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PHARMACOTHERAPY BASED PROBLEMS WITH THE RECENT ADVANCES IN THE MANAGEMENT OF DIABETIS MELLITUS

NAVEEN KUMAR . T[1]*, L.NAGAKRISHNA[2] ,LAKHAVAT SUDHAKAR[3] ,ANURAG THATIPALLI[4]

[1]Associate professor, department of pharmacology, Apollo Institute of Medical Sciences , Jubilee hills ,Hyderabad, A.P. India; [2]lecturer ,dep of pharmacology, Malla reddy Institute of medical sciences, hyderabad ,A.P.India;[3]NON medical assistant ,departmaent of pharmacology, Kakatiya medical college, warangal ,A.P, India;[4]Assitant professor Dept. of Forensic Medicnes , Apollo Institute of Medical Sciences ,Jubliee hills ,Hyderabad,A.P .Email- doctornaveen1@rediffmail.com

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ABSTRACT

Objectives : To review the drug treatments and some of the popular , non traditional remedies now available for type-2 diabetis mellitus, as well as selected investigational agents , to describe each medications place in the overal approach to treatment.
Material and Methods : Data source from english language journals, pharmacolgy text books, abstracts, review articles and news paper accounts.
Results :Older drugs like Sulfonyl ureas and Meglinitide analogues stimulate production and release of insulin.These drugs must be used in patients with intact pancreas and are associated with risk of hypoglycaemic .Biguanides (metformin) reduces hepatic glucose production and increases peripheral glucose utilization, but its use is hampered by a high percentage of adverse reaction like metallic taste and diarrhoea.Thiazolidinediones induce PPARɣ which express relevant genes increase glucose transport and utilization.but the disadvantage is increased risk of cardiovascular problems.£ -glucosidase inhibitors inhibit enzymes £ -glucosidases present in the intestinal brush borders and there by prevent the absorption and delay the digestion of carbohydrates .Abdominal distension and diarrhea had restricted their use.
Conclusion :. Hence there is continuous ongoing work in development of newer drugs ,which are safe ,efficacious and potent as well as free of undesirable effects such as sustained hypoglycemia. Fortunately there are newer drug , few of them approved while other still knocking the door from the classes of drug such as GLP1 Mimetic ,DPP-4 Inhibitors, SGLT-2 Inhibitors , insulin new class of drugs. Here we have tried to cover adverse effects and pharmacotherapy based problems in brief.

Key words: GLP-1 Mimetics, DPP-4 Inhibitors, SGLT-2 Inhibitors, Amylin Mimetics, Lispro insulin, Isophane insulin ,Glargine insulin.

INTRODUCTION

Modern life style with present days technological advances have made human life sedentary.This is causing increasing prevalence of obesity and physical inactivity among population.The number of cases of diabetes worldwide in the year 2000 among adults 20 years of age is estimated to be 171 million in recent reports and is said to rise to more than 300 million by 2025..Diabetis mellitus is a group of metabolic disorders characterized by chronic hyperglycemia associated with disturbances of carbohydrate , fat and protein metabolism resulting due to absolute or relative deficiency in insulin secretion, insulin action or both. The raised plasma glucose levels give rise to long term complications, dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart and blood vesels.There is an increase in the prevalence of type -1 diabetis also, but main cause of diabetis epidemic is type-2 diabetis mellitus, which accounts for more than 90 percent of all diabetis cases.The majority of cases of diabetis fall into two broad etipathogenetic categories now called type -1 and type- 2 DM. The etiologic classification of diabetis mellitus currently recommended by WHO and the ADA in 1997.

DIAGNOSIS AND CLINICAL PRESENTATION

Type 1 DM : Type 1 diabetes mellitus, results from insulin deficiency following destruction of the insulin-producing pancreatic beta cells and these patients depend on insulin for survival.On withdrawl of insulin they develop hyperglycemia ,ketoacidosis and coma.It most commonly presents in childhood but one-fourth of cases are diagnosed in adults. The genetic factors, autoimmunity and environmental factors play a role in causation and precipitation of type-1DM. Symptoms are caused by hyperglycemia and include polyuria, polydipsia, and weight loss despite increased appetite initially. The absence or poor response of glucogon stimulated C peptide levels are diagnostic of type-1 diabetis as these patients have low residual beta cell function.

