Hypoglycemia Associated with the Administration of Angiotensin-Converting Enzyme Inhibitor in a Diabetic Hemodialysis Patient

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Dear Sir,

Angiotensin-converting enzyme inhibitor (ACEI) is widely used in hypertensive diabetic patients because of not affecting glucose metabolism [1, 2]. Less is known, however, about hypoglycemia associated with use of ACEI. There are a few reports of hypoglycemia associated with the treatment of ACEI in hypertensive diabetic patients [3–5].

We report a diabetic hemodialysis patient who developed a hypoglycemic attack during the use of enalapril for the treatment of hypertension. As far as we know, this is the first case of hypoglycemia associated with the use of ACEI in hemodialysis patients.

A 44-year-old insulin-treated diabetic hemodialysis patient was treated with recombinant human erythropoietin for anemia from 30th October. Along with a rise in hematocrit from 18 to 30%, systolic hypertension was exacerbated from 170/80 to 200/80 mm Hg. To control blood pressure, 12.5 mg captopril per day was added to the previous therapy of daily 40 mg nifedipine on 8th April 1988. The dose of captopril was increased to 32.5 mg per day on 25th April. During captopril treatment, his blood glucose level was decreased several times to around 60 mg/dl. Thereby, the daily dose of subcutaneous insulin was reduced from 20 to 16 units.

Since blood pressure could not be well controlled, captopril was switched to 10 mg enalapril on 6th May, and nifedipine was increased from 40 to 80 mg on 16th May, respectively. On 23rd May, erythropoietin treatment was discontinued because hematocrit increased to 34%.

In the afternoon of 5th June, he went back home from playing pinball and lost his consciousness when eating an ice cream cone. His wife took him to Fukuoka Red Cross Hospital by an ambulance at 17.20 h.

On admission, blood pressure was 206/94 mm Hg and pulse rate 96/min. Pupils were round and isocoric. Ocular fundi were normal. The tendon reflexes of the extremities were symmetrical, and no abnormal reflexes were found.

Although he did not notice any signs of hypoglycemia such as palpitation, sweating and anxiety, blood glucose was extremely low (26 mg/dl). Soon after an intravenous injection of 20 ml of 50% glucose solution, his consciousness became clear and 10 min later, his blood glucose had

risen to 146 mg/dl. Thereafter, 3 sandwiches and 5 small rice balls were taken at 20.30 h and 10% glucose solution was injected intravenously at a rate of 50 ml/h until 24.00 h when blood glucose was 297 mg/dl. Next morning, fasting blood glucose was 64 mg/dl. Insulin was reduced from 16 to 10 units/day.

Enalapril was discontinued on 23rd July. Since then, blood glucose level elevated gradually and insulin was increased from 10 to 16 units/day on 16th November. Because of blood pressure elevation, 2.5 mg enalapril, being a quarter dose of the former use, was started on 16th November. No hypoglycemic episode developed thereafter.

Although ACEI was reported not to affect glucose metabolism [1, 2], there are a few papers describing hypoglycemic episodes induced by ACEI in hypertensive diabetic patients [3–5]. Ferrire et al. [3] first reported 3 hypertensive insulin-dependent diabetic patients treated with captopril, who developed unexplained hypoglycemia, and 1 hypertensive noninsulin-dependent diabetic patient treated with captopril, who necessitated withdrawal of hypoglycemic oral agents due to hypoglycemia. They also demonstrated the higher glucose disposal rate during treatment of captopril in all of the 5 nondiabetic patients and in 3 of the 4 diabetic patients, and suggested that captopril might induce an enhancement of insulin sensitivity [3]. McMurray and Fraster [4]

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reported 2 cases of diabetes who had to reduce the dose of insulin or hypoglycemic agents after the use of enalapril for hypertension. Rett et al. [5] reported 2 hypertensive noninsulin-dependent diabetic patients who developed unexplained hypoglycemia when captopril was added. ACEI inhibits an inactivation of bradykinin as well as a conversion of angiotensin I to angiotensin II. Rett et al. [6] demonstrated that administration of bradykinin or captopril increases muscular insulin responsiveness in streptozotocin-induced diabetic rats and in noninsulin-dependent diabetic patients as well, and suggested that the reduction of glucose levels with administration of ACEI is due to an elevating systemic kinin levels.

ACEIs such as captopril, enalapril and lisinopril are excreted via the kidney [7]. With chronic renal failure, significant delay in peak concentration or excretion rate occurs and drug concentration in blood increases [7]. Dose reduction is therefore recommended in patients with renal failure [7].

Enalapril is transformed into its active diacid metabolite, enalaprilat [8], and the maximum blood concentration or the area under the serum concentration curve in chronic renal failure patients is about 3 or 4 times as high as in control group [9]. Hemodialysis is effective in lowering the plasma concentrations of enalaprilat [10] and the clearance of enalaprilat by dialysis is around 60 ml/min [10]. However, a postdialysis rebound in plasma concentration occurs and a net reduction in its plasma concentration after dialysis is around 16% because of the reequilibration between tissue and plasma [10]. Thereby a marked accumulation of enalaprilat was found to occur in hemodialysis patients [10].

Diabetic patients with renal failure have another risk to develop a hypoglycemic attack, because the removal of insulin, which is degraded by the kidney, is delayed in the chronic renal failure [11]. It is suggested that a high dose of enalaprilat accumulated and resulted into a hypoglycemic attack in our patient. Although erythropoietin was concomitantly used, it was reported not to affect blood glucose [12]. Hypoglycemia with ACEI is a rare complication, but physician should be aware of the possible in-

creasing risk of hypoglycemia in diabetic patients. The close monitoring of blood glucose levels and the early reduction of insulin should be recommended especially when renal failure becomes prominent.

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