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Oral hypoglycemic drugs: An overview

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ABSTRACT

The aim of this study was to evaluate safety and efficacy of oral hypoglycemic agents in obese Type-2 diabetic patients. The objectives are to compare fasting and postprandial blood sugar (PPBS) levels, to compare body mass index in all the groups and to identify glycosylated hemoglobin levels and adverse drug reaction in all the groups. Diabetes mellitus is one of the world's major diseases. It currently affects an estimated143 million people worldwide and the number is growing rapidly. In the India, about 1-5% population suffer from diabetes or related complication. So there is need to cure this disease. Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral anti hyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors. Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in Type 1, which must be injected or inhaled. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Treatments include agents which increase the amount of insulin secreted by the pancreas, agents which increase the sensitivity of target organs to insulin , and agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Keywords: hypoglycemic, blood suger, insulin, diabetes mellitus, pancreas

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INTRODUCTION

Diabetes is a chronic progressive disorder, with multiple biological defects, which necessitates the use of a range of different classes of drugs in order to optimize disease control over the patients' life span. To date there have been oral drug classes such as the biguanides, sulphonylureas, and injectable insulin options such as human and analogue insulin, which have become household names in the treatment of diabetes. New treatment options that target the incretin system are now available. These now widen the choices for commencing treatment for Type 2 diabetes. We can choose the appropriate drugs for optimal control of diabetes.

We can choose the appropriate drugs for optimal control of diabetes targeting specific pathophysiological defects. It is important to understand the mechanism of action of these drugs to fully comprehend the mode and extent of glucose control that can be achieved as well as the side effects that could be anticipated.[1]

Defective insulin secretion and insulin resistance appear very too early in obese patients, and both worsen equally as diabetes progresses. An increase in overall fat tissue, especially in visceral as well as ectopic fat depots, is particularly associated with insulin resistance. The relationship between obesity and diabetes is of such interdependence that the term "diabesity" has been coined. [2] The prevalence of diabetes for all age groups worldwide diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and it will be 4.4% in 2030.

Diabetes affects approximately 200 million people worldwide, including more than a quarter of elderly living in developed countries. Diet and exercise are first line treatments along with oral hypoglycemic drugs to achieve the goal of improving glycogenic control and preventing both micro vascular and macro vascular complications. [3]

The term diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyper glycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non– ketotic hyperosmolar state may develop and lead to stupor, command, in absence of effective treatment, death. Often symptoms are not severe, or may be absent, and consequently hyperglycemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made.

As it is important to evaluate the benefits of hypoglycaemic agents in patients with various confounding risk factors, a comparative study is advantageous to choosing a right drug for the obese patient to reduce weight or put weight in control. The aim of this study was to evaluate safety and efficacy of oral hypoglycaemic agents in obese Type-2 diabetic patients. The objectives are to compare fasting and postprandial blood sugar (PPBS) levels, to compare body mass index (BMI) in all the groups and to identify glycosylated haemoglobin. [4]

Diabetes can cause serious health complications including heart disease, blindness, kidney failure, and lower-extremity amputations. Diabetes is the seventh leading cause of death in the United States.

SYMPTOMS OF DIABETES

People who think they might have diabetes must visit a physician for diagnosis. They might have SOME or NONE of the following symptoms:

- Frequent urination
- Excessive thirst
- Unexplained weight los
- Extreme hunger1
- Sudden vision changes
- Tingling or numbness in hands or feet
- Feeling very tired much of the time
- Very dry skin
- Sores those are slow to heal
- More infections than usual

Nausea, vomiting, or stomach pains may accompany some of these symptoms in the abrupt onset of insulin-dependent diabetes, now called Type 1 diabetes. [5, 6]

Pharmacotherapy

Pharmacotherapy Oral antidiabetic (OAD) agents that will be discussed include:

- Biguanides
- Sulphonylureas
- Non-sulphonylurea (Meglitinides)
- Thiazolidinediones
- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase IV (DPP-IV) inhibitors
- Glucagon-like peptide-1 (GLP-1) analogues

• Biguanides:

Biguanides are old agents that work by reducing hepatic glucose output and, to a lesser extent, enhancing insulin sensitivity in hepatic and peripheral tissues (ie, antihyperglycemics, hepatic insulin sensitizers). Phenformin was taken off the market in the United States in the 1970s because of its risk of causing lactic acidosis and the associated mortality (rate of approximately 50%). In contrast, metformin has proved effective and safe. [7, 8] It has been used in Europe for over thirty years, whereas in the United States it has been available since 1995. Metformin should be prescribed to all people with type 2 diabetes, unless contraindicated. Current recommendations of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) include metformin, diet and exercise as first-line therapy for the treatment of patients with type 2 diabetes, irrespective of the presence of overweight status. [9]

Mode of action

Metformin has a variety of metabolic effects, No clinically significant drug interactions have been some of which may confer clinical benefits that reported. However, agents affecting gut motility can extend beyond glucose lowering. At the cellular level, met-crease the glucose- lowering effect of acarbose. Metformin improves insulin sensitivity to some extent, an action mediated via post-receptor signaling path-3. Insulin Sensitizers ways for insulin. Recent data have suggested Insulin resistance is a prominent metabolic defect that adenosine 5′-monophosphate-activated protein.

Kinase (AMPK) is a possible intracellular target of nant glucose-lowering mechanism of action of metmetformin.[10] Through phosphorylation of key pro- formin is to reduce excessive rates of hepatic glutens, AMPK acts as a regulator of glucose and lipid core production. Metformin reduces gluconeogene metabolism and cellular energy regulation.[11] Since sis by increasing hepatic sensitivity to insulin (figure metformin lowers blood glucose concentrations 4) and decreasing the hepatic extraction of certain without causing overt hypoglycemia it is most ap- gluconeogenic substrates (e.g. lactate). Hepatic propriately classed as an anti-hyperglycemic – as glycogenolysis is also decreased by metformin. Indistinct from hypoglycemic – agent. The clinical sulin-stimulated glucose uptake in skeletal muscle is efficacy of metformin in patients with type 2 diabe- enhanced by metformin. This involves an increase tes requires the presence of insulin. The drug does in the movement of insulin-sensitive glucose transmit stimulate insulin release and a small decrease in porter molecules to the cell membrane; an increase fasting insulin concentrations is typically observed in the activity of the enzyme glycogen synthase in patients with hyperinsulinaemia. The predomi- promotes synthesis of glycogen. Metforminals Oral Antidiabetic Agents acts in an insulin-independent manner to suppress other class of oral antidiabetic agent or with insulin. Oxidation of fatty acids and to reduce triglyceride The drug is contraindicated in patients with imlevels in patients with hypertriglyceridaemia. paired renal function (i.e. serum creatinine This reduces the energy supply for hepatic gluco- >120–130 μmol/L, depending on lean body mass), neogenesis and has favourable effects on the glu- as a precaution against drug accumulation. Cardiac cose-fatty acid (Randle) cycle (in which fatty acids or respiratory insufficiency, or any other condition are held to compete with glucose as a cellular energy predisposing to hypoxia or reduced perfusion (e.g. source).[12] Glucose metabolism in the splanchnic hypotension, septicaemia) are further contraindicabed is increased by metformin through insulin-indetions, as well as liver disease, alcohol abuse and a pendent mechanisms. This may contribute to the history of metabolic acidosis. Metformin can beblood glucose-lowering effect of the drug, and in used in the elderly, provided that renal insufficiencyturn may help to prevent gains in bodyweight. Coland other exclusions are not present. A difficulty inlectively, the cellular effects of metformin serve to practice is that significant renal dysfunction may becounter insulin resistance and to reduce the putative present without the aforementioned elevation of se-toxic metabolic effects of hyperglycaemia (glucose rum creatinine.toxicity) and fatty acids (lipotoxicity) in type 2 diabetes.

Side effects:

1 Up to a third of patients on metformin experience gastrointestinal (GI) side effects, such as nausea, diarrhea, abdominal discomfort, and a metallic taste, which can be reduced by titrating the dose up slowly and by taking medication with or after meals?

2 The reported incidence of lactic acidosis with metformin is rare at 0.03 per 1000 patient-years of use. It is fatal in 30% to 50% of cases.8 A recent systematic review found no cases of lactic acidosis associated with metformin use in Type 2 diabetes when contraindications were observed.9 At high doses, especially in renal failure, it accumulates in mitochondria, inhibits oxidative phosphorylation and causes lactic acidosis (which can be further potentiated by alcohol).

