UNIT NO. 3

PHARMACOLOGY OF ORAL ANTI-HYPERGLYCAEMIC AGENTS & INSULIN

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ABSTRACT

Patients with type 2 diabetes require oral antihyperglycaemic drug therapy when diet and exercise fail to control glycaemia. As type 2 diabetes is a progressive condition in which beta-cell function deteriorates with increasing duration of diabetes, stepwise therapy with multiple pharmacologic agents is often needed over time to maintain target glucose control. Currently available oral agents for the treatment of type 2 diabetes include sulphonylureas, meglitinides, biguanide, thiazolidinediones, and alpha-glucosidase inhibitors. All oral anti-hyperglycaemic agents are currently not approved by the US FDA for use in pregnant women with gestational or type 2 diabetes. The risks of medications are often increased with advancing age. Therefore, it is often safer to consider initial low-dose, short-acting oral anti-hyperglycemic agents in the elderly. Metformin is the only oral anti-hyperglycemic agent approved by the US FDA for use in children with type 2 diabetes. Ultimately, up to 40% of type 2 patients may require insulin therapy, often in combination with oral agents, to achieve desired targets of glycaemic control. Only recombinant human insulin is recommended for pregnant women as well as women contemplating pregnancy.

INTRODUCTION

Patients with type 2 diabetes require oral antihyperglycaemic drug therapy when diet and exercise fail to control glycaemia. As type 2 diabetes is a progressive condition in which beta-cell function deteriorates with increasing duration of diabetes, stepwise therapy with multiple pharmacologic agents is often needed over time to maintain target glucose control. Ultimately, up to 40% of type 2 patients may require insulin therapy, often in combination with oral agents, to achieve desired targets of glycaemic control.

This article is focused on reviewing the pharmacology of currently available oral anti-hyperglycaemic agents as well as insulin preparations for treatment of patients with type 2 diabetes. The clinical issues in pharmacotherapy of diabetes (e.g. when to initiate therapy, role of combination therapy, treatment targets, etc.) will not be discussed here.

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ORAL ANTI-HYPERGLYCAEMIC AGENTS

Currently available oral agents for the treatment of type 2 diabetes include sulphonylureas, meglitinides, biguanide, thiazolidinediones, and alpha-glucosidase inhibitors.

Sulfonylureas

Sulphonylureas (e.g. tolbutamide, chlorpropamide, glibenclamide, glipizide, gliclazide, glimepiride) are oral insulin secretagogues which stimulate insulin release via activation of sulfonylurea receptor (SUR1) on the membrane of pancreatic b-cells. SUR1 is closely coupled to the ATP-sensitive, inward rectifying potassium K_{ATP} channel on the pancreatic b-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 b-cell membrane depolarizes and opens the voltage-sensitive calcium channels. The resultant calcium influx leads to a series of intracellular events that culminates in insulin secretion.

Sulfonylureas remain as a cornerstone class of drugs for treatment of type 2 diabetes. They are potent insulin secretagogues with mean HbA1c reduction of 1.5-2% reduction when used alone. As type 2 diabetes is a degenerative metabolic condition with progressive decline in pancreatic b-cell function over time, sulfonylureas are effective only if the patient still has adequate pancreatic b-cell reserves.

Chlorpropamide is a first generation sulfonylurea that has largely fallen out of favour due to significant adverse effects, especially severe and protracted hypoglycaemia and the syndrome of inappropriate anti-diuretic hormone (SIADH) secretion. The newer generation sulfonylureas generally have more acceptable side-effects profiles. However, hypoglycaemia remains a major concern, particularly with long-acting agents (e.g. glibenclamide) or short-acting drugs with active metabolites that have long half-life (e.g. glipizide).

Meglitinides

Meglitinides are short-acting non-sulfonylurea insulin secretagogues (e.g. nateglinide, repaglinide) which become available over the last few years. These drugs have unique rapid onset of action and are developed to target at postprandial hyperglycaemia.

Like sulfonylureas, meglitinides stimulate insulin secretion by closing the K_{ATP} channels on the membrane of the pancreatic b-cell via activation of the benzamido site on the 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, targeting at the postprandial hyperglycaemia caused by blunted "first phase" insulin secretion in patients with type 2 diabetes. Meglitinides can be taken just before the meal, thus allowing greater flexibility in mealtimes. Because of its short duration of action, it has lower tendency to induce hypoglycaemia and weight gain as compared to sulfonylureas.

Although meglitinides are generally safe and effective with mean reductions in HbA1c up to 1-2%, it may not provide adequate control of post-absorptive or fasting hyperglycaemia when used alone in patients with type 2 diabetes.

