Therapy with the Combination of Tolvaptan and Furosemide for Refractory Edema in Nephrotic Syndrome

Sir,

Edema, the chief clinical manifestation of nephrotic syndrome, often can be severe, more so in patients with steroid-resistant nephrotic syndrome (SRNS). Severe edema requires prolonged therapy with furosemide, which may be associated with adverse effects. While patients with hypovolemia benefit from administration of intravenous (IV) albumin with or without furosemide, the former is expensive and carries the risk of pulmonary edema in patients with oligouria. Tolvaptan, an antagonist of the arginine vasopressin receptor, increases free water excrection and diuresis.[1] Shimizu *et al*. first reported use of tolvaptan in an 8 year-old girl with nephrotic syndrome and refractory edema.[2] We report our experience with the combination of oral tolvaptan and IV furosemide in patients with nephrotic syndrome in whom the edema was refractory to IV furosemide alone.

We studied 10 patients (6 boys) with a median age of 7 (6–14) years, who received therapy with oral tolvaptan (0.5–1 mg/kg/day) and IV furosemide (3–4 mg/kg/day) for 48 h. Combination therapy was associated with significant increase in urine volume, from 1.2 (0.9–2.7) mL/kg/h at baseline to 2.4 (2.0–3.3) mL/kg/h at 48 h of therapy. There was a small but significant reduction in body weight from baseline 20.5 to 19.9 kg after 48 h. Serum

Table 1: Clinical parameters before and 48 h after therapy with oral tolvaptan and intravenous furosemide

Parameters	Before (*n*=10)	After (*n*=10)	*P**
Body weight (kg)	20.5 (18.6-38.9)	19.9 (18.4-36.5)	0.005
Urine volume (mL/kg/h)	1.2 (0.9-2.7)	2.4 (2.0-3.3)	0.02
Mean arterial pressure (mm Hg)	86 (83-90)	89 (84-98)	0.38
Hematocrit (%)	27.2 (22.2-33.4)	29.1 (24.6-33.4)	0.04
Blood levels			
Sodium (mEq/L)	133.0 (132-135)	140.5 (137-147)	0.004
Urea (mg/dL)	70.5 (43-78)	74.5 (47-90)	0.11
Albumin (g/dL)	1.4 (1.2-1.6)	1.5 (1.3-1.7)	0.14
Aspartate aminotransferase (U/L)	20 (16-32)	19 (14-32)	0.91
Alanine aminotransferase (U/L)	13.5 (9-27)	21.5 (10-23)	0.53
eGFR (mL/min/1.73 m^2)	93.9 (36.5-196.0)	93.8 (28.6-141.2)	0.15
Urine levels			
Sodium (mEq/L)	85 (73-93)	57 (25-82)	0.18
Potassium (mEq/L)	33 (26-42)	28 (18-34.5)	0.11

Value represent median (interquartile range), eGFR: Estimated glomerular filtration rate, *Wilcoxon sign rank test

sodium increased significantly from 133 mEq/L at baseline to 140.5 mEq/L after combination therapy. Three patient showed hypernatremia (serum sodium >145 mEq/L). Table 1 shows other parameters before and after combination therapy. None of the patients developed clinical evidence of hypovolemia during the study.

Our study demonstrates that combination therapy with oral tolvaptan and IV furosemide increases the urine output, without affecting renal function. Hypoalbuminemia in nephrotic syndrome results in impaired furosemide delivery to the tubular lumen at its site of action in thick ascending loop of Henle contributing to furosemide resistance. Since tolvaptan acts on the basolateral side of collecting duct and does not require secretion into the tubular lumen, its aquaretic action is not affected by the blood level of albumin. The therapeutic efficacy of vasopressin receptor antagonist is well demonstrated in the management of fluid retention in congestive heart failure and cirrhosis.[3] Recently, in a case series of 14 patients with nephrotic proteinuria secondary to diabetic nephropathy, improvement in furosemide refractory edema with tolvaptan therapy was described.[4]

Finding from this study shows that coadministration of tolvaptan and furosemide is effective in increasing urine output in patients with furosemide resistant edema due to nephrotic syndrome. While therapy is safe, careful monitoring of serum sodium is essential. Prospective controlled studies are required to examine whether tolvaptan is an effective and safe oral therapy for management of edema in nephrotic syndrome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Jitendra Meena, Aditi Sinha, Pankaj Hari, Arvind Bagga

Division of Nephrology, Department of Pediatrics, ICMR Center for Advanced Research in Nephrology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:
Prof. Pankaj Hari,
Room No. 3061, Division of Nephrology, Department of Pediatrics, ICMR Center for Advanced Research in Nephrology All India Institute of Medical Sciences, New Delhi, India.
E-mail: pankajhari@hotmail.com

References

1. Shoaf SE, Bramer SL, Bricmont P, Zimmer CA. Pharmacokinetic and pharmacodynamic interaction between tolvaptan, a non-peptide AVP antagonist, and furosemide or hydrochlorothiazide. J Cardiovasc Pharmacol 2007;50:213-22.
2. Shimizu M, Ishikawa S, Yachi Y, Muraoka M, Tasaki Y,

Iwasaki H, *et al*. Tolvaptan therapy for massive edema in a patient with nephrotic syndrome. Pediatr Nephrol 2014;29:915-7.
3. Yan L, Xie F, Lu J, Ni Q, Shi C, Tang C, *et al*. The treatment of vasopressin V2-receptor antagonists in cirrhosis patients with ascites: A meta-analysis of randomized controlled trials. BMC Gastroenterol 2015;15:65.
4. Takada T, Masaki T, Hoshiyama A, Toki T, Kamata Y, Shichiri M. Tolvaptan alleviates excessive fluid retention of nephrotic diabetic renal failure unresponsive to furosemide. Nephrol Carlton 2018;23:883-6.

Access this article online

Quick Response Code:

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_358_18

How to cite this article: Meena J, Sinha A, Hari P, Bagga A. Therapy with the combination of tolvaptan and furosemide for refractory edema in nephrotic syndrome. Indian J Nephrol 2020;30:53-5.

Received: 14-11-2018. **Revised:** 20-03-2019. **Accepted:** 17-05-2019. **Published:** 06-09-2019