Restoring post-prandial insulin release in type 2 diabetes

John Andrews

Tight blood glucose control is a primary aim of type 2 diabetes treatment. Combining metformin with the amino acid derivative, nateglinide, tackles both beta cell dysfunction and insulin resistance, and produces a greater decrease in haemoglobin A_{1c} levels than treatment with either drug alone.

Owing to the increasing age of the UK population and the rising level of obesity, the number of people with diabetes is expected to go up from the current 1.4 million to 3 million by 2010 (Amos et al, 1997). Of these patients, at least 80% will have type 2 disease.

While coronary mortality in the non-diabetic population is falling (British Heart Foundation Health Promotion Research Group, 2000), type 2 diabetes is associated with a 1.5–4-fold excess coronary mortality. At least half of all deaths in people with type 2 diabetes are caused by coronary heart disease and a further 15% by cerebrovascular disease (Nathan et al, 1997). Those with type 2 diabetes develop heart disease at a younger age than non-diabetics, have a higher rate of diffuse multi-vessel disease, are more likely to develop congestive heart failure and more likely to die after a heart attack (Nathan et al, 1997).

In addition to coronary disease and stroke, about 30% of type 2 diabetes patients have kidney disease (Viberti, 1996) and 15% develop foot ulcers (University of York NHS Centre for Reviews and Dissemination, 1999). Diabetes is also the most common cause of blindness in people of working age (University of York NHS Centre for Reviews and Dissemination, 1999).

Much of the cost of diabetes to the NHS arises from the management of such complications. Diabetes UK puts the annual cost of diabetes at £4.9 billion, and it has been estimated that diabetes is responsible for 9% of UK hospital costs, equivalent to £1.9 billion (Audit Commission, 2000).

What impact will recent additions to the range of treatments available for type 2 diabetes have on the personal, social and financial consequences of this escalating health problem?

Nateglinide (Starlix, Novartis Pharmaceutical UK Ltd, Frimley, Surrey) restores post-prandial, first phase insulin secretion from the pancreatic beta cells and is licensed for combination therapy with metformin in patients with type 2 diabetes which is inadequately controlled despite a maximally tolerated dose of metformin alone. The combination therefore targets both of the underlying mechanisms of type 2 diabetes – beta cell dysfunction and insulin resistance.

MANAGING DIABETES

The UK Prospective Diabetes Study (UKPDS, 1998a) showed the importance of tight blood sugar control in patients with type 2 diabetes. Over 10 years, haemoglobin A_{1c} (HbA_{1c}) was 7.0% in patients intensively managed with sulphonylureas or insulin compared with 7.9% in those less intensively managed. The reduction in HbA_{1c} was associated with a 12% lower risk of any diabetes-related endpoint (P=0.029) and a 25% lower risk of microvascular endpoints (P=0.0099).

In a sub-group of overweight patients treated with metformin (Glucophage, Merck Pharma, West Drayton, Middlesex), HbA_{1c} in the intensive management group was 7.4%, compared to 8.0% in those on conventional therapy. With intensive blood glucose control came a 32% fall in any diabetes-related endpoint (P=0.002) and a 29% reduction in microvascular endpoints (P=0.19) (UKPDS, 1998b).

Much of the benefit seen with metformin in obese patients and with sulphonylureas and insulin in non-obese patients occurred through their effects on microvascular rather than macrovascular complications. While metformin is increasingly seen as the 'gold standard' for type 2 diabetes patients whose blood sugar level is inadequately controlled by diet, further research is examining the potential for new treatments to reduce both microvascular and macrovascular complications.

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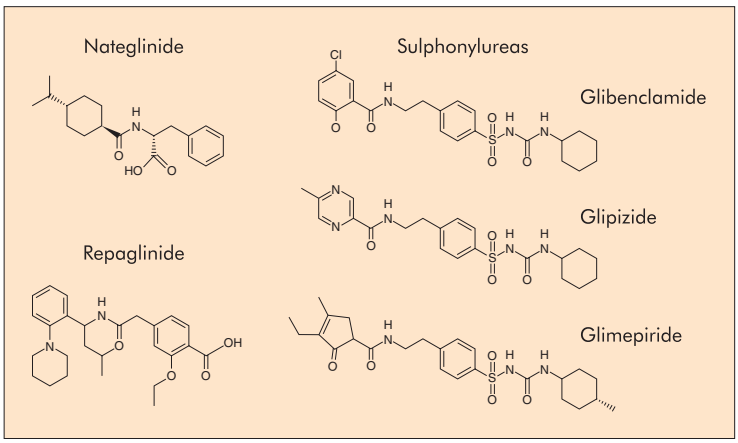


Figure 1. Chemical formulae for different treatments for diabetes for comparison with nateglinide.

