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DIABETES MELLITUS – RECENT THERAPEUTIC DEVELOPMENTS

SUMMARY

- **Optimal glycaemic, blood pressure and lipid control are major aims of diabetes care.**
- **The insulin analogues insulin aspart and insulin lispro have a rapid onset and short duration of action.**
- **Insulin glargine is an insulin analogue with a prolonged duration of action.**
- **The oral hypoglycaemic agents nateglinide and repaglinide stimulate insulin secretion.**
- **Pioglitazone and rosiglitazone are oral hypoglycaemic agents that reduce insulin resistance.**

INTRODUCTION

Diabetes mellitus is a serious, chronic illness which is increasing in prevalence.[1] Lowering blood glucose levels slows or prevents the development of diabetic complications. This was demonstrated in two large long-term randomised controlled trials – the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study.[2,3] Diabetes care is however complex and many issues, in addition to glycaemic control, must be addressed. These include lifestyle changes and control of blood pressure and blood lipids.[4,5,6]

This bulletin focuses solely on recently introduced therapies for glycaemic control. These include the insulin analogues - insulin aspart, insulin lispro and insulin glargine - and the new oral hypoglycaemic drugs: nateglinide and repaglinide, and the thiazolidinediones pioglitazone and rosiglitazone.

INSULIN ANALOGUES

Insulin analogues are modifications of soluble insulin (regular human insulin), where the amino acid sequence of the insulin molecule is altered in order to change its pharmacokinetic and pharmacodynamic properties.[7] The long-acting analogue insulin glargine provides a basal insulin supply over approximately 24 hours. The fast-acting analogues, insulin aspart and insulin lispro, provide a peak of insulin activity which is of short duration. The insulin analogues can thus mimic the basal secretion and mealtime surges of the normal, non-diabetic insulin profile more closely than previously available insulin formulations.[7,8,9,10] These preparations are usually initiated by specialists.

Fast-acting insulin analogues

Overview: The fast-acting insulin analogues insulin aspart (NovoRapid®) and insulin lispro (Humalog®) are absorbed more rapidly and have a faster onset and shorter duration of action than soluble insulin. The onset of action of insulin aspart is 10-20 minutes and the duration of action is 3-5 hours. Insulin lispro has an onset of action of approximately 15 minutes and a duration of action of 2-5 hours.[11,12,13] Insulin aspart is injected subcutaneously immediately before meals or, when necessary, soon after. Insulin lispro is injected subcutaneously shortly before meals or, when necessary, soon after. Insulin aspart and insulin lispro are normally used in combination with a longer-acting insulin, which provides the basal component of the insulin regimen. The dose of insulins aspart or lispro is individualised to the patient. The fast-acting analogues may also be used for continuous subcutaneous infusion using an insulin infusion pump.[11,12]

Biphasic preparations are also available (NovoMix 30®, Humalog Mix25® and Humalog Mix50®). These contain fast-acting (aspart or lispro) and intermediate-acting insulin analogues. [76,77]

Clinical trials: In two randomised, double-blind crossover trials in patients with type 1 diabetes, insulin aspart (injected immediately before a meal) improved postprandial glycaemic control when compared with soluble insulin (injected immediately before or 30 minutes before a meal).[14,15] Longer duration, open-label trials found improved glycaemic control with insulin aspart compared to soluble insulin. There were significant decreases in postprandial blood glucose levels, and slight, but significant, decreases in HbA_{1c} (glycated haemoglobin) levels.[16,17] HbA_{1c} is a measure of mean glycaemia over the previous 2-3 months. It is used to assess treatment efficacy and also as a

