Newer Oral Antidiabetic Agents

VS Reddy*, RK Sahay*, SK Bhadada*, JK Agrawal**, NK Agrawal***

Type 2 diabetes constitutes more than 95% of diabetic patients in our country. Its prevalence is constantly increasing and has already reached epidemic proportions, particularly in urban India. Possibly by the year 2025 India shall have approximately 57.2 million diabetics, the maximum number of diabetics in any one country. The long asymptomatic phase of type 2 diabetes gives a general misconception that it is a mild disease and the apathy towards treatment leads to a grim scenario, where 15-20% of patients present with micro/macrovacular complications at the time of diagnosis. The dreaded microvascular complications of diabetes are related to the degree of metabolic decompensation and can be prevented or postponed by achieving persistent and tight metabolic control. The need for achieving better control has been evident from the DCCT results. However, it is not easy to achieve this goal of persistent and tight metabolic control in a large proportion of patients. This is partly due to limitations of currently available modalities of treatment, and partly due to patient’s non-compliance with prescribed antidiabetic medications as well as with diet and exercise prescriptions. The initial treatment of type 2 diabetes has always been optimisation of diet and physical activity. However, the benefits of non-pharmacologic therapy are ill sustained with less than 10% patients maintaining an acceptable long term glycaemic control.

Currently available sulfonylureas (SU), the most commonly used pharmacologic agents in treatment of type 2 diabetes, have gradually increasing secondary failure rates reaching 50% at the end of 5 years of disease, though the initial response is good in 70-75% of patients. The biguanides are mainly used as adjuvants to sulfonylureas. The gastrointestinal intolerance limits their use in many patients. Thus, large number of patients with type 2 diabetes fail to achieve persistent good metabolic control. In the U.K. Prospective Diabetes Study (UKPDS) 28% and 53% of drug treated type 2 diabetes patients had a fasting plasma glucose concentration more than 140 mg % after 3 and 6 years and irrespective of mode of therapy, a steady increase in HbA1C was seen over 9 years follow-up.

The limitations of currently available pharmacological agents for control of blood glucose has stimulated research on novel antidiabetic agents with different mechanism of action. The magic word ‘CURE’ is no longer elusive and prevention is very much on the cards. Indeed for those who already have diabetes and are suffering with complications, much can be offered in the new millennium. The newer drugs, already developed or in the process of development for management of type 2 diabetes can be classified into (1) Insulin secretagogues, (2) Insulin sensitisers, (3) Drugs delaying GI glucose absorption, (4) Inhibitors of intermediary metabolism, (5) Insulinomimetic drugs. (Table I).

Table I : Newer Antidiabetic Agents in The New Millenium

1. Insulin secretagogues
   Newer sulphonylureas – glimeperide
   Non-sulphonylureas – repaglinide
   GLP-1
   GLP-1 receptor agonists (extendin 9-39)/DPP-IV
   Amylin antagonists
   Others
2. Insulin sensitisers
   - Biguanides
   - PPAR(α) antagonist – fibrates
   - PPAR(γ) antagonists – thiazolidinediones
   - Protein tyrosine kinase inhibitors – CLX 0300/0301/0900/0901
   - Antiobesity drugs
   - B-3 receptor antagonists

3. Inhibitors of intermediary metabolism
   - Antilipolytic and antihyperlipidaemic drugs
     - Fatty acid oxidation inhibitors (Lisophyllin)

