UNIT NO. 3

ORAL HYPOGLYCAEMIC AGENTS

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ABSTRACT

The management of glycaemia in people with type 2 diabetes depends not only on knowledge of oral antidiabetic agents. Clinical solutions to management of glycaemia require an intimate understanding of patient biological characteristics, co-morbidities, patient lifestyle preferences and requirements, and patient social support Oral antidiabetic agents can be categorised into: (a) Insulin Secretagogues – sulphonylureas and meglitinide analogues promote insulin release from beta cells via SUR1 receptors on beta cells. The soon to be launched dipeptidyl peptidase IV (DPP4) inhibitors promote insulin release by enhancing the effect of glucagon-like peptide 1 (GLP-1) on the beta cell via a site remote to SUR1 receptors; (b) Insulin Sensitisers – biguanides and thiazolidinediones improve insulin action at the muscle and the liver; and (c) Alpha-glucosidase Inhibitors – delay intestinal absorption of carbohydrates by inhibiting intestinal alpha-glucosidase. Oral antidiabetic agents should be begun in small doses. Doses should be increased gradually. Near maximal effects are often achieved with moderate doses. The MOH clinical practice guidelines recommend that initial pharmacotherapy in non-obese patients with type 2 diabetes should be by insulin secretagogues whereas for obese patients, metformin, thiazolidinedione or alpha-glucosidase inhibitor could be considered.

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Introduction

Impaired insulin action and relative insulin deficiency are recognised as key pathogenetic factors in the causation of type 2 diabetes mellitus[1,2]. Obesity and physical inactivity are key 'environmental factors' which can be modified by the genetically predisposed individual so that risks for acquiring insulin resistance and type 2 diabetes[3,4] can be reduced. Pathophysiology of type 2 diabetes revolves around impaired muscle glucose uptake, exaggerated endogenous glucose production (principally from the liver), relatively reduced insulin secretion[5] and impaired incretin action[6]. The relative contribution of each of these pathophysiologic features to hyperglycaemia varies between individuals, but it is generally thought that beta cell dysfunction tends to worsen over time in people with established type 2 diabetes[7].

Updated clinical practice guidelines on management of diabetes have recently been published by Ministry of Health, Singapore (MOH CPG)[8]. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have also recently released a joint statement on management of hyperglycaemia in type 2 diabetes[9]. Recent reviews on oral antihyperglycaemic (antidiabetic) agents[10,11], as well as an update on newer options in pharmacologic management of diabetes have also been published[12].

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MANAGEMENT OF GLYCAEMIA IN PEOPLE WITH TYPE 2 DIABETES

There is now clear evidence that improvement in glycaemia has a positive impact on clinical outcomes[13]. Hence, management of glycaemia should no longer just have avoidance of extreme hyperglycaemia and hypoglycaemia as objectives. It should be impressed upon patients that even though moderate degrees of hyperglycaemia may not be associated with symptoms, they do eventually lead to higher chances of chronic complications of diabetes. The association between hyperglycaemia and increased incidence of both microvascular as well as macrovascular complications was clearly observed in the UKPDS[14].

The management of glycaemia (avoiding hyperglycaemia, avoiding hypoglycaemia and maintaining glucose concentrations near-optimal to individualised targets) in people with type 2 diabetes depends not only on knowledge of oral antidiabetic agents. Clinical solutions to management of glycaemia require an intimate understanding of patient biological characteristics (e.g. age, body mass), patient disease characteristics (e.g. duration of diabetes, presence of symptomatic hyperglycaemia, presence of hypoglycaemia, renal function, liver disease and other co-morbidities), patient lifestyle preferences and requirements (e.g. activity status, dietary habits including regularity of meals), patient social support, etc; and matching these with a selection from the armamentarium of pharmacologic agents delivered via oral, injectable (insulin and others) and inhaled routes. The characteristics of the antidiabetic pharmacologic agent which need to be considered include effectiveness, rate at which effect can be achieved, ease of administration and convenience of dosing, safety, and tolerability.

