Clinical Forum

Drug therapy of type 2 diabetes mellitus in the new millennium

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Abstract

The incidence of type 2 diabetes mellitus is increasing due to changing life-styles. Today the slogan of all diabetologists is "strict glycaemic control" to prevent long term diabetic complications. The traditional agents- sulphonylureas, biguanides and insulin sometimes fail to achieve the recommended goal. However, newer insulin secretagogues (glimepiride, repaglinide, glucagan like peptide-1 agonists), drugs decreasing insulin resistance (thiazolidinediones), agents slowing carbohydrate absorption (miglitol, amylin analogues) and newer insulins (insulin lispro) have been developed for the management of type 2 diabetes mellitus. With the advent of these newer drugs, management of type 2 diabetes promises to scale new heights in the new millennium.

Keywords : *Type 2 diabetes, drugs, glycaemic control*

Type 2 diabetes mellitus (DM) is a common disorder associated with high morbidity and mortality. In developing countries its incidence is steadily increasing due to rapid changes in lifestyle. It is a heterogenous disorder and both environmental and genetic factors work in tandem in its pathogenesis. The impaired glucose homeostasis is the result of a dynamic interaction between insulin secretion and insulin action.[1] Lifestyle alterations such as modification in diet, patient education and regular physical activity remain important in the management of type 2 DM. Yet, in majority of patients drug therapy is often required. Failure of glycaemic control with the traditional agents - sulfonylureas, biguanides and insulin, paved the way for synthesis of newer agents. A number of these agents have already been marketed and several others are undergoing clinical trials. The new millennium promises to bolster the armamentorium with new antidiabetic agents. This article aims to review the traditional drugs and to give an overview of the newer agents for the management of type 2 DM

Received on: 19th October 1999
Accepted on: 23rd February 2000

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Sulphonylureas

These agents stimulate insulin secretion by interacting with specific receptors on the ß cell membrane by the closure of ATP sensitive potassium channels with the resulting depolarisation allowing influx of calcium ions into ß cells, thus triggering the release of insulin containing secretory granules.[2] Besides release of insulin, several extrapancreatic effects of sulphonylureas like lowering of insulin resistance have

also been described.[3] However, this mode of action of sulphonylureas remains controversial. Patients with type 2 DM have a combined insulin resistant as well as insulin deficient state. The sulphonylureas provide the rational choice to begin treatment in such patients. In responsive patients, glycated hemoglobin (HbA1c) is reduced by 1-2%. But subjects with high fasting blood glucose and obesity (BMI >=27 kg/m²) are less successful in attaining good glycaemic control with sulphonylureas. About 10% of type 2 DM patients per year fail to respond to sulphonylurea therapy[4] and this secondary sulphonylurea failure rate rises with increasing duration of diabetes.

The issue concerning choice of various sulphonylureas is beyond the scope of this article. Recently, interest has been focussed on the advantages and disadvantages of long acting agents used once daily versus short acting agents used three times daily. Glibenclamide and chlorpropamide are long acting agents with potent and prolonged hypoglycemic effect, while short acting sulphonylureas (tolbutamide, glipizide, gliclazide) require frequent dosing.[5] However, glipizide has been introduced in a slow-release form for once-daily administration and may improve patient compliance.[6] Also there is no consensus on maximum doses of various sulphonylurea preparations. Recent data indicate that maximum effect is reached even at lower doses.[7] The major adverse effect is hypoglycemia seen especially in the elderly.[8] It is more common with glibenclamide and chlorpropamide and is aggravated in the presence of alcohol consumption, inadequate food intake, renal impairment and use of drugs which potentiate effects of sulfonylurea e.g. fibrates, non-steroidal anti-inflammatory drugs etc.[9] Another major adverse effect is increase in body weight. Earlier, the University Group Diabetes Programme (UGDP) study[10] had raised the question of cardiovascular safety of sulfonylurea in diabetic patients. However, the recently concluded United Kingdom Prospective Diabetes Study (UKPDS) did not demonstrate any increase in cardiovascular mortality in this group of patients.[11]

