OBSERVATIONS

Implantable Pump Therapy Restores Metabolic Control and Quality of Life in Type 1 Diabetic Patients With Buschke's Nonsystemic Scleroderma

Buschke's nonsystemic scleroderma is an uncommon dermatosis characterized by thickened and indurate skin of unknown origin, mostly affecting upper parts of the body but also the abdominal area. While diabetes is rarely associated, subcutaneous insulin treatment may be hardly feasible and effective because of incomplete absorption of insulin (1).

After approval of our institutional ethical committees, four type 1 diabetic patients (one male and three female subjects) affected by this condition received Medtronic MiniMed implantable pumps (Northridge, CA) for intraperitoneal insulin delivery (2) between 1994 and 2004. The patients, aged 45.2 ± 2.9 years, had a mean duration of diabetes of 33.5 ± 1.3 years, including multiple microvascular complications. Biopsies of the affected skin, performed in three patients, confirmed expanded dermis with enlarged collagen bundles and, in one case, visible mucin. None had evidence of systemic sclerosis by biopsy and other investigations at baseline or during follow-up. Skin status was clinically assessed on a yearly basis, diabetes complications surveyed as required, and HbA_{1c} (A1C) measured using a high-performance liquid chromatography method (normal values <5.6%) on a quarterly basis.

From implantation time, improvement of glucose control was sustained as shown by mean yearly A1C moving from 9.3 ± 0.7% (baseline) to 7.9 ± 1.3% (2005). Microvascular complications remained stable or decreased. All patients experienced a dramatic decrease of skin induration as early as a few months after implantation. We found clinical improvement of the skin aspect in terms of redness, swelling, and induration, even if we did not have tools at our disposal to measure skin elasticity.

Several published case reports describe either poorly effective therapeutic options for Buschke's scleroderma (3,4) or the effective, albeit rather extreme, radiation therapy (5). Poor glycemic control may play a role in worsening of the skin condition, resulting in a vicious cycle of worsening control and worsening disease driven by poor absorption of insulin (6). Although not documented by pathological or biochemical skin analyses, our findings support previous hypotheses that glucose excess causes impairment through increased glycation alterations of tissue collagen, which are involved in Buschke's scleroderma, and that this process can be reversed with improved glucose control. We suggest implantable pump therapy as an option in patients with type 1 diabetes affected by this uncommon skin condition when optimized subcutaneous insulin treatment fails to achieve acceptable blood glucose control.

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Possible Problem With Optipen Pro-1

Should diabetic patients continue to use this product?

Insulin glargine is a modified basal insulin analog that has been recently introduced and is now available worldwide. Insulin glargine is available in 3-ml cartridges that can be used with the OptiPen Pro-1 (Sanofi-Aventis). The Medicines and Healthcare Products Regulatory Agency (MHRA; executive agency of the Department of Health in the U.K., which enhances and safeguards the health of the public by ensuring the effectiveness of medicines and medical devices) has received a significant number of reports concerning difficulties in the operation and use of the OptiPen Pro-1 insulin pen injection system. A fault was found with some batches of the OptiPen Pro-1 system, whereby the dosage button failed to engage at the end of an injection (1).

A total of 32 type 1 diabetic patients (age 17.0 ± 4.4 years [mean ± SD]) on multiple daily injection regimens, who had been treated with insulin for at least for 6 months and were insulin glargine naive, were transferred from NPH insulin to insulin glargine between May 2004 and March 2005. Two patients without any evidence of infection or of skipped insulin doses had ketosis on the 3rd and 4th month of insulin glargine treatment, respectively. When the patients were questioned about the reasons for ketosis, they stated leakage of insulin from the sides of the pen during injection.

