Hypoglycemia Associated with the Administration of Angiotensin-Converting Enzyme Inhibitor in a Patient with Diabetes Mellitus

Recently it has been stressed that angiotensin-converting enzyme inhibitors have benefits such as improvement of insulin resistance or delay in the progression of diabetic nephropathy (1, 2). On the other hand, it was reported that the administration of angiotensin-converting enzyme inhibitors such as captopril, may result in hypoglycemia (2). Here we describe a case of diabetes mellitus, which caused hypoglycemia associated with the use of alacepril, an angiotensin-converting enzyme inhibitor.

The case is a 59-year-old woman with non-insulin-dependent diabetes mellitus, who had been treated with oral hypoglycemic agent for seven years until she was transferred to our division. The control of diabetes mellitus was very poor (fasting plasma glucose 321 mg/dl and HbA1c 13.8%). Her urinary C-peptide level was low (2.4 μg/day). Insulin therapy was started in November 1994, but the blood glucose remained unchanged, requiring a large dose of insulin (mixture of 30% regular and 70% intermediate-acting insulin; Penfill 30R) as described below. The patient also had diabetic neuropathy, retinopathy and nephropathy: reduced creatinine clearance (39 ml/min) and overt proteinuria.

The blood pressure was high, requiring several antihypertensive agents, such as calcium blockers (nifedipine 20 mg/day, nilvadipine 5 mg/day), an angiotensin-converting enzyme inhibitor (alacepril 75 mg/day) and diuretics (furosemide 80 mg/day and spironolactone 25 mg/day), to control it from May 1995. When the dose of insulin reached 62 units/day, the blood glucose profile was suddenly improved, and the dose of insulin could be reduced gradually to 36 (Sept. 14), 32 (Sept. 26) and 20 U/day (Sept. 29). On Sept. 29, 1995, the patient suddenly developed hypoglycemia (plasma glucose 36 mg/dl) shortly after breakfast with the injection of 20 units of insulin. Alacepril was switched to temocapril (4 mg/day), another angiotensin-converting enzyme inhibitor on that day, which was stopped on October 4, considering the possibility of hypoglycemia induced by both angiotensin-converting enzyme inhibitors. Since then she has never developed any episode of hypoglycemia with injection of 10 units of insulin (intermediate-acting insulin; Penfill N), and gradually her blood glucose levels became higher again (postprandial glucose level: -250 mg/dl), requiring an increase in insulin dose (22 units/day: Penfill 30R) 5 days after the cessation of the angiotensin-converting enzyme inhibitors.

In 1985, Ferriere et al first reported a case of hypoglycemia associated with the administration of an angiotensin-converting enzyme inhibitor, captopril (2). Thereafter there have been several reports of hypoglycemia associated with the use of angiotensin-converting enzyme inhibitors (3), and hypoglycemia has been recognized as a side effect of angiotensin-converting enzyme inhibitors in Western countries (4). In contrast, in Japan there have been few reported cases of hypoglycemia with the administration of angiotensin-converting enzyme inhibitors, except for two cases with enalapril (5, 6). Here we describe a Japanese case of hypoglycemia associated with the use of alacepril, with which there has been no reports of hypoglycemia. A very recent report from the Netherlands (4) indicated that as many as 13.8% of all hospital admissions for hypoglycemia was attributable to use of angiotensin-converting enzyme inhibitors. A euglycemic clamp study was not performed in the present case, but the reduction of required dose of insulin during the use of alacepril and its increase after the cessation of alacepril suggests that the increased insulin sensitivity induced by alacepril might contribute to hypoglycemia. It has recently been suggested that the increased local bradykinin level in muscle is involved in the improvement of insulin sensitivity induced by angiotensin-converting enzyme inhibitors (7). In the present case, it is possible that impaired renal function exaggerated hypoglycemic action of the angiotensin-converting enzyme inhibitor. Whatever the mechanisms, we should be aware of the possibility of hypoglycemia with angiotensin-converting enzyme inhibitors in Japanese patients as well as Caucasian patients, especially in those associated with diabetic nephropathy (8).

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References