The measurement of glycated haemoglobin (HbA1c) is an important tool in the assessment of average exposure to glycaemia in the preceding three months. Many patients would also benefit from self-monitoring of blood glucose (SMBG), even in those who are not on insulin treatment. SMBG allows for recognition of glucose excursion patterns and allows for fine-tuning of treatment utilising adjustments of activity, diet and pharmacologic agents[15]. This ultimately translates into better HbA1c levels. SMBG also allows for detection of hypoglycaemia, which should be tackled so as to avoid hypoglycaemia unawareness[16], a debilitating sequel, more often seen in type 1 diabetes but also sometimes seen in people with type 2 diabetes.

Patient engagement is essential for chronic care[17]. Besides engaging the patient in an understanding of the overall care plan, an ongoing assessment of how much the patient and his caregivers can be empowered to modify diet, activity and even

dose of pharmacologic agents to improve glycaemia needs to be done. Although obviously not all patients can be empowered to the same extent, such empowerment goes a long way in improving control as the patient is able to make the necessary adjustments on his own on a day to day basis.

ORAL ANTIDIABETIC AGENTS

Oral antidiabetic agents can be categorised into:

a) Insulin Secretagogues – sulphonylureas and meglitinide analogues promote insulin release from beta cells via SUR1 receptors on beta cells. The soon to be launched dipeptidyl peptidase IV (DPP4) inhibitors promote insulin release by enhancing the effect of glucagon-like peptide 1 (GLP-1) on the beta cell via a site remote to SUR1 receptors[10].

b) Insulin Sensitisers – biguanides and thiazolidinediones improve insulin action at the muscle and the liver.

c) Alpha-glucosidase Inhibitors – delay intestinal absorption of carbohydrates by inhibiting intestinal alpha-glucosidase.

Some commonly used oral antidiabetic agents and their pharmacologic properties are listed in Table 1.

CLINICAL APPROACH

Newly Diagnosed Patient

In the patient recently diagnosed with symptomatic (weight loss, polyuria, etc) type 2 diabetes, it is important to consider whether ketosis is present. The possibility of type 1 diabetes may also need to be considered and immune markers such as

Table 1. Some commonly used oral antiodiabetic agents and their pharmacologic properties

Sulfonylureas (SUs)	Non-SU Secretogogues	Biguanides	a-Glucosidase Inhibitors	Thiazolidinediones
Mechanism of action				
Increased pancreatic insulin secretion	Increased pancreatic insulin secretion	Decreased hepatic glocose production	Decreased gut carbohydrate absorption	Increased peripheral glucose disposal
Advantages				
Well established	Targets postprandial glycaemia	Well established	Targets postprandial glycaemia	No hypoglycaemia
Decreases microvascular risk	Possibly less hypoglycaemia and weight gain than with SUs	Weight loss	No hypoglycaemia	Reverses prime defect of type 2 diabetes
Convenient daily dosing		No hypoglyacemia	Nonsystemic	Nonglycaemic benefits (decreased lipid levels, increased fibrinolysis, decreased hyperinsulinemia, improved endothelial function)
		Decreases microvascular risk		Possible b-cellpreservation
		Nonglycaemic benefits (decreased lipid levels, increased fibrinolysis, decreased hyperinsulinemia)		Convenient daily dosing
		Convenient daily dosing		
Disadvantages				
Hypoglycaemia Weight gain	More complex (3 times daily) dosing schedule	Adverse gastrointestinal effects	More complex (3 times daily) dosing schedule	Liver function test monitoring
Hyperinsulinemia (effect of this uncertain)	Hypoglycaemia	Many contraindications Lacticacidosis (rare)	Adverse gastrointestinal effects	Weight gain
	Weight gain			Oedema
	No Long-term data		No long-term data	Slow onset of action
	Hyperinsulinemia (effect of this uncertain)			No long-term data
Food and Drug Administration approval status				
Monotherapy	Monotherapy	Monotherapy	Monotherapy	Monotherapy
Combination with insulin, metformin, thiazolidinedione, a-glucosidase inhibitors	Combination with metformin	Combination with insulin, SU, non-SU, secretagogue, thiazolidinedione	Combination with SU	Combination with insulin (rosiglitazone at <4 mg daily or pioglitazone), SU, metformin