4. Inhibitors of GI glucose absorption
   - Glucosidase inhibitors
     - Amylin analogues (Pramlinitide)

5. Insulinomimetic drugs
   - Vanadium salts

---

**Insulin secretagogues**

**New SU insulin secretagogue: Glimeperide**

This is a third generation SU which binds to a 65 kd protein of the putative SU receptor different from the 140 kd protein targeted by other SU's. It has a three fold faster rate of association and nine fold faster rate of dissociation than glibenclamide and thus has rapid onset and prolonged duration of action, permitting once daily administration. Though its initial action is stimulation of insulin secretion, it has also an insulin-mimetic effect in peripheral tissues possibly mediated by GLUT-4 recruitment. The extrapancreatic effects may explain lesser degree of stimulated hyperinsulinaemia. Unlike glibenclamide, this drug prevents post-exercise insulin release, thereby decreasing the risk of hypoglycaemia. It is absorbed completely in either fasting or fed state. It does not accumulate in the body with reducing renal function (upto GFR 10 ml/min) and its hydroxy metabolite has negligible effects on blood glucose and are excreted equally by the liver and kidney. Hence it is safe in renal failure and in the elderly. It does not exhibit any drug interaction and because of its poor binding to extrapancreatic, myocardial, and vascular system ATP dependent K+ channels, the risk of coronary vasoconstriction and adverse cardiovascular events are reduced in comparison to other SU's. On a weight for weight basis glimeperide is the most potent SU with suggested doses between 1-6 mg once daily, but doses upto 8 mg may give additional glucose lowering effect.

**Non-sulfonylurea insulin secretagogues**

(i) **Repaglinide**

Repaglinide is a new chemical entity, a carbamoylmethyl benzoic acid derivative which differs structurally from the sulphonylureas and belongs to the meglinitide group of drugs. Its molecular formula is C\textsubscript{27} H\textsubscript{36} N\textsubscript{2} O\textsubscript{4} and it has a molecular weight of 452.6. The insulinotrophic action of repaglinide is mediated via the inhibition of ATP dependent potassium ion channels in the pancreatic beta cell membrane which results in the depolarisation of the cell membrane and an influx of calcium ions through voltage-gated calcium channels. Intracellular calcium concentration is therefore increased and along with it, the insulin secretion. Repaglinide binds with high affinity to a receptor which is distinct from sulphonylurea receptor. In addition, repaglinide binds with low affinity to the classic sulphonylurea receptor. This differential binding results in more potent stimulation of insulin release. It is rapidly absorbed from the GI tract and has a half life of less than 1 hour. It is metabolised primarily in the liver and is excreted predominantly in the bile, thus it is safer in renal failure and the elderly. It is an effective post prandial glucose regulator and can be administered 3 times a day before meals for an effective glycaemic control. Doses may vary from 1-4 mg twice or thrice a day. Adverse effects include GI intolerance and hypoglycaemia, though the
latter is not prolonged as with glibenclamide\textsuperscript{11,12}.

(ii) GLP-I

Glucagon like peptide (7-36) amide (GLP-1) is a potent gut hormone playing the role of incretin, i.e., stimulating meal related insulin release from the B cells\textsuperscript{13}. It potentiates the insulin releasing effect of glucose by stimulating adenylate clyase and increasing cAMP in the B cells\textsuperscript{13}. It also suppresses glucagon release. It exerts insulinomimetic effects on gluconeogenesis in liver and muscles and lipogenesis in the adipose tissues. Since the insulin release is glucose dependent, it does not lower blood glucose further from normal blood glucose concentrations, hence decreasing the risk of hypoglycaemia\textsuperscript{14}. It also reduces post prandial glycaemia by delaying gastric emptying\textsuperscript{11}. Because of its short duration of action and need for parenteral administration, it is not a viable option for routine management of type 2 diabetes. To overcome these drawbacks GLP-1 receptor agonists such as Extendin 9-39 for oral administration are being developed\textsuperscript{11}. Extendin is a 39 amino acid peptide derived from Heloderma suspectum venom. Another promising approach is prevention of deactivation of GLP-1. The enzyme responsible for deactivation is DPP IV and oral inhibitors of this enzyme are currently under development NVP-DPP 728 is one such inhibitor undergoing animal studies\textsuperscript{15}.

(iii) Other agents

The knowledge that islet amyloid polypeptide (IAPP, Amylin) suppresses insulin secretion and action and further it has been linked with the development of insulin resistance at very high concentrations, has led to the development of amylin antagonist (IAPP-8-37) which stimulates insulin secretion\textsuperscript{16}. It has been found to be effective in animal studies; human trials are ongoing\textsuperscript{16}.