Type 2 DM : Type -2 diabetis mellitus (T2DM) is the most common form of diabetes. The pathophysiological basis is a combination of impaired beta cell function , with marked increase in peripheral insulin resistance at receptor /post receptor levels and increased hepatic glucose out put production.The risk of developing T2DM increases with age, obesity, physical inactivity, and also shows strong familial tendency. C-peptide may be variable ranging from hyper to normoinsulinemic levels in a majority of the subjects.

Monitoring Of Blood Glucose :

Blood glucose testing*:* The glucose con-centration is 10-15 % higher in plasma or serum than in whole blood because structural components of blood cells are absent.

Venous blood sample : The laboratory methods commonly used for determining plasma glucose utilize enzymatic methods, colorimetric methods or automated methods.

Testing For Ketonuria /Ketonemia :

Most strips utilize a nitroprusside re-action that measures only acetone and acetoacetate. Although these tests do not detect β-hydroxybutyric acid, the semi quantitative estimation of the other ketone bodies is nonethe-less usually adequate for clinical assessment of ketonuria.

Glycosylated Hemoglobin

The major form of glycohemoglobin (HbA1C) is abnormally elevated in diabetics. Glyco-hemoglobin generally reflects the state of glycemia over the preceding 8-12 weeks, thereby providing a method of assessing chronic diabetic control[1].

Diagnostic Criteria

The diagnosis of diabetes mellitus is based on measuring venous plasma glucose in the fasting state and 2 hours after a 75 gram glucose load (recommended by the WHO). The details of the diagnostic criteria are given in Table 1.

In case of an abnormal test result, the test should be repeated on a different day.

Oral glucose tolerance test (OGTT) is recommended by WHO for epidemiological purposes.

Table 1: Diagnostic criteria for diagnosis of Diabetis Mellitus.

Category	WHO	ADA
Impaired fasting glucose (IFG)	100 to < 126mg/dl	100 to < 126mg/dl
Impaired glucose tolerance (IGT)	2hr post glucose > 140 mg/dl and < 200mg/dl	2hr post glucose > 140 mg/dl and < 200mg/dl
Normal	FPG =100mg/dl and PP < 140 mg/dl	FPG =100mg/dl and PP < 140 mg/dl

Management

Diabetes mellitus is condition associated with number of complications including coronary heart disease, retinopathy, neuropathy etc. It is now clear that tight control of blood glucose significantly reduces the risk of complications of diabetes.

Management Of Type 2 Diabetis Mellitus

Non- Pharmacological therapy : Non-pharmacological measures including diet, exercise and stress alleviation are importantinterventions for the management of diabetes.

PHARMACOLOGICAL THERAPY OF NEWER DRUGS

Oral agents(Newer drugs) for the treatment of hyperglycemia :

The mechanism of action of newer drugs for treating type-2 diabetis mellitus (T2 DM) can be divided into three categories :

1. Oral inhibitors of the enzyme dipeptidyl peptidase-4(DDP-4) which is widely expressed in many tissues, including kidney,liver, lung, and the small intestine Eg: Incretin mimetics.
2. Drugs that is used in type-1 diabetis mellitus (T1DM) on intensive insulin regimens is the injectable drug that suppresses glucagon secretion from pancreatic α cells ,there by attenuating hepatic glucose production. Eg:Amylin analogs.
3. Drug that mediates 90% of filtered glucose reabsorption in the convoluted segment of the proximal renal tuble.Eg;Sodium glucose co-transporter-2 inhibitors.
4. Insulin analogues given parenterally which cause glucose utilization Eg: Short acting, intermediate and long acting insulin preparations.

INDIVIDUAL DRUGS

Incretin Mimetics : includes Exenatide, sitagliptin, vidagliptin.

Exenatide : long acting analogue (resistant to DPP -1V degradation) obtained from Gila monster. Exenatide is approved solely for use in combination of metformin and a sulfonylurea, or the combination of metformin with a thiazolidinedione in resistant cases of type-2 diabetis mellitus patients [2],[3].It reduces only post meal glucose rise [4]. It is administered as a subcutaneous dose injection typically twice daily in doses of 5 to 10µg.

Adverse effects : In in vitro animal models ,GLP-1 and its analogues are associated with proliferative effects on pancreatic β cells [5]. Progressive islet dysfunction is a recognized phenomenon in T2DM and results in the eventual loss of glycemic control over time. In addition to functional abnormalities, an actual decrease in β-cell mass also has been demonstrated,likely the result of increased apoptosis combined with decreased regeneration [6].Therefore, any agent that alters this balance may delay or prevent the decline in insulin secretory capacity, potentially allowing a more durable effect on glucose control than conventional agents, most of which are associated with substantial therapeutic attrition over time. This hypothetical effect of the GLP-1 mimetics, however has not yet been demonstrated in long-term clinical trials.

