Annals Academy of Medicine

Current Therapeutic Strategies for Type 2 DM—K C Loh & M K S Leow

Abstract

Type 2 diabetes mellitus is now regarded a worldwide epidemic with diabetes-related complications exacting a heavy toll on those with poor metabolic control. Although there is no cure currently, the therapeutic armamentarium has expanded over the last few years to five classes of oral agents – sulfonylureas, biguanides, meglitinides, thiazolidinediones and alpha-glucosidase inhibitors. Sulfonylureas continue to be the mainstay oral hypoglycaemic agents for type 2 diabetics because they are potent insulin secretagogues and cost-effective. Metformin exerts its main effect by reducing hepatic glucose output and is proven to particularly benefit obese type 2 diabetics. Meglitinides are rapid-acting insulin secretagogues targeting at postprandial hyperglycaemia and this class of drug is useful for those who are at risk of hypoglycaemia with longer-acting sulfonylurea drugs. Thiazolidinediones constitute a new class of insulin sensitzers that work predominantly in improving glucose uptake by the adipose tissues and skeletal muscles. Alpha-glucosidase inhibitors delay the digestion and absorption of polysaccharides, thus attenuating postprandial hyperglycaemia. This review article briefly examines the nature of these oral agents, including the role of combination therapy and insulin where clinically indicated.

Introduction

Type 2 diabetes mellitus is recognised as a metabolic syndrome and although the treatment paradigm has shifted from one that focuses solely on glycaemic control to one addressing global cardiovascular risk factors in a particular individual, glycaemic control remains one of the key challenges that the physician faces in his daily practice. The practicing physician must be familiar with the basic pharmacology of the various classes of hypoglycaemic drugs to ensure its effective and rational use. This is becoming an increasingly complicated task given the rapid pace of progress in diabetes therapy. There is also a need to appreciate the pathophysiology of type 2 diabetes and the concept of insulin resistance and β-cell dysfunction, and how this may influence the choice of therapeutic agents in any particular patient. This review summarises the major drug classes and provides evidence-based approach in the management of type 2 diabetes.

The Burden of Type 2 Diabetes Mellitus

Type 2 diabetes is still not satisfactorily managed anywhere in the world, thereby accounting for the considerable morbidity and mortality from diabetes-related complications. Epidemiologically, the Asia-Pacific region alone accounts for nearly 50% of the world’s diabetic patients, 95% or more being type 2 diabetics. Singapore has one of the highest prevalence of diabetes in the region. The National Health Survey of Singapore in 1998 estimated an overall prevalence of 9.0% among adults 18 to 69 years of age, with rates highest among Indians (15.8%) and Malays (11.3%). Diabetes alone is the sixth commonest cause of death, excluding deaths secondary to cardiovascular and renal complications.

Relevance of Basic Pathophysiology of Type 2 Diabetes

Patients with type 2 diabetes mellitus have coexistent problems of insulin resistance and β-cell dysfunction, although to varying degrees. This may range from predominantly insulin resistance with relative insulin deficiency to predominantly insulin secretory defect with insulin resistance. In type 2 diabetes, insulin resistance plays a pivotal role in the pathogenesis of hyperglycaemia.
by reducing insulin-mediated glucose uptake and disposal in adipose tissues and skeletal muscles. Insulin resistance also leads to accentuated gluconeogenesis and hepatic glucose output in the liver. Insulin resistance is initially offset by hyperinsulinaemia, an adaptive counter-response of the pancreatic β-cells. However, this will ultimately lead to impaired β-cell secretory function and progressive insulinopaenia. Any pharmacologic intervention must therefore address these two related aspects adequately to be successful and effective.

Guidelines, Targets and End-points
The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have conclusively proven that intensive blood glucose control significantly decreases the risk of microvascular disease in both type 1 and type 2 diabetic patients respectively.6,7 These studies revealed that a 1% reduction in HbA1c translates into a 35% to 60% risk reduction for microangiopathy. Therefore, the glycaemic targets for patients with type 2 diabetes are not different from those patients with type 1 diabetes.