A-4166 (N-Trans-4-isopropylcyclohexylcarboxylphenylalanine) a phenylalanine analogue, stimulates meal related insulin release and decreases post prandial hyperglycaemia by 64\%\textsuperscript{17}. It is short acting and needs to be administered prior to meals in a dosage of 120 mg\textsuperscript{17}.

Guanidino related compounds (BTS 67582) act on a site different from SU receptors on the B-cells and offer an alternative mechanism to stimulate insulin release\textsuperscript{16}. They may have a promising role to play\textsuperscript{15}.

Attempts to treat defects of glucose sensing proinsulin biosynthesis and proinsulin processing by the B-cells, by pharmacological means are under development, but are still at a preliminary stage.

Insulin sensitisers

Insulin resistance is a universal feature in patients with type 2 diabetes mellitus. The key role played by peripheral and hepatic insulin resistance suggest that enhancement of insulin action might be an effective pharmacological approach for treatment of type 2 diabetes as well as an ideal way to manage the metabolic ‘syndrome’ of associated obesity, hypertension, and dyslipidaemia. These agents do not stimulate release of insulin from pancreatic B-cells but only increase the sensitivity of peripheral tissues to insulin. Moreover, sole peripheral action means, that these agents are unlikely to produce hypoglycaemia on their own.

Biguanides

They were introduced in 1958. Following UGDP study, they were out of favour because of fear of lactic acidosis, but have bounced back as they are known to significantly counteract insulin resistance. Metformin is preferred to phenformin as it does not inhibit mitochondrial oxidation of lactate and lactic acidosis with this drug is a rarity. Significant improvement in glycaemic control, lipid profile, and with no notable increase in plasma
lactate, serum insulin, weight gain, and frequency of hypoglycaemia have been observed with this group of drugs\textsuperscript{18}. Its major modes of action include (a) inhibition of gluconeogenesis, (2) reduction of hepatic glucose output, (3) reduction of weight\textsuperscript{19}; the improvement in insulin sensitivity is a byproduct of these alterations.

**Thiazolidinediones**

The discovery of peroxisome proliferator activated receptor (PPAR) and their subtypes has led to the discovery of a new generation of drugs. The two major PPAR receptors are \(\alpha\) & \(\gamma\) and both are expressed by obligate heterodimerisation with retinoic acid x receptor (Rx Rx\(\alpha\) and Rx Rx\(\gamma\)). The PPAR (\(\alpha\)) is primarily responsible for lipolysis by activation of enzymes such as acylCOA oxidase, lipoprotein lipase, malic enzyme, bifunctional enzyme, and medium chain acylCOA dehydrogenase. On the other hand, PPAR(\(\gamma\)) is primarily responsible for the adipocyte differentiation and at the metabolic level, in FFA and lipid anabolism and storage. The pronounced hypoglycaemic effect seen by PPAR(\(\gamma\)) agonists is attributed primarily to adiposite differentiation and/or activation\textsuperscript{20}.

The PPAR(\(\gamma\)) agonists, ciglitazone, pioglitazone, englitazone, troglitazone, and rosiglitazone are some of the members of this class. They decrease hepatic glucose output and increase peripheral glucose utilisation by improving insulin sensitivity at hepatic and muscle sites\textsuperscript{21}. They restore the sensitivity of phosphophenol pyruvate carboxy kinase (PEPCK) to insulin thereby decreasing glycogenolysis. They also increase peripheral triglyceride clearance and decrease hepatic triglyceride synthesis, independent of insulin\textsuperscript{21}. At the cellular level, they increase the binding and tyrosine kinase activity of insulin receptors, activate post receptor signaling proteins and enhance insulin induced translocation of GLUT-4 on to the plasma membranes\textsuperscript{16,21}. All these effects are dependent on insulin. These agents do not stimulate insulin secretion from \(\beta\)-cells and are therefore not effective in insulinopenic subjects\textsuperscript{22}. Troglitazone was marketed in USA, but was subsequently withdrawn due to hepatotoxicity. Rosiglitazone and pioglitazone are devoid of hepatotoxicity.

