Treatment of refractory congestive heart failure and normokalemic hypochloremic alkalosis with acetazolamide and spironolactone

M.I. KHAN, MB, D MED, MRCP, FRCP[C]

Combination therapy with a loop diuretic and an aldosterone antagonist can produce normokalemic hypochloremic alkalosis, a complication not previously documented in the literature. This report describes 74 patients who had severe congestive heart failure treated with a combination of furosemide and spironolactone in whom this complication developed. Acetazolamide corrected the metabolic abnormality. The combination of furosemide and spironolactone with intermittent courses of acetazolamide was very effective in the treatment of severe congestive heart failure complicated by normokalemic hypochloremic alkalosis.

Un traitement associant un diurétique dit de l'anse et un antagoniste de l'aldostérone peut entraîner une alcalose normokaliémique et hypochlorémique, une complication qui n'a pas été établie précédemment dans la littérature. Ce rapport décrit 74 patients souffrant d'insuffisance cardiaque grave et traités avec une association de furosémide et de spironolactone chez qui cette complication est apparue. L'acétazolamide permit de corriger cette anomalie. L'association de furosémide et de spironolactone avec des cures intermittentes d'acétazolamide s'est avérée très efficace dans le traitement de l'insuffisance cardiaque grave compliquée d'alcalose normokaliémique et hypochlorémique.

In most patients congestive heart failure can be adequately controlled by therapy with digitalis and a loop diuretic, such as chlorothiazide or furosemide. Significant potassium and chloride loss may develop and result in hypokalemic hypochloremic alkalosis, which can be corrected by the administration of potassium chloride.[1,2] However, some clinicians have given an aldosterone antagonist along with the loop diuretic to prevent hypokalemia and augment the urinary excretion of sodium.[3-7]

A few years ago hypochloremic alkalosis developed in 10 of our patients during treatment of refractory congestive heart failure (defined as congestive heart failure persisting for more than 2 weeks despite sodium restriction, bed rest, adequate digitalis therapy and combination diuretic therapy with furosemide and spironolactone). All 10 patients had normal serum potassium levels. We assumed that the hypochloremic alkalosis was one of the reasons for the relative lack of a response to furosemide, which had been given in daily doses of 160 to 200 mg.

Normokalemic hypochloremic alkalosis has not been documented as a complication of combination therapy with a loop diuretic and an aldosterone antagonist, and therefore no definite treatment has been outlined in the literature. Acetazolamide seemed an appropriate drug to try because it inhibits carbonic anhydrase,[8,9] thereby increasing the urinary excretion of sodium bicarbonate, with resulting hyperchloremic acidosis. It was used to treat congestive heart failure before the advent of loop diuretics.[10-15]

In this paper I have described the occurrence of normokalemic hypochloremic alkalosis in 74 patients with congestive heart failure treated with furosemide and spironolactone, the use of acetazolamide to correct this complication, and the effect of acetazolamide on refractory congestive heart failure when given with spironolactone alone or spironolactone and furosemide.

Patients and methods

In the period January 1971 to February 1979 patients admitted to a clinical teaching unit under our supervision because of severe congestive heart failure were assigned to this study if four conditions were met:

- If severe congestive heart failure (manifested by increasing shortness of breath, orthopnea, gross edema of both legs, a jugular venous pressure greater than 10 cm and compatible radiologic signs) was still present after 2 to 3 weeks of standard treatment of this condition (bed rest, restriction of dietary intake of sodium chloride to 2 g/d, and administration of digoxin, furosemide [80 to 160 mg/d] and spironolactone [100 to 200 mg/d]).
- If normokalemic hypochloremic alkalosis developed (serum potassium level 3.9 to 5.3 [normal 3.5 to 5.3] mmol/l, serum chloride level less than 93 [normal 96 to 106] mmol/l and total CO_2 content greater than 31 mmol/l).
- If there was no response to therapy with furosemide (160 mg/d for 4 days) — that is, if diuresis was inadequate, as judged from a weight loss of less than 1 kg in 4 days, and the jugular venous pressure remained greater than 8 cm.
- If the serum creatinine level was less than 2 mg/dl (177 μmol/l) and the patient had none of the following conditions known to cause refractory congestive heart failure: surgically correctable cardiac lesions, pulmonary embolism, thyrotoxicosis, infection, obstructive cardiomyopathy or constrictive pericarditis.

