Pediatrics & Therapeutics
ISSN: 2161-0665

Ogawa et al., Pediatr Ther 2017, 7:1
DOI: 10.4172/2161-0665.1000313

Research Article Open Access

Electrolyte Imbalance Caused by Diuretic Therapy in Infants with Congenital Heart Diseases

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Received date: Feb 02, 2017; **Accepted date:** Feb 13, 2017; **Published date:** Feb 15, 2017

Abstract

Background: Although furosemide and spironolactone are widely used to treat heart failure in infants and children because of their effectiveness and few side effects, there have been no prospective studies about the frequency and degree of serum electrolyte abnormality after the use of diuretics in pediatric patients.

Methods: We prospectively studied 126 infants at our outpatient clinic aged less than 2 months old with left-to-right shunt who received oral diuretics. All patients were started on furosemide at 0.5~3 mg/kg/day and spironolactone at 0.5~2 mg/kg/day, orally divided into two or three doses according to the degree of congestive heart failure.

Results: Serum sodium level ranged from 128 to 142 mEq/L (mean 136 mEq/L) and was <134 mEq/L in 18 of 126 patients (14.3%). Serum potassium level ranged from 4.5 to 6.9 mEq/L (mean 5.5 mEq/L) and was more than 5.5 mEq/L in 68 patients. Hyperkalemia (serum potassium level >6.0 mEq/L) was complicated in 19 patients. Eighteen patients with sodium levels of <134 mEq/L after diuretics showed lower body weight at the start of diuretics and lower postnatal age than the patients with serum sodium levels ≥ 134 mEq/L.

Conclusion: Although neither severe hyponatremia nor hypokalemia developed, there were a few patients with prolonged hyponatremia after diuretic therapy. It seems to be preferable to monitor serum electrolyte levels carefully after the start of diuretic therapy in infants with congenital heart disease.

Keywords: Congestive heart failure; Congenital heart disease; Diuretics; Furosemide; Hyponatremia

Introduction

Among congenital heart diseases, ventricular septa defect (VSD) is the most commonly encountered lesion if bicuspid aortic valve is excluded from consideration. Symptomatic congestive heart failure (CHF) due to pulmonary overcirculation and left-sided volume overload develops in children with moderate or large VSD. Although the definitive therapy for such patients is prompt resolution of the hemodynamic problems by intracardiac repair, many infants with CHF improve with medical therapy.

The mainstays of medical therapy for heart failure in children with large left-to-right shunts have historically been digitalis and diuretics [1]. Although diuretics have never been shown to improve survival in pediatric patients with CHF, their use is considered important because of the improvement of clinical symptoms by the decrease of pulmonary congestion and the effort of breathing [1]. Among the available diuretics, furosemide and spironolactone are widely used to treat CHF in infants and children because of their effectiveness and few side effects [2]. On the other hand, furosemide may produce clinically significant derangements in fluid and electrolyte balance, such as hypovolemia, hyponatremia, hypochloremia, hypokalemia and alkalosis [3]. Despite their widespread use, there have been no prospective studies about the frequency and degree of serum electrolyte abnormalities after the use of diuretics in pediatric patients. We studied serum electrolytes prospectively after the use of furosemide and spironolactone as the treatment of CHF in infants with large left-to-right shunts and examined factors that cause electrolyte imbalance.

Methods

We prospectively studied 126 infants at our outpatient clinic aged under 2 months old with left-to-right shunt who received oral diuretics between August 2005 and August 2011. The diuretics were indicated in infants with at least two symptoms or findings including tachypnea, retractions, growth failure, hepatomegaly, cardiomegaly on chest roentgenogram and ventricular hypertrophy on electrocardiogram. Patients were neither edematous nor had known renal disease. All patients fed almost normally.

All patients were started on furosemide at 0.5~3 mg/kg/day and spironolactone at 0.5~2 mg/kg/day orally divided into two or three doses according to the degree of CHF. Digitalis was used in 70 patients and no patient received angiotensin-converting enzyme inhibitors. Neither another diuretic therapy nor potassium chloride supplementation was given during the period of the study. Body weight, serum electrolytes and plasma human atrial natriuretic peptide (hANP) were assessed after almost 7 days of treatment. Peripheral venous blood was drawn from the antecubital fossa or dorsal digital veins.