• Metformin can interfere with vitamin B12 absorption and may lower serum vitamin B12 levels through unknown mechanisms, but is rarely of clinical significance. Anemia has been observed in 7% of people in clinical trials. It appears to be rapidly reversible with discontinuation of the drug. It is recommended to monitor hematological parameters. [13]

Contra-indications

Metformin is contraindicated in people with the following risk factors for lactic acidosis:

- Renal (serum creatinine ≥ 130 mmol/L in men, or ≥ 120 mmol/L in women)
- Hepatic impairment
- Respiratory insufficiency
- Severe infection
- Alcohol abuse
- Heart failure requiring pharmacological therapy
- Metformin should also be used with caution in elderly people (older than 80 years) with reduced lean body mass. It is recommended to monitor renal function upon initiating metformin and at least annually thereafter.[10]
- Any patient undergoing radio-contrast studies should have metformin withheld one day before the study and 48 hours after the study to avoid any potential lactic acidosis.

2 .Sulphonylurea secretagogues

The sulphonylurea group of drugs has been available for the last 50 years. All of them (glibenclamide, glipizide and gliclazide) have a similar mechanism of action that is mediated by inducing closure of the ATP-sensitive potassium (K+) channels. The intracellular retention of K+ changes the membrane potential resulting in depolarization of the ß-cell, and opening of the voltage-dependent calcium channels. This facilitates movement of Ca++ into the cell, stimulating exocytosis of insulin into the circulation.

Traditionally, sulphonylureas are classified into first- and secondgeneration depending on their duration of action. The latter group, in general, has a greater potency and improved safety.

Examples of the first-generation SUs include acetohexamide, tolbutamide and chlorpropamide. The latter drug has a long duration of action, up to 48 hours, and even its metabolites have active hypoglycaemic potential.

Examples of the second-generation group include glibenclamide (Daonil®), glipizide (Minidiab®), and gliclazide (Diamicron®). Glimepiride (Amaryl®) is classified as a third-generation SU.

All of them have a number of generics available, and most of the generics are of equal potency. All of them stimulate insulin release from pancreatic ß-cells that have residual function. They display, to some extent, a glucose-dependent effect, but still have a potential for serious hypoglycemia, which is especially a problem with chlorpropamide, especially in the context of skipped meals. Chlorpropamide use is thus best avoided. [14]

Mechanism of Action

SUs have a glucose independent mechanism of action, which means that they continue to exert their effects irrespective of ambient glucose concentrations in the circulation. They induce insulin release from beta cells by inhibiting ATP-dependent potassium channels. Besides pancreatic beta cells, these channels are present in various tissues of the body including cardiomyocytes and vascular smooth muscle cells (SUR2 isoform). Modern SU such as glimepride act predominantly upon SUR 1 isoforms.

SU also bind with an exchange protein called Epac 2, which interacts with Rap 1 protein to increase the number of insulin vehicles that fuse with beta-cell plasmalemma. This effect has been demonstrated for all SUs except gliclazide.