On this basis 74 patients were selected for study. Digoxin had produced toxic effects in six of the patients, but these were alleviated during the first week in hospital. The congestive heart failure was considered refractory in 38 patients because there was no significant improvement after 2 weeks of standard treatment; the jugular venous pressure was greater than 10 cm and there was gross edema of the legs or

From the department of medicine, University of Ottawa and Ottawa General Hospital

Reprint requests to: Dr. M.I. Khan, 381 Kent St., Ste. 504, Ottawa, Ont. K2P 2A8

massive generalized edema (anasarca). Of these 38 patients 33 had ischemic atherosclerotic heart disease, with at least two documented myocardial infarctions and at least two episodes of congestive heart failure in the 2 years before admission; the lack of response to therapy was attributed to poor left ventricular contractility.

In all 74 patients furosemide therapy was stopped but spironolactone continued to be given, in a dosage of 250 mg four times a day, throughout their hospital stay. For 4 days acetazolamide, 250 mg four times a day, was given and the effect on the normokalemic hypochloremic alkalosis was monitored; amelioration of the congestive heart failure was indicated by a weight loss of more than 2 kg in 4 days and a decrease in the jugular venous pressure. On the fourth day furosemide therapy was restarted, with lower daily doses (40 to 80 mg); further amelioration of the heart failure was indicated by a further weight loss of more than 2 kg in 4 days and a fall in the jugular venous pressure to less than 4 cm in 1 week.

Of the 38 patients with refractory congestive heart failure 13 had no response to this treatment regimen. They were given a much larger daily dose of furosemide (200 to 240 mg) as well as spironolactone, and if the heart failure persisted acetazolamide was added and the daily dose of furosemide reduced to 80 to 160 mg.

Results

Illustrative case

A 68-year-old man with refractory congestive heart failure was admitted to hospital. He had had increasing shortness of breath and edema for 2 weeks and was receiving digoxin (0.125 mg/d), hydrochlorothiazide (100 mg twice a day) and spironolactone (75 mg/d). This was his third admission in 2 years for congestive heart failure. Transmural anterior and inferior myocardial infarctions had occurred 5 and 3 years previously.

At the time of admission he was having difficulty breathing except when upright, the internal jugular veins were distended to the level of the earlobes when he was sitting or standing, and he had anasarca, a third heart sound, cardiomegaly and crepitations throughout the lungs. A chest roentgenogram confirmed moderate cardiomegaly and severe left ventricular failure. His hemoglobin level was 14.2 g/dl and his leukocyte count 6.0 $\times$ 10^9/l. Serial electrocardiograms and cardiac enzyme levels did not suggest a recent myocardial infarction but were in keeping with old transmural anterior and inferior infarcts. His blood pressure was 115/80 mm Hg. Infection, pulmonary embolism and digitalis toxicity were excluded; the serum digoxin level was 0.9 ng/ml (normal range 0.8 to 2.2 ng/ml). He may have increased his salt intake but denied not taking his medications.

Treatment was started with oxygen, modified bed rest, digoxin (0.25 mg 2 days a week and 0.125 mg 5 days a week), restriction of dietary sodium chloride intake to 2 g/d, furosemide (80 mg intravenously once a day for 2 days, then 120 mg/d orally for 3 days, and then 160 mg/d orally), spironolactone (25 mg four times a day) and isosorbide dinitrate (5 mg sublingually every 2 hours).

By the ninth day there was no improvement (he had lost only 1.8 kg) and normokalemic hypochloremic alkalosis had developed (Table I). Furosemide was discontinued and acetazolamide, 250 mg four times a day, was given for 4 days along with the spironolactone. Correction of the normokalemic hypochloremic alkalosis was complete on the 13th day, by which time his congestive heart failure had responded to treatment: the jugular venous pressure had fallen from 15 to 7 cm and his weight had dropped another 3.7 kg.