Statistical analysis

S. No	GA	BW (g)	Postnatal age (day)	Dose of furosemide (mg/kg)	Serum Na (mEq/L)	Dose of salt (g/kg)	Duration of salt (days)
1	36W5D	2544	26	1.9	128	0.06	21
2	36W5D	2620	29	1.2	129	0.1	52
3	40W4D	2832	9	1.3	130	0.03	35
4	39W5D	2840	17	1.3	131	0.1	20
5	37W0D	2370	21	1.1	131	0.2	21
6	41W3D	3416	10	1.1	131	0.09	NA
7	39W4D	3546	33	1.7	132	0.1	88
8	38W2D	2446	19	1.1	132	0.08	12
GA: Gestational Age (days), BW: Body Weight.							

Table 1: Administration of salt in patients with hyponatremia after starting diuretics.

The clinical data are expressed as mean ± standard deviation. Means were compared by Student's t test. Correlations between continuous variables were estimated by Spearman's test and linear regression analysis was used to quantify the effect of variables on serum electrolytes. Variables were considered statistically significant at a p value of less than 0.05 by using two-sided tests. Data were analyzed using Dr. SPSS II for Windows version 11.0.1 J.

Results

Patient profile

All 126 patients were between 36 and 42 weeks' gestation (median 39W4D) and weighed 1928 g to 4290 g (median 2982 g). Age at initiation of the diuretic therapy was between 5 and 56 days (median 21 days), with a weight of 2345 g to 5238 g (median 3560 g).

One hundred and nineteen patients had ventricular septal defect, four had atrioventricular septal defect and three had patent ductus arteriosus. Eleven patients had Down's syndrome. The mean oral dose of furosemide was 1.2 ± 0.33 mg/kg/day (range 0.46 to 2.8 mg/kg/day) and that of spironolactone was 1.0 ± 0.16 mg/kg (range 0 to 1.8 mg/kg/day). The median interval between the initiation of the diuretics and clinical assessment was 7 days (range 2 to 15 days). The clinical assessment was performed 4 to 9 days after the initiation of diuretics in 117 patients.

Serum electrolyte

Serum sodium level ranged from 128 to 142 mEq/L (mean 136 mEq/L) and was <134 mEq/L in 18 of 126 patients (14.3%) (Figure 1). No patient showed severe hyponatremia (serum sodium level <115 mEq/L). Salt (0.03 to 0.2 g/kg daily) was administered for 8 patients with serum sodium levels <132 mEq/L (Table 1). Although serum sodium level improved within one week after the administration of salt in 6 patients, salt was needed for 88 days owing to the prolongation of hyponatremia in one patient. In patient 5, serum sodium level was decreased again after the cessation of salt due to the improvement of serum sodium level. The time course of serum sodium level after the administration of salt was unknown because the patient was excluded from the study. Five of 7 patients with hyponatremia after the administration of salt needed intracardiac repair during infancy. Serum chloride level ranged from 92 to 106 mEq/L (Figure 1).

Serum potassium level ranged from 4.5 to 6.9 mEq/L (mean 5.5 mEq/L) and was more than 5.5 mEq/L in 68 patients and there was hyperkalemia (serum potassium level >6.0 mEq/L) in 19 patients (Figure 2). The hyperkalemia returned to the normal range within a few days in almost all cases. No patient showed hypokalemia (serum potassium levels <3.0 mEq/L).

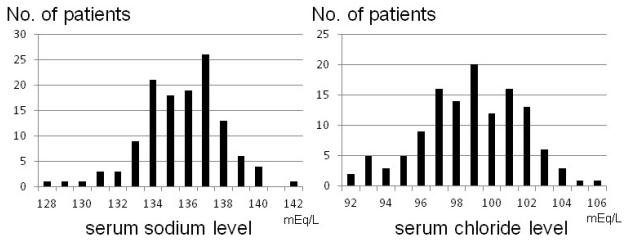

Figure 1: Serum sodium and chloride levels after starting diuretics.

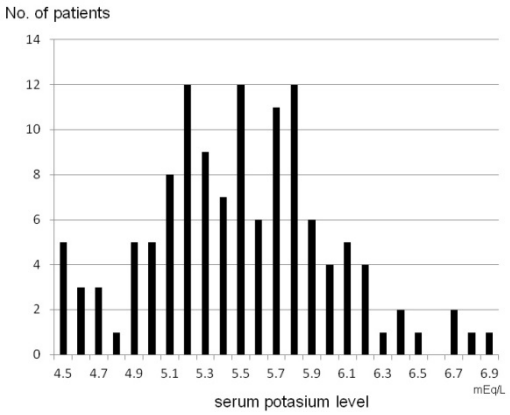

Figure 2: Serum potassium level after starting diuretics.

