Part 2
Management of Type II Diabetes Mellitus

Antonella Tonna B. Pharm (Hons.), Ph.D. (Aberdeen)
Senior Clinical Pharmacist, St. Luke's Hospital, G'Mangia
email: antonellatonna@hotmail.com

Keywords: diabetes, diet, sulphonylureas, biguanides, thiazolidinediones, alpha glucosidase inhibitors, repaglinide, insulin

There is currently no cure for diabetes mellitus (DM). Irrespective of whether type I or type II diabetes is treated, the overall goals of management and therapy are targeted towards patient wellbeing and may be summarised as follows: 1,3

• Avoiding symptoms of hypoglycaemia and hyperglycaemia
• Maintaining patients as close to euglycaemia as possible
• Slowing down of the progression of chronic complications associated with diabetes
• Normalisation of nutrition and achievement of ideal body weight
• Maintaining normal growth and development in children
• Maintaining a healthy, cheerful life free of the fear of DM

Diabetes care and prevention of complications
It has been recognised that chronic complications of diabetes are a major cause of kidney disease, vision loss and amputations in countries where prevalence of the disease exceeds 5%. 6 As a result, prevention of the onset has become one of the major goals of treatment. Consequently, European countries (including Malta) have collaborated to issue the “St. Vincent Declaration” where recommendations for the prevention of costly complications have been put forward. 7 These include a one third reduction in blindness due to diabetes, a one third reduction in people entering end stage diabetic renal failure and reduction in rate of limb amputations by one half.

Management of Type II diabetes
a) Diet and exercise
Reduction in total body fat by 5% may be associated with a significant improvement in glycaemic control. 2 In addition, it improves efficacy of oral or insulin treatment and helps in reducing dyslipidaemia and cardiovascular risks. A successful diet programme should be tailored around a patient’s needs and the advice of a nutritionist or dietician should be sought. The pharmacist is in an ideal position to offer advice concerning:

• Special diabetic products: including chocolates and biscuits – overall, these should be avoided as they are of limited benefit. Very often, such products contain other sugars as an alternative to glucose such as sucrose, sorbitol and mannitol, that offer no advantage to diabetics. Besides, sorbitol in particular is absorbed slowly from the intestine and may produce osmotic diarrhoea. 8,10
• Sweeteners: non-nutritive sweeteners such as aspartame should be recommended. 10
• Sugar content of liquid medicines (both OTC and prescription). Sweetening agents to be avoided include fructose, syrup, honey and glycerol. 11

b) Oral Hypoglycaemic Agents
The introduction of oral hypoglycaemic agents (OHA’s) is considered only after lifestyle modifications have failed to reach treatment goals after at least three months. Drug therapy should not be
instituted beforehand since this will expose the patient to adverse effects inappropriately. There are five classes of OHA's available that will be discussed briefly:

i. Sulphonylureas: These act primarily on the pancreas to increase the amount of insulin secreted in response to a given blood glucose level. Consequently, a degree of residual pancreatic function is required. There is no evidence that there is a difference in efficacy between drugs in this class. The major differences are in the half-life (which relates to the hypoglycaemic effect) and the site of metabolism (i.e. whether renal or hepatic). There are five classes of OHA’s available that will be discussed briefly:

Table I: Pharmacokinetic Data of sulphonylureas

<table>
<thead>
<tr>
<th>Name</th>
<th>Proprietary name</th>
<th>Max daily dose (mg)</th>
<th>Half life (hours)</th>
<th>Dosing Frequency (in 24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpropamide</td>
<td>Diabinese</td>
<td>500</td>
<td>35+</td>
<td>1</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>Daonil</td>
<td>15</td>
<td>4 - 13</td>
<td>1</td>
</tr>
<tr>
<td>(Glyburide)</td>
<td>Semidaonil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Amaryl</td>
<td>6</td>
<td>5 - 8</td>
<td>1</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Gibenese</td>
<td>20</td>
<td>3</td>
<td>1 - 2</td>
</tr>
<tr>
<td>Gliquidone</td>
<td>Gluennorm</td>
<td>60</td>
<td>12 - 24</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Rastinon</td>
<td>2000</td>
<td>7</td>
<td>2 - 4</td>
</tr>
</tbody>
</table>

ii. Biguanides: Metformin is the only biguanide available in the UK and has only been recently introduced in the USA. Phenformin was previously available but was withdrawn in the 1970’s due to the association with fatal lactic acidosis. The pharmacological actions of metformin are numerous and complex and proposed mechanisms include decreased intestinal absorption of glucose, increased glucose uptake form the blood into the tissues, decreased glucose production in the liver and decreased insulin requirements. The activity of the drug is therefore dependent on residual pancreatic activity. Metformin is the drug of choice in obese type II DM since it enhances weight loss. The efficacy of metformin is considered to be comparable to that of sulphonylureas. The main advantage of metformin is that it does not produce hypoglycaemia even when taken in overdosage. It does not undergo hepatic metabolism and is eliminated renally.