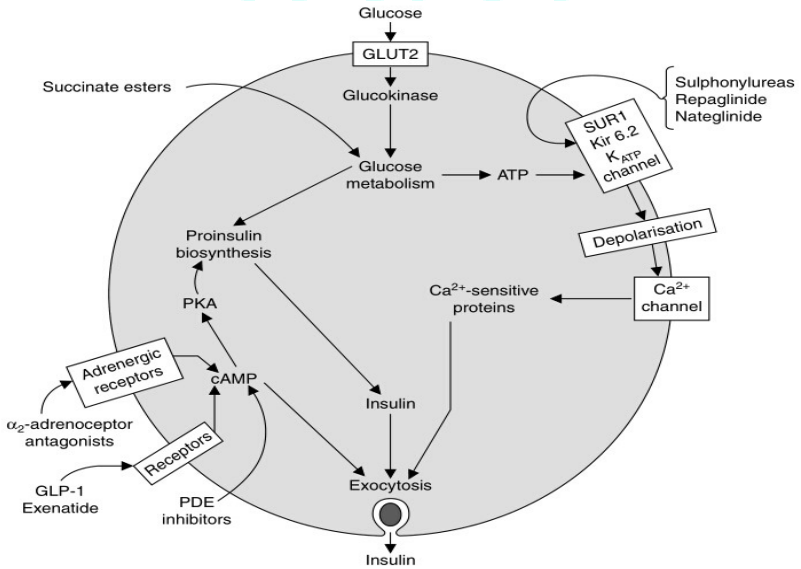


Fig. 2. The insulin-releasing effect of sulphonylureas and other agents on the pancreatic islet β cell. Sulphonylureas bind to the sulphonylurea receptor (SUR)-1 located within the plasma membrane. This closes Kir 6.2 potassium channels which reduces potassium efflux, depolarises the cell and opens voltage-dependent calcium influx channels. Raised intracellular calcium brings about insulin release. According to the stimulus-secretion model, metabolism of glucose generates adenosine 5′-triphosphate (ATP) leading to closure of potassium channels, permitting the normal β cell to link insulin secretion closely to glucose concentration. Sulphonylureas may also enhance nutrient-stimulated insulin secretion by other actions on the β cell. Other secretagogues, e.g. repaglinide, nateglinide, also stimulate insulin secretion via the SUR-Kir 6.2 complex. Other agents, e.g. phosphodiesterase (PDE) inhibitors, glucagon-like peptide (GLP)-1 (7–36 amide), act via cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) to promote proinsulin synthesis (reproduced from Krentz and Bailey,[4] with permission from the Royal Society of Medicine Press). **GLUT2** = glucose transporter-2.

Pharmacology

Pharmacological properties of various SUs are detailed in Table-2.

Drug	Dose	Duration of action	Renal excretion	Biliary excretion
Glibenclamide	1.25-20 mg	12-24 h	50%	50%
Glipizide	2.5-40 mg	12-18 h	80%	20%
Gliclazide	40-320 mg		80-90%	10-20%
Gliclazide MR	30-120 mg	24 h	80-90%	10-20%
Glimepride	1-8 mg	24 h	60%	40%

Table-2: Pharmacological properties of sulfonylureas.

Non-sulphonylurea secretagogues (Meglitinides)

These drugs, the so-called glinides, include repaglinide (NovoNorm®), a benzoic acid derivative, and nateglanide (Starlix®), a phenylalanine derivative. These agents are short-acting insulin secretagogues. Both have a similar action to SUs, acting on the same ß-cell receptors. They act on the ATP dependent potassium channels in pancreatic ß-cells, allowing opening of calcium channels and increased insulin release.

They are differentiated from SUs by their much shorter half-lives, and the absence in them of the sulphonic acid moiety, which allows them to be used where patients are allergic to sulphas. In view of their shorter duration of action, they have been used as 'prandial drugs', taken just before meals. Their rapid clearance reduces the potential for delayed hypoglycemia.

As a general rule, the glucose lowering effect of sulphonylureas plateaus after half the maximum dose is reached.

Pharmacology

The meglitinides are non-sulfonylurea hypoglycemic agents that lower blood glucose levels by stimulating the release of insulin from the pancreas. Action of these agents is dependent on actively functioning beta cells in the pancreatic islets.

The meglitinides bind to a non-sulfonylurea receptor on the pancreatic beta cell membrane. This leads to the closing of ATP-dependent potassium channels in the beta cell membrane and the opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue-selective with low affinity for heart and skeletal muscle.

Metformin (a component of Prandimet), is a biguanide-type hypoglycemic agent. It increases peripheral uptake and utilization of glucose, resulting in a reduction in hepatic gluconeogenesis, a reduction in glucose absorption from the gastrointestinal tract, and an improvement in insulin sensitivity of peripheral tissue.

Pharmacokinetics

Drug	Bioavailability (%)	Tmax (hr)	Half-life (hr)	Metabolism	Excretion (%)
metformin (Glucophage)[12]	50-60	--	6.2-17.6	None	urine: > 90
nateglinide (Starlix)[13,14]	73	≤1	1.5	Hepatic (2C9 and 3A4); less potent metabolites	urine: 83 feces: 10
repaglinide (Prandin)[15]	56	≤1	1	Hepatic (2C8 and 3A4); 3 metabolites which do not contribute to glucose lowering effect	urine: 8 feces: 90

Fixed-dose combination repaglinide/metformin (Prandimet) tablets are bioequivalent to the individual drugs administered together.

Side effects

In general, the SUs and non-SUs have similar side effects. Hypoglycaemia would tend to be more common in SUs with longer duration of action, for example with chlorpropamide rather than with the glinides.