PPAR(\(\alpha\)) agonists such as fibrates are not effective hypoglycaemic agents, but lowers LDL cholesterol and triglycerides and raise HDL, thus offering protection against increased coronary morbidity and mortality which is seen in type 2 diabetes\textsuperscript{21}.

Retinoids, which activate RxR receptors are being developed to control diabetes, one such product LG 100268 has shown significant promise, in that, in addition to being an insulin sensitisir it causes weight reduction in contrast to PPAR(\(\gamma\)) agonists\textsuperscript{22}.

A new class of drugs which are plant extracts and act through inhibition of protein tyrosine kinase are being investigated. In additon to hypoglycaemic effect it blocks the formation of proinflammatory cytokines such as TNF \(\alpha\). Compounds in this class includes CLX 0301, CLX 0302, CLX 0900, and CLX 0901. This group of drugs also lowers cholesterol and triglycerides. Again these are sensitisers and are not effective in type 1 diabetes\textsuperscript{23,24}.

**\(\beta_3\) adrenergic receptor agonists**

\(\beta_3\) adrenergic receptor present in brown and white adipose tissues, mediate catecholamine stimulated thermogenesis and lipolysis. A polymorphism in \(\beta_3\) adrenergic receptor due to missense mutation in the gene coding for it, has been identified in Finns and Pima Indians. This has been linked to lower basal metabolic rate, greater visceral adiposity, and early onset of type 2 diabetes in these ethnic groups. This observation has stimulated the use of selective \(\beta_3\) adrenoceptor agonists such as CL 316, 2443, which do not cross react with other \(\beta\)-adrenoceptor, for treating obesity and improving insulin senstivity\textsuperscript{25}. In obese diabetic animal models, \(\beta_3\) adrenergic receptor agonists reduce body weight by increasing energy expenditure and reduce fat depots without inducing a decrease in food intake. Reduction in blood glucose along with triglyceride concentration are observed within a week of their usage\textsuperscript{24}. Preliminary results in type 2 diabetes patients with...
these drugs have confirmed these beneficial effects25.

Inhibitors of intermediary metabolism
Type 2 diabetes is invariably associated with a disordered lipid metabolism. In the muscle, a glucose, fatty acid cycle has been recognised for many years. The oxidation of fatty acids decreases glucose uptake and utilisation through substrate competition, causing a post receptor insulin resistance. As the rate of fatty acids oxidation determines the rate of gluconeogenesis, a good correlation exists between raised fasting NEFA levels, impaired lipid oxidation, and re-esterification and hepatic glucose output (HGO) in patients with type 2 diabetes. Since increase in HGO is responsible for fasting hyperglycaemia in type 2 diabetes, drugs decreasing fatty acid levels or inhibiting fatty acid oxidation are attractive options for controlling fasting hyperglycaemia26.

Drugs decreasing fatty acids
These are anti-hypertriglyceridaemic drugs, e.g., acipimox and bezafibrate16. Acipimox is a long acting nicotinic acid analogue, which significantly reduces plasma NEFA and HGO26. Its effects on HGO are more sustained than nicotinic acid which has a variable effect on glycaemic control frequently worsening due to discrepant effects on glycogen breakdown and gluconeogenesis. In a study of 8 obese type 2 diabetic patients overnight suppression of plasma NEFA with acipimox significantly reduced lipid oxidation, HGO, and increased the glucose disposal rate27.

Bezafibrate, a PPAR(α) agonist is effective in reducing the dyslipidaemia of diabetes. However, it is important to note that these agents can be supplementary but cannot be used alone for therapy of diabetes21.

Fatty acid oxidation inhibitors
Suppression of fatty acid oxidation decreases hepatic gluconeogenesis and increases peripheral glucose utilisation. The drugs of this class inhibit carnitine palmitoyl transferase-1 (CPT-1) which is a rate limiting enzyme for the transfer of long chain fatty acids into mitochondria28. Etoximer is the prototype and this has been shown to be effective in reducing HGO, increase peripheral glucose utilisation, and pyruvate dehydrogenase activity. However, the drawbacks with this drug include fear of myocardial damage and refractory hypoglycaemia26. Studies however, are in progress to develop short acting inhibitors of long chain fatty acid oxidation which may help reduce ketogenesis in type 1 diabetes29. Lisofylline is one such drug which has shown promise in animal studies.

