

(3) ANTIDIABETIC AGENTS

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The National Institute for Clinical Excellence is expected to issue guidelines on glycaemic control in type 2 diabetes shortly and work on guidelines for type 1 diabetes is in progress. This article discusses current drug treatment

The aims of treating diabetes are to achieve present well-being and future health. Fasting blood glucose levels and levels two hours after a glucose tolerance test are used for diagnosis (7.0mmol/L and 11.1mmol/L, respectively). People with blood glucose levels 7.8mmol/L and <11.1mmol/L two hours post glucose load are said to have impaired glucose tolerance (IGT).

Type 1 diabetes is an auto-immune disease caused by the destruction of pancreatic islet cells. The landmark study that proved the benefits of treating hyperglycaemia was the Diabetes Control and Complications Trial (DCCT).¹ This showed that it was possible to achieve a satisfactory level of glycaemic control and maintain it over 10 years, and that intensive control could delay the onset and slow the progression of microvascular complications. Glycated haemoglobin (HbA1c) is used as a measure of diabetes progress and control but is not suitable as a diagnostic tool. The basis of the test is that glucose binds irreversibly to haemoglobin and the amount bound is directly proportional to blood glucose concentration. Because red blood cells have a lifespan of approximately 90 days, the HbA1c shows average blood glucose concentration during the eight to 12 weeks before the test. HbA1c levels should be 7 per cent or less. However, two people with similar HbA1c values could have very different blood glucose patterns. One could have a great number of highs and lows whereas the other could have kept better control. Frequent self monitoring of blood glucose at home will provide this detailed information.

In type 2 diabetes the cause of hyperglycaemia is a combination of insulin resistance and a loss of secretory function by pancreatic β cells. The UK Prospective Diabetes Study showed the progressive nature of type 2 diabetes despite intensive control and agreed with the DCCT in that treatment of hyperglycaemia delayed the onset of microvascular complications.² However, the study also demonstrated the macrovascular benefits of treating hypertension, eg, reduction in cardiovascular disease (CVD). When the risk of microvascular complications is plotted against blood glucose concentrations two hours after glucose challenge, the curve is flat through the range of normal values, but increases steeply at a concentration of around 11.1mmol/L. In comparison, the cardiovascular risk curve increases gradually over the whole range of glycaemia³ and the risk of mortality also increases across the whole range, even outside that associated with diabetes.⁴ Although both raised HbA1c levels and IGT are risk factors for the onset of CVD, research indicates that reduction of HbA1c has no marked impact on its onset or progression and treatment of hyperlipidaemia and hypertension is most effective. As a result, the treatment of type 2 diabetes has now been extended to tackle hypertension and dislipidaemias. IGT occurs as a result of loss of early phase insulin release and postprandial hyperglycaemia is accompanied by a postprandial increase in lipids and free radicals and an activation of a prothrombotic state. It has been proposed that reducing postprandial hyperglycaemia is more important than reducing fasting glycaemia, but this hypothesis has yet to be tested.

Current treatment should start with sensitivity to the psychological impact of the diagnosis. Education should be delivered at an appropriate level and prescribing should be tailored to the lifestyle of the individual. Newly diagnosed people are given dietary and exercise advice, but dietitians I have talked to believe that this stage of treatment in type 2 diabetes is not given enough priority even though it can delay the start of drug treatment and yield long-term benefits. Dietary advice has been discussed in a previous article and

ultimately the aim is to consume a well balanced diet.⁵ People should also be persuaded to exercise because it reduces insulin resistance and lowers blood glucose. Community pharmacists are often involved at an early stage through the supply of monitoring equipment, and can usefully reinforce positive lifestyle messages.