The targets of glycaemic control may be defined as ‘ideal’, ‘optimal’, ‘suboptimal’, and ‘unacceptable’, depending on the range of HbA1c and the respective pre-meal and 2-hour post-meal capillary blood glucose values (Table I). The American Diabetes Association (ADA) has recommended that action be taken when the fasting plasma glucose exceeds 7.8 mmol/L (140 mg/dL) and HbA1c exceeds 8%. The goals are a fasting glucose less than 6.7 mmol/L (120 mg/dL) and HbA1c below 7%.8 These targets should serve as general guidelines and the actual therapeutic goal should be individualised based on clinical variables such as age, renal function and other co-morbidities that may predispose an individual to hypoglycaemia.

Oral Pharmacotherapeutic Options
Table II summarises the classes of oral antidiabetic agents currently available for the treatment of type 2 diabetes. These are classified into sulfonylureas, meglitinides, biguanides, thiazolidinediones, and α-glucosidase inhibitors. Both sulfonylureas and meglitinides are insulin secretagogues; they work by stimulating the pancreatic β-cell secretion of insulin. These are true oral hypoglycaemic agents because they can potentially induce hypoglycaemia even when used as monotherapy. Metformin and thiazolidinediones are insulin sensitisers as they decrease plasma glucose levels by enhancing the action of insulin in vivo without stimulating endogenous insulin secretion. Alpha-glucosidase inhibitors retard the rate of digestion of dietary carbohydrates and hence prolong the absorption of glucose from the gut. However, the final amount of glucose absorbed and intake of total calories from carbohydrates remains unchanged.

Sulfonylureas – Quest for the Next Generation and Beyond
Sulfonylureas are still one of the cornerstone classes of drugs for the treatment of type 2 diabetes mellitus. As insulin secretagogues, they bind to the sulfonylurea receptor (SUR1) closely coupled to the ATP-sensitive, inwardly rectifying potassium Kir 6.2 channel, so-called K_ATP channel on the pancreatic β-cells. Under the normal resting state, the K_ATP channel opens with efflux of potassium. Activation of the SUR1 leads to closure of the K_ATP channel. By inhibiting the efflux of potassium, the β-cell membrane depolarises and opens the voltage-sensitive calcium channels. The intracellular calcium flux in turn leads to a series of vesicular trafficking that culminates in insulin secretion (Fig. 1).

The first-generation sulfonylureas, except for tolbutamide, have largely fallen out of favour due to significant adverse effects including protracted and refractory hypoglycaemia and the syndrome of
inappropriate anti-diuretic hormone (ADH) secretion (SIADH). The second-generation sulfonylureas (e.g. glibenclamide, glipizide, gliclazide) became available since the 1980s, and these agents generally have more acceptable side-effects profiles. However, hypoglycaemia remains an obligatory trade-off, especially with long-acting agents (e.g. glibenclamide) or short-acting drugs with active metabolites that have long half-lives (e.g. glipizide). Glimepiride is one of the latest additions to the sulfonylurea family and emerging clinical studies showed a lower risk of hypoglycaemia and less weight gain as compared to the older sulfonylureas. The commonly used sulfonylureas and their dosing guide are summarised in Table III.

Increasing awareness of the differential tissue selectivity of sulfonylureas has led to recent interest in elucidating tissue selectivity of sulfonylureas specific for SUR1 of the pancreatic β-cells. This is because in vitro patch clamp studies showed that closure of the K\textsubscript{ATP} channels in SUR2A of cardiac muscle cells and SUR2B of vascular smooth muscle cells, respectively, may lead to undesirable physiological consequences like worsening of tissue ischaemia. Sulfonylurea compounds with both sulfonylurea and benzamido moieties (e.g. glibenclamide and glimepiride) bind to both SUR1 and SUR2A/SUR2B subtypes, whereas drugs with pure sulfonylurea moiety alone (e.g. tolbutamide, gliclazide) bind with high affinity only to the SUR1. However, the clinical significance of these tissue specificities remains to be established.