Biguanide

Metformin is the only safe biguanide for clinical use after the withdrawal of phenformin and buformin due to the potentially high risks of lactic acidosis. Nevertheless, metformin has remained one of the cornerstone drugs for treatment of obese type 2 diabetic patients.

Although the exact cellular mechanism of metformin action is unclear, it primarily reduces hyperglycaemia by reducing hepatic glucose output. This is achieved by inhibition of gluconeogenesis, and to a lesser extent glycogen breakdown, by the liver. Secondarily, it also enhances peripheral glucose disposal and delays glucose absorption from the small intestine. 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.

Unlike the insulin secretagogues, metformin may reduce body fat mass and produce weight loss in obese subjects. The UK Prospective Diabetes Study (UKPDS) demonstrated particular benefit of metformin therapy in obese diabetics over the use of sulfonylureas or insulin therapy in reducing diabetes-related complications.

Metformin is contraindicated in any conditions that predispose an individual to lactic acidosis; e.g. renal failure, chronic hypoxaemic states, septicaemia, etc. Because of the potential danger of acute renal failure precipitated by intravenous iodinated contrast administration, patients are advised to temporarily discontinued metformin treatment before CT study with contrast.

Thiazolidinediones

Thiazolidinediones (glitazones for short) are activators of peroxisome proliferators-activated receptor gamma (PPARg). PPARg are nuclear hormone receptors located in adipose tissues, skeletal muscles and liver. These in turn act as a ligand-dependent transcription factor that controls the expression of a large array of genes involved in adipocyte differentiation and modulation of insulin sensitivity. Glitazones shows high affinity for PPARg receptor and constitute a new class of drug to reduce insulin resistance. Because its action is mediated through gene transcription, the onset of action is slow and it may take up to 2-3 months before maximal anti-hyperglycaemic action becomes evident. Glitazones achieve mean HbA1c reduction of 1-1.5%.

Like biguanides, glitazones do not affect insulin secretion. Its predominant antiglycaemic 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 PPARg agonist first introduced in 1997; this drug was subsequently withdrawn from the market in March 2000 because of its potential in causing fatal hepatotoxicity. Rosiglitazone and pioglitazone are the currently available glitazones for the treatment of type 2 diabetes, though only rosiglitazone is available in Singapore.

The adverse effects of glitazones include oedema, anaemia, and weight gain. Unlike troglitazone, hepatotoxicity is rare in the second generation glitazones. As a precautionary measure, liver enzyme measurement is recommended pre-treatment, and on periodic basis whilst on treatment. Because of fluid retention, glitazones are contraindicated in patients with moderate to severe cardiac failure.

Alpha-glucosidase Inhibitors

Alpha-glucosidase inhibitors slow the digestion and absorption of dietary polysaccharides by reversibly inhibiting the carbohydrate-digesting enzymes (amylase, sucrase, maltase, isomaltase) and thereby attenuating postprandial glycaemic excursions. This class of drugs delays the absorption of postprandial blood glucose via a non-systemic action, with digestion of carbohydrates most significantly retarded in the duodenum and jejunum. However, its glucose-lowering effect is only modest with mean HbA1c reduction of 0.5-1.0%. Alpha-glucosidase inhibitors are associated with a high prevalence of gastrointestinal side-effects like diarrhea, abdominal discomfort and flatulence.

Acarbose is the prototype alpha-glucosidase inhibitor and the only one available locally. Two newer drugs, miglitol and voglibose, are available in other countries. Despite its local action in the gut, these agents are absorbed systemically to some degree and they should not be used during pregnancy or in breastfeeding mothers. As a practical point, patients on combination therapy that includes an alpha-glucosidase inhibitor who develop hypoglycaemia should be reversed with glucose and not sucrose, given that the breakdown of sucrose into glucose and fructose will be retarded by the drug.

Table 1 provides a summary of the pharmacologic profile of oral anti-hyperglycaemic agents.

USE OF ORAL ANTI-HYPERGLYCAEMIC AGENTS IN SPECIAL POPULATIONS

Pregnancy

All oral anti-hyperglycaemic agents are currently not approved by the US FDA 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 with no gross deleterious or teratogenic effects on preliminary trials. Preliminary data on the safety of metformin use in pregnancy has been encouraging, this is especially so as it has been shown to reduce pregnancy loss in women with frequent spontaneous abortions. Until more concrete data on the safety of these oral agents are available, all women requiring pharmacologic therapy during pregnancy are advised to switch to insulin.