The most common adverse side effect is hypoglycaemia. The UKPDS reported an incidence of 1.2% in the SU-treated group.13 Hypoglycaemia is predisposed to by high doses, missed meals, excessive alcohol, and a history of renal or hepatic disease.

Weight gain is the other significant side effect, and is usually seen in the context of improved glycaemic control. The average weight gain on a SU is some 2–5 kg. Less common side effects include GI disturbance, photosensitivity, abnormal liver enzymes, flushing (especially with chlorpropamide and alcohol), and chlorpropamide induced hyponatraemia, especially in patients on concomitant diuretic therapy.[15]

Contraindications

Nateglinide (Starlix) and repaglinide (Prandin) are contraindicated in patients with type 1 diabetes, diabetic ketoacidosis, or a known hypersensitivity to the drug or its inactive ingredients. Repaglinide (Prandin, Prandimet) is contraindicated in patients also taking gemfibrozil. [16]

Any product containing metformin is contraindicated in patients with any of the following: renal disease or renal

dysfunction (serum creatinine > 1.5 mg/dL for males and > 1.4 mg/dL for females), acute or chronic metabolic acidosis, including diabetic ketoacidosis, acute myocardial infarction, septicemia, pregnancy, or known hypersensitivity to metformin or other ingredients in the drug formulation. Due to the metformin component, the labeling for combination repaglinide/metformin (e.g., Prandimet) contains a boxed warning related to an increased risk of lactic acidosis, especially in patients with renal or hepatic impairment, sepsis, dehydration, excessive alcohol intake, or acute congestive heart failure. If lactic acidosis is suspected, combination repaglinide/metformin should be discontinued and the patient should be hospitalized immediately. Because metformin can cause vitamin B12 deficiency, patients being treated with any product containing metformin should have hematological parameters assessed annually.

4. Thiazolidinediones

Thiazolidinediones (TZD) are selective peroxisome proliferator activated receptor (PPAR) gamma agonists. PPARs in humans are associated with gene transcription. Activation of these receptors regulates the transcription of insulin responsive genes involved in the control of production, transport, and use of glucose. [17]

The interactions of TZD result in an:

-Increased insulin-stimulated glucose uptake by peripheral tissues (skeletal muscle and adipose tissues) by improving insulin sensitivity

-Reduced hepatic glucose production

-Decreased lypolysis and

-Enhanced adipocyte differentiation

TZD currently available include pioglitazone (Actos®) and rosiglitazone (Avandia®). They can be prescribed as monotherapy or in combination with metformin or sulphonylureas. Its use with insulin is not recommended due to the excessive weight gain and fluid retention. [18] The weight gain may be mediated through a number of mechanisms:

- It usually involves deposition of fat in the peripheral subcutaneous site with a reduction in visceral fat deposition.
- It could also be due to an increase in plasma volume (i.e. oedema) because of the activation of PPAR receptors in the kidneys.
- The oedema may be due to a decrease in renal excretion of sodium and an increase in sodium and free water retention.

Fluid retention and pedal oedema occurs in 3% to 5% of people taking TZD. This can precipitate congestive heart failure in patients with compromised cardiac function. Rosiglitazone and pioglitazone differ in their effects on lipids:

- Rosiglitazone increases LDL-cholesterol (LDL-C) by 0.34–0.47 mmol/L, has no effect on triglycerides (TG), and increases HDL-cholesterol (HDLC) by 0.05-0.09 mmol/L.
- Pioglitazone has a neutral effect on LDLC, decreases TG by 0.29–0.60 mmol/L, and increases HDL-C by 0.09-0.14 mmol/ L.23 Both agents may reduce the level of small, dense LDL-cholesterol, which is thought to be the most atherogenic lipoprotein component in people with diabetes and may reduce macrovascular morbidity and mortality.

