Drugs of the Future 2007, 32(6): 563-569

CCC: 0377-8282/2007

Meeting Report

New developments in the management of diabetes

Highlights from the Diabetes UK Annual Professional Conference, held on March 14-16, 2007, in Glasgow, U.K.

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Abstract

The Diabetes UK Annual Professional Conference took place on March 14-16, 2007, in Glasgow, U.K. The meeting was devoted to basic science, clinical science and clinical care addressing different aspects in the field of diabetes. This report mainly concentrates on the development of new drugs and other measures to improve diabetes control and associated risk factors.

Introduction

Diabetes has become an important public health problem throughout the world. This substantial global burden brings with it the huge challenge of providing effective treatment strategies to those affected. We have evidence that intervention to lower glucose levels will improve outcome, and in clinical practice we continually strive to achieve optimal control of diabetes and other risk factors to reduce morbidity and mortality.

Incretin hormones and mimetics

Liraglutide is a long-acting GLP-1 analogue currently in late stages of clinical development as a once-daily treatment for patients with type 2 diabetes. Vilsboell *et al*. used liraglutide as monotherapy in 165 patients for 14 weeks. Glycosylated hemoglobin (HbA1c) was significantly lower on liraglutide than on placebo and the treatment was well tolerated. A dose-dependent weight reduction was observed with liraglutide. There were no reported episodes of major or minor hypoglycemia (1). The same group of researchers also noted a significant reduction in systolic blood pressure, triglyceride levels, plasminogen activator inhibitor-1 (PAI-1) and brain natriuretic peptide (BNP) concentrations with liraglutide (2). Liraglutide markedly improved β-cell function, first-phase insulin secretion and maximal β-cell secretory capacity (3).

In another interesting study, human pancreatic β-cells were exposed to liraglutide and it was found that native human β-cell differentiation occurs in response to liraglutide via GLP-1 receptors. Therefore, liraglutide might help to increase the β-cell numbers in type 2 diabetic patients (4). Observations from an animal study confirmed that GLP-1 regulates gene expression in clonal pancreatic β-cells, which may be a potential mechanism by which GLP-1 stimulates insulin secretion (5).

Glucose-dependent insulinotropic polypeptide (or gastric inhibitory peptide, GIP) is a key incretin hormone that is rapidly degraded *in vivo* by dipeptidyl-peptidase IV (DPP-IV). *N*-Acetyl-GIP is a potent DPP-IV-resistant analogue of GIP with improved antidiabetic activity in type 2 diabetic patients. In an animal study, it was found that *N*-acetyl-GIP did not have any effect in insulin-deficient streptozotocin-treated diabetic mice. This study thus suggests that the mode of action of this analogue is to stimulate insulin secretion from the β-cell (6). (Pro3)GIP is a potent and specific GIP receptor antagonist that improves glucose tolerance and insulin resistance and counters abnormalities of islet structure and function in *ob/ob* mice. Again, all these beneficial effects of (Pro3)GIP were not observed in streptozotocin-treated diabetic mice, suggesting that it acts through an insulin-dependent mechanism (7).

Oral hypoglycemic drugs

Rimonabant, the first selective cannabinoid CB_1 receptor blocker, significantly improved cardiometabolic risk factors in overweight/obese patients with type 2

diabetes receiving metformin or sulfonylurea. In the SERENADE study, rimonabant was given to treatment-naïve patients with type 2 diabetes for 6 months as monotherapy. There was a significant reduction in HbA1c, body weight and waist circumference. Rimonabant also improved the lipid profile and was well tolerated. The most common side effects were dizziness, nausea and upper respiratory tract infection (8). In another multicenter, randomized, double-blind, placebo-controlled trial, rimonabant significantly improved oral glucose tolerance compared with placebo in nondiabetic overweight/obese patients (9). Data from RIO-Diabetes, RIO-Europe, RIO-North America and RIO-Lipids revealed that rimonabant 20 mg/day significantly improved multiple cardiometabolic risk factors in patients with type 2 diabetes, as well as nondiabetic overweight/obese patients (10).

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor γ (PPARγ) agonists used for the treatment of type 2 diabetes. TZDs improve glycemic control by reducing insulin resistance in target tissues, although the mechanism of their action has not been fully elucidated. There is also growing evidence that TZDs directly improve endothelial function in insulin-resistant subjects, independent of improvement of glycemic control. Salt *et al.* demonstrated that rosiglitazone is able to acutely stimulate nitric oxide (NO) synthesis in cultured endothelial cells by an AMP-activated protein kinase-dependent mechanism, independent of PPARγ (11).

