Repaglinide: a novel oral antidiabetic agent

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Repaglinide is a novel oral antidiabetic agent, marking the development of a new class of drugs for type 2 diabetes. This article examines repaglinide and its position in the treatment of type 2 diabetes.

For the last three decades little has changed in the treatment of type 2 diabetes by oral hypoglycaemic agents. Despite a succession of 'new' sulphonylureas with postulated advantages based mainly on potency these were, in truth, minor variations on the theme started by chlorpropamide and tolbutamide in the 1950s. In the biguanide field metformin remains the only available agent following the withdrawal of phenformin approximately 20 years ago. A new agent for type 2 diabetes, repaglinide (NovoNorm®, Novo Nordisk, Crawley) was introduced late in 1998, heralding the development of a new class of drugs for this condition, prandial glucose regulators.

TRADITIONAL TREATMENTS

Sulphonylureas

Sulphonylureas are the largest class of drugs for the treatment of type 2 diabetes. Traditionally they fall into first and second (or perhaps more appropriately subsequent) generation sulphonylureas. Of the first generation, chlorpropamide and tolbutamide, the former is little used although tolbutamide is still used as a short-acting agent. Of the second generation gliclazide, glibenclamide and glipizide all enjoy more widespread use.

The mechanism of action is intriguing. In the short term they clearly lower blood glucose by enhancing insulin secretion. In the longer term, however, the improvement in glucose is maintained but the increased insulin secretion subsides to pre-treatment levels. This improvement in glucose without a major increase in insulin secretion is described as an improvement in insulin sensitivity, i.e. endogenous insulin is more efficient in its actions on metabolism. Thus sulphonylureas, introduced following the chance finding of hypoglycaemia during treatment with sulphonamides, and of uncertain mechanism of action for many years of use, apparently work in type 2 diabetes by actions directed against the two major elements of pathogenesis, diminished insulin secretion and impaired insulin action (Nattrass, 1996).

Metformin

Metformin also enhances insulin action. Hepatic glucose output is reduced, glucose uptake into the peripheral tissues of muscle and fat is enhanced, and there is a small effect upon glucose absorption from the gut. Since it acts directly upon the metabolic pathway or the effect of insulin on that pathway, blood glucose is lowered while at the same time insulin levels are reduced. Perhaps because of this metformin has less propensity to result in weight gain than the sulphonylureas.

Acarbose

Acarbose is an α-glucosidase inhibitor which lessens glucose uptake from the gut. Its major effect is therefore upon postprandial glucose excursions and it has little impact upon fasting blood glucose.

USES AND LIMITATIONS OF TRADITIONAL TREATMENTS

Before welcoming a new class of oral agents it is pertinent to consider whether the ones we have need improving upon. The answer has to be 'yes'. Most drugs are limited in their use by side-effects and oral hypoglycaemic agents are no exception.

Sulphonylureas

Of the many side-effects attributed to sulphonylureas only two are of major clinical signifi-

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cance. First sulphonylurea usage is associated with weight gain. This may be through the stimulation of insulin secretion in the early stages of their use but it is a common sequela of their use. As Skarfors et al (1991) demonstrated that 79% of people who developed diabetes were overweight, the prospect of further weight gain is not to be welcomed.

The second unwanted effect is hypoglycaemia. It seems harsh to call this a side-effect since the whole object of treatment is to lower blood glucose and the more potent the agent the greater the likelihood of an overshoot. In the early stages of treatment it is common on direct questioning to elicit a history of mild hypoglycaemic symptoms, particularly before lunch. This appears to pass and what is more worrisome is the hypoglycaemia occurring during chronic usage and often as a consequence of a missed meal in the elderly. The patient may present with coma or neurological deficit mimicking a stroke, which initially responds to intravenous glucose. Unlike insulin-induced hypoglycaemia, however, relapse is almost certain until the drug is metabolized and its effect removed. Sulphonylurea-induced hypoglycaemia is therefore rightly considered a medical emergency that necessitates admission and intravenous glucose infusion.

Among the many important conclusions and findings of the United Kingdom Prospective Diabetes Study (UKPDS) is one of major importance in the use of oral agents. In an early paper (UKPDS, 1995) looking at beta-cell function following instigation of treatment of type 2 diabetes, it is apparent that while one can see a one-off improvement in beta-cell function with a sulphonylurea, over the ensuing years there is a rather relentless decline in function. In other words although the sulphonylureas are effective in lowering blood glucose there is little evidence that they modify the natural history of the disease rather than simply buying a few years improvement (UKPDS, 1995).

Metformin

Metformin is relatively free of clinical side-effects. Fears that it might increase the incidence of lactic acidosis, as phenformin did before it, have largely proved unfounded and the majority of cases reported have been in patients with renal failure where the drug is contraindicated (Bailey and Nattrass, 1988). The most significant side-effect, which appears to be an idiosyncratic response rather than a dosage effect, is its ability to cause diarrhoea.

Acarbose

Acarbose is severely limited in its use by gastrointestinal side-effects.