measure of risk for the development of diabetic complications.[4,7,18] In all but one of the aforementioned trials, NPH insulin (isophane insulin) provided the basal component of the insulin regimens.[15,16,17] In one of the open-label trials, the incidence of major nocturnal hypoglycaemic events requiring parenteral treatment was lower with insulin aspart. This was also the case with late postprandial events.[16] The incidence of hypoglycaemic episodes seen in clinical trials with insulin aspart was comparable to, or lower than, the incidence with soluble insulin.[8]
In clinical trials of insulin lispro, the basal insulin component was NPH or ultralente insulin. In a 12-month open-label randomised clinical trial, insulin lispro was associated with significantly improved postprandial glycaemic control in patients with both type 1 and type 2 diabetes. HbA_{1c} levels were slightly but significantly lower with insulin lispro compared to soluble insulin in patients with type 1 diabetes. In patients with type 2 diabetes the decrease in HbA_{1c} was similar in both treatment groups.[20] In another 1-year, open-label trial in type 1 diabetes, glycaemic control (in terms of HbA_{1c} and fasting blood glucose (FBG)) was not different between insulin lispro and soluble insulin.[21] In the above trials the overall rate of hypoglycaemia with insulin lispro was less than, or similar to, the rate with soluble insulin.[20,21,22] A meta-analysis of data from eight trials in patients with type 1 diabetes found the incidence of severe hypoglycaemia was lower with insulin lispro than with soluble insulin. In three other trials insulin lispro caused significantly fewer episodes of nocturnal hypoglycaemia.[23]
Both insulin aspart and insulin lispro have been associated with improved treatment satisfaction compared to soluble insulin.[16,24]

Long-acting insulin analogue

Overview: The long-acting analogue insulin glargine (Lantus®) is administered subcutaneously once daily. It can be administered at any time, but it should be given at the same time each day. The dosage and timing of administration should be individualised to the patient. It is a *clear* solution which forms microprecipitates in the subcutaneous tissue, slowly releasing insulin glargine with no pronounced peak concentration.[25,26,27] It shows a constant concentration-effect versus time profile which lasts approximately 24 hours.[9] Insulin glargine can form the basal component of a basal-bolus insulin regimen, where a shorter-acting insulin provides the bolus component.[10] Insulin glargine is also used in combination with oral hypoglycaemic agents in type 2 diabetes.[27]

Clinical Trials: In open-label, randomised trials in patients with type 1 diabetes, insulin glargine produced significantly greater reductions in fasting plasma glucose (FPG) and FBG levels than NPH insulin.[28,29,30,31] In these trials patients also continued their previous, pre-prandial short-acting or fast-acting insulin regimen. Reductions in HbA_{1c} levels from baseline with insulin glargine compared to NPH insulin were similar in two studies (duration 16-28 weeks).[28,30] The incidences of nocturnal or symptomatic hypoglycaemia with insulin glargine were similar to or less than with NPH insulin in most of the aforementioned studies.
In randomised, open-label trials comparing insulin glargine with NPH insulin in patients with type 2 diabetes, patients continued treatment with oral hypoglycaemics or pre-prandial short-acting insulin. Insulin glargine (given once daily at bedtime) and NPH insulin (given once or twice daily) gave a similar degree of glycaemic control (reductions in HbA_{1c} and FBG). In three trials the incidences of symptomatic hypoglycaemia (in one trial) and nocturnal hypoglycaemia (in two trials) were lower with insulin glargine. Insulin glargine was also associated with similar or less weight gain compared with NPH insulin.[32,33,34] Greater treatment satisfaction has been reported with insulin glargine than with NPH insulin, in patients with both type 1 and 2 diabetes.[10,35]

ORAL HYPOGLYCAEMIC AGENTS

Nateglinide and repaglinide

Overview: Nateglinide and repaglinide act by stimulating insulin secretion from pancreatic ß-cells. Their mechanism of action is similar to the sulphonylureas.[36,37,38] They are administered shortly before meals, as they have a fast onset and short duration of action.[37,38,39] Their hypoglycaemic effect is therefore aimed at reducing postprandial hyperglycaemia, although they can also reduce fasting hyperglycaemia.[39,40]

