The Insulin Sparing Effect of Telmisartan in a Case of Type 2 Diabetes Mellitus Associated with Schizophrenia under Treatment of Risperidone

Kohei Yamaguchi and Etsuro Tsutsumi

Abstract

A male patient was diagnosed with diabetes mellitus at age 37 and insulin treatment was introduced at age 49. About 2 years after the introduction of insulin, the antihypertensive agent was switched from candesartan (4 mg/day) to telmisartan (20 mg/day). The alteration improved his glycemic control dramatically, with the HbA1c levels decreasing from 8.3% to 6.0% in 6 months. Gradual marked reduction in insulin requirement was observed as it was reduced from 62 U/day to 46 U/day in 6 months and to 18 U/day in 15 months. Also his body weight was reduced from 81 kg to 65 kg in 15 months without remarkable life-style modification. Throughout the whole clinical course mentioned above, he was under treatment for schizophrenia with drugs including risperidone which possibly affects glucose metabolism. The medication for schizophrenia was not changed during this period. We present here the marked glycemia improvement effect and insulin sparing effect of telmisartan in a case of type 2 diabetes mellitus.

Key words: telmisartan, insulin therapy, insulin sensitivity, schizophrenia, risperidone


Introduction

Increasing attention has been paid to the metabolic effects of telmisartan, an angiotensin II receptor blocker (1-3). However, as far as we know, there have been no reports indicating that telmisartan exhibited an unequivocal improvement in glycemic control associated with a marked reduction in insulin requirement. Here, we describe such a patient that showed marked glycemic improvement on response to telmisartan administration. The patient adhered to perform self monitoring of blood glucose (SMBG) 3-4 times a day. This enabled us to make meticulous observations of the process of glycemic improvement. He was also under treatment with risperidone, an atypical antipsychosis drug, which has been reported to induce metabolic abnormalities (4, 5). We discuss the possibility that telmisartan may have reversed the metabolic abnormalities induced by risperidone.

Case Report

We report a 51-year-old man whose antihypertensive agent was switched from candesartan to telmisartan. He was diagnosed with diabetes mellitus at the age of 37. He underwent treatment with an oral hypoglycemic agent for one year but he did not continue to use it for the next 3 years. After that he was under treatment at an outpatient clinic for several years. Thereafter he visited our hospital at age 48, showing poor glycemic control (HbA1c; 9.2%), mild obesity (BMI; 30 kg/m²) and hypertension (blood pressure; 146/84 mmHg). Even after the in-hospital treatment for one month, it was difficult to maintain good glycemic control (HbA1c; 9.2-11.5%).

When he was 49 years old, the insulin treatment was introduced to him and he started SMBG at that time. About 2 years after the introduction of insulin, the antihypertensive agent was switched from candesartan (4 mg/day) to telmisartan (20 mg/day). Around this point, his glycemic control...
was still not good (HbA1c levels in the preceding 3 months were in the range of 7.8-8.6%). Before telmisartan administration, the medications were as follows; felodipine 5 mg, candesartan 4 mg (which was switched to telmisartan), fluvastatin 30 mg, metformin 750 mg, and insulin (each preprandial ultrashort-acting insulin analog [insulin aspart: 16, 10, 10 U] and NPH insulin 26 U at bed time). The regimen of felodipine, fluvastatin and metformin was not altered throughout the entire course.

He was also under treatment for schizophrenia by a psychiatrist and the medication was as follows; clonazepam 9 mg and bronazepam 3 mg as benzodiazepines, levomepromazine 25 mg as a phenothiazine, risperidone 2 mg as an atypical antipsychosis drug, valpronate Na 300 mg as an emotional stabilizer, and piperidine as an antiparkinsonism drug. Of the above-mentioned drugs, risperidone is reported to affect glucose metabolism (4, 5). This drug had been administered to him for 3 years. The medication for schizophrenia was not altered at all during the entire course. The main symptoms of the disease were hypobulia and lack of spontaneity, and no obvious change in the symptom was observed by the psychiatrist in charge.

The clinical course is shown in Fig. 1, in which the starting point of telmisartan is depicted as “0 week”. The patient adhered to perform SMBG 3-4 times a day since the introduction of this procedure and he continued it during the clinical course shown in Fig. 1. The insulin dose was adjusted according to SMBG and HbA1c levels.

After the introduction of telmisartan, glycemic control was dramatically improved, although we did not aggressively modify his life-style. According to the information from his wife, there had been no remarkable change in his life-style of diet and exercise for this period. He was not employed and his pastime was car driving.

The HbA1c levels decreased from 8.3 ± 0.4% (mean ± S. D. in the 3 months preceding the switch to telmisartan) to 6% in 6 months (around 24th week in Fig. 1), and fine glycemic control continued thereafter as the HbA1c level was 4.9 % in 15 months (around 60th week in Fig. 1). The average of preprandial blood glucose calculated from the data of SMBG (determined 3 times every day) also decreased 177 mg/dL to 141 mg/dL in 6 months and 103 mg/dL in 15 months. Gradual reduction in insulin requirement and body weight were observed and each change was as remarkable as the former reduced from 62 U/day to 46 U/day in 6 months and 18 U/day in 15 months and the latter from 81 kg to 73 kg in 6 months and 65 kg in 15 months. The insulin therapy at 15 months consisted of each preprandial ultrashort-acting insulin (2, 3, 3 U) and NPH insulin at bed time (10 U). The blood pressure was controlled around 130/80 mmHg with both medications.