Another TZD, pioglitazone, was studied in a randomized, double-blind, placebo-controlled trial in subjects with impaired glucose tolerance. This study revealed that pioglitazone does not restore first-phase insulin response but decreases the second-phase insulin response and postprandial insulin:glucose ratio, possibly as a result of improved insulin sensitivity (12). The same group of researchers also found that there was significant improvement in the lipid profile, including a reduction in fasting triglycerides and increased HDL cholesterol, in pioglitazone-treated patients. Pioglitazone also suppressed nonesterified fatty acids (13).

In another study, combination therapy with pioglitazone (PPARγ agonist) and bezafibrate (PPARα agonist) was evaluated in type 2 diabetic patients. This combined therapy prevented the 60% decrease in liver triglyceride content measured by magnetic resonance imaging (MRI) previously reported for PPARγ agonist monotherapy. There was also significant improvement in fasting and postprandial glucose levels which was not additive and not dependent on changes in tissue triglyceride content (14). However, another study failed to show any effect of fenofibrate on insulin sensitivity in type 2 diabetic subjects as compared to atorvastatin (15).

There are concerns regarding the use of TZDs and insulin together, as this combination might increase the risk of edema and precipitate heart failure. Recently, the combination of pioglitazone and insulin was licensed in the U.K. for use in the treatment of type 2 diabetes. A prospective analysis examined the effect of pioglitazone combined with insulin in type 2 diabetic patients. There were significant improvements in HbA1c and triglyceride levels. The mean daily insulin dose fell significantly from baseline. Although mean weight gain was 2.9 kg, no patients were hospitalized (16). In another study, pioglitazone was added to the current insulin regimen in type 2 diabetic patients. After 18 months of follow-up, HbA1c had improved by an average of 17%, weight had increased by 5.5%, but the insulin requirement had fallen by 8%. One patient was able to stop insulin. Therefore, TZDs with insulin are an effective treatment in type 2 diabetic patients who are not well controlled otherwise (17).

Metformin-associated lactic acidosis occurs almost exclusively in patients with type 2 diabetes with concurrent renal and/or liver dysfunction, sepsis or hypoxic states. A case report demonstrated lactic acidosis in a patient who was on a modified-release preparation of metformin. As this metformin preparation is quite new and will be used more extensively, careful monitoring of patients who are at high risk is needed (18).

Metformin and glitazones can induce ovulation in women, leading to concern about unplanned pregnancies in women treated for type 2 diabetes. A retrospective study found that 3 of 37 women aged 20-46 years who used these drugs either alone or in combination became pregnant. Thus, type 2 diabetic women of child-bearing age should be counseled properly as to the potential of insulin sensitizers to increase the likelihood of conception (19).

Insulin preparations

Endothelial dysfunction, as assessed by reduced NO bioavailability, is associated with type 2 diabetes and vascular disease. Insulin-stimulated NO synthesis in the endothelium is impaired in patients with type 2 diabetes. Investigators from Glasgow suggested that insulin stimulates the protein kinase B (PKB)-mediated phosphorylation of endothelial NO synthase at Ser615 in human aortic endothelial cells and may contribute to insulin-stimulated NO synthesis in endothelial cells (20).

Individuals with type 1 diabetes are traditionally started on twice-daily biphasic insulin at diagnosis, progressing to basal bolus for greater flexibility. However, patients often resist the change to a more intensive regimen. Mealtime short-acting insulin was tried in newly diagnosed type 1 diabetic adult patients and found to be safe and effective. Therefore, this regimen may be a good alternative for flexible intensive insulin therapy (21). An interesting case report mentioned insulin resistance to short-acting insulin analogues such as NovoRapid® (insulin aspartate) and Humalog® (insulin lispro) because of insulin antibody formation, which improved with Apidra® (insulin glulisine). Therefore, if a patient needs a high dose of this type of insulin analogue, insulin resistance should be kept in mind and another insulin analogue may be a good option (22).

Proper glycemic control for diabetic patients who are admitted to the hospital is absolutely essential to reduce morbidity and mortality. Continuous intravenous insulin

treatment is the usual protocol in most U.K. hospitals. However, an audit revealed that continuous i.v. insulin is not properly monitored, leading to frequent episodes of hypoglycemia and hyperglycemia. Even when the protocol was followed carefully, glycemic control was not ideal. Thus, re-education of the staff and re-designing the protocol are needed to improve outcomes (23).

