

ORAL HYPOGLYCEMIC AGENTS IN 21ST CENTURY: A CRITICAL APPRAISAL

India is in the grip of epidemic involving lifestyle diseases such as diabetes mellitus, hypertension, obesity and cardiovascular diseases. Diabetes in particular has caught the attention of world as India has become world capital of this disease. The profile of Indian diabetic patients is different from that seen in west such as they are thinner, younger and metabolically obese having low BMI. The management of diabetes mellitus has evolved with time since the discovery of disease. The race to reach the most appropriate glycemic goal has been attended by consequent development of multiple agents in the armamentarium of treating physician. Oral hypoglycemic agents are available to treat diabetes since 1956 when first generation sulfonylurea was introduced in form of tolbutamide followed by biguanides a year after. Since the introduction of these agents there have been additions of numerous oral hypoglycemic agents such as third generation sulfonylurea, glitazones, alpha glucosidase inhibitors. As of today physicians have choice for treating DM including new generation sulfonylurea (glipizide, gliclazide, glimepride), metformin, pioglitazone, rosiglitazone, acarbose, miglitol, voglibose, netiglinide and repaglinide. Latest in the armamentarium of physicians are dipeptidyl peptidase inhibitors which have come in clinical practice in last two years. Future looks bright as in the 21st century physicians will not only have access to newer antidiabetic drugs from existing classes of drugs but also have novel agents like glycosuric agents which are being researched vigorously.

The pathogenesis of type2 diabetes involves three primary defects: insulin resistance, beta cell dysfunction and hepatic glucose overproduction. None of the currently available treatment options address the problem of islet cell dysfunction and they have their attending problems of lack of efficacy and side effects, hence there remain critical unmet medical needs in the treatment of this disease. Beta cell function is lost more than 50%, once hyperglycemia is diagnosed and unattainable glycemic control is often the result of ongoing deterioration of beta cell function. A novel approach in treating diabetes mellitus is to utilize the physiological actions of endogenous incretin hormones; glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), the intestinal hormones released in response to nutrient ingestion. Although the incretin defect was noticed long ago its therapeutic value has been recognised very recently. GIP is secreted by K cells from upper small intestine and GLP-1 is by L cells located in distal intestine when stimulated by intraluminal glucose. Incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose in the gut. The observation that an oral glucose load was more effective at releasing insulin compared with the same amount of glucose given intravenously led to this theory. Studies prove that both GIP and GLP-1 stimulate insulin release in glucose dependent manner in humans, contributing 50 – 70% of the postprandial insulin response and both are necessary for maintenance of normal glucose tolerance. Incretins stimulate insulin secretion only in presence of hyperglycemia with no response in normal or low glucose levels. Pathophysiology of diabetes mellitus also encompass a recently understood defect in incretin effect with decreased insulinotropic effect of GIP and decreased

blood levels of GLP-1. Research shows a 15% reduction in post prandial levels of GLP-1 in patients with diabetes mellitus. Although hyperinsulinaemia is a hallmark of the first years after diagnosis, the first-phase insulin response (peak after a glucose load) is impaired or absent early in the disease. This first-phase insulin response is caused by incretins secreted from the small intestine after an oral glucose load. GIP and GLP-1 are rapidly inactivated by dipeptidyl peptidase 4 (DPP 4), a member of serine peptidase family. Different pharmacologic strategies to enhance incretin effect in management of diabetes include continuous administration of GLP-1, DPP4 resistant GLP-1 analogues and DPP4 inhibitors. The DPP-4 inhibitors approach GLP-1 insufficiency by enhancing incretin instead of mimicking it. By inhibiting DPP-4, the enzyme responsible for the breakdown of GLP-1, agents such as sitagliptin and vildagliptin can prolong the action of GLP-1 and increase circulating levels. One of the major differences between the GLP-1 analogues and the incretin enhancers is that the former are proteins that must be injected, and the latter are chemicals that can be taken in pill form. Also, exenatide, being a protein must be kept in the refrigerator, while sitagliptin doesn't require any special storage. DPP-4 inhibitors tend to be weight neutral with no effect on appetite and gastric emptying, while GLP-1 analogues seem to cause weight loss in overweight individuals owing to their unique action of delayed gastric emptying and suppression of appetite by a yet unknown central action.