Metformin

Metformin is a biguanide which improves insulin sensitivity by the reduction of fasting blood glucose and insulin levels. However, it is not effective in the absence of insulin. In type 2 DM it may decrease hepatic glucose output, increase peripheral utilisation of glucose, reduce fatty acid oxidation, increase the number of GLUT 4 (allows transport of glucose into muscular and adipose cells) and decreased alimentary glucose absorption. It has a favourable action on various disorders associated with insulin resistance such as high triglyceride levels, reduced HDL and high plasminogen activator inhibitor (PAI-1) levels seen frequently in type 2 DM with abdominal obesity.[12]

As obese type 2 DM is associated with insulin resistance, metformin therapy may be more appropriate in such circumstances. Recent observations suggest that it may also be useful in non-obese type 2 diabetic patients. Recent metformin therapy trials have demonstrated a decline in HbA1c by 1.7 to 1.8%.[13] The UKPDS group observed similar improvement of glycaemic control with metformin as that obtained with sulfonylureas or even once daily insulin therapy.[14]

Adverse effects are mainly gastrointestinal which include nausea,

bloating, diarrhoea and abdominal cramping. These side effects may disappear with time in many patients. Hence the dosage (taken with meals) may be progressively increased from 500-850 mg/day to 1500-1700 mg/day[15]. In contrast to sulfonylureas no gain in body weight is observed. Lactic acidosis is also an uncommon complication when compared with phenformin.[16] The drug is excreted by the kidneys and is contraindicated in patients with renal disease (serum creatinine >1.5 mg/dl) liver disease, and cardiac or respiratory insufficiency.[16,17] According to some authors the drug should not be used in the elderly (beyond 65-70 years).[18]

Acarbose

Alpha(α) glucosidase inhibitors (of which Acarbose is the prototype) bring about a dose-dependent inhibition of glucosidase enzyme of the small intestine which is responsible for the breakdown of non-absorbable monosaccharides. This leads to reduced and delayed rise in post-prandial blood glucose and insulin levels. Because these drugs do not cause hypoglycaemia, they should be called oral antidiabetic agents and not oral hypoglycemic agents. Acarbose is a pseudo-tetrasaccharide of microbial origin. In patients with type 2 DM treated with diet, sulfonylurea or insulin, it brings about a reduction in postprandial blood glucose and HbA1c levels, reduces plasma insulin responses, and improves indices of blood glucose stability without inducing hypoglycaemia.[19]

Gastrointestinal intolerance such as flatulence, diarrhoea and mild pain in the abdomen are the major adverse effects. The intolerance is caused by the osmotic effect and bacterial fermentation of undigested carbohydrates in the distal bowel. In order to improve drug compliance, dosage has to be increased very slowly.

Insulin

Several aspects of insulin therapy still remain controversial and why, when and how to prescribe insulin in patients with type 2 DM is still not clear. In type 2 DM, ongoing beta cell damage culminates in the decline of insulin secretion and insulin secretagogues are no more effective and fail to evoke the desired insulin release. Thus, exogenous insulin therapy is the rationale to compensate for the secretory failure of the beta cells in the presence of marked insulin resistance. Hence insulin therapy may be used as an alternative to oral drugs after sulfonylurea failure or when oral agents are contradicated.[20] The use of single morning intermediate acting insulin has been challenged and several authors prefer bedtime insulin in combination with sulfonylureas.[20] UKPDS demonstrated that once daily insulin was effective and acceptable initial therapy after diet failure.[14] Sometimes twice or multiple injections may have to be used and the feasibility and benefits of intensive insulin therapy in type 2 DM have been clearly demonstrated.[21]

The major adverse effects of insulin therapy are an increase in body weight and hypoglycaemia. Perhaps the concern for hyperinsulinaemia induced atherosclerosis was overemphasised in the past.[22] The "Diabetes mellitus Insulin - Glucose infusion in Acute Myocardial Infarction (DIGAMI)" study documented a beneficial cardiovascular effect of intensive insulin therapy in the year following myocardial infarction.[23] Similarly UKPDS found no increase in cardiovascular events or mortality with insulin therapy.

Combined Therapy

Four major classes of conventional agents (sulfonylureas, biguanides, α-glucosidase inhibitors and insulin) are available for the management of type 2 DM. To achieve ideal glycaemic control, these drugs may be used individually or in combination in a stepwise fashion. Recently there has been renewed interest in combination therapy. Of these, combinations of sulfonylurea and insulin especially at bedtime have been most extensively studied.