TYPE 1 DIABETES

Treatment of type 1 diabetes is initiated in hospital where patients usually receive a lot of support. Most patients are started on a pre-mixed insulin preparation (containing an intermediate and a short acting insulin), injected twice daily until their diabetes is controlled, but regimens should be tailored to meet the needs of the individual. Duration of action can vary between individuals and treatment must be assessed. Requirements will also change with infection, stress, renal impairment etc. A major innovation has been the introduction of the very rapidly acting insulin analogues, insulin lispro and insulin aspart. These can be injected immediately before a meal and tailored to the specific insulin demands of that meal in that individual. Because of this and their very short duration of action there are fewer risks of hypoglycaemia and weight gain. A regimen in which a long or intermediate acting insulin is given at bedtime and a short-acting insulin given before each meal, is termed "basal bolus". Although these regimens are intensive and require a lot of monitoring they are popular with properly trained patients because they give a high level of control and freedom. Infusion pumps avoid the need for multiple injections. They allow continuous basal infusion, with the patient activating preprandial doses. However, pumps are not available on the NHS and are not suitable for many patients. NICE is currently investigating the clinical and cost effectiveness of insulin pump therapy.

TYPE 2 DIABETES

If after three months, diet and exercise has not worked, drugs are prescribed in type 2 diabetes. In patients of normal weight with some pancreatic function, sulphonylureas are used first line. In those who are overweight and have little residual β cell function, metformin is used. If treatment with one antidiabetic fails, another drug or a combination of drugs is used. Because of the progressive nature of type 2 diabetes, five per cent of those taking oral antidiabetics will suffer a secondary failure of treatment each year and the clinician should warn patients of this and prepare them for the possibility of eventually having to be treated with insulin.

Sulphonylureas Sulphonylureas act by stimulating insulin secretion from β cells and during long-term administration may also enhance insulin activity. All are capable of causing hypoglycaemic attacks and patients should be made aware of the symptoms of a "hypo" and understand the dangers of delaying or missing meals. The most commonly prescribed sulphonylurea is gliclazide. It has a duration of action of up to 24 hours and is popular because it rarely causes "hypos" and can be taken once or twice a day. It takes four to five hours to achieve a peak response so taking it before breakfast gives good cover for lunch and the evening meal. Sulphonylureas can upset the gastrointestinal tract and most tend to cause weight gain. The manufacturers of Amaryl (glimepiramide) claim that it does not have the same risk of weight gain. Glimepiramide and controlled release gliclazide are licensed for combination therapy with insulin. Sulphonylureas are primarily metabolised in the liver and should be used with caution in the presence of hepatic dysfunction.

Metformin The biguanide metformin acts by inhibiting gluconeogenesis, increasing peripheral utilisation of glucose and, possibly, by

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reducing appetite. It is taken with food and the dose is titrated up gradually to minimise gastrointestinal side effects. Used alone, it can reduce HbA1c levels by up to 17 per cent but it can also be used with insulin, sulphonylureas or thiazolidinediones. Use is discontinued in the presence of renal failure because of the risk of lactic acidosis.

Acarbose Acarbose is an intestinal α -glucosidase inhibitor that inhibits the absorption of starch and sucrose. It has a small effect on blood glucose but gastrointestinal side effects make it an unpopular choice.

Thiazolidinediones Rosiglitazone and pioglitazone (glitazones) act by activating peroxisomal proliferator activated receptor gamma (PPAR γ), a nuclear receptor that regulates the expression of several genes involved in metabolism. PPAR γ controls adipocyte differentiation, lipid storage, and insulin sensitisation. Glitazones enhance insulin sensitivity in two ways. They increase adipose mass by inducing the uptake of fatty acids and, although this seems illogical in view of the association of obesity with insulin resistance, fatty acid uptake by adipose tissue results in reduced systemic availability, less fatty acid uptake by muscle and therefore reduced insulin resistance. What is not known is whether there is a critical adipose tissue mass beyond which there is renewed onset of insulin resistance (or even glitazone resistance) and drugs that decrease insulin resistance without increasing adipose mass are being researched.

Sensitisation mainly occurs through an improvement in insulin-stimulated glucose disposal rates into peripheral tissues. It is less clear whether these drugs suppress hepatic glucose output. An attractive feature of the glitazones is their synergy with other antidiabetics. When added to current treatment in patients whose glycaemic control remained unsatisfactory despite sulphonylureas, metformin, insulin, or a combination of these agents, glitazones were effective, decreasing serum levels of glucose, insulin, and HbA1c. And in fact, glitazones are only licensed for use in dual therapy with either metformin or sulphonylureas. However, glitazones are not licensed for use with insulin. NICE has issued guidance on the use of both drugs. In about a quarter of patients there is no blood glucose response to these new drugs. Non-responders are more obese and have a longer-standing insulin resistance with depleted pancreatic insulin reserves. In those who do respond, improvements in control can take six months and patients need encouragement to continue treatment. Although glitazones may delay the need to move to insulin, where failing insulin release is apparent, insulin must be used and glitazones should not be introduced.