Clinical trials: In a randomised double-blind trial, nateglinide plus metformin significantly reduced HbA_{1c} from baseline (by up to 0.51%). There was little or no change in HbA_{1c} with metformin plus placebo.[41] Another randomised double-blind study compared nateglinide, metformin, the combination of both or placebo. Metformin produced greater reductions in HbA_{1c} and FPG than nateglinide (0.8% vs 0.5% and 1.6 mmol/L vs 0.7 mmol/L respectively). However, combination therapy lowered HbA_{1c} and FPG levels more effectively than either monotherapy (by 1.4% and 2.4mmol/L respectively).[42] Nateglinide seems to have little stimulatory effect on insulin secretion when administered in the fasting state.[36,43]
In a single-dose study in healthy volunteers, nateglinide was found to have a faster onset and shorter duration of action than repaglinide.[44] The clinical significance of this is unknown, although, theoretically, it could result in less risk of postprandial hypoglycaemia with nateglinide.[44,45,46]
In randomised double-blind trials of up to 1 year in duration, patients receiving repaglinide monotherapy achieved similar glycaemic control (in terms of changes in HbA_{1c}, FPG and FBG) to those receiving glibenclamide.[48,49,50] Repaglinide was associated with greater glycaemic control than glipizide in a one-year randomised double-blind

trial.[51] In the above trials, the incidence of hypoglycaemia with repaglinide was similar to that seen with the sulphonylureas.[48,49,50,51] A randomised double-blind study compared repaglinide, metformin, or a combination of both in patients inadequately controlled on metformin monotherapy. The combination of repaglinide and metformin showed a significant reduction from baseline in HbA_{1c} levels (1.4%) and FPG (2.2 mmol/L). In this study there were no significant changes in HbA_{1c} or FPG from baseline with either drug as monotherapy.[52]

Indications: Nateglinide is indicated for combination therapy with metformin in type 2 diabetes patients. It should be taken within 1 to 30 minutes before meals. The dose is individualised to the patient.[37] If a meal is missed, the dose should be omitted.[39]
Repaglinide is indicated in type 2 diabetes patients either as monotherapy or in combination with metformin. It should be taken before main meals. The dose is titrated individually to the patient's requirements.[38] If a meal is missed, the dose should be omitted.[39,53]

Contraindications: Hypersensitivity to the active ingredient or any of the excipients. Type 1 diabetes. Diabetic ketoacidosis. Pregnancy and lactation. Severe hepatic impairment. Concomitant use of repaglinide with gemfibrozil. Repaglinide is contraindicated in children less than 12 years of age.[37,38]

Adverse effects: Hypoglycaemia. Hypersensitivity. Elevations in liver enzymes. Gastrointestinal disorders and visual disturbances with repaglinide.[37,38]

Interactions: Drugs which influence glucose metabolism. Nateglinide may interact with inhibitors of cytochrome P450 enzymes (predominantly CYP2C9 inhibitors).[37] Repaglinide is primarily metabolised by CYP2C8, and also by CYP3A4 and interaction with inhibitors or inducers of these enzymes may occur. Concomitant use of repaglinide with gemfibrozil is contraindicated. Gemfibrozil, an inhibitor of CYP2C8, markedly enhances and prolongs the hypoglycaemic effect of repaglinide.[38,39,54]

Thiazolidinediones (glitazones)

Overview: The thiazolidinediones (TZDs) pioglitazone and rosiglitazone exert their effects through gene transcription. They increase the insulin sensitivity of adipose tissue, skeletal muscle and the liver.[55,56,57,58] They may take several weeks to have their maximum effect.[46,56]