Furosemide therapy was restarted at a daily dose of 80 mg, and moderate diuresis continued without postural hypotension. Eight days later the jugular venous pressure was normal and there were no symptoms or signs of congestive heart failure. He had lost 5 kg in the 10 days since the end of acetazolamide therapy, compared with 1.8 kg in the 10 days before its start. He was discharged on the 24th hospital day taking

Table I—Data for patient with refractory congestive heart failure

Variable	Hospital day									
	1	3	6	8	9	10	12	13	14	22
Levels of serum constituents										
Creatinine, mg/dl (mmol/l)	1.5 (133)	1.4 (124)	1.6 (141)	1.6 (141)	–	1.8 (159)	1.9 (168)	–	–	1.5 (133)
Total CO_2, mmol/l	30	34	33	32	33	32	28	23	18	26
Chloride, mmol/l	96	89	92	92	91	94	97	101	104	99
Potassium, mmol/l	4.2	3.5	3.9	4.1	4.2	4.0	4.1	4.2	3.8	4.0
Sodium, mmol/l	138	140	139	136	139	137	139	136	139	134
Serum level of digoxin, ng/ml	0.9	–	–	–	–	–	1.7	–	1.6	1.4
Blood pH	7.446	–	–	–	–	–	–	7.385	–	–
Jugular venous pressure at 45°, cm	15	–	15	–	15	–	13	7	5	1–2
Daily dose of medications										
Furosemide, mg	80*	120	160	160	–	–	–	80	80	80
Acetazolamide, g	–	–	–	–	1	1	1	–	–	–
Spironolactone, mg	100	100	100	100	100	100	100	100	100	100
Weight, kg	68	–	67.5	67.5	66.2	65	63	62.5	59.4	58

*Intravenously for 2 days.

digoxin (0.25 mg/d), furosemide (80 mg/d) and spironolactone (100 mg/d).

Findings in the entire group

The mean changes in body weight and serum electrolyte levels in the 74 patients are shown in Table II. After 2 to 3 weeks of standard treatment in hospital (including spironolactone and furosemide) the mean weight loss in 1 week (± the standard deviation) was 0.7 ± 0.2 kg, but after 4 days' treatment with acetazolamide and spironolactone the mean weight loss was 4.0 ± 0.6 kg. This greater loss in weight was accompanied by a reduction in the jugular venous pressure and a lessening of the signs and symptoms of congestive heart failure. During the next 7 days, with spironolactone and furosemide therapy, a further 5.5 kg was lost on average. The metabolic abnormality was corrected in all 74 patients by the fourth day of acetazolamide therapy.

In 61 (82%) of the 74 patients diuresis continued for the 4 days of acetazolamide and spironolactone therapy, with amelioration of the congestive heart failure, as judged by the weight loss and the reduction in the jugular venous pressure from more than 10 cm to less than 4 cm. When furosemide therapy was reintroduced at a lower dose 61 (82%) of the 74 patients had a substantial increase in diuresis, a weight loss of more than 4 kg in 1 week and complete clearing of the congestive heart failure.

Only 1 of the 13 patients with refractory congestive heart failure showed resolution of the heart failure when the daily dose of furosemide was increased greatly. The other 12 had a substantial weight loss and resolution of the heart failure during a 2-week period of therapy with an intermediate daily dose of furosemide (80 to 160 mg), as well as spironolactone (100 to 200 mg/d) and, intermittently, acetazolamide. It was necessary to give the 4-day course of acetazolamide twice during the 2-week period to achieve normal serum levels of chloride and total CO_2.

Discussion

Hypokalemic hypochloremic alkalosis, a well recognized complication of the use of loop diuretics, is corrected by the administration of potassium chloride supplements.[1,2] However, the diuretic complication I have described in 74 patients is best termed normokalemic hypochloremic alkalosis to emphasize that the serum potassium level is normal and that potassium chloride supplementation is not the preferred treatment; our study confirms that this complication of combined therapy with a loop diuretic and an aldosterone antagonist is effectively corrected by acetazolamide administration.