PRANDIAL GLUCOSE EXCURSIONS AND DIABETES COMPLICATIONS

In any diurnal studies of patients with type 2 diabetes it is readily apparent that there may be two major abnormalities of blood glucose. First, the fasting blood glucose is abnormally high and second there is an increased postprandial glucose excursion. Furthermore there is a strong relationship between the two such that the higher the fasting glucose the greater is the postprandial glucose excursion (Owens et al, 1985). The latter undoubtedly comes about through a failure of early insulin release following ingestion of food. The impaired early insulin release allows a greater glucose excursion, and we should note here that it has further consequences upon circulating insulin levels (see below).

While it is readily accepted that a chronically elevated fasting glucose will contribute to protein glycation and the development of specific diabetic complications, the significance of elevated postprandial blood glucose is less clear. Any attribution of specific effects is acknowledged as somewhat tenuous, nevertheless there are grounds for implicating postprandial glycaemia in the long-term consequences of diabetes.

Hyperglycaemia enhances glomerular hyperfiltration (Wiseman et al, 1985) and retinal blood flow (Grunwald et al, 1990) which may be important in the subsequent development of microvascular complications. Most diabetologists will be familiar with the impairment of motor nerve conduction velocities that accompany diagnosis or periods of poor control and which improve with lowering of blood glucose (Ward et al, 1971).

In the area of macrovascular disease there is evidence for a long-term effect of glycated haemoglobin on the development of, and mortality from, coronary heart disease (Kuusisto et al, 1994).

Sulphonylureas and metformin have little impact upon postprandial glucose excursions. One consequence of the increased glycaemic excursion is that the insulin level is also raised for a significant portion of the day. It is thought that hyperinsulinaemia is one of the factors that may play a major role in the onset and development of atherosclerotic disease (Massi-Benedetti and Frederici, 1999). Thus the wisdom of condoning or allowing hyperinsulinaemia remains questionable.

PRANDIAL GLUCOSE REGULATORS

Repaglinide is the first of a new class of prandial glucose regulators. It is a carbamoylmethyl benzoic acid (CMBA) from the non-sulphonylurea moiety of glibenclamide. The predominant mechanism of action is through stimulation of insulin secretion. Repaglinide closes ATP-sensitive K+ channels in pancreatic beta cells, causing calcium channels to open. The subsequent influx of calcium ions stimulates insulin release from the pancreatic beta cell. In contrast to the sulphonylureas, repaglinide does not stimulate insulin release independent of its effect upon ATP-sensitive K+ channels (Fuhlendorff et al, 1998) nor does it inhibit insulin biosynthesis (Louchami et al, 1998). Following oral administration there is rapid absorption with a t_{max} within 1 hour post administration and a half life of approximately 1 hour. Thus repaglinide is a rapid onset, short duration insulinotropic agent.

It is effective in improving diabetic control in diet-treated patients with modest diabetic control. Fasting blood glucose was lowered by 3.9 mmol/litre (P<0.001), haemoglobin A_{1c} was reduced by 2.1%, from 6.98 to 4.87% (P<0.002 absolute), and 2-hour postprandial glucose was lowered by 6.2 mmol/litre (P<0.001; Van Gaal et al, 1995). In a series of 1-year studies comparing sulphonylureas and repaglinide the latter was of similar efficacy to glibenclamide and gliclazide and significantly better than glipizide in mean change of HbA1c (0.6%, P<0.05) and fasting blood glucose (0.9 mmol, P<0.05) (Dejgaard et al, 1998; Marbury et al, 1999; Wolffenbuttel and Landgraf, 1999; data on file, NovoNordisk, 1997). However, it is worth noting that repaglinide was administered in a fixed dosing regimen and so the benefits of flexible dosing were not observed (*Figure 1*).

The five 1-year studies demonstrated an increase in weight of 3% in sulphonylurea-naïve patients. However, when a flexible dosing regimen is implemented there is no significant change in body weight from baseline in treatment-naïve patients treated with repaglinide (Moses et al, 1999a).

In type 2 patients who were inadequately controlled on metformin, the addition of repaglinide brought about significant improvement, reducing haemoglobin A_{1c} by 1.4% (absolute P=???) (Moses et al, 1999b) (*Figure 2*).

Thus repaglinide is effective first-line monotherapy for type 2 diabetic patients, has an equivalent or superior effect compared with sulphonylureas (Dejgaard et al, 1998; Marbury et al, 1999; Wolffenbuttel and Landgraf, 1999; data on file, NovoNordisk, 1997), and is effective in combination with metformin in patients not controlled on metformin alone.

Pooled data from a number of studies indicate similar rates of mild hypoglycaemia compared to the sulphonylureas but a significantly lower rate of severe hypoglycaemia (1.31% of 761 patients on repaglinide *vs* 3.27% of 367 patients on glibenclamide, glipizide or gliclazide — demonstrating a relative risk ratio 2.8 times higher for the sulphonylurea group) (Smedegaard Kristensen et al, 1999). There was no increased incidence of hypoglycaemia in the elderly and pharmacokinetic studies show that repaglinide can be used in patients with mild or moderate renal insufficiency.