**Meglitinides – The Prandial Glucose Regulators**

The loss of the acute insulin response, otherwise called “first phase” insulin secretion, constitutes the basis of postprandial hyperglycaemia in type 2 diabetics. The meglitinides are developed to target at postprandial hyperglycaemia in a way similar to the use of rapidly acting insulin analogues before a meal.

Like sulfonylureas, meglitinides stimulate insulin secretion by closing the K\textsubscript{ATP} channels on the membrane of the pancreatic β-cell via activation of the benzamido site on SUR1. Its unique pharmacokinetic profile of rapid absorption coupled with extensive hepatic biotransformation translates into a drug with rapid-onset and rapid-offset effect. This property makes it an ideal prandial glucose regulator, allowing greater flexibility in mealtimes to accommodate a wider range of eating habits. Preprandial dosing may reduce the risk of hypoglycaemia should a meal be missed, and forestall hyperglycaemic excursions when additional meals are consumed. When used as monotherapy, however, meglitinides may not provide adequate control of post-absorptive or fasting glycaemia.

The currently available meglitinides are repaglinide and nateglinide. For treatment naïve patients, the initial starting dose of repaglinide is 0.5 mg just prior to a meal. The dose recommended in those switching over from sulfonylureas is 1 mg before each main meal, with the maximum daily dose up to 16 mg. The usual starting dose of nateglinide is 120 mg before each meal (Table IV).

Reductions in HbA1c of up to 1% to 2% can be expected
of the meglitinides, an efficacy fairly similar to that of sulfonylureas. This group of agents can act synergistically in combination with metformin and thiazolidinediones. However, meglitinides are not useful in patients with primary or secondary failure to sulfonylureas. Meglitinides are generally safe and well tolerated; however, it is contraindicated in severe renal and hepatic failure, pregnancy and lactation. Weight gain may occur though this is generally less severe compared to sulfonylureas.

**Biguanides—The Return of Metformin**

Metformin has remained one of the most efficacious antidiabetic agents, despite the withdrawal of phenformin and buformin because of potential adverse effect of lactic acidosis. Metformin is hydrophilic and is eliminated rapidly by the kidneys; this dissimilarity leads to a significantly reduced risk of lactic acidosis estimated at 3 cases per 100,000 patient years.\(^{14,15}\)

Metformin reduces hyperglycaemia predominantly by reducing hepatic glucose output. This is achieved by inhibition of gluconeogenesis and to a lesser degree of glycogenolysis by the liver. Secondarily, it also reduces hyperglycaemia by increased insulin-mediated glucose disposal at the adipose tissue and skeletal muscle through upregulation of glucose transporters.\(^{16}\) It can also interfere with glucose absorption from the small intestine and reduce postprandial glycaemic excursions. Besides improving glycaemic control, metformin leads to favourable reductions in serum triglycerides concentrations via decreases in very low density lipoprotein (VLDL) synthesis, as well as mild decrease in total cholesterol and slight increase in high density lipoprotein (HDL) levels.\(^{17}\) Because free fatty acid oxidation result in the accumulation of acetyl co-enzyme A and citrate, which in turn inhibit glycolytic enzymes and contribute to insulin resistance, metformin can reduce insulin resistance by lowering free fatty acid levels. Metformin does not cause weight gain; it may actually reduce the body fat mass and produce weight loss in obese subjects. The UKPDS showed particular benefit of metformin therapy in obese diabetics over the use of sulfonylureas/insulin therapy in reducing both micro- and macrovascular endpoints.\(^{7}\)

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**TABLE III: SUMMARY OF THE COMMONLY USED SULFONYLUREAS FOR TYPE 2 DIABETES**