Table II—Mean changes in weight and serum electrolyte levels after 4 days' treatment with acetazolamide, 250 mg four times a day, in 74 patients whose severe congestive heart failure was unresponsive to furosemide therapy*

Variable	Mean ± standard deviation		
	Before acetazolamide treatment	On day 4 of acetazolamide treatment	On third day after acetazolamide treatment
Weight, kg	70.3 ± 2.12	66.3 ± 1.51	60.8 ± 2.08
Serum level, mmol/l			
Sodium	136 ± 0.58	–	134 ± 0.45
Potassium	4.3 ± 0.10	4.2 ± 0.06	4.3 ± 0.08
Chloride	91 ± 0.52	103 ± 0.35	102 ± 0.42
Total CO_2	34 ± 0.32	23 ± 0.55	26 ± 0.55

*Spironolactone, 250 mg four times a day, was given throughout the hospital stay.

The 74 patients had been treated with a combination of furosemide (80 to 160 mg/d) and spironolactone (100 to 200 mg/d) for 2 to 3 weeks when normokalemic hypochloremic alkalosis developed. We had chosen to prevent the loss of potassium due to loop diuretics by administering an aldosterone antagonist at the same time. An added factor in the conservation of potassium in our group of patients may have been their slightly impaired renal function, indicated by the serum creatinine levels, which ranged from 1.4 to 1.9 mg/dl (124 to 168 μmol/l).

A potassium deficit can exist in a patient with a normal serum potassium level;[16] however, patients with metabolic alkalosis and a mean serum potassium level of 4.3 mmol/l, as was the case in our group of 74 patients, are unlikely to have a low total potassium content, especially when taking a potassium-sparing diuretic. We emphasize the importance of the serum potassium level because it is abnormalities in this level that dictate alterations of the potassium gradient across the myocardial cell membrane and can result in electrocardiographic manifestations of cardiac dysfunction.[17-20]

Normokalemic hypochloremic alkalosis has not been documented in the literature as a complication of combination therapy with loop diuretics and aldosterone antagonists. Statson and associates[6] described two patients with hyponatremia and hypochloremia as complications of combination therapy with furosemide and spironolactone but did not state the serum potassium levels or whether alkalosis was present.

Possible ways of treating normokalemic hypochloremic alkalosis include the administration of one of four agents: potassium chloride, ammonium chloride, arginine monochloride and acetazolamide. To our knowledge there have been no studies showing the usefulness of potassium chloride in the management of this condition, but patients with a normal serum potassium level who are receiving aldosterone antagonists should not be given potassium chloride supplements because of the definite risk of life-threatening hyperkalemia.[21,22] This risk is greatly increased if the blood urea nitrogen level is greater than 25 mg/dl (8.9 mmol/l).[21] Ammonium chloride has been used to correct hypochloremic alkalosis due to mercurial diuretics.[23-26] Laragh and his colleagues[5] stated that additional chloride supplementation with ammonium chloride or arginine monochloride might be needed to correct hypochloremic alkalosis caused by loop diuretics. However, ammonium chloride can cause gastric irritation, is nauseating and does not add to natriuresis

in patients with congestive heart failure.[11] Also, deaths have been reported with the use of L-arginine, particularly when combined with spironolactone.[27] Acetazolamide had been used both to correct hypochloremic alkalosis caused by mercurial diuretics[28] and to manage congestive heart failure before the advent of loop diuretics.[10-15]

Kassirer and associates[29] have emphasized that it is difficult, if not impossible, to restore normal potassium balance and acid–base equilibrium in a patient depleted of chloride; this is likely to happen in edematous patients with a low dietary intake of sodium chloride who are receiving diuretics.

A mildly depressed serum chloride level (93 to 95 mmol/l) in patients taking diuretics for heart failure does not necessitate treatment if there is no other electrolyte abnormality or edema and the heart failure has resolved. The reduction or cessation of diuretic therapy may restore the chloride balance.

Thus, in this study the requirements for treatment with acetazolamide were hypochloremia (serum chloride level less than 93 mmol/l), metabolic alkalosis (serum total CO_2 content greater than 31 mmol/l in the absence of respiratory acidosis), normokalemia (serum potassium level 3.9 to 5.3 mmol/l), congestive heart failure with the jugular venous pressure exceeding 5 cm, and definite edema of the legs. The results of the study showed: that the combination of acetazolamide and spironolactone corrected the normokalemic hypochloremic alkalosis, increasing the mean serum chloride level from 91 ± 0.52 to 103 ± 0.35 mmol/l; that the drug combination had a diuretic action sufficient to ameliorate the congestive heart failure, as shown by a substantial weight loss and reduction in jugular venous pressure; and that the patients with refractory congestive heart failure (those who had a poor response to treatment with 160 to 200 mg/d of furosemide) showed an improvement, with an enhanced response to furosemide, after two 4-day courses of acetazolamide.