DOSING

Repaglinide is usually taken immediately before a main meal although it can be taken up to 30 minutes before a meal. The recommended dosing range is 0.5–4 mg with meals, two, three or four times a day. Patients should miss out or add a repaglinide dose if they miss or add a meal.

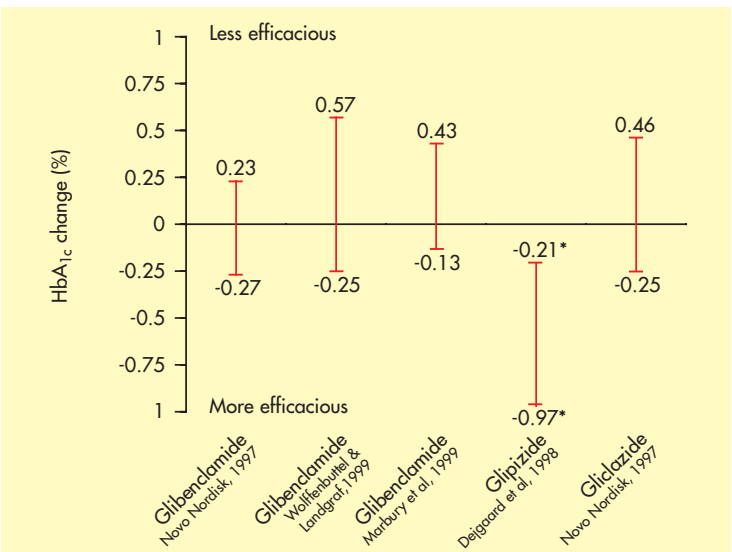

*Figure 1. Efficacy of repaglinide in 1-year studies compared with sulphonylureas. HbA_{1c} = haemoglobin A_{1c}. * significant improvement compared with repaglinide treatment (P<0.05).*

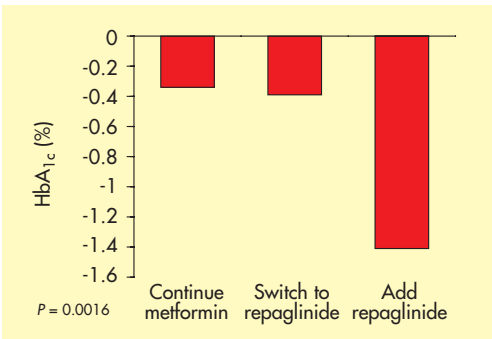

Figure 2. Efficacy of repaglinide on haemoglobin A_{1c} (HbA_{1c}) in metformin failures. From Moses et al (1999b).

One potential benefit of repaglinide, particularly in patients who are being encouraged to lose weight but also for those who eat irregularly (Moses et al, 1999a) is the concept of flexible dosing. The rapid action and short duration means that by the time of the next meal there is no significant concentration of the drug unless a further dose is taken. Thus the meal can be voluntarily omitted, not supplied, or simply forgotten without a major risk of hypoglycaemia occurring if the drug is not taken (Damsbo et al, 1999). Thus the concept of its use includes 'one meal, one dose — no meal, no dose'.

The flexible dosing regimen of repaglinide is of particular relevance to those patients with irregular eating habits, or those whose religion recommends a period of fasting or abstinence from certain foods. Muslims observing Ramadan (28–30 days) each year are required to abstain not only from eating and drinking between sunrise and sunset, but also from consuming oral medications and intravenous nutritional fluids. As repaglinide can be taken flexibly, two, three or four times a day, it can be taken by Muslim patients before meals at sunrise and sunset. Therefore repaglinide allows these patients to participate in the fast without risking hypoglycaemia.

CONCLUSION

Repaglinide is the first in a new class of oral hypoglycaemic agents. It has been shown to be effective monotherapy in patients poorly controlled on diet, and in combination with metformin in those poorly controlled on metformin.

The action of the drug is of rapid onset and short duration and the predominant effect is through an enhancement of insulin secretion.

The incidence of severe hypoglycaemia in clinical trials of the drug appears to be over half that seen with the most widely used sulphonylureas.

In the light of it being a rapid acting insulin secretagogue there is no carry-over of effect to the next meal. Thus a more flexible approach to meals can be instigated with no dose being taken in the event of meals being skipped. **HM**

Conflict of interest: Dr Nattrass is a member of the NovoNorm Advisory Board and has also spoken at a number of diabetes meetings sponsored by Novo Nordisk.

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KEY POINTS

- Repaglinide is a novel agent, marking the development of a new class of drugs for the treatment of type 2 diabetes.
- Repaglinide has been shown to have an equivalent or superior efficacy to sulphonylureas.
- When the flexible dosing regimen allowed by repaglinide is implemented, there is no significant change in body weight in treatment-naïve patients.
- Patients treated with repaglinide demonstrated a significantly lower rate of severe hypoglycaemia compared to patients treated with sulphonylureas.