<table>
<thead>
<tr>
<th>Sulfonylureas</th>
<th>Starting dose</th>
<th>Maximum dose</th>
<th>Duration of action</th>
<th>Mean HbA1c reduction</th>
<th>Common adverse effects</th>
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<tr>
<td>Tolbutamide</td>
<td>250 mg bid</td>
<td>1000 mg tid</td>
<td>6-16 h</td>
<td>1% to 2 %</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>5 mg</td>
<td>20 mg bid</td>
<td>12-24 h</td>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td>Glipizide</td>
<td>10 mg bid</td>
<td>20 mg bid</td>
<td>12-24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1-2 mg om</td>
<td>8 mg om</td>
<td>24 h</td>
<td></td>
<td></td>
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</table>

MR: modified release preparation

**TABLE IV: THE OTHER CLASSES OF ANTIDIABETIC AGENTS (NON-SULFONYLUREAS)**

<table>
<thead>
<tr>
<th>Starting dose</th>
<th>Maximum dose</th>
<th>Duration of action</th>
<th>Mean HbA1c reduction</th>
<th>Common adverse effects</th>
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<tr>
<td>Meglitinides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.5 mg bid-qid (with meals)</td>
<td>4 mg qid (with meals)</td>
<td>1-4 h</td>
<td>1-2%</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>60 mg tid (with meals)</td>
<td>120 mg tid (with meals)</td>
<td>1-4 h</td>
<td>1-2%</td>
</tr>
<tr>
<td>Biguanides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>250 mg bid-850 mg om</td>
<td>850 mg tid-1000 mg tid</td>
<td>1.7-4.5 h</td>
<td>1-2%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>4 mg om</td>
<td>8 mg om</td>
<td>24 h</td>
<td>1-1.5%</td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td>25 mg tid (with meals)</td>
<td>100 mg tid (with meals)</td>
<td>6 to 12 h</td>
<td>0.5-1%</td>
</tr>
</tbody>
</table>
The half-life of metformin varies between 2 and 5 hours, with nearly 90% excreted via the kidneys. Due to its frequent gastrointestinal side effects such as diarrhoea, nausea and anorexia, it is recommended that metformin should be initiated at a low dose and titrated upwards gradually. The maximum daily dose is about 2.5 to 3 g in divided doses (Table IV). It is contraindicated in hepatic, renal, cardiac and respiratory failure, and should be used with great caution in any clinical setting associated with tissue hypoxia. Physicians using metformin should screen their patients for these contraindications, and monitor the renal function regularly, particularly in geriatric patients.

**Peroxisome proliferator-activated receptor gamma (PPAR-γ) Agonists and the ‘Glitazones’**

Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear hormone receptor acting as a ligand-dependent transcription factor that controls the expression of a large array of genes involved in adipocyte differentiation, lipid storage, cell proliferation, inflammatory processes, and modulation of insulin sensitivity. PPARγ are located in adipose tissues, skeletal muscles and liver and are activated by a number of naturally occurring fatty acid derivatives. Synthetic compounds called thiazolidinediones (the “glitazones” for short) show high affinity for PPAR receptor and constitute a new class of oral therapeutic agent to reduce insulin resistance.

Like biguanides, thiazolidinediones do not affect insulin secretion. Its predominant antglycaemic action is via increased expression of glucose transporters for peripheral glucose uptake. Glitazones also reduce hepatic glucose output by inhibiting gluconeogenesis. Troglitazone was the prototype PPARγ agonist, but was discontinued from the market in March 2000 because of its potential in causing fatal hepatotoxicity. Rosiglitazone and pioglitazone are the currently available glitazones for therapy of type 2 diabetes, though only rosiglitazone is available locally.

The usual starting dose for rosiglitazone is 4 mg daily; the dosage can be doubled if indicated (Table IV). Because its action is mediated through gene transcription, the onset of action is slow and it may take up to 8 to 12 weeks before maximum benefit is attained. It is thus necessary to observe for improvement in glycaemic control over this period of time before titrating the dosage of the glitazone. Similarly, the insulin sensitising effect of glitazones persists for several weeks after discontinuation. On the average, the HbA1c can be expected to decrease by 1% to 1.5%.