glutamic acid decarboxylase (GAD) antibody may need to be performed. In such circumstances, insulin therapy should be started until the situation becomes clear. In symptomatic patients who are not ketotic, an insulin secretagogue may be useful as they are more rapidly effective than a biguanide[11] and is likely to relieve symptoms faster. When type 2 diabetes has been confirmed, a biguanide may then be added or substituted as hyperglycaemia comes under control.

For the patient with-newly diagnosed type 2 diabetes who has asymptomatic hyperglycaemia, it has been conventional to encourage patients to embark on a trial of dietary modification (medical nutritional therapy) and appropriate physical activity before institution of pharmacologic treatment. In the UKPDS, 74% of people newly diagnosed with diabetes who were allocated to 'diet only', were able to remain on diet only, but only 24% had fasting blood glucose 7.7 mmol/L and below after 3 years[18]. It appears reasonable to try this approach in assymptomatic patients as some do indeed make the necessary lifestyle changes to stay off medications for some years. However, if glycaemic targets are not met within 4 months, it is reasonable to add on pharmacotherapy[8]. Since insulin resistance appears to be the prominent feature in people recently diagnosed with type 2 diabetes, it is reasonable to start with metformin in low dose unless clinical judgement suggests that relative insulin deficiency is the main feature[9]. Metformin has the advantage of being able to limit weight gain although some patients may not be able to tolerate it on account of gastrointestinal adverse effects, particularly diarrhea. A recently published observational study suggests that metformin may be equally effective in non-obese as in obese subjects with type 2 diabetes[19].

The MOH CPG recommends that initial pharmacotherapy in non-obese patients with type 2 diabetes should be by insulin secretagogues whereas for obese patients, metformin, thiazolidinedione or alpha-glucosidase inhibitor could be considered (Fig 1)[8].

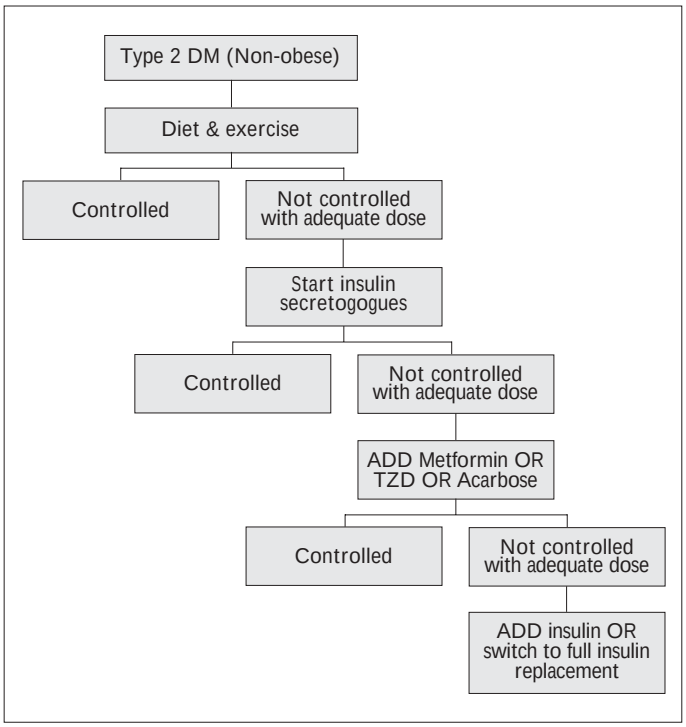
Combination Therapy

While benefit may be derived from escalation from low dose of a specific antidiabetic agent to moderate dose, it is probably counterproductive to try increase monotherapy to high doses, as there is often little further improvement in glycaemia whilst potential for adverse effects increases[10]. In addition, the pathophysiology of type 2 diabetes is complex and multiple pathways are involved. Hence, using two or more oral antidiabetic agents at moderate doses targeted at two or more pathophysiologic pathways appear to be intuitively more appropriate than escalating a single agent to its maximum tolerated dose.

