Original Article

Pharmacology Section

Short-Term Furosemide Therapy in Chronic Renal Disease; Implications of Hypomagnesia and Potential for Improving Hyperkalaemia

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ABSTRACT

Background: Several long term studies on the effect of furosemide in chronic renal diseases exist. Furosemide has been noticed to lead to early electrolyte balance in several long-term studies. Further, some studies have shown that an early, rapid decrease in potassium (K) levels is seen with furosemide therapy.

Objectives and Methods: Hence, a short term study was undertaken to study the potential effect of a short, 3-day therapy with furosemide on chronic renal failure (CRF) and nephrotic syndromes. The study evaluated the clinical implications of a short-term furosemide therapy in terms of electrolyte imbalance, and as to whether a rapid decrease in potassium levels can be achieved and may be potentially used to cure hyperkalaemia. The study included 100 subjects, out of which 50 were CRF patients and the rest had nephrotic syndrome.

Results: A 3-day course of furosemide showed a rapid decrease in potassium (K) and magnesium (Mg) levels in both the groups. However, the response was protective in patients with CRF, who showed higher pretreatment K and Mg levels, but the nephrotic syndrome patients had normal pretreatment levels (K, Mg). The results were suggestive that furosemide led to hypokalaemia and hypomagnesia. Hence, while caution is needed with furosemide, as it has the potential to cause early hypokalaemia/hypomagnesia, on the other hand, it also depicted a potential of treating hyperkalaemia, as was seen in the CRF patients. Further, a simultaneous decrease in Mg levels suggests a need to supplement Mg in patients who were treated with furosemide, because K supplementation is refractory if Mg is not supplemented. This also undermines a need to monitor the Mg levels in the serum (normally not done), which might be as important as the regular monitoring of the sodium, potassium, and calcium levels, as recommended for loop diuretics. Lipid derangements which are seen with early, short-term furosemide treatments, suggest the need for an early monitoring of the lipid profile, which might be adversely affected; even in case of a short therapy with furosemide.

Conclusion: The rapid potential of furosemide for treating hyperkalaemia needs to be reinforced in large-sampled studies

Keywords: Chronic Renal Disease, Furosemide therapy, Hyperkalaemia

INTRODUCTION

Chronic renal failure (CRF) and nephrotic syndrome are chronic kidney diseases where loop diuretics are given (e.g furosemide) to manage the oedema, due to an increase in the extracellular fluid volume. In fact, patients with chronic renal insufficiency have increased extracellular volume even in the absence of oedema [1] and loop diuretics like furosemide are useful. Further, since loop diuretics maintain their efficacy even in advanced stages of renal failure when the filtration rates are markedly reduced, [2], [3] they are the preferred diuretics in the settings of CRF and nephrotic syndrome. However, the overall natriuretic effect of furosemide, particularly in conventional doses, is markedly diminished in chronic renal insufficiency and hence, high doses may be needed. The administration of furosemide in nephrotic syndrome has been shown to improve renal function markedly, probably due to the regression of the intrarenal oedema. [4] However, the response to furosemide in nephrotic syndrome is also frequently decreased due to the altered pharmacokinetics (albumin binding reducing the bioavailability), thus causing the requirement of high doses.[5]

Importantly, the adverse effects of loop diuretics in terms of electrolyte imbalance include hypokalaemia, hypomagnesaemia, hypocalcaemia and hyponatraemia, and higher doses are expected to cause more rapid and early electrolyte imbalances. [5] However, the common notion is that electrolyte imbalances take some time and that the monitoring of electrolytes with furosemide therapy is normally advocated at periodic monthly intervals. Though some early, short-term studies with furosemide did show early effects on electrolyte imbalance, grossly, the picture remains unclear. [3] An interesting fact in terms of electrolyte changes with loop diuretics (furosemide causing hypokalaemia), is the potential of using loop diuretics (furosemide) in treating hyperkalaemia due to renal insufficiency. [6] Hyperkalaemia due to other reasons have also been shown to respond to furosemide (loop diuretic) therapy.[7], [8]

With this background, a short term study (3 day course of high dose furosemide in chronic renal failure and nephrotic syndrome) was undertaken with an objective of observing the short term effects of high dose furosemide therapy on electrolyte imbalance, and its implications. The secondary objectives included comparing the effect of furosemide in CRF and nephrotic syndrome, and evaluating the potential of short-term furosemide therapy in treating hyperkalaemia.