The common adverse effects of glitazones include fluid retention and weight gain; the latter being contributed by factors such as fluid retention, fat deposition and overall improved metabolic control. Unlike troglitazone, hepatotoxicity is rare in rosiglitazone and pioglitazone. As a precautionary measure, the glitazones are contraindicated in any patient who has baseline alanine aminotransferase (ALT) above 2.5 times the upper limit of normal. Liver enzyme measurement is recommended pre-treatment, and two monthly thereafter for a year. As glitazones are expensive drugs with a relatively high incidence of adverse effects, it is more prudent to use glitazones as add-on therapy to patients who fail conventional combination oral therapy.

**Alpha-glucosidase Inhibitors – Acarbose**

Alpha-glucosidase inhibitors such as acarbose, miglitol and voglibose delay the digestion and absorption of dietary polysaccharides by reversibly inhibiting the carbohydrate-digesting enzymes (glucoamylase, sucrase, maltase and isomaltase) and thereby attenuating postprandial hyperglycaemic excursions.

This class of drugs delays absorption of postprandial blood glucose via a non-systemic action, with digestion of carbohydrates most significantly retarded at the duodenum and jejunum. However, its glucose-lowering effect is modest with mean reduction in HbA1c of 0.5% to 1.0% only. Acarbose can be initiated at a dose of 25 mg three times daily with meals, and the dose gradually titrated upwards if necessary to a maximum dose of 100 mg thrice daily in patients weighing over 60 kg (Table IV). In other countries, two more newer α-glucosidase inhibitors, miglitol and voglibose, are also available for the treatment of type 2 diabetes.

Alpha-glucosidase inhibitors are relatively costly and they are associated with a high prevalence of gastrointestinal side-effects like diarrhoea, abdominal discomfort and flatulence. Since α-glucosidase inhibitors target at the polysaccharide-digestive enzymes that reside only at the brush border of the gut, their antglycaemic action is essentially non-systemic. Despite some degree of intestinal absorption, it is important to appreciate that α-glucosidase inhibitors exert no further glycaemia-blunting effect in the bloodstream due to the absence of polysaccharide-digestive enzymes in the systemic circulation. However, because these agents are absorbed systemically, they should not be administered during pregnancy and it is also not advisable to prescribe them to lactating women who breast-feed their babies. Generally, these drugs are relatively safe for patients with mild to moderate liver or renal impairment, though they should be avoided in severe renal failure as the plasma drug levels can be markedly elevated. As a practical point, patients on combination therapy that includes an α-glucosidase inhibitor who develop hypoglycaemia should be reversed with glucose and not sucrose (cane sugar), given that the breakdown of sucrose into glucose and fructose will be retarded by the α-glucosidase inhibitor.
Use of Oral Antidiabetic Agents in the Reproductive Female

All oral hypoglycaemic agents are currently not approved by the US Food and Drug Administration for use in pregnant women with gestational or type 2 diabetes. Amongst the sulfonylureas, glibenclamide is found to cross the maternal circulation to a negligible extent, and because preliminary clinical trials showed no gross deleterious or teratogenic effects of glibenclamide in pregnancy, this drug may perhaps be accepted for use in pregnancy in future. Until then, all patients requiring pharmacologic therapy during pregnancy should switch to insulin therapy.

It is important to note that women in the reproductive age group with polycystic ovarian syndrome (PCOS) may resume normal ovulatory cycles when treated with insulin sensitisers such as metformin and/or glitazones. In fact, metformin is now considered one of the primary treatment modalities in PCOS. Due to the possibility of ovulation induction, precautionary advice should be given regarding alternative and adjuvant methods of contraception to women with reproductive potential when prescribed with any of the insulin-sensitising drugs.

Oral Antidiabetic Combination Therapy

Oral combination therapy is useful for patients who have failed monotherapy by exploiting the synergistic effect of drugs with distinctive mechanisms of actions. When oral agents are combined, considerations must also be given to adverse effects profile (which might be exaggerated), dosing schedules, and costs factors that may impact upon patients’ compliance.