Side effects of exenatide include nausea and vomiting, particularly at the initiation of therapy. Recently, postmarketing reports of pancreatitis occurring in exenatide-treated patients have emerged, with most patients having at least one risk factor for this condition. A causal association with exenatide is not clear. Because of its glucose-dependent effect, exenatide does not increase the risk of hypoglycemia.

Among patients with T2DM requiring insulin therapy, exenatide exhibits less potent HbA1c reduction compared with its combination with oral agents an expected observation because such individuals tend to be more insulin deficient with less available insulin secretory reserve[7].

Cardiovascular Impact Of Incretin Mimetics

GLP-1 receptors have been demonstrated in cardiac myocytes and in certain regions of the brain that regulate autonomic function[8].

In animal models, GLP-1 receptor agonists have been reported to increase blood pressure and heart rate as a result of activation of sympathetic outflow[9].

In addition to this chronotropic effect, a positive inotropic effect also has been attributed to direct myocardial activity. Clearly, long-term safety data are required before we fully understand any potential benefits (or risks) to the cardiovascular system from exenatide and other GLP-1–based therapies.

DPP-4 Inhibitors

Sitagliptin (100mg od before meals) or Vildagliptin (50mg, od before meals) are orally active selective inhibitors of DPP-4 enzyme there by enhancing meal-related circulating concentrations of biologically active GLP-1and GIP.They are used along with metformin and /or sulfonylureas for resistant cases of type -2 diabetis mellitus patients. DPP-4 inhibitors increase effective incretin levels into a more physiological range [10]. Their metabolic effects include the glucose-dependent stimulation of pancreatic insulin secretion and suppression of glucagon output[11].

The current members of this class that are either available for clinical use (sitagliptin) or in advanced phases of development (vildagliptin, saxagliptin, alogliptin) have reasonably high selectivity for DPP-4, and few adverse effects in humans have been demonstrated thus far in clinical trials [12], [13] ,[14].

As mentioned ,the DPP-4 inhibitors appear to be ,at least at the early point in their development, reasonably safe medications [15].

Recently, postmarketing reports of anaphylaxis, angioedema, and rashes, including Stevens-Johnson syndrome, in sitagliptin-treated patients have emerged. A causal link to the drug, however, is not known.

Other adverse effects include nasopharyngitis (because substance –P is also asubstrate for DPP-4 whose level gets elevated),git distress and diarrhea.Successful sitagliptan therapy requires adequate levels of GLP-1 which may not be feasible inpatients taking strict carbohydrate free diet[16].

Amylin Mimetics

Another new antihyperglycemic used predominantly by patients with type 1 diabetes mellitus (T1DM) on intensive insulin regimens, is the injectable pramlintide. Pramlintide is a synthetic analogue of human amylin, a β-cell peptide co-secreted with insulin [17]. Amylin mimetic have the same actions of amylin a protein that is normally produced by the pancreas. Amylin slows down the movement of food through the intestine .This slows down the absorption of glucose from the intestine ,which reduces sudden increase in blood glucose.

Amylin is used (15-60µg s.c before meals as an adjuvant to insulin in type-1 diabetis mellitus cases) with insulin in insulin requiring type-2 diabetis mellitus patients [18]. Because of the effects on satiety and gastric emptying, hypoglycemia may occur in patients also receiving insulin. Accordingly, the prandial insulin dose should be pre-emptively reduced when pramlintide is initiated.

The role of pramlintide in the therapy of type-2 diabetis mellitus is not clear. Because pramlintide requires thrice-daily self-injections (which cannot be combined in the same syringe as

insulin), it is unlikely to play a major future role in the management of type-2 diabetis mellitus. The most frequent and severe adverse effect of pramlintide is nausea which occur mostly at the beginning of treatment and gradually reduces .Other adverse effects are diarrhea and headache.

Conclusion : while prescribing new drugs for diabetis careful supervision ,especially for Exenatide which is commonly prescribed especially cvs and git adverse effects should be taken in to consideration for type-2 diabetis mellitus patients, and amylin mimetic pramlitide for type-1 diabetis mellitus patients for risk of hypoglycemia with insulin .

Sodium Glucose Cotransport 2 Inhibitors

SGLT-2 inhibitors (eg;dapaglifozin, serglifozin and remoglifozin) are newer antidiabetic drugs that have successfully cleared phase -111 clinical trials.