Obese type 2 diabetic patients are difficult to control despite massive doses of insulin because of severe insulin resistance. A large volume of insulin causes weight gain, being an anabolic hormone, and local discomfort. In these situations, concentrated insulin therapy is a good alternative. In a case report, an obese patient (body mass index [BMI] = 35) who was receiving 1400 U of insulin had an HbA1c of about 10.3%. When U500 Actrapid insulin (250 U twice a day) was used in this patient for 6 months, HbA1c fell to 7.8%. Therefore, concentrated insulin is a novel alternative for type 2 obese patients who have severe insulin resistance to improve their diabetes control and compliance (24).

Time-action profiles of different premixed formulations of biphasic insulin aspart (30%, 50% and 70% insulin aspart) were investigated in type 1 diabetic patients. Increasing ratios of rapid-acting insulin in these premixed formulations resulted in greater early-phase metabolic effect and a shorter duration of action, which helps to optimize insulin therapy according to individual needs (25).

Insulin glargine, a long-acting insulin analogue, is used frequently to treat both type 1 and type 2 diabetic patients. The NICE (National Institute for Health and Clinical Excellence) has published guidelines on insulin glargine. An analysis revealed that HbA1c decreased by 1%, weight decreased by 1 kg and there was also a significant reduction in hypoglycemic episodes following treatment with insulin glargine (26). Another retrospective analysis also confirmed the beneficial effects of insulin glargine. Maximum improvements were noted in diabetic patients who were on insulin glargine alone or in combination with other drugs (27). However, when NovoRapid® was mixed with insulin glargine in the same syringe by a patient prior to injection, it affected the potency of the insulins, resulting in higher doses. This may have been due to the acidic pH of insulin glargine. Thus, it is very important to explain this undesirable effect to the patient when recommending two different kinds of insulin (28). In a retrospective study of 30 type 1 diabetic patients, insulin glargine was used during pregnancies. Insulin glargine was found to be very safe and was not associated with any adverse effects in the mother or the baby (29).

Insulin detemir, another long-acting insulin analogue, is increasingly prescribed for diabetic patients. PREDICTIVE (Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation) is an international observational study in diabetic patients assessing the safety and efficacy of insulin detemir in clinical practice. This study found a significant reduction in HbA1c, fasting blood sugar, fasting blood sugar variability and the incidence of hypoglycemia in insulin detemir-treated patients. There was no significant weight gain in both type 1 and type 2 diabetic patients (30). Unfortunately, there was a case report of erythema multiforme secondary to insulin detemir, a life-threatening complication (31).

In an observational study, the effect of insulin detemir and insulin glargine was compared in insulin-naïve type 2 diabetic patients. Both were found to be equally effective in improving glycemic control in diabetic patients, with no significant weight gain (32). Another pilot study compared traditional twice-daily regimens with basal bolus and carbohydrate counting in overweight type 2 diabetic patients. Basal bolus insulin therapy with carbohydrate counting initially improved glucose control and total insulin dose was reduced by 4.7 U. Therefore, this option appears to be a good alternative for type 2 diabetic patients (33). In spite of the increasing use of insulin in different combinations for type 2 diabetic patients, a retrospective study revealed that, although insulin therapy resulted in significant improvement in glycemic control, optimal control was not achieved and was associated with significant weight gain. Thus, new therapeutic strategies are needed (34).

In the PREFER Treat-to-Target study, investigators attempted to define the recommended doses of biphasic insulin aspart 30 (BIAsp30) and insulin detemir (IDet) and insulin aspart (IAsp) as a basal bolus regimen in type 2 diabetic patients. This was a 26-week, multicenter, open-label, randomized, parallel-group trial involving 715 poorly controlled type 2 diabetic patients. At the end of the trial, total daily insulin doses were 0.63 U/kg for BIAsp30 and 0.86 U/kg for IDet/IAsp. BIAsp30 titration resulted in a 50:50 split between breakfast and dinner. For IAsp, the final split between meals was: breakfast 35%, lunch 29% and dinner 36%. Final IDet doses were 0.353 U/kg when used once daily, and 0.201 U/kg at breakfast and 0.356 U/kg at dinner when used twice daily. It is interesting to note that the doses of BIAsp30 and IAsp were distributed equally between meals. The great majority (87%) of the patients who were on a basal bolus insulin regimen remained on once-daily IDet (35).

Although insulin pump therapy is a very important modality for treating diabetic patients who are not well controlled with other options, cost-effectiveness and the long time scale of projected benefits are a concern. A study evaluated the cost-benefit ratio of insulin pump therapy by directly monitoring the effects on healthcare use. Benefits within the time frame for secondary care providers were apparent. It was also suggested that the methods used could be of value to other health communities starting a pump service (36).