The outmoded mercurial diuretics were known to lose their natriuretic effect when hypochloremic alkalosis developed.[24-26,30] This so-called refractoriness was corrected by administering ammonium chloride[23-26,30] or acetazolamide[28] before using the mercurial diuretic again. A similar refractoriness to furosemide in the presence of hypochloremic alkalosis has not been established, although in experiments with dogs furosemide has induced the urinary excretion of 1240 μmol of sodium per minute in the presence of metabolic acidosis but only 970 μmol/min in the presence of metabolic alkalosis.[31] It can certainly be argued that a dog's response in an experiment may not simulate the response of a patient with severe congestive heart failure and anasarca refractory to a standard treatment regimen that includes the administration of 200 mg of furosemide per day.

In this study acetazolamide corrected the hypochloremic alkalosis in all 74 patients, and diuresis and weight loss were enhanced by this correction. Although these results do not prove that the hypochloremic alkalosis caused refractoriness to modest doses of furosemide, the evidence is suggestive. Further studies are required to elucidate the mechanisms. Obviously a study involving a placebo would be foolhardy in very ill patients with refractory congestive heart failure; therefore, controlled comparative therapeutic trials cannot be done with such patients.

There may be other explanations for the favourable diuretic response. In particular, a few days after diuretic therapy is stopped, fluid balance may be partially corrected by the mobilization of edema fluid into the intravascular compartment, which may then allow a natriuretic response to diuretic therapy. However, the patients in this study had a mean weight loss of 4.0 kg during the 4 days that they took acetazolamide and spironolactone but not furosemide. Their hypochloremic alkalosis was corrected and they subsequently appeared to be more responsive to furosemide, having a further weight loss of 5.5 kg, on average, in the next 7 days. Others[5,6,32] have shown that the natriuretic effect of furosemide can be increased by various combinations of hydrochlorothiazide, acetazolamide and spironolactone.

In summary, then, combination therapy with acetazolamide and spironolactone will correct normokalemic hypochloremic metabolic alkalosis and ameliorate congestive heart failure, and the combination of furosemide, spironolactone and intermittent acetazolamide therapy is effective in managing severe congestive heart failure: with this regimen diuresis and weight loss can be maintained without potassium and chloride depletion or alkalosis.

References

1. SCHWARTZ WB, VAN YPERSELE DE STRIHOU C, KASSIRER JP: Role of anions in metabolic alkalosis and potassium deficiency. *N Engl J Med* 279: 630, 1968
2. KASSIRER JP, HARRINGTON JT: Diuretics and potassium metabolism: a reassessment of the need, effectiveness and safety of potassium therapy. *Kidney Int* 11: 505, 1977
3. EARLEY LE, ORLOFF J: Thiazide diuretics. *Annu Rev Med* 15: 149, 1964
4. Idem: Diuretics. *N Engl J Med* 276: 966, 1967
5. LARAGH JH, CANNON PJ, STATSON WB, et al: Physiologic and clinical observations on furosemide and ethacrynic acid. *Ann NY Acad Sci* 139: 453, 1966
6. STATSON WB, CANNON PJ, HEINEMANN HO, et al: Furosemide: a clinical evaluation of its diuretic action. *Circulation* 34: 910, 1966
7. LIDDLE GW: Aldosterone antagonists and triamterene. *Ann NY Acad Sci* 139: 466, 1966
8. MILLER WH, DESSERT AM, ROBLIN RO JR: Heterocyclic sulfonamides as carbonic anhydrase inhibitors. *J Am Chem Soc* 72: 4893, 1950
9. MAREN TH: Pharmacological and renal effect of Diamox, new carbonic anhydrase inhibitor. *Trans NY Acad Sci* 15: 53, 1952
10. FRIEDBERG CK, HALPERN M, TAYMOR R: The effect of intravenously administered 6063, the carbonic anhydrase inhibitor, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide, on fluid and electrolytes in normal subjects and patients with congestive heart failure. *J Clin Invest* 31: 1074, 1952
11. FRIEDBERG CK, TAYMOR R, MINOR JB, et al: The use of Diamox, a carbonic anhydrase inhibitor, as an oral diuretic in patients with congestive heart failure. *N Engl J Med* 248: 883, 1953