Adverse Effects

Increased urine volume (up to 400 ml) was observed in clinical studies with dapagliflozin, associated with increased hematocrit and urea, suggesting slight volume depletion. Electrolyte imbalance is also a consideration because physiological studies have shown increased sodium loss with as sodium -glucose cotransporter has been inhibited. A phase II trial reported one case of dehydration and prerenal azotemia, which resolved with oral rehydration and withholding angiotensin-converting enzyme inhibitor and diuretic therapy [19].

Whether patients with diabetes mellitus who have neuropathy, hyporeninemic hypoaldosteronism, and nephropathy could be rendered more vulnerable to sodium wasting and hypovolemia will need to be assessed further. A statistically significant increase in magnesium (0.18 ± 0.16 mEq/liter; $P < 0.001$) and decrease in uric acid levels (−1.14 ± 1.15 mg/dl; $P < 0.001$) were reported in a phase II trial with dapagliflozin compared with placebo. In terms of bone metabolism, an increase in parathormone concentration (range, 0.6–7.0 pg/ml above baseline of 31.1–35.0 pg/ml) has been noted, which was greater than the 0.8 pg/ml increase than placebo. There was no change in serum 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D values from baseline, and the mean changes in the 24-h urinary calcium-to-creatinine ratio were similar to those with placebo [20].The long-term effects on bone health will also need to be clarified by ongoing phase III trials.

The apparent presence of SGLT2 in the placenta does raise concern about its safety in women of child-bearing age.Another important question is whether increased glucosuria would predispose to UTIs or genital fungal infections.

In vivo studies have not shown a higher prevalence of bacteriuria among diabetic patients with glucosuria compared with patients without glucosuria. Defects in the local urinary cytokine secretions and an increased adherence of the microorganisms to the uroepithelial cells have been proposed to increase the incidence of UTI in patients with diabetes[21], [22].

This suggests that risk of UTI may not be increased in patients taking SGLT2 inhibitors, and this has been borne out by the available clinical data.

Symptomatic vulvovaginal candidiasis is more prevalent in patients with diabetes compared with the normal population [23], [24].But it is unknown whether circulating glucose concentrations or the presence of glucosuria is the critical factor.

INSULINS

Management of Type -1 diabetis mellitus

Insulin is the only therapy available for patients with type 1 diabetes.Insulin replacement in patients with type 1 diabetes has been less than optimal because it is not possible to completely reproduce the normal physio-logic pattern of insulin secretion into the portal vein. The problem of achieving optimal insulin delivery remains unsolved with the present state of tech-nology. Immunogenicity has been markedly reduced with the use of highly purified hu-man insulin preparations, thereby reducing complications associated with impure insulins. Human insulin is now been produced by recombinant DNA technology. All human and pork insulins currently available are “purified.” The more highly purified insulins currently in use preserve their potency quite well; therefore, refrigera-tion while in use is not necessary. Four principal types of insulin are available: (a) Short-acting insulin, with rapid onset of action; (b) Intermediate-acting insulin; and (c) Long-acting insulin, with slow onset of action (Table 2). [25].

Table 2 : Characteristics of newer insulin preparations.

	Type	On set	Peak (hr)	Duration of action (hr)
Rapid acting	Lispro	5-15 min	1	3-5 hrs
	Aspart	10 -15 min	1	3-5 hrs
	Glulisine	5 – 15 min	1	5-6 hrs
Intermediate acting	Isophane	2 hrs	1 hr	16-18 hrs
	Lente	2 hrs	1 hr	16-20 hrs
Long acting	Glargine	1 -2 hrs	No peak	24 hrs
	Detemir	2-3 hrs	6-8 hr	24hrs

COMMON ADVERSE REACTIONS ASSOCIATED WITH NEW INSULIN PREPARATIONS

General

Hypoglycemia, hypokalemia, lipodystrophy and hypersensitivity are among the potential clinical adverse effects associated with the use of all newer insulin preparations.

Hypoglycemia and Hypokalemia-Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control . Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia. Severe hypoglycemia can result in temporary or permanent impairment of brain function and death. Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Since intravenously administered insulin has a rapid onset of action, increased attention to hypoglycemia and hypokalemia is necessary. Therefore, glucose and potassium levels must be monitored closely when insulin is administered intravenously.

Allergy

Local Allergy - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of insulin.

Systemic Allergy - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.

Laboratory tests : As with all insulin therapy, the therapeutic response should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin recognition and management of hypoglycemia and hyperglycemia, adherence

to meal planning, complications of insulin therapy is recommended for the monitoring of long-term glycemic control. Urine ketones should be monitored frequently.