Other favourable effects of incretin hormones may have a therapeutic role in type 2 diabetes mellitus like inhibition of glucagon release, decreased hepatic gluconeogenesis, slowing of gastric emptying, central action in suppressing appetite with consequent weight loss, stimulation of replication and neogenesis and inhibition of apoptosis of beta cells of pancreas, later quality signifying importance as potential agent for the prevention of type2 diabetes. As incretin receptor activation is only coupled to stimulation of insulin secretion in the presence of elevated blood glucose, therapies that are based on incretin enhancement have a low risk of hypoglycemia, which is a problem with current therapies. As confirmed from studies, DPP4 inhibitors increase meal stimulated active GLP-1 and GIP levels by two to three fold, increase insulin and c-peptide levels, reduced plasma glucagon levels, reduced glycemic excursion following glucose tolerance test, dose dependently reduced HbA1c and fasting plasma glucose. DPP4 inhibitors may have a beneficial disease modifying effects of attenuating loss of beta cell mass and function and normalizing beta-alpha cell ratio on chronic therapy for 2-3 months. Thus, DPP4 inhibitors have the potential both for assisting in achieving glycemic goals in anti-diabetic therapy and for modifying underlying disease course by correcting the islet cell dysfunctions characteristic of the disease.

Studies have proven their role as monotherapy and as complementary adjuncts to ongoing oral therapy for diabetes mellitus. DPP4 inhibition have demonstrated even delay in the onset of overt diabetes, improvement in insulin sensitivity and reversal of glucose toxicity speculating their use in humans as a potential agent for the prevention of type 2 diabetes. Because of the efficiency, safety, tolerability and oral route of administration, it is expected that DPP4 inhibition may

be the first-line treatment of the early stage of type 2 diabetes, particularly in combination with metformin or thiazolidinediones. Concerns have been raised on selectivity of DPP IV inhibitors and side effect profile as inhibition of DPP8 and DPP9 (enzymes of same family as DPP4) have evoked severe toxicities in animal species. Thus, pharmaceutical efforts focused on identifying a highly selective DPP4 inhibitor for clinical development. Optimization of this series led to the discovery of sitagliptin (MK431) and vildagliptin (LAF237), highly selective DPP4 inhibitors for the treatment of type 2 diabetes, others in final stages of development are saxagliptin (BMS477118), alogliptin, demiglitin, SYR322, PHX1149, GRC8200, ilethiozolidide. DPP4 inhibitors may have the greatest impact in patients who are early in the disease process; however, whether these agents are enough to get more patients to reach their target HbA1c levels or they simply delay the start of insulin therapy remains in question. GLP-1 analogue, exenatide is available in injection form only and its cost is prohibitive for average Indian diabetic patient. However it scores over other oral drugs such as sulphonylurea by reducing weight in obese diabetic patients and not causing hypoglycaemia. Oral DPP4 inhibitors available in India for patients include Sitagliptine and vildagliptine. Both these agents are equally effective and comparable in their adverse effect profile. The emerging aspect of these agents is their potential role in beta cell preservation. In patients with type 2 diabetes mellitus who had moderately severe hyperglycemia inadequately controlled by metformin alone, the addition of sitagliptin 100 mg once daily or vildagliptine 50 mg twice daily provided significant and sustained improvements in HbA1c and other glycemic endpoints, including fasting glucose and post prandial glucose. In addition, sitagliptin provided statistically significant improvements in markers of β -cell function. Overall, the addition of sitagliptin to ongoing metformin therapy was well-tolerated with neutral effects on body weight relative to placebo, low incidence of hypoglycemia, and no worsening of gastrointestinal adverse events. Sitagliptin 100 mg once daily added to ongoing pioglitazone therapy was effective and well tolerated in these patients with type 2 diabetes who had not achieved adequate glycemic control with pioglitazone alone. Another study provides add-on efficacy and safety results for sitagliptin, compared with a standard sulphonylurea agent, glipizide, in patients with inadequate glycaemic control on metformin monotherapy. The study results demonstrate that sitagliptin was non inferior to glipizide in HbA1c-lowering efficacy. Although both treatments were generally well tolerated, sitagliptin had a considerably lower risk of hypoglycaemia relative to glipizide and produced weight loss compared with weight gain with glipizide. In one study sitagliptin 100 mg once daily significantly improved glycemic control and beta cell function in patients with type 2 diabetes with inadequately controlled on glimepiride or glimepiride plus metformin therapy. The addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycaemia and body weight, consistent with glimepiride therapy. Sitagliptin is not currently indicated for use with insulin although there are clinical trials in progress evaluating this combination. While consensus agrees that there is a strong scientific rationale of sitagliptin use even in patients taking insulin, proactive promotion of DPP4 inhibitors use in combination with insulin should be avoided until we have the phase III clinical trial on this combination.