NEW ALTERNATIVES

In the last year, three new products have been introduced for the treatment of type 2 diabetes. Two of these (rosiglitazone and pioglitazone) improve blood glucose control by reducing insulin resistance while the third (nateglinide) improves early phase insulin secretion in response to meals.

There is growing evidence that these two underlying mechanisms of type 2 diabetes – insulin resistance and beta cell dysfunction – begin at an early stage of the disease and develop in parallel. Newly diagnosed patients recruited to UKPDS had already lost 50% of their beta cell function at diagnosis, and it was calculated that the damage had started 12 years before diagnosis (UKPDS, 1995).

It would seem logical, therefore, to manage type 2 diabetes in ways which will:

- Increase sensitivity to insulin in muscle, fat and liver cells
- Restore the physiological pattern of insulin secretion from the beta cells of the pancreas
- Suit the needs of the growing proportion of type 2 diabetes patients who are also obese
- Provide tight blood glucose control with a low risk of hypoglycaemia.

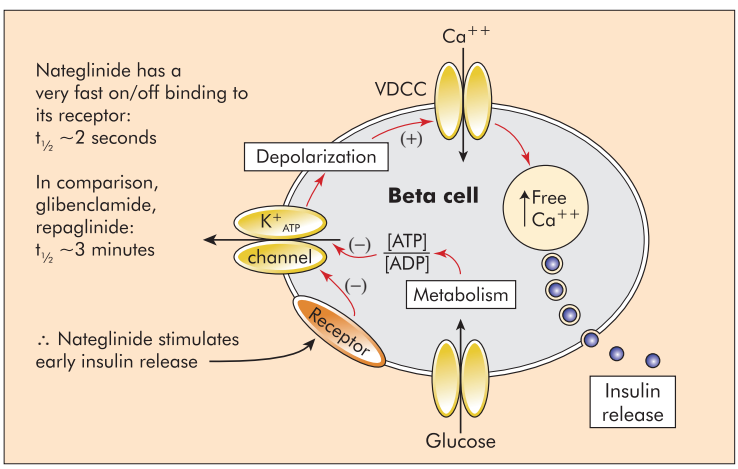


Figure 2. Nateglinide rapidly binds to and dissociates from the beta cell. ADP = adenosine diphosphate; ATP = adenosine triphosphate; Ca++ = calcium ions; K+ = potassium ions; $t_{1/2}$ = half life; VDCC = voltage-dependent calcium channel.

NATEGLINIDE

Chemistry and pharmacokinetics

Nateglinide is a derivative of the amino acid, D-phenylalanine, and is chemically and pharmacologically dissimilar to the sulphonylurea receptor analogues (glibenclamide, glipizide, glimepiride) and the meglitinides (repaglinide) (*Figure 1*).

Nateglinide is rapidly absorbed and minimally affected by meal composition. It has the same pharmacokinetic profile in renally and hepatically impaired patients, however, it cannot be prescribed for patients with severe hepatic impairment.

Ten per cent of nateglinide is excreted unchanged by the kidney, with the remainder metabolized rapidly in the liver: 70% by CYP 2C9 and the remainder by CYP 3A4.

Mode of action

Nateglinide has a 'rapid on, rapid off' action on the pancreatic beta cell, binding to its receptor for just 2 seconds, compared with 3 minutes for glibenclamide and repaglinide. Nateglinide depolarizes the beta cell by closing the ATP (adenosine triphosphate)-dependent potassium channels in the beta cell membrane. This leads to opening of the calcium channels, and the resulting calcium influx enhances insulin secretion (Hu et al, 2000) (*Figure 2*).

Nateglinide-induced insulin secretion by pancreatic beta cells is glucose responsive, with significantly greater insulin secretion when nateglinide is taken before a meal than in the fasted state (Keilson et al, 2000).

When taken 1–30 minutes before a meal, nateglinide restores the physiological early phase post-prandial insulin secretion which is lost in patients with type 2 diabetes, leading to a reduction in the post-prandial glucose spikes typically seen in the disease (Hollander, 2000) (*Figure 3*). However, there is no prolonged reduction in glucose levels between meals, comparable with that seen with sulphonylureas, which can lead to increased hypoglycaemia between meals.

The importance of glucose spikes

About 1 in 3 patients with type 2 diabetes have raised post-prandial glucose in the absence of abnormal fasting plasma glucose (FPG) (DECODE, 1999a). Data on some 25 000 type 2 diabetes patients in the Diabetes Epidemiology: Collaborative study showed that 2-hour post-prandial glucose measurement is a better predictor of cardiovascular risk than FPG (DECODE, 1999b) (*Table 1*).