Lactic acidosis is of major concern with biguanide treatment since it is a rare but fatal complication with a 30-50% fatality rate. The incidence of lactic acidosis occurring with metformin treatment is much less than that with phenformin mainly because about 9% of Caucasians exhibit a genetically conferred hepatic defect of phenformin hydroxylation. This does not apply to metformin since it is not hepatically metabolised. However, this is largely preventable by a strict observance of the contraindications, all of which are conditions that predispose to development or potentiation of lactic acidosis. These include:

- acute illness (e.g. dehydration, shock, heart failure) which results in increased tissue lactate production
- renal impairment resulting in accumulation of biguanide - in practice metformin is usually stopped when serum creatinine is in the range of 150-160µmol/l
- hepatic impairment where there is a reduced lactate excretion
- use of X-ray contrast media which may predispose to acute renal
Thiazolidenediones: These drugs normally develop. It is therefore recommended to start treatment at a low dose and increase gradually until a recommended to be much safer possibly because they interact with a slightly different nuclear receptor than troglitazone. The FDA recommends intermittent monitoring of liver function but does not specify at what intervals. It is recommended to repeat liver function tests every three months. If the alanine aminotransferase (ALT) is 1.5 times above the normal value, this should be repeated within one week. The drug should be stopped if ALT levels are three times above normal values.

The National Institute of Clinical Excellence (NICE) has issued guidelines on both the use of rosiglitazone and pioglitazone. NICE recommends that the glitazones be used in combination with metformin or sulphonylureas when the combination of metformin/sulphonylurea fails to lower glucose levels within the range required. This combination therapy may be introduced before insulin is added on. In obese patients, combining glitazone to metformin is preferred over the combination with sulphonylurea.

Alpha glucosidase inhibitors:
Acarbose is the only available drug in this group. Migitol is also available in the USA but still not available in Europe. Acarbose acts on the brush border of the small intestine where it competitively binds to α-glucosidase enzymes and inhibits absorption of starch and sucrose. It has less effect on lactose than on other carbohydrates. This delayed absorption results in a decrease in post prandial glucose levels. Since there is no effect on insulin secretion, using the agent alone will not result in hypoglycaemia. Overall it is a very safe drug to use with a mild adverse effect profile.

v. Repaglinide: This is a novel benzoic acid derivative and is the only drug available in its group. It is an insulin secretagogue, which stimulates the secretion of insulin but only in the presence of glucose. Consequently, when taken at meal times, it lowers the post prandial glucose concentration. It is given on a 'one meal, one tablet; no meal, no tablet basis.'

c. Stepwise treatment: With the gradual and steady deterioration of β cell function over time, the patient usually requires additional therapy. After failure of monotherapy, combining OHA's is the first choice. When control is not achieved in this way, combining an OHA to insulin may be considered provided the patient still has some residual pancreatic function. Insulin is normally started as a night time dose to suppress the hepatic output with subsequent increase when glycaemic control is not achieved. Table II shows the currently recommended/licensed combinations of treatment.

d. Insulin: required when the secretion of endogenous insulin is not sufficient. The indications for insulin treatment are as follows:
- non ketotic hyperosmolar coma
- pregnancy
- failure of oral treatment
- acute myocardial infarction
- during and after major surgery
- acute illness
- fasting blood glucose >17mmol/l

A detailed discussion of insulin therapy will be presented in the third and final part of this series.

Table II: Recommended Combination Therapy in Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Sulphonylureas</th>
<th>Metformin</th>
<th>Glitazones</th>
<th>Acarbose</th>
<th>Repaglinid</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>b</td>
<td></td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>r</td>
</tr>
<tr>
<td>Metformin</td>
<td>b</td>
<td>b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glitazones*</td>
<td>r</td>
<td>b</td>
<td>b</td>
<td></td>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Acarbose</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>r</td>
<td></td>
<td>r</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>b</td>
<td>r</td>
<td>b</td>
<td>r</td>
<td>r</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>r</td>
</tr>
</tbody>
</table>

b = combination recommended or licensed; r = combination not recommended.

*In the USA, licensed for use as monotherapy but may only be used in combination as per European license.
References