OBSERVATIONS

Dramatic Improvement of Subcutaneous Insulin Resistance with Nafamostat Ointment Treatment

Subcutaneous insulin resistance is characterized by a lack of biological efficacy of subcutaneously injected insulin, with retained sensitivity to intravenously injected insulin. The existence of increased insulin-degrading activity has been suggested as a possible underlying mechanism (1). It has been reported that protease inhibitors exert beneficial effects on the absorption of subcutaneously injected insulin (1). Although the effect of an ointment containing a protease inhibitor has been shown in normal volunteers (2), there has been no report on the ointment's effect in patients with subcutaneous insulin resistance. This is the first report showing that nafamostat ointment is markedly effective in patients with subcutaneous insulin resistance.

A 52-year-old woman (156 cm, 79 kg) with type 2 diabetes was admitted to our hospital for glycemic control. A1C level was 14.0% under the treatment of subcutaneously injected insulin (335 units/day). Anti-insulin antibody was not detected. In spite of the severe resistance to subcutaneously injected insulin, hypoglycemic efficacy of intravenous insulin was retained. We diagnosed this subject as having subcutaneous insulin resistance and performed possible therapeutic trials using nafamostat ointment. For the preparation of nafamostat ointment (0.1%, wt/wt), Futhan (nafamostat mesilate) injection (Ono Pharmaceutical, Osaka, Japan) was mixed with Azunol (azulene) ointment (Nippon-Shinyaku) as previously described (2). Nafamostat ointment was applied to the skin 30 min before insulin injection. After subcutaneous injection of 20 units of insulin lispro without nafamostat ointment, plasma insulin level was 20.3 μU/ml at 0 min, 18.0 μU/ml at 60 min, 22.7 μU/ml at 120 min, and 19.0 μU/ml at 180 min. Plasma glucose level was 525 mg/dl at 0 min, 432 mg/dl at 60 min, 425 mg/dl at 120 min, and 418 mg/dl at 180 min. With the application of nafamostat ointment, however, insulin absorption dramatically improved and its hypoglycemic effect was markedly increased. After subcutaneous injection of 20 units of insulin lispro with nafamostat ointment, plasma insulin level was 16.4 μU/ml at 0 min, 120.6 μU/ml at 60 min, 102.6 μU/ml at 120 min, and 57.1 μU/ml at 180 min. Plasma glucose level was 407 mg/dl at 0 min, 408 mg/dl at 60 min, 306 mg/dl at 120 min, and 255 mg/dl at 180 min. A similar effect was observed with regular insulin after nafamostat pretreatment.

Nafamostat is a protease inhibitor usually given to patients with disseminated intravascular coagulation or pancreatitis. Its low molecular weight enables it to easily permeate skin and produce an efficacy of ointment form. It has the advantages of convenient preparation and application and of exerting beneficial effects continuously. It is likely that application of nafamostat ointment to the skin is a very promising method to improve the absorption efficacy of subcutaneously injected insulin in patients with subcutaneous insulin resistance.

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