Inhibitors of gastro-intestinal glucose absorption
Alpha glucosidase inhibitors
These drugs competitively inhibit the glucosidases at the small intestinal brush border, responsible for breakdown of complex polysaccharides (Starches) and sucrose into glucose30. This results in decrease of postprandial glycaemia. The drugs approved in this class for clinical use are acarbose & miglitol.

Acarbose
Originally developed in Germany, is being widely used for post prandial glucose regulation. It is usually used in type 2 diabetes either as a monotherapy or in conjunction with SU’s or biguanides30. The average decrease in post prandial blood glucose during acarbose treatment in diet treated type 2 diabetic patients was 3 mmol/1 and maximal decrease in HbA1C was 1%. Acarbose is recommended thrice daily in doses of 50-200 mg with the first bite of each major meal30. Titration of dose is important to optimise benefits and minimise its side effects, which include flatulence, cramping, and diarrhoea30.

Miglitol
This is a newer-glucosidase inhibitor, derived from 1-deoxy nojirimycin and is structurally similar to
glucose\textsuperscript{11}. It is almost completely absorbed from GI tract, is short acting and hence is expected to have less GI side effects than acarbose. The usual dose is 50-100 mg. daily\textsuperscript{31}.

**Insulinomimetic drugs**

**Vanadium salts**

Vanadium is an ultra trace element. Its compounds such as vanadyl orthovandate, metavandate and peroxovanadate have been shown to have insulinomimetic effects on adipocytes, hepatocytes, and the skeletal muscles as well as in hyperinsulinaemic and hypoinsulinaemic animal models of the diabetes. They act by a mechanism independent of insulin and near euglycaemia is achieved in animal models within 1-2 weeks. In animal models, vanadium salts induce decrease in body weight, attributed to its central anorectic effects\textsuperscript{32}. These salts act by increasing the phosphorylation of insulin receptor either by activation of the intrinsic tyrosine kinase activity or by inhibition of the phosphotyrosyl phosphatase that dephosphorylates the receptor\textsuperscript{32} and may also act on post receptor sites (mitogen activated protein kinase and cytosolic insulin independent tyrosine kinase)\textsuperscript{32}. Importantly these compounds are effective even in situations where the insulin signal transduction pathway is defective\textsuperscript{16}. Usual dosage is 100 mg/day and the effects lasts for upto 2 weeks after discontinuation. Major side effects are gastrointestinal; however, there are fears of its mitogenic potential, as it stimulates tyrosine kinase. A synthetic organic complex of vanadyl (bis maltatato) oxovanadium with high lipophilicity and peroxovanadium compounds appear promising\textsuperscript{32}.

IGF-1 receptor agonists are also being developed for selective hypoglycaemic action, prolonged duration of effects, and perhaps for use by the oral route.

Additionally, new drugs are being developed to counter complications in diabetes. These include aminoguanidine, tenisetam, OPB-9195 which are AGE receptor antagonists; protein kinase C inhibitors (LYS 333531, WAY 151003, and Cremophor EL), nerve growth factors, octreotide, hismanal, topical clonidine, picotamide, and a lot of research is focused on antioxidants such as vitamin E and \(\alpha\) lipoic acid\textsuperscript{33}.

In conclusion, the management and approach for diabetes mellitus is on the threshold of a revolution. Increasing realisation of the need for optimal glycaemic control and the pitfalls of available therapeutic options in type 2 diabetes has led to active search for newer modalities of therapy. Despite simultaneous research on oral antidiabetic agent having different mechanisms of action, in order to overcome the deficiencies of currently available antidiabetic medication only glimeperide, repaglinide, thiazolidenediones, and acarbose have been introduced for routine use. It is hoped that some of the other such agents would be soon introduced in India at an affordable price; the remainder and perhaps many newer formulations may be available a few years later down the road.

**References**

8. Muller G, Wied S. The sulfonylurea drug glimeperide stimulates glucose transport, glucose transporter translocation and dephosphorylation in insulin resistant


