Type III Allergy to Insulin Detemir

Allergy to insulin has become rare with human recombinant insulin or its analogs, with an estimated incidence of <1%. The most common clinical situation is related to the type I allergic reaction in the Gell and Coombs classification and usually consists of a local wheal-and-flare eruption at injection site with induration, pruritus, and burning sensation that appear a few minutes after the injection and last for 1–2 h; this reaction is rarely systemic, with urticaria, angioedema, or anaphylactic shock. Insulin can also be infrequently responsible for a late type III Arthus’ reaction, characterized by the development of subcutaneous nodules at the injection site 2–6 h after administration (1). And last, insulin allergy may be rarely related to a type IV T-cell–mediated delayed reaction that appears 8–12 h after injection, peaks at 24 h, and lasts for several days with painful, itchy, local mononuclear infiltration.

To our knowledge, we report the first case of type III allergy to the new long-acting insulin analog detemir. A 31-year-old man with type 1 diabetes for 20 years was admitted for uncontrolled diabetes. He had no history of any allergy. He had been treated by glargine (Lantus; Sanofi-Aventis) once daily and aspart (Novorapid; Novo Nordisk) before each meal for 2 years. We decided to switch insulin glargine for detemir to optimize glycemic control. Six hours after the first injection of detemir, the patient presented a subcutaneous small, subdermal, nonpruriginous, slightly painful nonerythematous nodule with central hematoma at injection site (left arm). On the 2 following days, the same localization occurred 4–6 h after the detemir injection (right arm, left thigh), although no reaction to aspart was noticed. Local factors such as poor injection technique, misuse of insulin injector, or use of impure alcohol were ruled out. Detemir was then switched back for glargine. The nodules spontaneously disappeared in ~48 h. We did not perform skin tests because of the explicit clinical presentation of a type III allergy and because of the potential risk of serum sickness after re-introducing detemir. However, we cannot exclude that an excipient rather than insulin detemir itself could be responsible for this allergy. Nevertheless, the only additive present in detemir preparation and not in glargine or aspart preparations is mannitol, and allergy to mannitol is exceptional and related to IgE-mediated anaphylaxis (type I reaction) (2). To our knowledge, we report here the first case of allergy with insulin detemir.

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References

Efficacy of Pitavastatin, a New HMG-CoA Reductase Inhibitor, on Lipid and Glucose Metabolism in Patients With Type 2 Diabetes

Type 2 diabetes is one of the risk factors for macrovascular disease. Treatment of hypercholesterolemia is important in patients with type 2 diabetes to prevent macrovascular disease. The 3-hydroxy-3-methyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are key drugs to lower the cholesterol level not only in nondiabetic patients but also in patients with type 2 diabetes. However, some statins might worsen glycemic control (1) whereas some of them might be neutral (2) or improve glycemic control (3), and their effects on glucose metabolism are controversial. Pitavastatin, an HMG-CoA reductase inhibitor, has been available in Japan since 2003 (4) and the Republic of Korea since 2005, and its effect on glucose metabolism in diabetic patients remains unknown. Since safe use of statins is important for patients, we evaluated the effects of pitavastatin on lipid and glucose metabolism in this study.

A total of 79 type 2 diabetic patients (47 men and 32 women; mean age ± SD 61.7 ± 12.1 years; BMI 26.7 ± 4.2 kg/m²) with hypercholesterolemia who had never been treated with statins and attended one of five outpatient diabetic clinics were enrolled. Informed consent was obtained from all subjects. This study was designed as a 8-week intervention period with new administration of pitavastatin (1 or 2 mg/day). Fasting plasma glucose, HbA1c, LDL cholesterol, HDL cholesterol, triglycerides, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl-transferase, and creatine phosphokinase levels were measured both before and after 8 weeks of pitavastatin treatment. Differences in these parameters pre- and posttreatment were analyzed using Wilcoxon’s matched-pair signed-rank test.