	Na<134	Na ≥ 134	P value
No. of patients	18	108	
Gestational age (day)	275 ± 10	276 ± 8	0.796
Birth weight (g)	2879 ± 393	3040 ± 421	0.126
Postnatal age (day)	20 ± 8	26 ± 13	0.011
BW at first diuretics (g)	3246 ± 489	3644 ± 698	0.005
Doses of furosemide (mg/kg)	1.2 ± 0.2	1.2 ± 0.3	0.819
BW change (g/day)	6.1 ± 18	2.2 ± 21	0.42
hANP (pg/ml)	312 ± 237	268 ± 216	0.551

Table 2: Comparison of clinical characteristics related to hyponatremia after starting diuretics.

Factors in electrolyte imbalance

Eighteen patients had serum sodium levels <134 mEq/L after diuretics. These patients showed a lower body weight at the start of diuretics (p=0.005) and a lower postnatal age (p=0.011) than the patients with serum sodium levels ≥ 134 mEq/L (Table 2). No significant differences were observed with regard to gestational age, birth weight, dosage of furosemide, change of body weight after starting diuretics and atrial natriuretic polypeptide. Down's syndrome was not a risk factor for hyponatremia after starting diuretic therapy.

Sixty-eight patients had serum potassium levels ≥ 5.5 mEq/L after starting diuretics. These patients showed lower postnatal age than the patients with serum potassium levels <5.5 mEq/L (p=0.003) (Table 3).

	K<5.5	K ≥ 5.5	P value
No. of patients	58	68	
Gestational age (day)	277 ± 8	274 ± 8	0.058
Birth weight (g)	2996 ± 419	3034 ± 422	0.619
Postnatal age (day)	29 ± 14	22 ± 11	0.003
BW at first diuretics (g)	3611 ± 596	3568 ± 621	0.69
Doses of furosemide (mg/kg)	1.2 ± 0.4	1.2 ± 0.3	0.232
BW change (g/day)	0.67 ± 19	4.5 ± 22	0.294
hANP (pg/ml)	280 ± 181	269 ± 241	0.785

Table 3: Comparison of clinical characteristics related to potassium levels after starting diuretics.

Discussion

Diuretics represent a mainstay of therapy for acute and chronic heart failure and are effective in relieving symptoms of fluid overload and sodium retention in adult patients [4]. Although no published clinical studies are available concerning the effectiveness of diuretics in reducing mortality or improving symptoms in pediatric patients with heart failure, diuretics are also widely used to treat heart failure in infants and children [2]. Diuretics may cause side effects such as volume depletion with prerenal azotemia, electrolyte and acid-base disorders, metabolic abnormalities and ototoxicity, as well as nephrocalcinosis. In children, various side effects such as cholelithiasis in premature infants receiving total parenteral nutrition concomitantly, secondary hyperparathyroidism and bone disease, drug-induced fever and sensorineural hearing loss in infants with respiratory distress were reported [5-7]. The chronic adverse effects of diuretics on serum electrolytes are well known and numerous reports documented the occurrence of diuretic-induced hyponatremia in adult patients [8-11]. The elderly seem to be at increased risk and several series found that 80% of patients are women [9-12].

Diuretic-associated hyponatremia is usually slow to develop and generally subsides with cessation of the diuretic unless the patient is ingesting excessive quantities of water. Although the decrease in serum sodium after starting diuretic therapy is usually modest, severe hyponatremia (serum sodium level <115 mEq/L) can develop in a susceptible subgroup of outpatients [8,9,11]. Thiazides have been implicated most often and combinations of thiazides with amiloride or triamterene may also be responsible [12]. Sonnenblick et al. reported that 73% of cases were attributable to thiazide congeners or chlorthalidone alone, 6% to furosemide and only 1% to spironolactone [11]. Thiazide-induced severe hyponatremia developed within 14 days in most adult patients and half of them showed low levels of serum sodium within 5 days [11]. Although furosemide is a more powerful natriuretic agent than thiazide, severe hyponatremia is less common than with thiazide [11].

Furosemide is one of the least toxic diuretics in pediatrics and is used most commonly in children. The addition of spironolactone can be helpful to minimize potassium loss. It has been shown that levels of both sodium and water excretion induced by furosemide are greatest during the first few days of therapy and then subsequently decline [3]. The plasma clearance of furosemide in a newborn infant is remarkably slow compared with that in older children and adults because of immature renal and hepatic function. The plasma half-life and elimination rates of furosemide in a newborn infant are similar to those in an adult with advanced renal failure [13]. Therefore, chronic therapy of furosemide in infants may induce adverse effects more frequently.