12. BELSKY H: Use of a new oral diuretic, Diamox, in congestive heart failure. *N Engl J Med* 249: 140, 1953
13. RELMAN AS, LEAF A, SCHWARTZ WB: Oral administration of a potent carbonic anhydrase inhibitor ("Diamox"): its use as a diuretic in patients with severe congestive heart failure. *N Engl J Med* 250: 800, 1954
14. SCHWARTZ WB, RELMAN AS, LEAF A: Oral administration of a potent carbonic anhydrase inhibitor ("Diamox"). III. Its use as a diuretic in patients with severe congestive heart failure due to cor pulmonale. *Ann Intern Med* 42: 79, 1955
15. SELDIN DW: Management of congestive heart failure. Management designed to avoid serious disturbances of electrolyte and water balance. *Arch Intern Med* 95: 385, 1955
16. CASSEY TH, SUMMERSKILL WH, ORVIS AL: Body and serum potassium in liver disease. I. Relationship to hepatic function and associated features. *Gastroenterology* 48: 198, 1965
17. GETTES LS, SURAWICZ B, SHIUE JC: Effect of high K, low K and quinidine on QRS duration and ventricular action potential. *Am J Physiol* 203: 1135, 1962
18. BUTCHER WA, WAKIM KG, ESSEX HE, et al: The effect of changes in concentration of cations on the electrocardiogram of the isolated perfused heart. *Am Heart J* 43: 801, 1952
19. ST GEORGE S, FREED SC, ROSENMAN RH, et al: Influence of potassium deprivation and adrenalectomy on potassium concentration of the myocardium. *Am J Physiol* 181: 550, 1955
20. SURAWICZ B, KUNIN AS, SIMS EA: The effects of hemodialysis and of glucose–insulin administration on plasma potassium and on the electrocardiogram. *Circ Res* 12: 415, 1963
21. GREENBLATT DJ, KOCH-WESER J: Adverse reactions to spironolactone. A report from the Boston Collaborative Drug Surveillance Program. *JAMA* 225: 40, 1973
22. LAWSON DH: Adverse reactions to potassium chloride. *Q J Med* 43: 433, 1974
23. ETHRIDGE CB, MYERS DB, FULTON MN: The modifying effect of various inorganic salts on the diuretic action of Salyrgan. *Arch Intern Med* 57: 714, 1936
24. SCHWARTZ WB: Role of electrolyte balance in the response to mercurial diuretics in congestive heart failure. *Bull N Engl Med Center* 12: 213, 1950
25. SCHWARTZ WB, WALLACE WM: Electrolyte equilibrium during mercurial diuresis. *J Clin Invest* 30: 1089, 1951
26. WESTON RE, ESCHER DJW, GROSSMAN J, et al: Mechanisms contributing to unresponsiveness to mercurial diuretics in congestive heart failure. *J Clin Invest* 31: 901, 1952
27. BUSHINSKY DA, GENNARI FJ: Life-threatening hyperkalemia induced by arginine. *Ann Intern Med* 89: 632, 1978
28. RUBIN AL, THOMPSON HG JR, BRAVEMEN WS, et al: The production of hyperchloremic acidosis to restore the diuretic effect of mercurial agents in patients with refractory edema. *Clin Res Proc* 2: 94, 1954
29. KASSIRER JP, BERKMAN PM, LAWRENZ DR, et al: The critical role of chloride in the correction of hypokalemic alkalosis in man. *Am J Med* 38: 172, 1965
30. MUDGE GH, WEINER IM: The mechanism of action of mercurial and xanthine diuretics. *Ann NY Acad Sci* 71: 344, 1958
31. HOOK JB, WILLIAMSON HE: Influence of probenecid and alterations in acid–base balance of the saluretic activity of furosemide. *J Pharmacol Exp Ther* 149: 404, 1965
32. DETTLI L, SPRING P: Therapy with combinations of diuretic agents: comparative studies. *Ann NY Acad Sci* 139: 471, 1966