Clinical Trials: A systematic review of 11 studies found that pioglitazone, both as monotherapy and in combination therapy, produced decreases in HbA_{1c} and FBG.[61] A double-blind placebo-controlled trial found that pioglitazone monotherapy significantly reduced FPG and HbA_{1c} compared to placebo.[62] In two 16-week randomised double-blind placebo-controlled studies in patients with poorly-controlled diabetes, the addition of pioglitazone to either metformin or a sulphonylurea, reduced HbA_{1c} and FPG.[63,64] Pioglitazone plus metformin significantly reduced HbA_{1c} (by a mean of 0.83%) and FPG (by 2.09mmol/L) compared with metformin plus placebo. Some patients were treated with pioglitazone plus metformin for a further 72 weeks in an open-label extension study. Further decreases in HbA_{1c} and FPG were observed.[63] Pioglitazone in combination with a sulphonylurea, reduced HbA_{1c} by up to 1.3% and FPG by up to 3.2mmol/L, compared with a sulphonylurea plus placebo.[64]
In double-blind randomised placebo-controlled trials, rosiglitazone monotherapy significantly reduced HbA_{1c} (by up to 1.5%) and FPG compared to placebo.[65,66,67] Rosiglitazone added to therapy with either a sulphonylurea or metformin, in patients not adequately controlled by one of these drugs, improved glycaemic control.[68,69] In one 26 week double-blind, placebo-controlled parallel-group study, rosiglitazone plus a sulphonylurea produced significant decreases in FPG (up to 2.09 mmol/L) and HbA_{1c} (up to 1.03%), compared with a sulphonylurea plus placebo.[68] In a double-blind, placebo-controlled trial, metformin plus rosiglitazone significantly reduced HbA_{1c} (by up to 1.2%) and FPG (by up to 2.9 mmol/L) compared to metformin plus placebo.[69]

Effects on lipids: Pioglitazone use was found to be associated with reductions in triglycerides (TG) and increases in HDL-cholesterol (HDL-C).[61] Pioglitazone plus metformin or a sulphonylurea reduced TG concentrations and increased HDL-C concentrations compared to placebo plus metformin or a sulphonylurea.[63,64] In trials rosiglitazone (as monotherapy or combination therapy) increased total cholesterol, HDL-C and LDL-cholesterol (LDL-C). It reduced circulating levels of free fatty acids, and increased or decreased plasma TG levels depending on the baseline values.[36,70] The total:HDL cholesterol ratio did not change significantly in most studies.[70] A change to larger, more buoyant, less atherogenic LDL-C particles has been observed in studies of both pioglitazone and rosiglitazone.[71,72]
Two open-label studies compared pioglitazone with rosiglitazone in patients previously treated with troglitazone (a TZD). Glycaemic control and weight gain were similar with both pioglitazone and rosiglitazone.[73,74] In one study, mean total cholesterol levels decreased significantly with pioglitazone, but increased with rosiglitazone.[73] In the other study mean cholesterol, TG and LDL-C levels decreased in the pioglitazone group and increased in the rosiglitazone group. Mean HDL-C increased with pioglitazone and decreased with rosiglitazone therapy.[74] To date no double-blind randomised controlled trials have been published comparing pioglitazone and rosiglitazone.[70]

Indications: TZDs are indicated as oral monotherapy in type 2 diabetes patients, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin in inappropriate because of contraindications or intolerance. TZDs are also indicated for oral combination therapy in patients with insufficient glycaemic control despite maximal tolerated dose of either metformin or sulphonylurea monotherapy. They are used in combination with metformin particularly in overweight patients, or in combination with a sulphonylurea only in patients who are intolerant of metformin or for whom metformin is contraindicated.[57,58]

Contraindications: Hypersensitivity to the active ingredient or any excipients. Cardiac failure or history of cardiac failure (NYHA stages I to IV). Use in combination with insulin, as this may increase the risk of heart failure. Hepatic impairment. Pregnancy and lactation. Rosiglitazone is also contraindicated in patients with severe renal insufficiency and pioglitazone is contraindicated in dialysed patients.[56,57,58]