Elderly

The risks of medications are often increased with advancing age. For instance, decline in renal function is often not reflected in a measurable change in serum creatinine concentration because of an accompanying decline in muscle mass. Because of this, metformin should be used with caution in elderly patients. In addition, decline in cardiac function and risks for volume overload can be occult in the elderly and may become clinically apparent with the use of thiazolidinediones. Therefore, it is often safer to consider initial low-dose, short-acting oral anti-hyperglycemic agents in the elderly.

Children

Metformin is the only oral anti-hyperglycemic agent approved by the US FDA for use in children with type 2 diabetes.

Patients with co-morbidities

Renal dysfunction increases the risk for hypoglycemia in particular with the use of insulin secretagogues. One should substitute high-dose, long-acting sulfonylureas (e.g. chlropropamide, glibenclamide) with short-acting ones (e.g. tolbutamide), or rapid-acting insulin secretagogues (e.g. repaglinide, nateglinide). Metformin is also usually contraindicated in patients with renal dysfunction whereas alpha-glucosidase inhibitors need to be used with great caution. Thiazolidinediones may be an option, but the potential risks of fluid retention need to be considered.

In patients with cardiopulmonary failure, metformin is to be avoided because of the risks of lactic acidosis in presence of tissue hypoxia. Thiazolidinediones is contraindicated in subjects with moderate to severe cardiac failure.

Hepatic insufficiency increases the risks of lactic acidosis and hypoglycaemia and influences the metabolism of many oral anti-hyperglycemic agents.

Table 1. Pharmacologic Profile of Oral Anti-Hyperglycaemic Agents

	Elimination Half-life (hr)	Site of Metabolism	Site(s) of Elimination	Major Adverse Effects
A. Sulfonylureas				
1) Chlorpropramide	~ 36	Liver	Renal>>gut	Hypoglycaemia (severe) SIADH
2) Tolbutamide	~ 4-8	Liver	Renal>>gut	Hypoglycaemia (less)
3) Glibenclamide	~ 6-10	Liver	Renal>>gut	Hypoglycaemia
4) Glipizide	~ 2-5	Liver	Renal>>gut	Hypoglycaemia
5) Gliclazide	~ 8-12	Liver	Renal>>gut	Hypoglycaemia
B. Meglitinides				
1) Repaglinide	~ 1	Liver	Gut	Hypoglycaemia (less)
2) Nateglinide	~ 1	Liver	Gut	Hypoglycaemia (less)
C. Biguanide				
1) Metformin	~ 6	unchanged	Renal	Lactic acidosis; nausea; vomiting; diarrhoea
D. Thiazolidinediones				
1) Rosiglitazone	~ 4	Liver	Gut>renal	Fluid retention; weight gain; transaminitis
2) Pioglitazone	~ 24	Liver	Gut>renal	Fluid retention; weight gain; transaminitis
E. a-Glucosidase Inhibitors				
1) Acarbose	~ 2	Gut	Gut>renal	flatulence; diarrhoea
2) Miglitol	~ 2	Gut	Gut>renal	flatulence; diarrhoea

INSULIN THERAPY IN TYPE 2 DIABETES

Patients with type 2 diabetes may require insulin either for acute glycaemic control (eg. during intercurrent illness or peri-operative period), or for long-term therapy due to secondary failure of oral agents. Besides recombinant human insulin which replaced the beef or pork insulin preparations since the 80's, new human insulin analogues have become available over the last couple of years and these will be briefly discussed below. Only recombinant human insulin is recommended for pregnant women as well as women contemplating pregnancy.

Insulin in solution is relatively short acting because of its rapid clearance. Therefore, circulating insulin levels and its delivery to tissues is dependent primarily on the rate of entry of insulin into the circulation. This in turn is dependent on factors affecting insulin absorption from its injection site. Besides insulin types, factors like insulin dose, route of administration, anatomical site and other variables (e.g. temperature; exercise; massage; lipodystrophy; etc.) can affect the onset, degree, and duration of insulin activity. Insulin predominantly exists in hexameric form containing two zinc ions at the injection site. A 5,000-10,000 fold dilution of regular hexamers in the subcutaneous tissues is necessary to form monomers which can readily diffuse across capillary walls into the circulation. This need to dissociate the hexamers into dimers and monomers in the subcutaneous tissue explains the reason why the action of regular insulin is delayed by about 45 minutes.

Regular or soluble insulin are short-acting insulin and their action profile can be modified by the introduction of protamine (e.g. neutral protamine Hagedorn or NPH insulin) or zinc (e.g. IZS lente) to become intermediate-acting insulin. Premixed insulin preparations contain stable mixtures of fixed proportions of short-acting insulin and intermediate-acting insulin and these are particularly useful for patients who require both bolus (prandial) and basal insulin supplement. Pointers on the self mixing of insulin preparations are provided below.