It has been calculated that for each 1 mmol/litre rise in post-prandial, 2-hour glu-

cose, there is a 7% increase in relative risk of cardiovascular mortality and morbidity, irrespective of FPG level (DECODE, unpublished observations, 1998). Other studies have also shown a link between post-prandial glucose levels and cardiovascular risk:

- In the 12-year Diabetes Intervention Study, patients with diabetes who died from a myocardial infarction had a significantly higher post-prandial blood glucose level at recruitment than those who survived. But no similar relationship was seen between FPG and cardiovascular risk (Hanefield et al, 1996)
- In the Honolulu Heart Study of 8000 men without diabetes, 23-year follow-up showed that men with the highest 1-hour glucose challenge results had twice the age-adjusted risk of fatal coronary heart disease than those with the lowest levels (Honolulu Heart Program, 1999).

CLINICAL TRIALS

Effects of nateglinide monotherapy on blood glucose control

In a 12-week, double-blind, placebo-controlled dose ranging study in 289 patients with type 2 diabetes, the effects of nateglinide 30 mg, 60 mg and 120 mg before meals were compared. At the end of the study, dose-dependent reductions in HbA_{1c} were significantly greater in the treatment than in the placebo group (–0.45%, –0.62%, –0.64% respectively, $P<0.05$) (Hanefield et al, 2000).

In a double-blind, 6-month trial of nateglinide 120 mg before meals and metformin 500 mg three times a day, in 701 patients with type 2 diabetes, comparable reductions in HbA_{1c} of about 1% were seen with nateglinide and metformin *vs* placebo. Nateglinide achieved this largely through reducing 2-hour plasma glucose while with metformin it occurred via a fall in FPG (Horton et al, 2000) (*Figure 4*).

Nateglinide and metformin combination treatment: effects on blood glucose control

In a small study of 12 type 2 diabetes patients, acute treatment with nateglinide 120 mg before meals and metformin 500 mg three times a day was associated with significantly greater reductions in post-prandial glucose levels than were seen with either drug alone ($P<0.001$), especially after lunch and dinner (Hirschberg et al, 2000).

This effect was confirmed in a larger, placebo controlled 6-month trial of nateglinide 120 mg before meals and metformin 500 mg three times a day, in over 700 type 2 diabetes patients (Horton et al, 2000). Combination treatment was associated with significantly ($P\leq0.0001$) greater reductions in FPG and 2-hour plasma glucose than those seen with either drug alone, and with an overall reduction in HbA_{1c} of 1.9% compared with placebo (Horton et al, 2000) (*Figure 5*). The greatest improvement was seen in patients with the highest levels of HbA_{1c} (>9.5%) where a reduction of 2.5% was achieved (Horton et al, 2000).

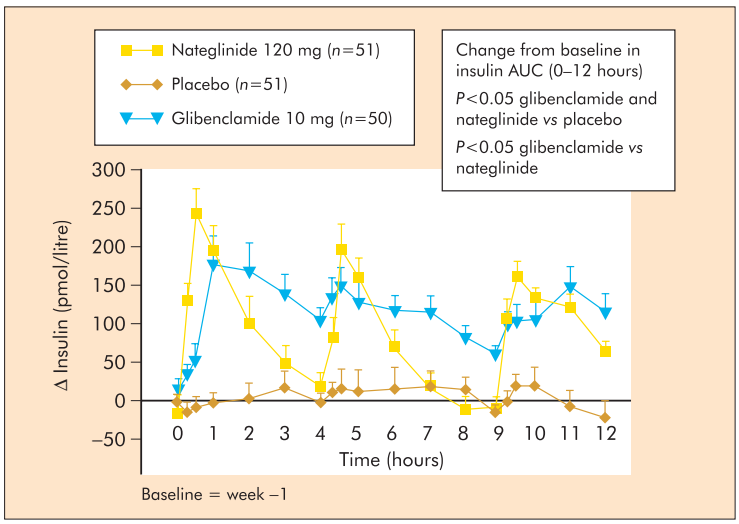


Figure 3. Effect of nateglinide, glibenclamide and placebo on insulin response after solid meal challenges 7 weeks post treatment. AUC = area under curve.

Safety and tolerability of nateglinide

In clinical trials, nateglinide was well tolerated. As monotherapy, nateglinide was associated with confirmed hypoglycaemia (plasma glucose of <3.3 mmol/litre) in <2% of patients, while in combination studies with metformin, the incidence was about 3% (Horton et al, 2000).