The MOH CPG has specific recommendations for combination therapy for people who are non-obese and obese[8]. However, for the non-obese patient on an insulin secretagogue, the obvious choice for a second agent would be metformin as it tends to improve glycaemia without the propensity for weight gain. For obese patients who are on metformin and who are not able to attain glycaemic targets, addition of a thiazolidinedione or alpha-glucosidase inhibitor is

Fig 1: Algorithm for pharmacotherapy of Type 2 Diabetes Mellitus (Adapted from ref 8)

It is recommended that each treatment is allowed 6 weeks to work before stepping up therapy.



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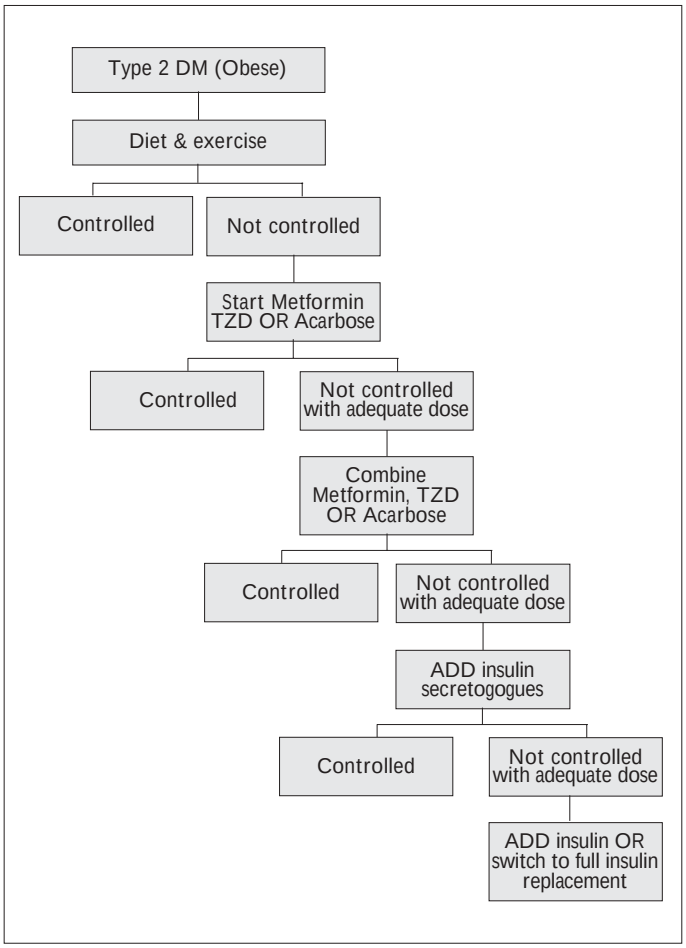

recommended, although alpha-glucosidase inhibitor is relatively milder in its effect and has the propensity to cause flatulence. On the other hand, thiazolidinediones are potent but its onset of action is slower (over weeks); and it has the propensity to cause weight gain and oedema.

However, over time, as duration of diabetes increases, current pathophysiologic models indicate that ongoing deterioration of beta cell dysfunction occurs[7]. Again intuitively, by then, insulin secretagogues and even insulin should be considered as part of pharmacologic therapy if they have not been previously included.

Renal Impairment

Metformin depends almost solely on the kidneys for excretion[10]. Hence, renal function should be evaluated regularly while patients are on metformin for fear of increased risk for lactic acidosis. Some authorities recommend that as creatinine clerarance decreases below 50 ml/min, metformin dose should be decreased and when creatinine clerarance is below 30 ml/min, metformin should be discontinued[20]. As age is a major factor in the estimation of renal function, caution should also be exercised in elderly people who are on metformin, even if the serum creatinine appears to be within the reference range.