The addition of vildagliptin to on-going metformin therapy produced clinically meaningful dose-related reductions in HbA1c and fasting plasma glucose and appeared to reduce metformin-related GI adverse effects. Metformin patients who added vildagliptin (50mg qd or bid)

also experienced a beneficial effect on blood pressure, relative to placebo. Although suggestive, the influence of vildagliptin on blood pressure remains to be clarified. Two 24-week studies examining the combination of vildagliptin and pioglitazone showed that vildagliptin produces clinically meaningful reductions in HbA1c when combined with reduced-dose pioglitazone in drug-naïve patients and when added to full-dose glitazone treatment. A comparative trial versus rosiglitazone showed that vildagliptin produced a similar reduction in HbA1c, improved lipid measures, and did not produce weight gain compared with rosiglitazone. The addition of vildagliptin to insulin treatment produced a significant reduction in HbA1c that was particularly marked in older patients and appeared to reduce the frequency and severity of hypoglycaemia.

The most common adverse effects with the use of DPP4 inhibitors are upper respiratory tract infection (6.3% in the sitagliptin-pioglitazone group vs. 3.4% in the pioglitazone-only group), nasopharyngitis (5.2% in the sitagliptin group vs. 3.3% in the placebo group), urinary tract infections and headache (5.1% in the sitagliptin pioglitazone group vs. 3.9% in the pioglitazone-only group). Gastro intestinal side effects including nausea, abdominal pain, and diarrhoea have also been reported in some studies. DPP4 is a ubiquitous cell-membrane protein, expressed in many tissues, including lymphocytes, which has raised some concerns about the long-term effects of DPP4 inhibitors especially on immune function. It has been classified as schedule 4 prescription only medicine in poison schedule. DPP4 enzyme family also includes other members such as DPP8, DPP9 and QPP, and selective inhibition of DPP4 is highly desirable, because inhibition of two other enzymes, DPP8 and DPP9 has resulted in fatal toxicities in animal studies. The DPP 8/9 selective inhibitor produced alopecia, thrombocytopenia, reticulocytopenia, multiorgan histopathological changes, enlarged spleen and mortality in rats. This inhibitor also produced gastrointestinal toxicity in dogs. Furthermore, the DPP2 selective inhibitor produced reticulocytopenia in rats. The reported incidence of hypoglycemia in subjects receiving sitagliptin or vildagliptine is similar to that in control subjects.

