*Case Report*

# Nonketotic Hyperosmolar Coma and Frusemide Therapy

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SUMMARY

**Nonketotic hyperosmolar diabetic coma developed in a patient with congestive cardiac failure who was treated with frusemide. With the introduction of large doses of frusemide for resistant edema the authors suggest that particular care be taken to exclude the development of diabetes mellitus. Hyperglycemia in a patient with an already established diuresis may lead to lethal hyperosmolar coma. DIABETES *23*: 247-48, March, 1974.**

Diabetes mellitus is a well recognized complication of diuretic therapy. There have been reports of nonketotic hyperosmolar coma in patients receiving thiazides and chlorthalidone.[1,2] Although frusemide is known to produce glucose intolerance,[3] its association with nonketotic hyperosmolar diabetic coma has not been reported in the English literature. Due to the increasing use of large doses of frusemide and the high mortality of patients with nonketotic hyperosmolar diabetic coma,[4] we feel that it is important to record this association in a patient receiving frusemide for the treatment of cardiac failure.

## CASE REPORT

In January 1971 a sixty-nine year old man presented with dyspnea on exertion. He had evidence of ischemic heart disease and congestive cardiac failure. There was no glycosuria. The patient was treated with digoxin and hydrochlorothiazide. A urine test four months later was normal. In May 1972 he suffered from an episode of left ventricular failure and was admitted to another hospital. The symptoms were alleviated with frusemide, and the patient was discharged taking 40 mg. daily of this drug. Again there was no glycosuria.

In October 1972 there was a further exacerbation of pulmonary edema which was controlled by frusemide 80 mg. daily by mouth. Thereafter the patient suffered from thirst, polyuria, anorexia, weight loss, postural dyspnea and syncope. After one week, spironolactone 50 mg. and hydroflumethiazide 50 mg. were added to his treatment. The condition of the patient slowly deteriorated over the next three weeks, and by the time he was admitted to our hospital he was in coma.

The patient had gross fluid depletion and peripheral vascular failure. The pulse rate was 73 per minute and blood pressure 80/0 mm. Hg in the horizontal position. When sitting upright the patient had a pulse rate of 140 per minute and a blood pressure of 50/0. His central venous pressure was 4 cm. above the right atrium. There was left ventricular hypertrophy and the fundi showed marked arterial tortuosity. The patient exhibited a coarse tremor of all limbs but there were no localizing neurologic signs or other abnormal clinical findings. Urine testing showed heavy glycosuria without ketones or protein. Urine microscopy was normal.

Laboratory investigations on admission gave the following results: blood glucose 990 mg./100 ml., plasma sodium 141 mEq./L., potassium 5.0 mEq./L., bicarbonate 27 mEq./L., urea 246 mg./100 ml., osmolality 394 mOsm./kg., hemoglobin 16.5 gm./100 ml., and total white cell count 8,500/cm.$^3$ Midstream urine was sterile. Chest X ray showed cardiac enlargement but was otherwise normal. Electrocardiogram showed sinus rhythm and left bundle branch block; there was no change from the tracing first obtained in 1971.

A diagnosis of nonketotic hyperosmolar diabetic coma was made, and the patient was treated with intravenous fluids and insulin. He was also given heparin because of the high incidence of thromboembolism in this condition.[4] In the first twenty-four hours the patient received 5 L. of normal saline followed by 10 L. of 5 per cent dextrose and a total of 320 mEq. potassium. He only required two injections of soluble insulin, 60 units on admission and 20 units after five hours, with none subsequently. Over the first twenty-four hours the patient passed 850 ml. of urine.

He then made a rapid recovery. After forty-eight hours, investigations were as follows: blood glucose 170 mg./100 ml., plasma sodium 143 mEq./L., potassium 3.7 mEq./L., bicarbonate 30 mEq./L., urea 38 mg./100 ml., creatinine 1.5 mg./100 ml., hemoglobin 11.7 gm./100 ml. Within twenty-four hours his tremor had completely subsided.

He was given a 120 gm. carbohydrate 30 mEq. sodium diet, and the blood glucose remained initially within normal limits. However, he again developed cardiac failure which required treatment with frusemide 80 mg. daily. Overt diabetes mellitus could then be controlled only by the addition of tolbutamide 500 mg. twice a day. He was eventually discharged on this regimen and remains well.

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## DISCUSSION

The etiology of hyperosmolar coma in this case is uncertain. Frusemide may have contributed to the hyperosmolar state directly by evoking an excessive salt and water diuresis; the addition of the relatively small doses of spironolactone and hydroflumethiazide may have further exacerbated this. Suppression of insulin excretion by frusemide and the thiazide diuretic is likely to have been responsible at least in part for the nonketotic diabetic state and consequent hyperosmolar coma. There was no family history of diabetes. The patient may have been a latent diabetic, but there was no evidence of the existence of diabetes mellitus before treatment with frusemide.

There are two previous reports of nonketotic hyperosmolar diabetic states in association with frusemide therapy.[5,6] The first was a patient with advanced alcoholic cirrhosis who developed nonketotic hyperosmolar diabetic coma after treatment with frusemide, bendrofluazide, spironolactone and cortisone.[5] He responded to treatment initially and was not overtly diabetic when subsequently given smaller doses of diuretic without steroids. The patient died three months later in hepatic coma. The second report described a case of nonketotic diabetes in a patient receiving frusemide for cardiac failure. There was moderate hyperosmolarity but no clear evidence of coma. As in the present case, diabetes recurred on the reintroduction of frusemide. There is also a report of a nondiabetic hyperosmolar coma in a patient receiving frusemide for heart failure, who developed severe fluid depletion as a result of a urinary tract infection.[7]

It is suggested that patients receiving large doses of frusemide be closely monitored for evidence of diabetes mellitus. Although the present case and three previous cases of hyperosmolar states associated with frusemide all survived, it remains a potentially lethal condition.

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