Efficacy:

Bennett et al reviewed RCTs comparing glitazones or thiazolidinediones (TZDs) (pioglitazone and rosiglitazone) and second-generation sulfonylureas (glibenclamide, glimepiride, and glyburide). The review found both treatments had similar effects on HbA1c.Five RCTs with up to 1 year or less in duration, compared glitazones and a SFU, showing greater weight gain with glitazones, favoring SFUs. Five RCTs compared rosiglitazone or pioglitazone with a SFU, indicating a greater increase in LDL with glitazones relative to a SFU. Eight RCTs compared rosiglitazone or pioglitazone with a SFU, indicating a favorable increase in HDL with glitazones relative to a SFU. Pioglitazone is favored for a greater decrease in TG over SFUs in 6 RCTs. However, when comparing rosiglitazone and SFUs, Bennett et al found conflicting evidence for benefits of TG lowering. In one RCT, while both rosiglitazone (at 8mg dose) and a SFU were associated with a decrease in TG, the differences were non-significant; in another RCT a lower dose (4mg) of rosiglitazone lowered TG relative to a SFU, however, at a dose of 8mg, rosiglitazone increased TG relative to SFU with no statistical significance reported.The ADOPT study showed all-cause mortality and cardiovascular mortality to be similar for rosiglitazone and glyburide at 2.3% and 2.2%, respectively.As above, it should be noted that the FDA has placed a boxed warning for all thiazolidinedione agents, including rosiglitazone and pioglitazone for risk of congestive heart failure.

Safety:

Five RCTs determined a greater risk of mild to moderate hypoglycemia with SFUs over glitazones with an OR of 3.9. Although the ADOPT study with over 1300 participants in each arm reported no statistical significance for outcome of hypoglycemia between rosiglitazone and glyburide. Bennett et al reviewed 4 RCTs looking at outcome of CHF with glitazones versus SFU and found an increase of CHF incidence with glitazones over SFUs with an OR of 1.68.While the review did not show statistical significance, clinical significance could not be ruled out.Three RCTs did not show a consistent difference in the occurrence of diarrhea between groups treated with pioglitazone or rosiglitazone and glyburide.

5. α-Glucosidase Inhibitors

α-Glucosidase inhibitors include acarbose and miglitol. They act on α-glucosidase, an enzyme found in brush border cells of small intestine, cleaving more complex carbohydrates into sugars. αGlucosidase inhibits the breakdown and absorption of carbohydrates (dextrins, maltose, sucrose and starch; no effect on glucose); their largest impact is on postprandial hyperglycemia and their effect on FPG levels is modest. They have been associated with a reduction in HbA1c by 0.7 to 1.0 percent and FPG levels by 35 to 40 mg per dL (1.9 to 2.2 mmol per L). These agents are thus most useful in patients who have mild FPG elevations or in patients with predominant postprandial hyperglycemia. However, the main side effects of α-glucosidase inhibitors are flatulence, abdominal discomfort, bloating and diarrhea, which reduce compliance in treated patients. As for metformin, patients should be instructed to take this medication with food, starting with the lowest effective dose and titrated slowly over intervals of two to four week. Although hypoglycemia is not typically associated with monotherapy with α-glucosidase inhibitors, it can occur in combination with other drugs; it is important, to inform patients that the

traditional treatment for hypoglycemia may be blocked during treatment with α-glucosidase inhibitors and only glucose should be consumed in this condition.

Mode of Action:

1. Acarbose blocks the digestion of starch, sucrose and maltose. The digestion of carbohydrate is delayed and occurs throughout the small intestine, rather than upper part of jejunum. Absorption of glucose and other monosaccharides in not affected. The net result is a decrease in post prandial rise in blood glucose. Most of the carbohydrate is eventually absorbed and that which is now absorbed is metabolised by the bacteria in the colon to short chain fatty acids which are then absorbed in the colon.

2. Acarbose decreases meal stimulated secretion of gastric inhibitory polypeptide and other gastrointenstinal peptide (inhibitors) hormones. There is smaller increase in post prandial blood sugar level that leads to smaller increase in insulin level.

3. Acarbose does not cause weight gain with the therapeutic doses.

Efficacy:

Van de Laar et al. and Bolen et al. reviewed 2 RCTs comparing submaximal dosed metformin and maximally dosed acarbose showing no significant differences in HbA1c reduction between the two treatment groups.No statistically significant differences were observed for weight reduction with either AGIs or metformin.Reviews by Van de Laar et al and Bolen et al, found no benefits to HDL or TG with either therapy. One study, using submaximal doses of metformin and maximum doses of acarbose showed a reduction in LDL favoring acarbose. No evidence is available to determine all-cause or CV mortality benefits with either treatment.