Pitavastatin treatment resulted in a significant decrease in LDL cholesterol levels (from 4.28 ± 0.69 to 2.70 ± 1.03 mmol/l, P < 0.0001) and triglyceride levels (from 1.71 ± 0.76 to 1.54 ± 0.99 mmol/l, P < 0.0001), whereas the change in HDL cholesterol levels did not reach statistical significance (from 1.29 ± 0.32 to 1.33 ± 0.33 mmol/l, P = 0.055). Concerning glycemic control, changes in fasting plasma glucose levels (from 8.20 ± 2.71 to 8.27 ± 2.10 mmol/l) and HbA1c levels (from 7.25 ± 1.60 to 7.27 ± 1.47%) were not statistically significant. Changes in other available parameters were also not statistically significant. No subject terminated the trial because of adverse events.

Our results showed that pitavastatin is a potent agent for lowering LDL cholesterol level and that it does not affect glycemic control in patients with diabetes. Although statins have been widely prescribed all over the world and are regarded as the first choice for hypercholesterolemia, physicians must pay attention to the adverse effects of these agents, e.g., myotoxicity, liver dysfunc-
tion, and worsened glycemic control, which might be related to the cytochrome P450–mediated metabolic pathway (4,5). The results in this study are an important observation for patients with diabetes and are consistent with another report that pitavastatin, which is metabolized with little involvement of cytochrome P450 isoenzymes (4), did not show these major adverse effects (6). Because pitavastatin has been marketed for only a few years, further studies with a greater number of subjects and a longer duration are needed to establish the safety of this agent.

In conclusion, pitavastatin is effective in lowering LDL cholesterol and triglyceride levels without affecting glycemic control in patients with diabetes. We believe that this agent must also help prevent the development of macrovascular disease in diabetic patients, as has been seen with other statins, but this still requires confirmation in a controlled clinical trial.

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References

Twelve-Hour Glycemic Profiles With Meals of High, Medium, or Low Glycemic Load

D iets of low glycemic load may dampen the postprandial glycemic response, thereby avoiding high blood glucose concentrations that could be detrimental to health (1). We compared blood glucose profiles of two nondiabetic subjects (A and B) consuming meals of high (baguette, strawberry jam, and melon) and medium (baked potato, cheese, and Coca Cola), or low (chickpeas, tuna, vinegar, and oil) glycemic load at regular intervals throughout the day.

Three test meals contained the same calorie content but different glycemic load for each subject: A: glycemic load = 92, 49, and 19; B: glycemic load = 115, 66, and 24). For each glycemic load category, three full portions of the test meal with a 4-h interval in between and six half-portions with a 2-h interval in between were consumed on 2 different days. For each subject, six 12-h blood glucose profiles deduced from the interstitial glucose in subcutaneous abdominal tissue measured by MiniMed continuous glucose monitoring system were obtained.

A relatively stable blood glucose profile was observed throughout the day with low–glycemic load meals for both subjects (Fig. 1). Consumptions of high– and medium–glycemic load meals were usually followed by peaks of blood glucose. However, there did not appear to be an obvious dose-response effect between the actual glycemic load and the height of the peaks (either full portion versus half portion or high glycemic load versus medium glycemic load), suggesting a possible “threshold” effect (2). Nibbling diets with small frequent meals may only help avoid hyperglycemia when the meal glycemic load is below a certain threshold level. Compared with the glucose response of the first meal, some of those triggered by each subsequent but identical meal appeared to be lower. This apparently greater “breakfast” glycemic response may be due to higher ACTH and glucocorticoid levels before awakening. Since glycemic index values of food are derived in the fasting state, the glycemic load formula may give better prediction of the postprandial glycemic response for breakfast than those for lunch or dinner.

Calculated meal glycemic load may deviate from the actual glycemic response of food combinations. Potential limitations of the continuous glucose monitoring system also need to be considered when interpreting our glycemic profiles (3). In this study, 25% of the sensor–derived blood glucose concentrations deviated by ≥15% from the corresponding fingerstick glucometer values (for calibration) among 48 paired values.

Our pilot study suggests that a stable blood glucose profile can be maintained by consuming a low–glycemic load diet. However, meal glycemic load may need to be below a certain threshold to be of benefit. Identical meals may produce different blood glucose responses at different times of the day, indicating that the glycemic load formula may not predict the postprandial glycemic response for meals eaten in the nonfasting state.

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