Painful peripheral neuropathy, a well-described manifestation of insulin neuritis, can result from rapid improvement in diabetes control following initiation of insulin. However, autonomic neuropathy is not a recognized manifestation of insulin neuritis. A 38-year-old type 2 diabetic women developed autonomic neuropathy after starting Novomix® 30, indicating that autonomic neuropathy may be a manifestation of rapid improvement in glycemic control after initiation of insulin (37). Another complication associated with human insulin was highlighted in a case

report. A 23-year-old type 1 diabetic women developed lipoatrophy when she was treated with biphasic insulin. This was successfully treated with dexamethasone. This type of skin change is cosmetically unacceptable and can cause erratic absorption of insulin, which should be kept in mind and managed properly (38).

Other modes of treatment and intervention

Improvements in both sensorimotor and autonomic neuropathy have been reported in recipients of either pancreas or simultaneous pancreas-kidney transplant, as reflected by improvements in nerve conduction velocities and measures of autonomic function. However, chronic painful neuropathic symptoms persisted in 2 type 1 diabetic patients even after pancreas transplant and long-term euglycemia (39). A retrospective chart and database assessment evaluated the effect of pancreas transplantation in diabetic patients in Ireland and found that it significantly improved HbA1c, lipid profile, creatinine and blood pressure levels (40). The study by Zhao *et al.* could detect stem cell-like cells in human adult pancreas, which may be valuable in extending the life of islets after transplantation and as a source of new islets available for transplantation (41).

The beneficial effect of Roux-en-Y gastric bypass surgery on morbid obesity and uncontrolled diabetes was established in a case report. A grossly obese women (BMI = 44.3) was receiving metformin and insulin and developed severe insulin resistance. She underwent Roux-en-Y gastric bypass surgery and lost almost 26 kg. At follow-up 30 months post-surgery, her diabetes control was excellent (HbA1c = 7.4%) on diet alone. Therefore, this kind of surgery should be considered early on for patients with diabetes and gross obesity (42).

The early ACTID study revealed that, compared with published data from normal, overweight and obese subjects employed in sedentary occupations, physical activity was lower in individuals with type 2 diabetes (43). A population-based screening project for type 2 diabetes subjects revealed that as self-reported levels of total physical activity increased, there was a corresponding decrease in HbA1c. This project also suggested that it is the total amount of activity that is important rather than the type of activity (44). Another study found that a supervised exercise program reduced insulin resistance and decreased fasting β-cell response (45). Furthermore, a retrospective analysis evaluated the effects of orlistat in obese patients with type 2 diabetes. Treatment with orlistat for 6 months improved micro- and macrovascular risk factors and the drug was well tolerated (46).

At 6 months, the Dose Adjustment For Normal Eating (DAFNE) study in type 1 diabetic patients showed improved glycemic control without increasing severe hypoglycemia, while significantly reducing the negative impact of diabetes on quality of life (QoL) and improving other patient-reported outcomes (PROs). When the long-term efficacy of this training program was evaluated, QoL and other PROs were well maintained over approximately 4 years (47). The REACCT (Re-Education And Carbohydrate Counting Training) program covers similar principles of the DAFNE study over two 2-h sessions, 6 weeks apart. Groups of 5-10 patients with their partners receive education from a specialist dietician and a diabetes specialist nurse. This course has had positive clinical and lifestyle benefits in a highly cost-effective manner (48). Another study showed that low-carbohydrate diets can maintain significant weight loss and HbA1c over 9 months (49). Dhindsa *et al.* compared the effect of a very-low-calorie diet with orlistat in obese patients with poorly controlled type 2 diabetes. They found that an intensive very-low-calorie diet resulted in significant reductions in body weight, blood pressure and total cholesterol, and improvement in HbA1c. All these benefits were maintained for 1 year (50).

Previous studies have identified an association between dysglycemia, vascular dysfunction and oxidative stress. Aspirin is known to reduce vascular disease and improve dysglycemia at high doses, and may attenuate endothelial dysfunction. Raghavan *et al.* suggested that aspirin, when administered at 300 mg for 2 weeks, had a differential/positive effect on antioxidant status (51). Aspirin does not significantly increase the risk of retinal hemorrhage, gastrointestinal bleeding or hemorrhagic stroke. Despite all the benefits of aspirin, a clinical analysis revealed that patients with type 2 diabetes and high cardiovascular risk are not always on antiplatelet therapy despite the recommendation, particularly for primary prevention (52).

Painful diabetic neuropathy is a common complication of both type 1 and type 2 diabetes and its management is not satisfactory. Tricyclics and anticonvulsants are only partially effective and the place of opioids remains controversial. Harvey and Hanna treated 338 patients with moderate to severe painful diabetic neuropathy with combination therapy, adding modified-release oxycodone to gabapentin, and found a significant improvement (53).