Renal /Hepatic/Biliary/Pancreatic impairment:

The dose of insulin preparations need to be reduced in patients with diabetes and hepatic or renal impairment and careful glucose monitoring may be necessary due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Disadvantages And Important Adverse Effects With Short Acting Insulin Preparations

Short acting insulins should only be used if it is clear and colorless. Due to the risk of precipitation in some pump catheters short acting insulins is not recommended for use in insulin pumps.

Hyperglycemia, diabetic ketoacidosis, or diabetic coma may develop if the patient takes less short acting insulins than needed to control blood glucose levels. This could be due to insulin demand during illness or infection, neglect of diet, omission or improper administration of prescribed insulin doses. A developing ketoacidosis will be revealed by urine tests which show large amounts of sugar and acetone. The symptoms of polydipsia, polyurea, loss of appetite, fatigue, dry skin and deep and rapid breathing come on gradually, usually over a period of some hours or days. Severe sustained hyperglycemia may result in diabetic coma or death.

Disadvantages Of Existing Intermediate Acting Insulin Preparations

The most widely used intermediate-acting human insulin is isophane insulin (NPH insulin), which is administered twice daily in many cases to provide a 24-h basal insulinemia. However, because regular insulin or short acting insulin has a duration of action of more than 8 h in some patients, three mealtime injections during the day can compensate for the insulin waning effect of a single isophane insulin at night. With the introduction of the short-acting monomeric form, the too-short duration of action of isophane insulin has become obvious. In a study in 66 type 1 diabetic patients treated with lispro insulin(short acting) at mealtime, isophane insulin injections were based on blood glucose determinations before main meals. After 5 months, there was a 43% increase in the isophane dose, and the number of isophane injections increased from a mean of 1.4 to 3.1 per day compared with the previous regimen using regular insulin before meals [26].

The number of injections of isophane insulin might not be so important to achieve a constant 24-hr basal insulinemia, apart from patient comfort and convenience. However, the action profile of isophane insulin, with its peak action observed 5–7 h after injection might be much more of a concern [27].This means that isophane insulin injected at 10:00 p.m. would result in its maximum hypoglycemic action at 3:00–5:00 a.m., a time when insulin requirements are low. Indeed, nocturnal hypoglycemia occurs in a disproportionately high number, 50%, of all hypoglycemia events in type 1 diabetic patients [28], [29]. A decrease in the night time isophane insulin dose might overcome nocturnal hypoglycemia but as a consequence emphasizes the relative insulin deficiency between 5:00 and 8:00 a.m. at a time where insulin sensitivity decreases [30]. The well-known overall effect of this isophane insulin shortcoming is morning fasting hyperglycemia.

The diurnal blood glucose profile of diabetic patients with insulin therapy varies considerably and can be accounted for to a large extent by the high intrasubject and intersubject variability of absorption[31], [32]. The variability is more pronounced with intermediate- and long-acting insulin formulations than with short-acting insulins [33], [34] .

Disadvantages And Important Adverse Effects With Glargine (Long acting insulin preparations)

Insulin glargine is produced by recombinant DNA technology utilizing a non pathogenic laboratory strain of Escherichia coli.It is indicated for once daily subcutaneous administration in the treatment of patients over 17 years of age with Type 1 or Type 2 diabetes mellitus who require basal (longacting) insulin for the control of hyperglycemia. Glargine is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue and may delay recovery from hypoglycemia. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. Glargine must not be mixed with any other insulin or diluted with any other solution. If glargine is diluted or mixed, the solution may become cloudy, and

the pharmacokinetic/ pharmacodynamic profile (e.g., onset of action, time to peak effect) of glargine and/or the mixed insulin may be altered in an unpredictable manner.

Antibody Production: Insulin administration may cause insulin antibodies to form. In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed in both intermediate (NPH) human insulin and insulin glargine treatment groups with similar percents of increased and decreased titers.Such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycemia or hypoglycemia.

Transfering Patients From Other Insulins

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, timing of administration, manufacturer, type (e.g., regular, intermediate, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted. As with all insulins, when transferring to glargine, the early warning symptoms of hypoglycemia may be changed, be less pronounced, or absent.

CONCLUSION

The availability of new options for diabetis therapy provides a chance for successful therapy in a large number of patients.How ever it is important to consider how much true benefit these new forms of treatment will have on the diabetic community.The best choice for a patient remains controversial.

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