Insulin-metformin combination may be tried in obese subjects to reduce insulin resistance.[24] Acarbose-insulin combination helps to reduce blood glucose fluctuations, especially post-prandial hyperglycaemia and late hypoglycaemia.[25] Some authors have advocated the use of "triple therapy" i.e. a combination of bed time insulin along with sulfonylurea and biguanides.[26]

Newer Approaches

While a number of pharmacological approaches are currently available, none are ideal for the management of type 2 DM. The old adage “necessity is the mother of invention” is clearly exemplified by the generation of new drugs aimed to increase insulin release, improve insulin sensitivity and delay carbohydrate absorption.

I Insulin Secretagogues

(a) New sulphonylurea compounds

Glimepiride is a new sulphonylurea compound which binds to a different protein of the sulphonylurea receptor and has a similar insulin secretory action like glibenclamide.[27] The effect of once daily oral administration is similar to that of twice daily regimen, hence is used in dosages of 1, 4 and 8 mg once daily, which induces an effective hypoglycaemic effect and has a good safety profile in type 2 DM patients.[28] Glimepiride is a pancreas selective agent having a specific effect on potassium regulated ATP channels (K-ATP) in pancreatic islet cells with no effect at cardiovacular, K-ATP channels.[29]

(b) Nonsulphonylurea Insulin Secretagogues

Repaglinide, a member of the meglitinide family is a non-sulphonylurea hypoglycaemic agent. It regulates ATP sensitive potassium channels via a different binding site from the sulphonylurea receptor. The plasma concentration is rapidly increased due to the rapid and complete absorption of the drug from the gastrointestinal tract. It is metabolised in the liver and excreted via bile and its metabolites have no hypoglycaemic effects. The plasma half life of the drug ($t_{1/2}$) is < 1 hour, hence it can be used in patients with impaired renal function.[30]

YM-026, a stereoisomer of phenylalanine derivative, has been developed in Japan.[31] Compared to sul-phonylureas, it has a rapid hypoglycaemic action and has a shorter duration. BTS-67582, another novel agent decreases fasting and postprandial hyperglycaemia, reduces HbA1c, in a dose dependent manner in type 2 DM patients.[32]

(c) α_2 Adrenergic Antagonists

It has been observed that adrenaline acts on ß cells of pancreas and decreases insulin secretion. α_2 blockers increase glucose-induced insulin secretion in both nondiabetic and type 2 DM individuals. However, the hypoglycaemic effect may be due to interaction with ATP sensitive potassium channels in beta cells similar to sulfonylureas.[33] Besides, these agents can menacingly increase blood pressure.

Therefore, as a class of hypoglycaemic agents they are less attractive.

(d) Glucagon-like Peptide-1

Glucagon-like Peptide-1 (GLP-1) is a fragment of proglucagon molecule and has two shorter forms, 7-36 and 7-37 amides which are strong glucose dependent stimulators of insulin release. GLP-1 is a hormone released post-prandially from the lower intestines which potentiates insulin secretion and reduces gastric emptying rate. It promotes insulin release even after sulfonylurea failure in type 2 DM patients.[34] No hypoglycaemia is observed as insulin release is glucose dependent.[35] The major drawbacks are parenteral mode of administration and short duration of activity. Hence once daily injection of slowly absorbable GLP-1 or transdermal/transepithelial adminis-tration would overcome these drawbacks. Alternately, in future we may have oral nonpeptide agonists of GLP-1 receptor.[34,35]

II Agents decreasing Insulin Resistance

(a) Thiazolidinediones

These are a new class of compounds which enhance insulin action and promote glucose utilisation in peripheral tissues without any effect on insulin secretion. They act as agonists of the nuclear receptor, peroxisome proliferator activator (PPAR)-gamma.[36,37] Several compounds of this class have been developed such as pioglitazone, darglitazone, ciglitazone, englitazone, troglitazone, rosiglitazone etc.

Troglitazone, administered orally in dosage of 200 mg bid improves insulin resistance and glucose tolerance in obese individuals and type 2 DM.[37] In clinical trials troglitazone achieved significant reduction in fasting blood glucose, glycated haemoglobin and plasma insulin values without weight gain or hypoglycaemia. Although the drug is generally well tolerated, it may be associated with serious idiosyncratic hepatic cellular injury, necessitating regular monitoring of liver functions. Besides this, nausea, vomiting, abdominal distension, diarrhoea and anaemia may adversely affect patient compliance.

