassium excretion. There was only 1 episode of mild hyperkalemia (serum potassium 5.6 mEq/L) and rapidly resolved after cessation of spironolactone[23].

The review of the study of spironolactone in PD patients found that it cannot slow the decline of residual renal function nor urine volume. The favorable effect of spironolactone in peritoneal dialysis patients is that it tends to have good results in cardiac function and preserve peritoneal membrane function.

Kidney Disease Outcomes Quality Initiative (KDOQI) published guidelines for peritoneal dialysis patients in 2006, focusing on the deterioration of residual renal function. It is recommended that monitoring of renal function should be done closely. Try to slow the deterioration of kidney function, blood pressure control with angiotensin converting enzyme inhibitor or angiotensin receptor blocker and maintain euvolemic state[24]. The main approach is to restrict salt and water, adjust peritoneal dialysis prescription for adequate fluid and solute removal and preserve kidney function in order to provide enough urine output to control sodium and water balance.

Discussion

Control of sodium and water balance in PD patients is critical for treatment and it has an effect on treatment outcome. Using various types of diuretics appropriately can increase the amount of urine. At present, there is not much data on combined diuretic used to control volume status in ESRD patients. This is an opportunity for research leading to improve quality of management in peritoneal dialysis patients.

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บทคัดย่อ

บทบาทของยาขับปัสสาวะในการควบคุมสมดุลน้ำในผู้ป่วยล้างไตทางช่องท้อง

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ยาขับปัสสาวะถูกนำมาใช้อย่างแพร่หลายเพื่อควบคุมสมดุลน้ำและเกลือแร่ให้แก่ผู้ป่วยล้างไตทางช่องท้อง การได้รับยาอย่างเหมาะสมช่วยเพิ่มปริมาณปัสสาวะให้แก่ผู้ป่วย อีกทั้งเพิ่มการขจัดเกลือโซเดียม ช่วยให้ผู้ป่วยปราศจากภาวะน้ำเกิน ส่งผลดีต่อการรักษา บทความนี้นำเสนอเกี่ยวกับกลไกการออกฤทธิ์ของยาขับปัสสาวะ ข้อมูลการใช้ยาขับปัสสาวะชนิดต่างๆ ในผู้ป่วยล้างไตทางช่องท้อง งานวิจัยที่เกี่ยวข้อง รวมถึงการนำไปประยุกต์ใช้ในทางคลินิก

คำสำคัญ: ยาขับปัสสาวะ, สมดุลน้ำ, การล้างไตทางช่องท้อง