Vildagliptin was generally well tolerated in phase III trials. One case of significant peripheral edema was reported. The most common adverse events reported with vildagliptin were mild and included nasopharyngitis, headache, and dizziness. Vildagliptin has been associated with very few episodes of hypoglycemia when used as monotherapy or in combination with other antihyperglycemic medications. No significant laboratory abnormalities have been observed during or resulting from trials involving vildagliptin. Potential of DPP4 to also cleave other bioactive may cause adverse events on administration of DPP4 inhibitors related to increased blood pressure, neurogenic inflammation, and immunological reactions however, no such adverse events have been reported in animal studies or in humans using DPP4 inhibition. Other reported adverse reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment, with some reports occurring after the first dose. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay. Isolated case reports of renal failure and rhabdomyolysis with sitagliptin and simvastatin exposure are quoted.

Very few case reports from Philippines also report fatal haemorrhages, leukaemia, eosinophilia, erythema, skin exfoliation during sitagliptin use raise suspicion.

There are few unsettled issues about DPP4 inhibitors. There are reports that commonly used antidiabetic drugs can affect circulating DPP4 activity. Metformin has been reported to reduce DPP4 activity in patients with type2 diabetes and in diabetic animal models. Metformin increased active levels of GLP-1 in obese, non-diabetic human males and reduced inactivation of exogenously administered GLP-1 in obese-diabetic (*ob/ob*) mice. There are reports of reduced serum DPP4 activity brought about by the thiazolidindiones, meglitinide, and nateglinide. There is theoretical risk of aggravation of hypertension. Sitagliptin, by blocking dipeptidyl peptidase IV, prevents metabolism of neuropeptide Y_{1-36} and thereby increases the effects of neuropeptide. Y_{1-36} released from renal sympathetic nerves on Y_1 receptors leading to augmentation of neuropeptide Y_{1-36} induced enhancement of the renovascular effects of angiotensin II. The renal effects of dipeptidyl peptidase IV inhibitors in hypertensive diabetic patients merit a closer examination. To add to debate, a study in non diabetic hypertensives shows a decrease in blood pressure on administration of sitagliptin. Although presently not indicated for use in type1 diabetes, benefits have been suggested in combining DPP4 inhibitors with insulin therapy.

FUTURE ORAL AGENTS FOR DIABETES MELLITUS

Glycosuric agents: The kidney is important for the body's energy control. Glucose filtered from the blood in the glomerulus is reabsorbed mainly in the S1 segment of the kidney's proximal tubule, but when the capacity for glucose reabsorption reaches saturation, excess glucose is excreted in the urine. Two types of sodium glucose cotransporters mediate this reabsorption. The low-affinity sodium glucose cotransporter (SGLT2) is found almost exclusively in the kidney, and several mutations in the human SGLT2 gene can cause renal glucosuria. Although the high-affinity sodium glucose cotransporter (SGLT1) is expressed to some extent in the kidney and contributes to glucose reabsorption, it is mainly expressed in the small intestine. Although several reports concerning genetic mutations in human SGLT2 suggest that this molecule plays some role in glucosuria, pharmacological validation in intact animals is needed to support SGLT2 playing a critical role in renal glucose reabsorption. Several researchers have focused on the renal glucose reabsorption system as a way of improving hyperglycemia in type 2 diabetes mellitus, and SGLT inhibitors have been developed. Enhancement of urinary glucose excretion via SGLT2 inhibition leads to a negative energy balance, which is not really achieved by any existing clinical pharmacological inventions. Phlorizin lowers blood glucose without increasing insulin secretion and thus a SGLT2 inhibitor might improve hyperglycemia without hypoglycemia being caused by excessive insulin secretion. Thus, KanjuKastuno et al attempted to obtain compounds without unwanted properties of phlorizin (selectivity, bioavailability, and GLUT1-inhibitory effect of its aglycon). In this study, to elucidate the role of SGLT2 in renal glucose reabsorption, authors investigated the potency and properties of sergliflozin as a selective SGLT2 inhibitor in vitro and in vivo, and also evaluated the potency and properties of sergliflozin as an antidiabetic drug. In an oral glucose tolerance test in diabetic rats, sergliflozin exhibited glucose-lowering effects independently of insulin secretion. Any

glucose excretion induced by sergliflozin did not affect normoglycemia or electrolyte balance. These data indicate that selective inhibition of SGLT2 increases urinary glucose excretion by inhibiting renal glucose reabsorption. As a representative of a new category of antidiabetic drugs, sergliflozin may provide a new and unique approach to the treatment of diabetes mellitus.