Diabetic foot ulcers are difficult to treat and sometimes methicillin-resistant *Staphylococcus aureus* (MRSA) colonization occurs in these ulcers, particularly when they are chronic. Researchers form Manchester, U.K., demonstrated the high success rate of larval treatment in eradicating MRSA colonization from chronic diabetic foot ulcers (54).

Type 1 diabetes results from autoimmune T-cell-mediated destruction of pancreatic β-cells. In animal models, T-cell target peptides derived from β-cell antigens have successfully been used to treat this condition. However, reports of anaphylaxis following treatment have raised concerns about safety in humans. In a phase I trial, proinsulin peptide microeluted from HLA-DR4 molecules was given to patients with type 1 diabetes. All the subjects tolerated low-dose proinsulin peptide well, except for transient localized erythematous reactions at the injection site. No patient developed anti-proinsulin peptide antibodies. Thus, it is safe to administer proinsulin peptide in human subjects in order to determine its efficacy as a diabetic vaccine (55).

Hypertriglyceridemia is a component of dyslipidemia in diabetic patients, contributing to increased cardiovascular risk. Metformin, commonly used in obese type 2 diabetes, has a minor effect on the lipid profile. In a randomized, double-blind, placebo-controlled trial, fenofibrate was used in increasing doses along with metformin in 381 type 2 diabetic patients. The combination of metformin with increasing doses of fenofibrate effectively reduced lipid risk factors while maintaining diabetes control (56). Rosuvastatin has been shown to be the most effective statin for treating dyslipidemia, but its safety in South Asian patients has been questioned. A study from London, U.K., demonstrated that rosuvastatin 10 mg was safe and well tolerated, reduced total cholesterol and LDL cholesterol and increased HDL cholesterol significantly in this population (57). Niacin reduces triglycerides and LDL cholesterol and increases HDL cholesterol levels. However, there are concerns about a potential worsening of glycemic control. A study using an extended-release preparation of niacin (Niaspan) in diabetic subjects found improvement in both glycemic control and dyslipidemia (58).

Low testosterone levels are frequently found in men with coronary artery disease and type 2 diabetes. Testosterone replacement therapy has been shown to improve insulin sensitivity and glycemic control in men with type 2 diabetes. Androgens are synthesized from cholesterol and it has been postulated that treatment with statins could decrease testosterone levels by reducing the availability of cholesterol. Therefore, low testosterone levels and the widespread use of statins in the diabetic population may be related. Stanworth *et al.* found that, although statin use was associated with lower total testosterone levels, bioavailable testosterone and calculated free testosterone were not significantly reduced. Thus, this study illustrated the importance of measuring bioavailable or free testosterone in the assessment of hypogonadism in men with diabetes treated with statins (59). The same group of investigators also demonstrated in their epidemiological data that testosterone is positively associated with HDL cholesterol in men with type 2 diabetes and the dominant effect of testosterone in men with type 2 diabetes may be to increase HDL cholesterol (60).

Intensive glycemic control and the management of other cardiovascular risk factors reduces major complications in people with diabetes. In spite of all the newer drugs and treatment strategies, the management of diabetic patients as a whole is not ideal. A retrospective cohort study revealed that many people with type 2 diabetes receive inadequate monitoring and are uncontrolled on oral agents and/or insulin (61). Another independent patient record study examined relative HbA1c attainment across 5 major European countries. It was found that glycemic control across Europe remains suboptimal, with over two-thirds of patients receiving oral hypoglycemic monotherapy failing to achieve the target HbA1c levels. Patients in the U.K. have significantly higher individual HbA1c targets, mean HbA1c levels and less frequent HbA1c testing. Thus, despite the implementation of GMS in the U.K., the management of type 2 diabetes remains unsatisfactory (62).

Diabetic nephropathy is the leading cause of end-stage renal failure, with premature mortality and increased morbidity from cardiovascular disease. Intensive management with appropriate drugs can slow disease progression. An analysis concluded that the management of high-risk groups has improved in the U.K. since 2003, but is still short of national targets and more intensive treatment is necessary (63). The benefit of proper control of dyslipidemia in reducing the risk of cardiovascular complications in type 2 diabetes is well demonstrated. Another analysis looked at the management of lipid abnormalities in type 2 diabetic patients using NICE guidelines and found that treatment targets are not being met in a large proportion of patients (64).

Acknowledgements

I am extremely grateful to Prithu Banerjee for editing, correcting and giving me continuous inspiration to write this manuscript.

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