There have been few reports of liver toxicity with rosiglitazone and pioglitazone but liver function tests are advised before treatment and at regular intervals thereafter. The glitazones are contraindicated in hepatic impairment, history of heart failure, in combination with insulin and in pregnancy and breast feeding. Glitazones cause an increase in weight and rosiglitazone causes an increase in low density lipoprotein (LDL) cholesterol though the manufacturers claims this is a non-atherogenic fraction of LDL. Pioglitazone will induce CP3A4 which is partly responsible for its metabolism. Other drugs metabolised by this enzyme include erythromycin, calcium channel blockers, corticosteroids, ciclosporin, statins and triazoles so care must be taken with concurrent use.

Prandial glucose regulators Repaglinide (Novonorm) and nateglinide (Starlix), two new products, also work by stimulating insulin release. Although the names of these compounds sound similar they are chemically distinct and have different mechanisms of action. Repaglinide stimulates the same secretory mechanism as sulphonylureas but does not promote insulin release in absence of glucose. Nateglinide is an amino acid derivative and works by restoring early phase insulin release. It has a synergistic action with metformin. Both compounds have very short actions which deal effectively with postprandial glycaemic peaks and are omitted if a meal is missed. Weight gain is minimal and there is little risk of hypoglycaemia. I have seen no use of these compounds in my pharmacy but they could be useful in that this type of oral "basal bolus" treatment allows greater flexibility of lifestyle even if reducing postprandial glucose does not produce the expected benefits.

Insulin Ultimately 50 per cent of patients will end up on insulin due to β cell exhaustion. It is important to identify this promptly and

commence insulin immediately rather than let patients suffer years of ill health. Insulin is started in a similar manner as in type 1 diabetes but in the presence of insulin resistance, doses are much higher. Metformin is often prescribed concurrently to reduce the insulin dose. Community pharmacists can help patients anxiously awaiting treatment with insulin by reassuring them that their hyperglycaemia will improve so dramatically that they will feel a huge improvement in their health. Patients who have a fear of needles may benefit from being shown the modern pen devices. Some patients have high levels of fasting glycaemia due to unrestrained overnight hepatic gluconeogenesis. Their preprandial glucose levels will not be particularly elevated. In these patients it is worth trying to reduce nocturnal gluconeogenesis by administering a night time dose of isophane insulin while continuing normal daytime oral treatments.

THE FUTURE

Future management of diabetes seems centred around three aims: a better method of insulin delivery, new mechanisms of treatment and hopefully, a cure. For many patients, having to inject insulin is distressing and researchers have been working on alternatives such as insulin inhalers. The glycaemic effects of substances such as amylin analogues, insulin-like growth factor I, glucagon-like peptide I and β_2 -adrenoceptor agonists have also been examined. Pancreatic transplantation in poorly controlled patients with type 1 diabetes has led to insulin independence and islet cell transplants are under investigation. However, there are considerable problems with rejection, the need for long-term immunosuppression and donor availability. Work is being done to engineer a supply of insulin producing cells, and as with many chronic illnesses, the answer may lie in gene therapy. In the nearer future, it is predicted that there will be such a large increase in people with type 2 diabetes and using insulin, and that there will be a great strain on resources. Although pharmacists currently do not have much input into insulin treatment, I believe that there is an opportunity for us to become more involved.

CONCLUSION

Treatment of glycaemia in diabetes has become quite complex. With the need also to treat hypertension and dislipidaemia, polypharmacy is common. Whether or not we choose to play an enhanced role in diabetes, we do have a role as medicines expert and our strength lies in our ability to advise on all medicines and their effect in diabetes, eg, the masking effect of β blockers on tremor in hypoglycaemia. Finally we must not lose sight of the need to treat the patient and not the disease. Treatment often involves a change in behaviour. How many of us would willingly embrace the complex therapy, frequency of monitoring and adjustment in lifestyle that we are inflicting on others in the name of treating their diabetes?

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