Scientists in Australia (unpublished reports) have produced results that could silence the current debate about exactly how fat molecules clog up muscle cells, making them less responsive to insulin. The finding is an important milestone in understanding the mechanisms of obesity related insulin resistance, a precursor of Type 2 diabetes. These scientists have added to evidence that fat molecules clog up the cytosol, but not the mitochondrion, Kraegen and colleagues made one small change to a single muscle in one leg of a rat, allowing that muscle to burn fat molecules better. To do this, they overexpressed a protein (CPT1) that acts like a "gate" or "tap" to control entry of fat molecules into mitochondria.

The changed muscle burned more fat molecules and became significantly more responsive to insulin than the equivalent muscle in the opposite leg, which had not been re-engineered.

There is continuous interest in glucagon receptor antagonists, glucokinase activators, inhibitors of gluconeogenesis and glycogenolysis and activators of insulin signal pathways and coming few decades could see some new agents emerging from these. To conclude, in 21st century sulfonylurea are arguably the most cost effective glucose lowering agents either as monotherapy or in combination with insulin sensitizers. If incretin mimetics and DPP4 inhibitors are proven to have beta cell preservation then these agents could play an important factor in how the prescriptions for type 2 DM are written. For other future therapies such as glucosuric agents, GPPR 119 agonists, glucagons receptor antagonists etc. we need to wait and watch for their possible role in management of diabetes mellitus.

RECOMMEDED READING

1. **Ahren B.** Dipeptidyl Peptidase-4 Inhibitors Clinical data and clinical implications. *Diabetes Care.* 2007; (30): 1344-1350.
2. **Ramachandran A, Snehlata C, Latha E, et al.** Rising prevalence of NIDDM in an urban population in India. *Diabetologia* 1997;4:232-237.
3. **Kenji Katsuno, Yoshikazu Fujimori, Yukiko Takemura, et al.** Sergliflozin, a Novel Selective Inhibitor of Low-Affinity Sodium Glucose Cotransporter (SGLT2), Validates the Critical Role of SGLT2 in Renal Glucose Reabsorption and Modulates Plasma Glucose Level. *J Pharma Exp Ther* 2007; 320; 323-330.
4. **Kendall DM, Cuddihy RM, Bergental RM.** Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. *Am J Med.* 2009 Jun;122(6 Suppl):S37-50. Review.
5. **King H, Aubert RE, Herman WH.** Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414-1431.
6. **Moller DE.** New drug targets for type 2 diabetes mellitus and metabolic syndrome. *Nature* 2001; 414:821-827.
7. **Nathan DM, Buse JB, Davidson MG, et al.** Management of hyperglycemia in type 2 diabetes mellitus: a consensus algorithm for initiation and adjustment of therapy. *Diabetes care* 2006;29:1963-1972.
8. **American Diabetes Association.** Standard medical care in DM. *Diabetes care* 2009; suppl.
9. **Overton HA, Fyfe MC, Reynet C.** Another new molecule being studied for its use in diabetes is GPR119, a novel G protein-coupled receptor. *Br J Pharmacol.* 2008;153 Suppl 1:S76-81.
10. **Overton HA, Fyfe MC, Reynet C.** Another new molecule being studied for its use in diabetes is GPR119, a novel G protein-coupled receptor. *Br J Pharmacol.* 2008; 153 Suppl 1:S76-81.

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