MATERIAL AND METHODS

This prospective, comparative study was carried out in the Department of Nephrology, Government Rajaji Hospital, Madurai (South India), with the approval of the hospital ethical committee. The study evaluated the short-term effect of furosemide in patients suffering from chronic renal disease (CRF and nephrotic syndrome) on fluid and electrolyte imbalance, and the potential of short-term furosemide in treating hyperkalaemia. The secondary objectives included a comparative efficacy of the drug between chronic renal failure and nephrotic syndrome.

A total of 100 patients were enrolled, out of which 50 patients had nephrotic syndrome, and the other half were CRF patients. The enrolled patients included both the urban as well as the rural population in and around Madurai city. The patients who were included had the clinical signs and symptoms of volume overload. Only patients with volume overload and who were in need of diuretic therapy, were included. Both males and females and patients of all age groups were included. Patients who had a prior exposure of diuretic usage were not included. Patients with illnesses such as diarrhoea and severe vomiting, who were likely to already have electrolyte disturbances, were also excluded. Patients with high blood urea and serum creatinine who needed immediate dialysis to prevent further renal damage, patients having anuria and those who were unresponsive to a trial dose of loop diuretics, were also not enrolled.

The patients were evaluated through history, clinical examination, and investigations, as per the protocol. The biochemical investigations included renal function tests, liver function tests, and lipid profile, apart from an electrolyte profile. All investigations were done at the Department of Clinical Biochemistry by using an auto- analyzer and chemical tests. Other investigations included ultrasound of the abdomen to assess the kidney size. Eligible patients were enrolled in the study after the above evaluation and after obtaining their informed consent. The pre-study, baseline values of the various biochemical parameters patient are depicted in [Table/Fig 1]. Other baseline findings in terms of pre-study weight and urine output, along with post-treatment values, are also depicted in [Table/Fig 2].

Eligible patients were given 2mg-6mg/kg body weight/ per day of furosemide for 3 days, (higher than standard diuretic dose) depending on the severity of the oedema. Serum electrolytes, renal function tests, liver function tests, and lipid profile were repeated 72 hours after furosemide therapy. The results were separately analyzed for patients with nephrotic syndrome and for CRF patients and a comparative efficacy of the drug between CRF and nephrotic syndrome was also analyzed. Statistical analysis was carried out by using the 'Z' test (large sample test) for evaluating whether the differences were significant.

RESULTS

The CRF patients showed a significant clinical improvement in terms of the difficulty in breathing and increased urinary output, and showed weight reduction. In terms of the electrolyte profile, serum sodium (Na) showed a statistically significant fall after the treatment, as against normal levels before the treatment in these patients. Patients who were mostly hyperkalaemic showed a significant fall in the potassium (K) levels, with the levels reaching normal limits after furosemide therapy. Magnesium (Mg) levels also showed similar changes as potassium, with most patients achieving almost near normal values after treatment. Serum calcium (Ca) and bicarbonates did not show any significant changes. [Table/Fig 1] Though serum creatinine and blood urea were increased pre-treatment, no statistically significant change was seen after treatment. The lipid parameters were normal before treatment, but a statistically significant rise was seen after treatment. Liver function tests and blood gas analysis (pH and pO2 and pCO2) did not show any statistical change before and after therapy. [Table/Fig 1].

In nephrotic syndrome patients also, increased urine output with significant weight reduction, was seen. Serum electrolytes showed a statistically significant fall in both serum sodium and potassium levels after treatment (hypokalaemia, hyponatremia) as compared to the normal values pre-treatment. Serum magnesium levels also showed a statistically significant fall (hypomagnesaemia) from the normal. However, no changes in serum Ca and serum bicarbonates (seen to be normal pre-treatment) were seen after therapy in these