An inquiry form regarding OptiPen Pro-1 was given to all subjects on the 6th month of therapy. Leakage from the sides of the pen was noted by 58.8% of subjects, and a problem with the dosage button not locking when it was fully depressed following injection of the desired dose of insulin was reported by 38.2%. The patients were asked to rate

their degree of satisfaction with the pen on a scale from 0 (worst) to 5 (best). Overall, 9% of patients rated the pen as 5, 38.4% as 4, 26.4% as 3, 11.7% as 2, 8.8% as 1, and 2.9% as 0. A significant amount (61.7%) of subjects exchanged their OptiPen Pro-1 for an insulin syringe or insulin detemir.

In the U.K., the MHRA has issued an alert about possible problems with the OptiPen Pro-1. Possible damage to an internal component of the pen during assembly could mean that the dosage button fails to engage at the end of an injection. This could lead people to believe that an injection has not been successful and, therefore, subsequently duplicate the dose. The MHRA asked all National Health Service boards (confidential health advice and information service for Scotland) and pharmacists to ensure that patients using the system were aware of the potential for dose button failure (1). The leakage and dosage button problems observed with OptiPen Pro-1 raise uncertainty as to whether diabetic patients should continue to use this product.

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Improvement of Type 2 Diabetes in a Lung Cancer Patient Treated With Erlotinib

A 72-year-old woman, with BMI 30 kg/m^2, had established type 2 diabetes for 2 years before her diagnosis of non–small cell lung cancer (NSCLC). Initially, her HbA_{1c} (A1C) was 10.3%. After treatment with pioglitazone and glyburide for 1 year, she attained an A1C of 8.2%, with average fasting glucose levels of 130–160 mg/dl. She presented to our care with metastatic NSCLC. After two cycles of chemotherapy with carboplatin and paclitaxel, her tumor progressed, and subsequently her treatment was changed to 150 mg erlotinib once a day. Within the first 4 weeks of erlotinib use, the patient noted frequent episodes of hypoglycemia, and her premeal glucose levels decreased to <90 mg/dl. Notably, her appetite and nutritional intake were not changed, her weight remained stable, and no other medications known to affect glucose metabolism had been introduced. A morning cortisol level and renal and hepatic functions were also found to be normal. Glyburide at 10 mg twice a day was eventually discontinued. Her fasting glucose levels stabilized at ~90–110 mg/dl. The patient achieved a small reduction in the size of her tumor burden with erlotinib. After 8 months of erlotinib therapy, and while continuing 30 mg pioglitazone once a day, her A1C was measured at 6.5%. Unfortunately, 1 month later, symptomatic leptomeningeal central nervous system lesions progressed and the patient was transferred to a hospice program.

Erlotinib (Tarceva; OSI Pharmaceuticals) is an analinoquinazolone inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase and has been approved as second-line treatment in NSCLC (1). Hypoglycemia or glucose derangements were not reported as side effects in the phase III randomized trial (1) or in the available literature of these specific tyrosine kinase inhibitors (2). However, of interest to this case, the crystal structure of the kinase activation loop of EGFR adopts a conformation similar to that of the phosphorylated active form of the kinase domain of the insulin receptor (3). Downstream targets of EGFR, such as Akt (protein kinase B) and extracellular signal–regulated kinase, are also involved in the complex pathway of insulin signaling (4). Of note, regression of type 2 diabetes has been described with the use of another tyrosine kinase inhibitor, imatinib mesylate (Gleevec; Novartis) (5). Further investigation of the possible connection of EGFR-mediated pathways active in cancer and in the pathogenesis of diabetes as well as the possible use of analinoquinazolone EGFR inhibitor compounds in hyperglycemic states may be warranted.

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Insulin Allergy and Immunologic Insulin Resistance Caused by Interleukin-6 in a Patient With Lung Cancer

Simultaneous occurrence of insulin allergy and immunologic insulin resistance has been reported in a few cases (1). A 62-year-old man with type 2 diabetes, who had been treated with insulin (premixed insulin of 30% aspart and 70% protaminated insulin aspart) for 3 months, noticed urticariform erythema and induration of the skin at the insulin-injection site. Erythema appeared imme-