Human Insulin Analogues

Rapid-acting Insulin Analogues. Two rapid acting insulin analogues, insulin lispro and aspart have been developed with a reduced tendency to self-association of their molecules. Insulin lispro is produced by a switch in the positions of lysine at position 28 and proline at position 29 of the b-chain; whereas insulin aspart is produced by substituting the proline at position 28 of the b-chain with negatively charged aspartic acid. Because these analogues rapidly dissociate into monomers and dimers on subcutaneous injection, they demonstrate faster absorption kinetics and can therefore be injected just before meals. They also attain higher concentrations after subcutaneous injection compared to conventional human insulin and they reduce post-prandial glucose to a greater extent. The shorter duration of action of these rapid-acting insulin analogues also lead to a lower incidence of hypoglycaemia.

Long-acting Insulin Analogues

Insulin glargine and insulin detemir are long-acting insulin analogues that have virtually no plasma peak. Insulin glargine is the only long-acting insulin analogue currently available in Singapore and its duration of action is about 20-22 hours. Its long duration of action coupled with its peakless profile make it ideal to cover basal insulin requirement. These new long-acting insulin analogues provide more predictable glycaemic control with lower intra-subject variation and reduced risk of hypoglycaemia compared with the conventional preparations of intermediate-acting and long-acting insulin.

Pointers on Mixing of Different Insulins

The compatibility of different insulin preparations must be established before one provides any advice on the mixing of different types of insulin. This is especially so for newer formulations of insulin analogues. In general, the mixing of short-acting insulin analogues with insulin zinc suspensions (e.g. Lente human insulin or Ultralente human insulin) is not advised as the zinc component may retard the overall rate profile of the faster-acting insulin. Likewise, it should be noted that the new long-acting insulin analogue, insulin glargine, should not be mixed with any other forms of insulin due to the low pH of its diluent.

Table 2. Pharmacologic Profile of Insulin Preparations

	Onset	Peak	Duration of action
A. Recombinant Human Insulin			
1) Short-acting insulin (e.g. Regular or soluble insulin)	30-60 min	2-4 hr	6-8 hr
2) Intermediate-acting insulin (e.g. NPH or Lente insulin)	1-4 hr	8-12 hr	12-20 hr
3) Long-acting insulin (e.g. Humulin U or Ultratard)	3-5 hr	10-16 hr	18-24 hr
B. Human Insulin Analogues			
1) Rapid-acting insulin (e.g. Insulin lispro; insulin aspart)	5-20 min	1-3 hr	3-5 hr
2) Long-acting insulin (e.g. Insulin glargine)	4-8 hr*	"peakless"	20-24 hr

**Onset time for initial dose; steady state reached after 2-4 days of once daily administration*

SUGGESTED READINGS

ARTICLES BY THE AUTHOR:

1. Loh KC, et al. Current Therapeutic Strategies for Type 2 Diabetes Mellitus. Ann Acad Med Singapore 2002; 31:722-30.
2. Loh KC, et al. Alpha-glucosidase inhibitor and treatment of diabetes mellitus: a drug review. Endocrine Practice (USA) 1998; 4:287-93.

SUCCINCT REVIEW ARTICLES ON THE NEWER PHARMACOLOGIC AGENTS OR INSULIN:

1. Lebovitz HE. Rationale for and Role of Thiazolidinediones in Type 2 Diabetes Mellitus. Am J Cardiol 2002; 90(suppl):34G-41G.
2. Owens DR, et al. Drug Focus: Insulin Glargine. Int J Clin Pract 2002; 56:460-6.
3. Mudaliar SR, et al. Insulin Aspart (B28 Asp-Insulin): A Fast-Acting Analog of Human Insulin. Diabetes Care 1999; 22:1501-6.

LEARNING POINTS

- **Patients with type 2 diabetes require oral anti-hyperglycaemic drug therapy when diet and exercise fail to control glycaemia.**
- **Stepwise therapy with multiple pharmacologic agents is often needed over time to maintain target glucose control.**
- **Ultimately, up to 40% of type 2 patients may require insulin therapy, often in combination with oral agents, to achieve desired targets of glycaemic control.**
- **Currently available oral agents for the treatment of type 2 diabetes include sulphonylureas, meglitinides, biguanide, thiazolidinediones, and alpha-glucosidase inhibitors.**
- **All oral anti-hyperglycaemic agents are currently not approved by the US FDA for use in pregnant women with gestational or type 2 diabetes.**
- **The risks of medications are often increased with advancing age. Therefore, it is often safer to consider initial low-dose, short-acting oral anti-hyperglycaemic agents in the elderly.**
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