Overall, in completed trials, symptoms consistent with hypoglycaemia were reported in 10.4% with nateglinide monotherapy, 14.5% with nateglinide and metformin combination, 6.9% with metformin alone, 19.8% with glibenclamide alone, and 4.1% with placebo (data on file, Novartis Pharmaceuticals UK Ltd, 2001).

Nateglinide is associated with minimal weight change; in trials of nateglinide in combination with metformin, the average weight gain was 0.17 kg. As monotherapy, a change of less than 1 kg compared with baseline was recorded over 6 months treatment (Horton et al, 2000).

TABLE 1.
Predicting mortality risk in patients with diabetes

	Mortality risk (hazard ratio)			
	Newly diagnosed diabetes		Impaired glucose tolerance	
	Men	Women	Men	Women
ADA criteria	1.81	1.79	1.21	1.08
WHO criteria	2.02	2.77	1.51	1.6

American Diabetic Association (ADA) criteria: fasting plasma glucose alone (> 7 mmol/litre); World Health Organisation (WHO) criteria: fasting plasma glucose alone (> 7 mmol/litre) and a 2-hour post oral glucose tolerance test

Nateglinide does not interact with other drugs commonly used in diabetes (data on file, Novartis Pharmaceuticals UK Ltd, 2001).

Other adverse events observed in clinical studies were of a similar incidence in nateglinide-treated and placebo-treated patients. They included gastrointestinal complaints (e.g. abdominal pain, dyspepsia, diarrhoea), headache and events, such as respiratory infections, which were consistent with concomitant conditions in patient populations.

ONGOING RESEARCH

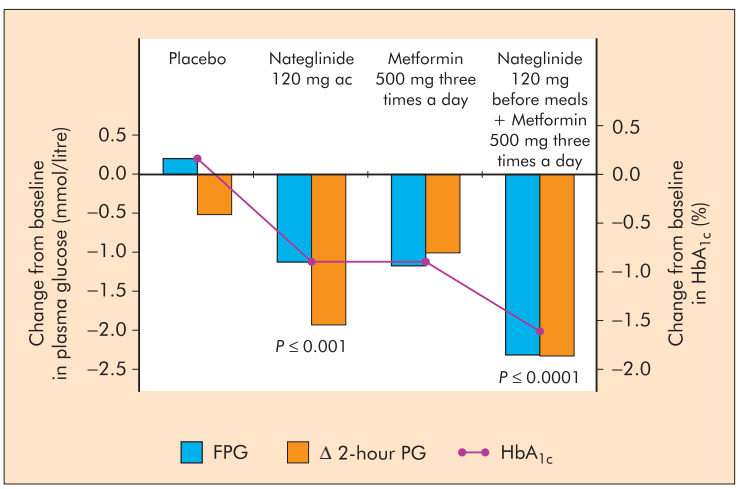
An extensive programme of clinical research is continuing to investigate the efficacy of nateglinide in comparison with other oral hypoglycaemic agents (e.g. sulphonylureas, metformin, acarbose), with other combinations of antidiabetic agents (e.g. rosiglitazone) and on the progression of impaired glucose tolerance to type 2 diabetes and the development of cardiovascular complications.

CONCLUSIONS

Nateglinide is a new amino acid derivative which is indicated for combination therapy with metformin in patients with type 2 diabetes inadequately controlled despite a maximally tolerated dose of metformin alone.

Used in combination with metformin, nateglinide produces clinically important reductions in HbA_{1c} which are superior to those achieved with either drug alone. It restores the physiological pattern of insulin secretion from the failing beta cells of type 2 diabetics and it may have the potential for reducing cardiovascular mortality and morbidity. **HM**

Figure 4. Effects on haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG) and 2-hour plasma glucose (PG) in patients not controlled on diet alone. From Horton et al (2000).



KEY POINTS

- Nateglinide is an amino acid derivative which restores the physiological, post-prandial, early phase of insulin secretion from the pancreatic beta cells.
- It therefore reduces the post-prandial glucose spikes commonly seen in type 2 diabetes and thus may have the potential to reduce cardiovascular mortality and morbidity in type 2 diabetes.
- It is indicated for combination therapy with metformin in patients with type 2 diabetes inadequately controlled despite a maximally tolerated dose of metformin.
- A combination of metformin and nateglinide produces significantly greater reductions in haemoglobin A_{1c} than those achieved with either drug alone.
- Used in combination with metformin, nateglinide is well tolerated with a low incidence of hypoglycaemia, weight gain and gastrointestinal disturbances.

Conflict of interest: Dr Andrews has received support for his research from Novartis Pharmaceuticals.

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