Examples of effective combinations include sulfonylureas with metformin, sulfonylureas with α-glucosidase inhibitors, metformin with α-glucosidase inhibitors, metformin with meglitinides, metformin with thiazolidinediones, or sulfonylureas with thiazolidinediones with or without metformin.

Insulin Therapy and Regimens for Type 2 Diabetes Mellitus

The natural history of type 2 diabetes dictates that many patients may eventually require insulin therapy, based on the 5% to 10% of annual secondary failure rate with insulin secretagogues. The time to initiation of insulin therapy varies amongst diabetic patients depending on variables such as rate of β-cell exhaustion, factors aggravating insulin resistance, and pharmacogenetic differences.

When oral combinations fail to achieve desired glycaemic goals, insulin can be added to oral therapy, or one can completely switch over to insulin therapy. In type 2 diabetics, the lowest dose of insulin capable of achieving glycaemic control should be used to avoid hyperinsulinaemia and its long-term sequelae. Prior to initiating insulin therapy, the patient should understand the basis for insulin therapy, and be familiar with insulin dose adjustment and the management of hypoglycaemia. The patient should preferably learn and adopt home blood glucose monitoring to facilitate insulin dose titration.

Conversely, patients with type 2 diabetes may be switched from insulin to oral agents when their glycaemic control shows significant improvement associated with decline in insulin resistance and glucose toxicity. This is because a type 2 diabetic patient may only require insulin on a temporary basis during periods of increased insulin resistance such as sepsis or other forms of acute stress. The basis behind this “step-up and step-down” therapeutic strategy lies in the dynamic nature of glucotoxicity, insulin sensitivity and β-cell function (Fig. 2).

Bedtime Insulin and Daytime Sulfonylureas (BIDS) Strategy

BIDS may serve to normalise fasting plasma glucose and improve the effectiveness of sulfonylureas to control daytime hyperglycaemia. Intermediate-acting insulin is administered at bedtime and its dose may be calculated empirically with the number of units of insulin similar to the value of the fasting capillary glucose in mmol/L. This is then adjusted by 2 to 4 units every 3 to 4 days until the target fasting capillary glucose is attained (e.g. 4 to 8 mmol/L). In patients with satisfactory fasting and pre-meals blood sugar levels but elevated (>11 mmol/L) post-dinner or bedtime readings, using premixed regular and intermediate-acting insulin pre-dinner may be more effective than giving intermediate-acting insulin at bedtime. BIDS is likely to work well in patients with a fasting glucose level usually under 15 mmol/L. This regimen can also be used as an induction for patients who may require insulin.
eventually require two or more doses of insulin administration daily.

**Multiple Insulin Injections**

When glycaemic control remains poor despite BIDS regimen, it is reasonable to discontinue oral insulin secretagogues and switch to insulin therapy. However, insulin sensitizers can be used in conjunction with exogenous insulin administration to minimise the insulin dose. The most common insulin regimen consists of twice daily insulin administered before breakfast and dinner. For obese type 2 diabetics, the average daily dose of insulin approximates 1 U/kg body weight, while lean patients may be controlled with half the amount. Unless there is a definite pattern of hyperglycaemia and low blood glucose values, it is reasonable to split this dose equally between pre-breakfast and pre-dinner injections. In patients requiring more than 30 units of insulin daily, it might be preferable to use a mixture of short and intermediate acting insulins rather than intermediate or long-acting insulin only. This has been made convenient for the patients with availability of pre-mixed insulin preparations (e.g. Mixtard (30/70), Humulin (30/70) and Humalog Mix 25). Fine-tuning of insulin doses is best determined by home blood glucose monitoring profile and the glycaemic trend over time.