Adverse effects: Fluid retention. Cardiac failure has been reported, but is an uncommon adverse event. Patients should be observed for symptoms and signs of heart failure, particularly those with reduced cardiac reserve.[57,58] Weight gain – although bodyweight is increased overall, increases are in subcutaneous, not visceral fat, and hepatic fat is decreased. Weight should be closely monitored.[57,58,70,71] Anaemia.[57,58]
Troglitazone, the first TZD, was voluntarily withdrawn shortly after its launch in the UK (and later worldwide) because of evidence that it could cause serious, sometimes fatal, hepatotoxicity. Clinical trials have shown no evidence of serious hepatotoxicity with pioglitazone or rosiglitazone, but a few cases of liver dysfunction have been reported since their launch.[56,75] The manufacturers recommend monitoring of liver enzymes prior to initiation of therapy, every two months for the first year of therapy, and periodically thereafter.[57,58]

Interactions: Rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 as a minor pathway. Concomitant administration of TZDs with nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of oedema.[57,58]

CONCLUSIONS

The main aim of diabetes therapy is improved glycaemic control, as this has been shown to reduce the incidence and slow the progression of diabetic complications. To achieve this goal, treatment with insulins and/or oral hypoglycaemic agents must be individualised to the patient. A number of factors affect the choice of therapy, including pharmacological and pharmacokinetic profiles, effectiveness, tolerability, contraindications, prescribing precautions and cost.

COSTS *(from GMS prices for August 2003)*

NovoRapid® (insulin aspart) (100units/ml) vial 10ml x 1	€26.41
NovoRapid Flexpen® (100 units/ml) pre-filled pen 3ml x 5	€44.80
NovoRapid Novolet® (100 units/ml) pre-filled pen 3ml x 5	€47.15
NovoRapid Penfill® (100 units/ml) cartridge 3ml x 5	€42.63
NovoMix 30 Flexpen® (insulin aspart/protamine-crystallised insulin aspart) (100 units/ml) prefilled pen 3ml x 5	€49.96
NovoMix 30 Penfill® (100 units/ml) cartridge 3ml x 5	€45.23
Humalog® (insulin lispro) (100 units/ml) vial 10ml x 1	€21.86
Humalog® (100 units/ml) cartridge 1.5ml x 5	€18.64
Humalog® (100 units/ml) cartridge 3ml x 5	€41.09
Humalog-Pen® (100 units/ml) pre-filled pen 3ml x 5	€46.40
Humalog Mix 25® (insulin lispro/insulin lispro protamine suspension) (100 units/ml) cartridge 3ml x 5	€39.16
Humalog Mix 25® Pen (100 units/ml) 3ml x 5	€43.30
Humalog Mix 50® Pen (100 units/ml) 3ml x 5	€44.67
Lantus® (insulin glargine) (100 units/ml) vial 10ml x 1	€41.18
Lantus OptiSet® (100 units/ml) prefilled pen 3ml x 5	€64.04
Lantus® (100 units/ml) cartridge 3ml x 5	€62.20

Starlix® (nateglinide) tablets 60mg x 84	€31.13
Starlix® (nateglinide) tablets 120mg x 84	€33.27
Starlix® (nateglinide) tablets 180mg x 84	€33.27
NovoNorm® (repaglinide) tablets 0.5mg x 120	€35.98
NovoNorm® (repaglinide) tablets 1mg x 120	€38.90
NovoNorm® (repaglinide) tablets 2mg x 120	€41.80
Actos® (pioglitazone) tablets 15mg x 28	€39.50
Actos® (pioglitazone) tablets 30mg x 28	€58.75
Avandia® (rosiglitazone) tablets 4mg x 28	€41.60
Avandia® (rosiglitazone) tablets 4mg x 56	€83.19
Avandia® (rosiglitazone) tablets 8mg x 28	€75.03

References available on request. Date prepared: Aug/Sept. 2003