		Chronic renal failure			Nephrotic Syndrome		
Biochemical Tests	Normal Serum Values	Before Treatment; Mean ± SD (Baseline)	After Treatment; Mean ±SD	p value	Before Treatment; Mean ± SD (Baseline)	After Treatment; Mean ± SD	p value
Serum Electrolytes							
Serum sodium	136-148 meq/l	136.8± 1.22	132 ± 0.96	p < 0.01	142.6 ± 0.68	137.4 ± 1.07	p < 0.01
Serum potassium	3.6 – 5 meq/l	5.4 ± 0.1	3.9 ± 0.1	p < 0.01	4.5 ± 0.08	3.8 ± 0.08	p < 0.01
Serum calcium	8.5 -10.5 meq/l	9.6 ± 0.2	9.2 ± 0.2	p=NS	9.3 ± O.11	9.1 ± 0.1	p=NS
Serum magnesium	1.4 -1.9 meq/l	4.9 ± 0.16	2.2 ± 0.13	p < 0.01	1.7 ± 0.13	0.8 ± 0.08	p < 0.01
Serum bicarbonate	16- 28 meq/l	17.8 ± 1.54	18.5 ± 1.63	p=NS	17.4 ± 0.4	19.3 ± 0.61	p=NS
Renal function test							
Blood urea	15- 40 mg %	112.8 ± 4.6	123.8 ± 4.8	p=NS	30.3 ± 2.4	28.8 ± 2.7	p=NS
Serum creatinine	0.4- 1.4 mg%	7.3 ± 0.7	7.4 ± 0.61	p=NS	0.7 ± 0.15	0.5 ± 0.23	p=NS
Liver function tests							
Serum total protein	6- 7.5 gm	5.7 ± 0.14	5.6 ± 0.14	p=NS	3.9 ± 0.13	3.8 ± 0.11	p=NS
Serum albumin	3.5- 5 gm	3.2 ± 0.08	3.2 ± 0.08	p=NS	1.6 ± 0.08	1.4 ± 0.08	p=NS
Serum globulin		2.5 ± 0.14	2.5 ± 0.1	p=NS	2.3 ± 0.08	2.3 ± 0.08	p=NS
Lipid profile							
Serum cholesterol	152- 200mg %	176.6 ± 6.9	197.4 ± 6.7	p < 0.05	402.9 ± 9.9	420.2 ± 9.4	p=NS
Serum triglycerides	80 - 150 mg%	116. 9 ± 7.7	153.4 ± 8.4	p < 0.01	242 ± 14.5	266 ± 13.8	p=NS p=NS
Serum HDL	30 -40 mg%	29.8 ± 1	34.9 ± 0.7	p < 0.01	32.6 ± 1.8	37.6 ± 1.3	p < 0.05
Serum LDL	< 130mg %	123.2 ± 11.5	131.9 ± 6.9	p=NS	321.8 ± 9.6	328.9 ± 9.3	p=NS
Serum VLDL	30mg%	23.5 ± 1.5	30.6 ± 1.9	p < 0.01	48.4 ± 2.8	53.3 ± 2.8	p=NS
Blood Gas Analysis							
pH	7.35 -7.45	7.3 ± 0.03	7.3 ± 0.03	p=NS	7.3 ± 0.03	7.4 ± 0.03	p=NS
pO2	75-100 mm Hg	94.9 ± 3.5	97.3 ±3.2	p=NS	105.5 ± 1.6	95.3 ± 1.8	p=NS
pCO2	35-45 mm Hg	25.9 ± 1.3	27.3 ± 1.2	p=NS	20.2 ± 1.9	22.6 ± 2.5	p=NS

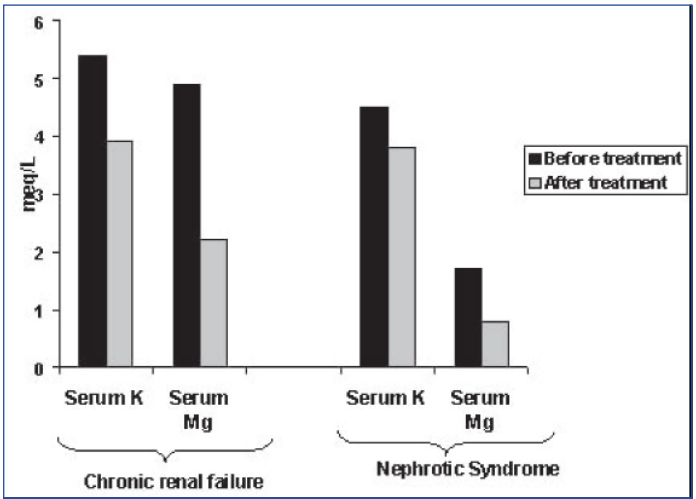
[Table/Fig-1]: Changes In Biochemical Parameters Seen With Furo Semide Short Term 3 Day Therapy
HDL, High density lipoprotein; LDL, Low density lipoprotein; VLDL, Very low density lipoprotein; CRF, Chronic renal failure, NS, Not significant; SD, Standard deviation.