**Insulin Analogues**

Rapid-acting insulin analogues, such as lispro and aspart insulin, can be injected just prior to meals and thus obviate the need to wait 30 to 45 minutes before eating. Unlike regular human insulin, these analogues rapidly dissociate into monomers and dimers on subcutaneous injection, thus facilitating rapid absorption into the capillaries. Insulin lispro has a weaker tendency for self-association than human insulin because of the switch in the positions of lysine at position 28 and proline at position 29 of the β-chain. Insulin aspart is produced by substituting the proline at position 28 of the β-chain of insulin with negatively charged aspartic acid. Due to the rapid onset and shorter duration of action, these rapid-acting insulin analogues have a lower risk of hypoglycaemia than regular insulin. The potency of insulin lispro and insulin aspart is equivalent to regular insulin, except that it has much more rapid activity.

Long-acting insulin analogues, such as insulin glargine, which will be available soon in Singapore, mimics the insulin pump by providing basal insulin throughout the day due to its “peakless” pharmacokinetic profile. It is soluble and precipitates after injection, resulting in a long half-life with about 50% activity 24-hour post-injection. Clinical trials of insulin glargine in both type 1 and type 2 diabetic patients confirmed its efficacy in improving fasting blood glucose control and reducing the incidence of nocturnal hypoglycaemia. While rapid-acting insulin analogues are generally not required for patients with type 2 diabetes mellitus, long-acting insulin analogues are expected to benefit patients with type 2 diabetes by providing a steady basal insulin delivery, thus reducing the risk of hypoglycaemia.

**Summary and Practical Points**

Although lifestyle modification with diet and exercise constitutes the cornerstone of type 2 diabetes management, pharmacologic interventions are inevitably required in the majority of patients. All the antidiabetic agents discussed can be used as monotherapy or in combination with one another. The choice of initial oral agent should be individualised and weighed upon various factors including the desired therapeutic targets, potential adverse effects, cost, compliance issues, etc.

Sulfonylureas and metformin continue to be the mainstay oral hypoglycaemic agents for type 2 diabetes because they are potent, cost-effective, and have established long-term efficacy and safety records. Metformin reduces hepatic glucose output and is particularly useful for obese type 2 diabetics. Alpha-glucosidase inhibitors, meglitinides and thiazolidinediones are newer classes of drugs with a unique place in the armamentarium for type 2 diabetes patients. Meglitinides are useful for patients with predominantly postprandial hyperglycaemia who are also at risk of hypoglycaemia with sulfonylurea therapy. Alpha-glucosidase inhibitors have a role in controlling post-meal hyperglycaemia, and may be used as monotherapy for those with mild diabetes. Thiazolidinediones constitutes a new class of insulin sensitisers and are particularly useful as add-on therapy in patients who failed to achieve satisfactory control with conventional combination therapy. If combination therapy with these available oral agents fail to attain glycaemic goals, adding on or switching over to insulin may be necessary. However, insulin therapy may be used upfront if the level of hyperglycaemia is clinically judged to be difficult to control using oral agents.

**REFERENCES**

QUESTIONS

1. Regarding the use of thiazolidinediones:
   a) The onset of hypoglycaemic action is rapid
   b) They have a gradual washout period
   c) Contraindicated when ALT/AST > 2.5x upper limit of normal
   d) Are safe in patients with congestive heart failure

2. Hypoglycaemia is unlikely with monotherapy of the following agents:
   a) Rosiglitazone
   b) Acarbose
   c) Metformin
   d) Metiglinides

3. Compared with sulfonylureas, metiglinides:
   a) Bind to a different receptor on the pancreatic β-cell
   b) Are more potent insulin secretagogues

4. The following antidiabetic agents are licensed for use in the pregnant diabetic:
   a) Acarbose
   b) Insulin
   c) Metformin
   d) Sulfonylureas

5. True statement(s) concerning α-glucosidase inhibitors include:
   a) Non-systemic antiglycaemic action
   b) No effect on the absorption of dextrose
   c) Sucrose is effective in reversing hypoglycaemia in patients on acarbose
   d) Contraindicated in advanced renal failure

ANSWER SHEET

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<th>Question 3</th>
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