Safety:

One RCT reported a low incidence of hypoglycemia risk with both agents, however, provided no statistical analysis. Van de Laar et al and Bolen et al reviews based on two trials, report higher rate of side effects for acarbose, favoring metformin. For total adverse events, one study reported an odds ratio of 1:5 in favor of metformin. Van de Laar et al reviewed one RCT comparing miglitol (AGI) and metformin, in which no statistically significant differences in GI adverse events were observed.Another study reports the incidence of withdrawal from the study due to GI adverse effects was 58% for acarbose arm and 14.8% for metformin.

6. Dipeptidyl peptidase IV (DPP-IV) inhibitors

DPP-4, described in 1966 and also known as CD26 regarding its activity in immune system, is a 110 kDa plasma membrane-spanning cell surface glycoprotein ectopeptidase, ubiquitously expressed in tissues such as liver, lung, kidney, intestinal brush-border membranes, lymphocytes, and endothelial cells. DPP-4 rapidly degrades and inactivates GLP-1, GIP, and other peptides in vivo via cleavage of N-terminal two amino acids. Inhibition of this enzyme leads to an increase in circulating endogenous GLP-1 and GIP levels; so that DPP-4 inhibitors are not incretin mimetics, but incretin enhancers. Unlike other GLP-1 based therapies, can be administered orally. Sitagliptin, vildagliptin and saxagliptin are DPP-IV inhibitors that are approved as initial pharmacologic therapy for the treatment of type 2 diabetes; as a second agent in those who do not respond to a single agent, such as a sulfonylurea, metformin or a thiazolidinedione; and as a third agent when dual therapy with metformin and a sulfonylurea does not provide adequate glycemic control. The usual dose of sitagliptin is 100 mg once daily, with reduction to 50 mg for moderate to severe renal insufficiency (GFR <30 to 50 mL/min) and 25 mg for severe renal insufficiency (<30 mL/min).The usual dose of saxagliptin is 2.5 or 5 mg once daily, with the 2.5 mg dose recommended for patients with moderate to severe chronic kidney disease (GFR ≤ 50 mL/min) and for patients taking strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole). DPP-4 inhibitors mimic the therapeutic effects of incretin mimetics including stimulation of insulin secretion, inhibition of glucagon secretion, possibly preservation of β-cell mass and inhibition of apoptosis. These drugs display quite similar efficacy in lowering HbA1C (≤1% reduction) compared with other antihyperglycemic agents, but they are weight neutral and have a low potential for hypoglycaemia when used as monotherapy. One safety concern involves the potential of DPP-4 inhibitors to interfere with immune functions: a meta-analysis of pooled clinical trial data for sitagliptin and vildagliptin indicates an increased risk for infection (nasopharyngitis and urinary tract infection) and headache. Other adverse effects occurring with more frequency in sitagliptin—treated patients versus those receiving placebo include, back pain, osteoarthritis, and extremities pain

Efficacy:

Bennett et al reviewed one 12-week moderately-sized double-blind RCT compared high dose sitagliptin with maximum dose glipizide and found similar reductions in HbA1c, -0.77% versus -1.00%, for DPP-4 inhibitor and SFU, respectively. Additional studies comparing DPP-4 inhibitor or SFU add-on therapy to metformin have shown similar results for reduction of HbA1c, not favoring either agent. Evidence indicates a benefit for weight reduction with a DPP-4 inhibitor over SFU, either as monotherapy and as combination therapy with metformin. However, due to lack of direct monotherapy comparative data, unable to determine true effect. Bennett et al review of lipid profile indicated an increase in LDL and HDL with sitagliptin over SFU, while the increase in TG with sitagliptin was less than the increase with SFU (3.6% versus 7.0%). However, in all lipid measures reviewers found an overlapping CI after placebo-subtracted change from baseline in each group. There is insufficient data to determine all-cause mortality benefits for this comparison.

Safety:

Sitagliptin consistently has a better hypoglycemic profile compared to SFUs as monotherapy and as combination therapy with metformin. Additionally, reduced incidence of hypoglycemia with sitagliptin versus glipizide or glimepiride was observed during Ramadan in a multi-center study. This is a specialized patient population since observers of Ramadan abstain from food or water from dawn until dusk for the duration of the month of Ramadan. No differences in GI sideeffects have been observed with DPP-4 inhibitors and SFU as monotherapy or combination therapy.