Although the pharmacokinetics of furosemide in pediatric patients including premature newborn infants was investigated in detail [14], there are few reports about the efficacy and safety of the continuous use of furosemide, despite its extensive use in infants with congenital heart disease [15-17]. Only two reports refer to electrolyte imbalance caused by oral furosemide therapy in pediatric patients. Kongrad et al. reported that one patient (an 8-year-old boy) showed simultaneous hypokalemia, hyponatremia and hypochloremia while receiving 2 mg/kg/day, among 8 orally treated patients [16]. Engle et al. reported a large study of furosemide in 62 children with heart disease of varying etiology and 44 children with renal disease [17]. During oral furosemide therapy in thirty-four patients, six patients had mild biochemical abnormalities (hypokalemic alkalosis, hypochloremia and mild azotemia) and one renal patient exhibited moderately severe azotemia with a transient rise in BUN level from 23 to 80 mg/dl. These studies were carried out on a small number of pediatric patients of various ages and lacked descriptive data about electrolyte abnormalities due to furosemide. Our study demonstrated that 14.3% of patients showed mild hyponatremia (128~133 mEq/L) after the diuretic therapy with furosemide and spironolactone. Increase of sodium excretion by furosemide and insufficient sodium intake are thought to be causes of hyponatremia. In our study, no relationship between serum sodium level and body weight change after the start of diuretics was observed. Our study revealed the relationship among hyponatremia after diuretics, body weight at the start of diuretics and postnatal age. Hyponatremia might depend on the immaturity of renal function. However, the correlation between hyponatremia and immaturity of renal function might be weak. A marked interindividual difference in the degree of diuresis produced following treatment with furosemide has been observed in infants with congestive heart failure [18]. Green et al. reported that this interindividual difference originated from both decreased delivery of the drug to the tubule in some patients and decreased responsiveness to drug in the lumen in others [19]. It might be difficult to predict hyponatremia after diuretic therapy in infants with congenital heart disease because of the interindividual differences in the intake of milk in addition to the interindividual differences in the degree of diuresis produced following treatment with furosemide.

In those children who develop hyponatremia, supplementation with oral salt was effective in restoring serum sodium levels. However, a few

infants needed sodium supplementation for over 50 days. Further investigation of patients with prolonged hyponatremia after diuretic therapy is needed.

Furosemide causes an increase in the urinary excretion of potassium, which may result in hypokalemia [3]. Loggie et al. reported that infants with congenital heart disease, treated on a chronic basis in the newborn period with diuretics (chlorothiazide or furosemide), rarely had serum potassium levels low enough (<3.5 mEq/l) to warrant the addition of potassium [20]. They suggested that this might be, in part, because the healthy newborn infants consume a diet high in potassium. Similar to their results, in the present study, no patient showed hypokalemia caused by diuretic therapy. Our result suggested that routine supplementation with potassium may not be necessary in diuretic therapy using furosemide and spironolactone. In contrast, we found that 15% of patients showed hyperkalemia (serum potassium level >6.0 mEq/L) after diuretic therapy. As marked hyperkalemia returned to the normal range within a few days in almost all cases, hemolysis during the taking of blood samples may be relevant to marked hyperkalemia after diuretic therapy.

The most prominent symptoms in infants with CHF due to left-to-right shunts are feeding difficulties and tachypnea, intercostal retractions caused by pulmonary edema. Although enlargement of the liver secondary to systemic congestion is usually present, edema is not common in such patients. That is different from adult patients with CHF. So the influence to serum electrolytes by diuretics may be different between infants with left-to-right shunts and adult patients with CHF. The prevalence of hyponatremia in adult patients hospitalized with CHF is 19%-25% [21]. However, hyponatremia in such patients is multifactorial in origin and associated with chronic diuretic therapy. There is no prospective study in adult patients with CHF regarding the short-term effects of diuretics on serum electrolytes. We could not compare the prevalence of electrolyte imbalance caused by diuretic therapy between infants and adult patients with CHF.

Conclusion

Electrolyte imbalance after the start of diuretic therapy in infants with CHF was not so rare. There were a few patients with prolonged hyponatremia after diuretic therapy. It seems to be preferable to monitor serum electrolyte levels carefully after starting diuretic therapy in infants with congenital heart disease.

Study Limitations

We did not measure serum electrolytes before starting diuretics, so we could not conclude that electrolyte abnormalities were caused by diuretics.

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