Clinical Parameters	Chronic Renal Failure			Nephrotic Syndrome		
	Before treatment Mean ± SD (Base-line)	After treatment Mean ± SD	p value	Before treatment Mean ± SD (Base-line)	After treatment Mean ± SD	p value
Weight (kg)	52.92 ± 1.16	51.84 ± 1.18	p=NS	27.74 ± 2.02	26.48 ± 1.97	p= NS
Urinary output (ml/per day)	892.6 ± 28.96	1235 ± 41.01	p <0.05	890.5 ± 36.66	1112.5 ± 39.75	P <0.05

[Table/Fig-2]: Baseline and Post treatment values of weight and urine output

nephrotic syndrome patients. No statistically significant differences were seen in urea and creatinine levels and no improvement in serum proteins was noticed after therapy. In terms of the lipid profile, serum total cholesterol, serum triglycerides, serum LDL (low density lipoproteins) and serum VLDL (very low density lipoproteins) levels were already raised pre-treatment, and derangements were noticed after treatment, though they were not significant. Blood gas analysis also did not show any significant change. [Table/Fig 1]

Comparative analysis showed a significantly greater fall of sodium levels in nephrotic syndrome patients than CRF, while the fall in potassium levels were significantly greater in CRF patients than in the nephrotic syndrome patients. A significant fall from the pretreatment hyperkalemic levels was seen. Hence, both the groups of patients showed a decrease in the potassium levels, but in the CRF patients, the decrease was from the higher pretreatment values to normal, but in nephrotic syndrome, it led to significant hypokalaemia from the normal pretreatment values. [Table/Fig 1] [Table/Fig 3].



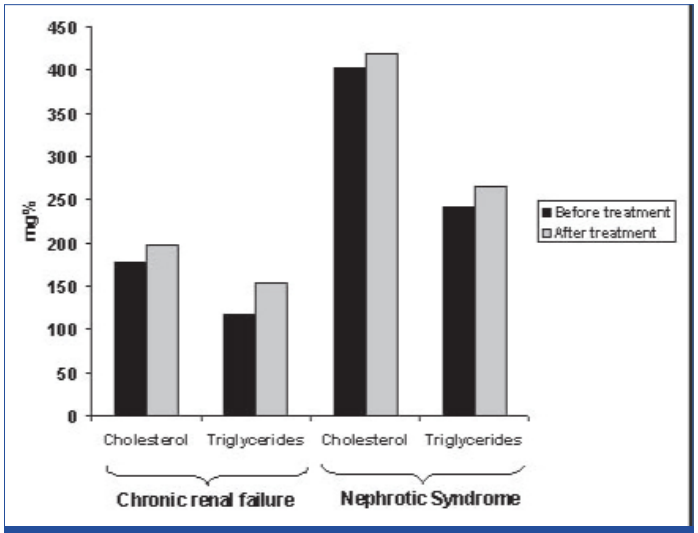
[Table/Fig-3]: Changes in potassium and magnesium levels seen before and after furosemide therapy in CRF and nephrotic patients

Serum calcium and serum magnesium showed a significant fall in both the groups, though the levels stayed within the normal range for calcium. Magnesium levels showed a similar picture as that of potassium. [Table/Fig 3] No major or significant changes in bicarbonates, liver function tests or blood urea/creatinine were seen, except for urea/creatinine levels showing an increase posttreatment in the CRF patients. High serum cholesterol further increased in CRF and nephrotic syndrome patients after treatment, though it was not statistically significant, and triglyceride levels also showed an increase. [Table/Fig 1] [Table/Fig 4]

Apart from the findings of imbalances in the biochemical parameters, no other significant side effect was reported in any of the study groups. The patients did not complain about any drug-associated adverse reactionand they seemed to tolerate the high doses of the furosemide well.