(b) Lipid interfering agents

A large majority of type 2 DM patients are obese with presence of increased non-esterified fatty acid (NEFA) levels which may contribute to hyperglycaemia by impairing peripheral glucose disposal and enhancing gluconeogenesis. Antilipolytic agents reduce concentration of NEFA by decreasing production and/or oxidation of NEFA and may improve the glycaemic control especially in obese type 2 DM.[38] Long term trials with antilipolytic agents such as nicotinic acid have been disappointing. Nevertheless, interfering with fatty acid oxidation remains an interesting approach to correct one of the metabolic abnormalities in type 2 DM.

(c) Glucagon Antagonists

Elevated glucagon levels in diabetes contributes to hyperglycaemia by stimulating hepatic glucose output. Therefore, blockade of glucagon action is an attractive approach to attain normoglycemia. The action of glucagon may be inhibited by 1) blocking synthesis and secretion of hormone; and 2) receptor blockade.[39] Presently no suitable compounds are available with any of the above mentioned features. But in future, such agents might be an important addition to antidiabetic agents.

(d) Vanadium Compounds

These compounds have insulinomimetic properties. Amongst the several biological effects of vanadium, it has been shown to stimulate glucose uptake, glycogen synthesis, glucose oxidation in adipose tissues and skeletal muscles. These compounds have been effective in obese but not in non-obese type 2 DM.[40] Gastrointestinal symptoms are the major adverse effects.

(e) Anti Tumour Necrosis Factor α Agents

Studies suggest that overproduction of tumour necrosis factor (TNF) α agents may contribute to impairment of insulin action. TNF-α may be a major component of the obesity-DM molecular link.[41] Favourable results with anti TNF α agents have been obtained in rodents but have not been substantiated in human studies.[42]

III Agents Slowing Carbohydrate Absorption

(a) 1-Deoxynojirimycin Derivatives

Miglitol derived from 1-deoxynojirimycin is structurally similar to glucose. Its effect on gastrointestinal glucosidase enzymes is similar to acarbose but unlike the latter it is completely absorbed from the gastrointestinal tract. No pancreatic or extrapancreatic effects have been demonstrated. In type 2 DM patients with suboptimal glycaemic control with conventional therapy, miglitol 50 mg three times daily may be an effective adjuvant therapy.[43] Presently it is undergoing clinical trials.

(b) Amylin Analogues

The ß cells of pancreas secrete not only insulin but also amylin, a 37 amino acid polypeptide.[44] Pramlintide, a synthetic human amylin has been utilised for clinical study. It is hypothesised that it exercises its effects by decreasing gastric emptying rate and slowing the absorption of nutrients. After iv/sc administration it prevents the rise in blood glucose after a mixed meal but not after intravenous glucose. The need for three times daily injection and significant gastrointestinal side effects are the limiting factors of Pramlintide therapy.

IV Newer Insulins (Insulin Lispro)

A high incidence of hypoglycaemia is observed even with regular insulin because of its property to self-aggregate into hexamers, resulting in a slow absorption from subcutaneous tissues with a peak action at 2 hours and duration of activity as long as 6-8 hours. There have been several attempts to create an insulin which will not self aggregate and will exist in monomer form, get absorbed quickly and dissipate rapidly to mimic a physiological release of insulin. Insulin lispro, the first such "designer" insulin has been created by reversing the amino acid sequence of human insulin at B-28-29 from proline-lysine to lysine-proline. Its major feature is its quick onset and short duration of action, which allows a better post-prandial diabetic control with a lower incidence of hypoglycaemia. An additional advantage is that it can be administered just before meals or even after meals and allows greater flexibility and convenience to the patient.[45]

Conclusions

Management of type 2 DM has been a complex issue for physicians over the decades, but with the introduction of newer agents the scene is changing rapidly. It is conceivable that with the increase in the number of antidiabetic agents, combined therapy with a multi-pronged approach will gain momentum.

Numerous pharmacological agents are presently under investigation. Hence in the future, physicians will have a wider choice in selecting a suitable antidiabetic regime for type 2 DM patients.

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