Chlorpropamide should no longer be used as an antidiabetic agent as it has a higher propensity for causing hypoglycaemia even in people with normal renal function. In fact, even glibenclamide should be used with caution, particularly in older folks, and other insulin secretagogues which are safer can be substituted.

Hepatic Disease

There are several considerations to bear in mind for patients with hepatic disease. Firstly, drug metabolism may be impaired. Secondly, hepatic glucose production could be reduced and there may be increased risks for hypoglycaemia, particularly early morning hypoglycaemia. Hence, insulin secretagogues and agents which depend on hepatic metabolism to a major extent for elimination of effect should be used cautiously. Thirdly, there is increased risk for lactic acidosis, and metformin should also be used cautiously.

Heart Failure

In overt heart failure, thiazolidinediones and metformin are contraindicated. However when heart failure is controlled, metformin can be considered. There is some epidemiological data that metformin may in fact be beneficial in terms of reducing incidence of heart failure, but this inference was derived from clinical database analysis and subject to more definitive studies[21].

The Elderly

The elderly often have multiple co-morbidities. Besides needing to consider possible organ dysfunction when planning pharmacotherapy for glycaemia, the potential for drug interaction in the context of polypharmacy also needs to be contended with[22]. Realistic glycaemic targets should be set. Moderation of dose and simplicity of regimen are useful principles to adhere to.

NEW ORAL ANTIDIABETIC AGENTS

The soon to be launched oral DPP4 inhibitors reduce the metabolism of GLP-1 and enhance its effect on promoting insulin release and reducing glucagon secretion[23]. In clinical trials, these group of agents have been used successfully in combination with metformin and thiazolidinediones. It would be interesting to observe how these new agents would improve current pharmacotherapy when they become available.

SUMMARY

As a class, oral antidiabetic agents are an important component of the overall treatment strategy of type 2 diabetes mellitus. Other components include dietary modification, physical activity, insulin therapy and use of other injectables. Patient engagement and patient monitoring are other important facets of management. It should also be impressed upon patients that mere avoidance of extreme hyperglycaemia and hypoglycaemia are insufficient and that achievement of near-optimal glycaemia based on customised targets of HbA1c and glucose are essential to reduce risk of chronic complications.

Oral antidiabetic agents should be begun in small doses. Doses should be increased gradually. Near maximal effects are often achieved with moderate doses. For insulin secretagogues, long acting agents such as chlorpropamide should be avoided and glibenclamide should also be used with caution. For patients on metformin, regular evaluation of renal function is important. Early combination therapy with agents from two or more classes of oral agents are useful. Clinical judgement is required so that insulin is initiated once insulinopenia sets in. Caution is required when managing patients with renal dysfunction and in patients who are elderly. Finally, besides managing glycaemia, attention should also be paid to optimising body weight, blood pressure and LDL cholesterol as well as encouraging smoking cessation and considering antiplatelet therapy.

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LEARNING POINTS

- **Clinical solutions to management of glycaemia require an intimate understanding of patient biological characteristics, co-morbidities, patient lifestyle preferences and requirements, and patient social support.**
- **The MOH CPG recommends that initial pharmacotherapy in non-obese patients with type 2 diabetes should be by insulin secretagogues, whereas for obese patients, metformin, thiazolidinedione or alpha-glucosidase inhibitor could be considered.**
- **Oral antidiabetic agents should be begun in small doses. Doses should be increased gradually. Near maximal effects are often achieved with moderate doses.**
- **For insulin secretagogues, long acting agents such as chlorpropamide should be avoided and glibenclamide should also be used with caution.**
- **For patients on metformin, regular evaluation of renal function is important.**
- **Early combination therapy with agents from two or more classes of oral agents are useful.**
- **Besides managing glycaemia, attention should also be paid to optimising body weight, blood pressure and LDL cholesterol as well as encouraging smoking cessation and considering antiplatelet therapy.**