DISCUSSION

Patients with chronic renal failure and nephrotic syndrome showed significant improvements in the clinical signs and symptoms. Though short term effects had not been observed earlier except in some isolated studies, the improvement in these clinical parameters



[Table/Fig-4]: Changes seen in lipid parameters seen with short-term furosemide in both CRF and nephrotic syndrome patients

following a short-term, high dose, 3-day furosemide therapy, were in accordance with the acute effects of furosemide as seen in earlier kidney dysfunction studies. [9]-[11] Loop diuretics are considered as the ideal choice pharmacotherapeutic agents for the correction of excess Na and water load in oedematous patients of CRF and nephrotic syndrome, with furosemide being a preferred and widely used drug. Loop diuretics are advantageous in these clinical conditions as they maintain efficacy in advanced renal failure [i.e.] even if the (glomerular filtration rate) GFR is less than 30ml/ hour. [12] This is possibly because loop diuretics do not suppress GFR, probably by abolishing the tubuloglomerular feed back response, and by the inhibition of the Na+-K+-2Cl cotransporterwhich is involved in transduction, in the loop of Henle. [2] However, patients with advanced renal failure require higher doses of furosemide than the normal dose, as was seen in our study. This could be due to the inability of the drug to achieve adequate concentration at the target site of action, as a number of endogenous acids accumulate in advanced CRF and these compete with diuretics for their secretion by the proximal tubule. Similarly, higher doses are required in nephrotic syndrome also, because of the binding of the 70% drug within the tubular lumen to the filtered protein. [5]

Though several studies have focused on the long-term effects of furosemide on serum electrolytes, some interesting short-term effects of furosemide in CRF and nephrotic syndrome patients which were seen in this study could have useful therapeutic clinical implications. Physiologically, the major site of potassium reabsorption is the ascending loop of Henle, which is the primary site of action of furosemide. It is important to understand that the reabsorption of potassium at this site is ultimately driven by the activity of magnesium dependent Na+ K+ ATPase, and that the cellular depletion of magnesium in these cells may contribute to renal potassium wasting. [13] Hyperkalaemia and hypermagnesaemia which are associated with CRF and nephrotic syndrome due to a defect in renal elimination [14], need to be aggressively managed, as high potassium levels predispose to cardiac arrhythmia and hypermagnesaemia leads to many neurological and cardiac complications. [15],[16]

High dose furosemide in our study, was able to bring both potassium and magnesium levels to normal in the CRF patients within 3 days,

thus minimizing any adverse complications which were otherwise seen. The potential of furosemide to decrease the K and Mg levels is supported by other earlier observations. [17],[18] But a simultaneous and significant decrease in the K and Mg levels was seen with the treatment with furosemide (loop diuretics) [19] in as short as 3 days in this study, thus implicating the necessity of monitoring these serum levels early, rather than at periodic monthly intervals. The acute hypomagnesia and hypokalaemia which are seen with furosemide, as was demonstrable in the nephrotic syndrome patients (Serum K decreased to 3.8 from 4.5 and serum Mg decreased to 0.8 from 1.7; $p<0.01$), may also lead to cardiac complications. [20]-[22]

Further, it is important to keep in mind that K deficiency which is seen with short-term furosemide usage, may fail to respond to supplementation, if magnesium depletion is not corrected and would affect adversely. [23],[24] Potential hypokalaemia which is seen with long-term diuretic usage also may fail to respond to the potassium supplements, unless magnesium is supplemented.

[25] This undermines a need for the monitoring of the serum magnesium levels [26] (otherwise not routinely included in the electrolyte profile of renal and other oedematous conditions) and this should be given as much importance as other electrolytes, including sodium, potassium, calcium and bicarbonate. Further, due to the early electrolyte changes which are induced, the electrolyte profile should be done early with furosemide therapy, rather than in the usual normal way.