During the above-mentioned course, telmisartan was reswitched to candesartan temporarily for 4 weeks (the 18th to 21st week). The glycemic control had been improved.

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**Figure 1.** Clinical course showing the changes in HbA1c, average of preprandial blood glucose, body weight and insulin dose. Preprandial blood glucose levels were calculated as the average of 42 determinations every 2 weeks.
The lipid profile improved without any changes in drugs affecting lipid metabolism after the administration of telmisartan. The average levels of HDL-cholesterol, LDL-cholesterol and triglycerides changed from 32 ± 7 mg/dL, 160 ± 10 mg/dL and 191 ± 42 mg/dL to 38 ± 2 mg/dL, 104 ± 4 mg/dL and 91 ± 39 mg/dL, respectively (each value represents an average of 3 determinations).

The serum prolactin level was relatively high (50.8 ng/mL, normal range in males; 3.6-12.8 ng/mL) probably due to risperidone administration (6). Considering diabetic complications, only neuropathy was positive.

Discussion

The changes following telmisartan administration in the present case can be summarized as follows: 1) telmisartan exhibited insulin sparing effect, 2) the body weight reduced gradually but definitely, and 3) the lipid profile improved. Additionally, risperidone which may induce metabolic abnormalities (4, 5) was administered throughout the entire clinical course.

As the above-mentioned data are the results of observational study, they may be criticized for chance occurrences. Against this criticism, however, we can argue that the improvement of glycemic control was proven by meticulous SMBG data, and that the second telmisartan administration brought about similar insulin sparing and glucose reducing results as observed in the first one. Pershadsingh and Kurtz also stated that switching of telmisartan to valsartan for 5 weeks reversed the improvement in insulin sensitivity and triglycerides obtained with telmisartan (1).
reported that in obese mice fed a high fat diet, glycemic improvement, reduction of serum levels of free fatty acid, triglycerides and insulin, and decrease of splanchnic fat mass occurred simultaneously by telmisartan (12).

Although the results of these studies are compatible to the findings in the present case, they do not explain the extreme effects of telmisartan seen in our case.

We then considered the weight reducing effect of telmisartan because weight reduction associated with this drug was observed in our case. The favorable effect of telmisartan on body weight control has been already reported (11, 13, 14). Different from thiazolidinediones, telmisartan does not induce obesity (13). Sugimoto et al (14) also asserted that telmisartan attenuated dietary-induced visceral obesity and weight gain, and they suggested that the drug as partial agonists (mixed agonists/antagonists) of PPARγ may have the capacity to improve glucose and lipid metabolism while attenuating a weight gain. It is evident that weight reduction plays an important role in improving insulin sensitivity especially in type 2 DM (15, 16). Therefore, weight reduction may account to some extent for the glycemic improvement associated with telmisartan in our case.

It is important to ascertain whether the insulin secretory function was restored after glycemic improvement in our case. By observing not only the absolute levels of serum CPR but also the CPR/BG ratio, we suppose the effect of exogenous insulin administration on endogenous insulin was canceled to some extent. Moreover the CPR response to glucagon infusion was deficient. Therefore, endogenous insulin can be considered to have remained deficient. Nonetheless, the insulin requirement decreased. This clearly indicates improvement of insulin sensitivity. This marked insulin sparing effect is the most conspicuous change following telmisartan administration in the present case (17, 18). Such various factors as PPARγ (19, 20), some kinds of adipokines and uncoupling protein 1 (3, 11, 20, 21) are said to involve improving insulin sensitivity on telmisartan administration. However, they do not seem to explain the extreme effects seen in our case.

On the other hand, increasing attention has been paid to the metabolic effects of risperidone (4, 5, 22-24). Risperidone has been reported to decrease insulin sensitivity (22), promote a weight gain (23), raise LDL-cholesterol levels (23) and increase the risk of diabetes mellitus (24). In other words, telmisartan and risperidone may have opposite effects on weight control, lipid metabolism and insulin sensitivity (22-24). Although the mechanisms of metabolic impairment induced by risperidone have not been fully elucidated, the direct effect on β-cells of pancreas has been virtually denied (22). As for possible mechanisms, the following have been suggested: insulin resistance due to body weight gain (23, 24) and a direct effect on insulin-sensitive target tissues (5).

In this context, the phenomenon after the administration of telmisartan in the present case seems to be the reverse of the metabolic effects of risperidone. This interpretation could account for the extreme effects of telmisartan in our case. We therefore speculate that the metabolic effects of telmisartan seen in our case were brought about, at least partially, through overcoming the metabolic effects of risperidone.

In conclusion, we presented the marked insulin sparing effect of telmisartan in a patient with type 2 diabetes mellitus. As this patient was under treatment of risperidone, the metabolic effects of telmisartan seem to require further study with regard to its interaction with risperidone. To our knowledge, this is the first report suggesting the possibility that the metabolic effects of risperidone may be reversed with telmisartan administration.

References