• Glucagon-like peptide-1 (GLP-1) analogues

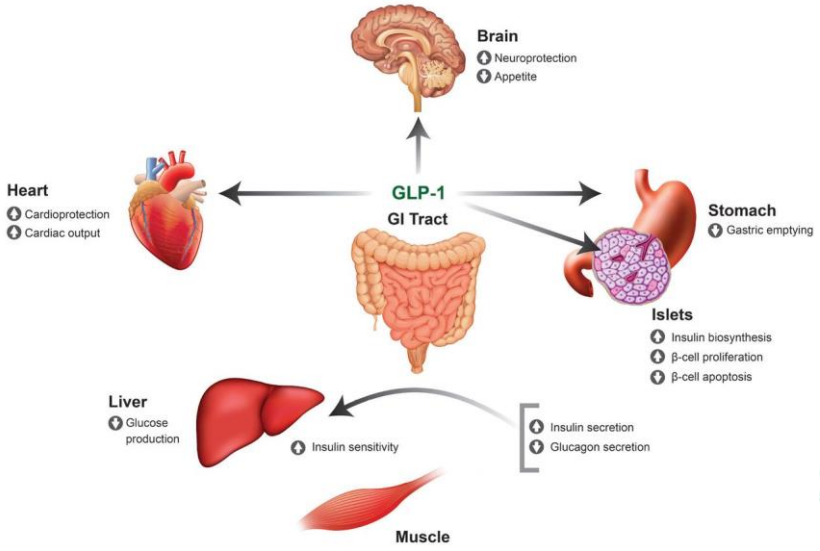
Glucagon-like peptide-1 (GLP-1) analogues are one of the more recent additions to the type 2 diabetes armamentarium and work by mimicking the incretin system to lower glucose and increase insulin. The drug class also exerts associated non-glycaemic advantages, such as weight loss. The first GLP-1 analogue was approved for use in Australia in 2007 and has been subsidised by the Pharmaceutical Benefits Scheme since 2008, yet its use remains relatively low. This article discusses the mode of action of GLP-1 analogues, their use in Australia and how to use and initiate GLP-1 analogues in people with type 2

diabetes, using case studies.Benefits Scheme since 2008, yet its use remains relatively low. This article discusses the mode of action of GLP-1 analogues, their use in Australia and how to use and initiate GLP-1 analogues in people with type 2 diabetes, using case studies.

Pharmacological Effects of GLP-1

GLP-1 has a number of potentially beneficial effects in the setting of type 2 diabetes. Intravenous administration of exogenous GLP-1 to patients with type 2 diabetes was shown to reduce plasma glucose concentrations to the normal fasting range, even in patients who had an inadequate response to oral antihyperglycemic drugs. The effects of exogenous GLP-1 observed after administration to patients with type 2 diabetes include:

- Decreased glucagon concentrations
- Improved insulin sensitivity
- Decreased A1C
- Slowed gastric emptying
- Increased satiety
- Decreased free fatty acid concentrations
- Decreased body weight



Actions of GLP-1 in target tissues. Adapted with permission GI, gastrointestinal.

Use in Combination Therapy

As dual therapy, GLP-1 receptor agonists are recommended in combination with metformin for patients who do not achieve A1C goals with metformin alone. For patients requiring triple therapy, GLP-1 receptor agonists can be combined with metformin and a sodium–glucose cotransporter 2 inhibitor in patients with persistent hyperglycemia. This triple combination is particularly well suited for overweight patients trying to control their weight. Additionally, incretin use with basal insulin may delay the use of bolus (mealtime) insulin with reduced risk of hypoglycemia. This simplified regimen reduces the need for matching mealtime insulin to specific carbohydrate ratios and also helps mitigate the weight gain often seen with insulin use. [19]

DISCUSSION

The first line of treatment is lifestyle modifications and metformin. If metformin alone cannot achieve a good glycemic control or it is not tolerated or is contraindicated, a second drug selected among the sulfonylureas, thiazolinediones, incretin mimetics and incretin enhancer drugs must be used. What is particularly relevant, anyway, is to avoid therapeutic inertia, thus therapy should be modified as soo+n as possible to keep glycemic control HbA1c at about 7%. In this second step, various factors such risk of hypoglycemia, comorbidities, age of patients, and presence of diabetic complications and cost of treatment must be properly considered to individualize treatment

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