Isolated study findings on the short-term effects of furosemide on electrolyte and water excretion in renal insufficiency patients with oedema corroborate our study findings. Gregory et al., [3] showed that short-term furosemide induced an increase in urine flow and increased Na/K excretion; however, K excretion appeared to be a function of increased urine flow, rather than an increased concentration of potassium in urine. [3] Hence, the early effects of an increase in K excretion do not seem to be dependent on the changes in the intricate kidney function mechanisms which are induced, and seem to be a result of increased urine flow which is induced by furosemide. This suggests the potential of furosemide in treating hyperkalaemia, even in situations without any compromised kidney function. However, the ability of furosemide to increase K excretion even when the filtration rate reduces considerably, is definitely advantageous and would benefit severely, renal-compromised patients who require the normalization of K. [3] A potential fast and early management of hyperkalaemia by furosemide would decrease associated cardiac complications like arrythmias, and early research studies have emphasized the importance of the fast, safe, and effective treatment of hyperkalaemia.[27] Carvalhana et al., [8] used furosemide to manage severe hyperkalaemia within 8 hrs in normal kidney function patients, and suggested that severe hyperkalaemia could be managed with conservative treatment, without the need for dialysis. [8] Selective early effects of furosemide on increased K excretion which were seen in our study, embeds the beneficial, fast potential of furosemide in treating hyperkalaemia in morbid situations, and these could be exploited clinically. However, since potassium levels decrease dramatically with furosemide therapy, it has to be carefully monitored, especially while using furosemide in patients having normal K levels, as these patients are susceptible to furosemide-induced hypokalaemia and subsequent complications.

The cardioprotective and neuroprotective effects of furosemide also seem to be due to increased Na excretion, apart from the effect on decreasing water load. However, diuretic-induced lipolysis and enhanced cholesterol levels [28], [29] could be the likely reason for the derangements which are seen in the lipid profile. Further, proteinuria/albuminuria which is associated with nephrotic syndrome due to a damaged glomerular basement membrane, inhibits lipolytic enzyme function, thus leading to dyslipidaemic changes. [30] Hence, the lipid profile should also be closely monitored in patients who are on a short-term, high dose furosemide, to prevent any potential vascular and cardiac complications.

Short term furosemide, as used in our study, seems to be highly effective in improving the clinical signs and symptoms in both CRF and nephrotic syndrome, including relief from dyspnoea, increase in urinary output, weight-loss and oedema clearance. However, comparatively, furosemide seems to be more effective and protective in CRF patients than in nephrotic syndrome patients, by potentially restoring hyperkalaemia and hypermagnesaemia to near normal levels, as was seen. But this could be due to the normal pretreatment baseline K and Mg levels which were seen in nephrotic syndrome patients and furosemide further led to adverse lowering (hypokalemia, hypomagnesia); while CRF patients had elevated serum levels which became normal due to increased K/Mg excretion. Hence, this may not have any other clinical implications, except that it necessitates cautious early monitoring and seems to confer it with a potential for treating hyperkalaemia, as is already discussed.

The side effect profile of short term furosemide treatment seems to be limited to electrolyte disturbances, as no other significant drug-related side effects were observed. However, even though it seems that furosemide was well-tolerated in short term treatment, this could be also due to any missed observation due to a lack of follow-up. In terms of efficacy, though the shortterm effect of furosemide on clinical parameters like dyspnoea and oedema in chronic renal disease patients may provide symptomatic improvement, the symptoms may return after the therapy with furosemide is discontinued due to the chronic nature of the disease. The other limitation of the study seems to be the small sample size, and larger short-term studies are suggested, especially to see the potential and the early effects of furosemide in treating hyperkalaemia.

REFERENCES

[1] Mitch WE, Wilcox CS. Disorders of body fluids, sodium and potassium in chronic renal failure. Am J Med. 1982;72:536-50.
[2] Schlatter E, Salomonsson M, Persson AE, Greger R. Macula densa cells sense luminal NaCl concentration via furosemide sensitive Na+2Cl-K+ cotransport. Pflugers Arch. 1989;414:286-90.
[3] Gregory LF, Jr., Durrett RR, Robinson RR, Clapp JR. The short-term effect of furosemide on electrolyte and water excretion in patients with severe renal disease. Arch Intern Med 1970;125:69-74.
[4] Lowenstein J, Schacht RG, Baldwin DS. Renal failure in minimal change nephrotic syndrome. Am J Med. 1981;70:227-33.
[5] Keller E, Hoppe-Seyler G, Schollmeyer P. Disposition and diuretic effect of furosemide in the nephrotic syndrome. Clin Pharmacol Ther1982;32:442-9.
[6] Wilcox CS. New Insights into Diuretic Use in Patients with Chronic Renal Disease. J Am Soc Nephrol. 2002;13:798-805
[7] Hollander-Rodriguez JC, Calvert JF, Jr. Hyperkalemia. Am Fam Physician. 2006;73:283-90.
[8] Carvalhana V, Burry L, Lapinsky SE. Management of severe hyperkalemia without hemodialysis: case report and literature review. J Crit Care. 2006;21:316-21.
[9] Bulow HH, Ladefoged SD. [Loop diuretics. Rational pharmacotherapy]. Ugeskr Laeger. 1993;155:3563-6.
[10] Silverberg DS, Ulan RA, Baltzan MA, Baltzan RB. Experiences with high doses of furosemide in renal disease and resistant edematous states. Can Med Assoc J. 1970;103:129-33.
[11] Russo D, Minutolo R, Andreucci VE. Role of loop diuretics in chronic renal failure. Cardiology. 1994;84 Suppl 2:162-70.
[12] Knauf H, Cawello W, Schmidt G, Mutschler E. The saluretic effect of the thiazide diuretic bemetizide in relation to the glomerular filtration rate. Eur J Clin Pharmacol. 1994;46:9-13.
[13] Ryan MP. Interrelationships of magnesium and potassium homeostasis. Miner Electrolyte Metab. 1993;19:290-5.
[14] Mountokalakis TD. Magnesium metabolism in chronic renal failure. Magnes Res. 1990;3:121-7.
[15] Tackett RL. Enhanced sympathetic activity as a mechanism for cardiac glycoside toxicity in hypomagnesemia. Pharmacology. 1986;32:141-6.
[16] Chvilicek JP, Hurlbert BJ, Hill GE. Diuretic-induced hypokalaemia inducing torsades de pointes. Can J Anaesth. 1995;42:1137-9.
[17] Musso CG. Magnesium metabolism in health and disease. Int Urol Nephrol. 2009;41:357-62.
[18] Schwinger RH, Erdmann E. Heart failure and electrolyte disturbances. Methods Find Exp Clin Pharmacol. 1992;14:315-25.
[19] Knauf H, Mutschler E. Saluretic effect of the loop diuretic torasemide in chronic renal failure. Interdependence of electrolyte excretion. Eur J Clin Pharmacol. 1990;39:337-43.
[20] Brucato A, Bonati M, Gaspari F, et al. Tetany and rhabdomyolysis due to surreptitious furosemide--importance of magnesium supplementation. J Toxicol Clin Toxicol. 1993;31:341-4.

[21] McGovern B. Hypokalemia and cardiac arrhythmias. Anesthesiology. 1985;63:127-9.
[22] Whelton PK, Watson AJ. Diuretic-induced hypokalemia and cardiac arrhythmias. Am J Cardiol. 1986;58:5A-10A.
[23] Solomon R. The relationship between disorders of K+ and Mg+homeostasis. Semin Nephrol. 1987;7:253-62.
[24] Whang R, Flink EB, Dyckner T, Wester PO, Aikawa JK, Ryan MP. Magnesium depletion as a cause of refractory potassium repletion. Arch Intern Med. 1985;145:1686-9.
[25] Dorup I, Skajaa K, Thybo NK. [Oral magnesium supplementation to patients receiving diuretics--normalization of magnesium, potassium and sodium, and potassium pumps in the skeletal muscles]. Ugeskr Laeger. 1994;156:4007-10, 4013.
[26] al-Ghamdi SM, Cameron EC, Sutton RA. Magnesium deficiency: pathophysiologic and clinical overview. Am J Kidney Dis. 1994;24:737-52.
[27] Sood MM, Pauly RP. A case of severe hyperkalemia: fast, safe and effective treatment is required. J Crit Care. 2008;23:431-3.
[28] Hudig F, Bakker O, Wiersinga WM. Amiodarone-induced hypercholesterolemia is associated with a decrease in liver LDL receptor mRNA. FEBS Lett. 1994;341:86-90.
[29] Stone NJ. Secondary causes of hyperlipidemia. Med Clin North Am. 1994;78:117-41.
[30] Warwick GL, Packard CJ. Pathogenesis of lipid abnormalities in patients with nephrotic syndrome/proteinuria: clinical implications. Miner Electrolyte Metab. 1993;19:115-26.

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