

Volume No. 2

Symposium On Diabetes

Oral Hypoglycaemic Agents

Introduction

We are thankful for your overwhelming response for our new initiative “**Symposium on Diabetes**”. As a leader in diabetes care we feel responsible to join hands with the medical fraternity in disseminating information on diabetes and thereby help them detect & control it.

The maiden volume of symposium on diabetes dwelled on the topic of **Diagnosis & Classification** wherein we discussed new classification of diabetes as recommended by American Diabetes Association.

The book further discussed on the diagnostic values and salient features of various types of diabetes. It was emphasized in the book that doctors should test for diabetes in all individuals at aged 45 and above, as early diagnosis of diabetes is important so that the associated complications may be prevented or delayed.

The current volume on **Oral Hypoglycemic Agents** reviews the role of OHAs and its limitations. The elaboration on various OHAs and guidelines for their usage makes it useful for your day-to-day clinical practice. The book also contains details on OHA failure and its management.

We are hopeful that you will find this issue interesting and relevant in your clinical practice.

Happy reading!

Oral Hypoglycaemic Agents (OHA)

Type 2 (NIDDM), the most common form of diabetes mellitus accounts of over 95% of all diabetics in India. Due to its insidious onset and lack of dramatic symptoms, the disease often remains undiagnosed for many years and patients may have complications at first presentation.

Drugs used to treat Type 2 diabetes aim to correct the underlying metabolic disorders, namely insulin resistance and inadequate insulin secretion. Therapy for diabetes should be used in conjunction with dietetic adjustments and exercise.

OHAs are usually not the first line therapy in diabetes diagnosed during situations of stress, such as infections and myocardial infraction, since the recommended therapy is insulin. OHAs are also not recommended for diabetes diagnosed in pregnancy, as they are not proven to be safe.

There are three different types of OHAs available in India:

1. Biguanides

- Biguanides do not stimulate insulin secretion, and lower glucose by increasing tissue utilization of glucose or reduced absorption of glucose from GI tract (known as antihyperglycaemic agent). It is useful as first line treatment in the obese diabetic. e.g., Metformin
- Metformin dosage

Initial dose	500mg daily increasing to 500mg twice daily in one week to reduce gastro intestinal side effects. The side effects can be further reduced by taking it with food.
Usual therapeutic dose	500mg three times daily.
Maximum dose	1.0 three times daily.

Caution:

- Not recommended in elderly patients (>70 years)
- Must not be used in patients with impaired renal function (creatinine >300 mmol/L), liver cirrhosis, congestive cardiac failure, recent myocardial infraction respiratory impairment, vascular disease and severe infections or any conditions known to cause lactic acid accumulation.

- Vitamin B12 deficiency may occur if metformin is given to patients who have had partial gastrectomy and terminal ileal disease.
- If serum creatinine increases, stop the drug.

2. Sulphonylureas

- Sulphonylureas have been used since 1950s. Sulphonylureas lower plasma glucose by stimulating insulin secretion by the islet cells of pancreas, and by reducing hepatic glucose production.
- Sulphonylureas can be combined with metformin, acarbose or insulin to improve control if indicated.
- Side effects with sulphonylureas are hypoglycaemia, hepatitis, SIADH, blood dyscrasia.

Table 1: Sulphonylureas and their recommended dosage:

First Generation		
	Minimum dose	Maximum dose
Tolbutamide	500 mg TDS	1 gm TDS
Chlorpropamide	125 mg OD	500 mg OD
Second Generation		
Glibenclamide	2.5 mg OD	10 mg OD
Gliclazide	40 mg OD	160 mg OD
Glipizide	2.5 mg OD	10 mg OD
Glimepiride	1-2 mg OD	4 mg OD

- Chlorpropamide and tolbutamide are excreted by the kidneys and are contraindicated in renal impairment.
- Glibenclamide is metabolized by the liver but its metabolites are active and excreted by the kidneys. The dose must be reduced in renal impairment. Second generation sulphonylureas (Gliclazide and Glipizide) are metabolized by the liver and may still be used in renal impairment.

Caution:

- Sulphonylureas cause hypoglycaemia because they increase insulin secretion. The risk is higher in the presence of renal impairment or liver cirrhosis or with the use of long acting preparations in the elderly.

- Sulphonylureas should be avoided in the obese because they increase appetite and lead to weight gain.
- Sulphonylureas are contraindicated in patients known to be allergic to sulpha drugs.
- Sulphonylurea drugs are mostly protein bound. Administration of drugs that have potential to displace them (e.g. antithyroid drugs, sulpha drugs, anticoagulants, NSAIDs and β blockers) can thus increase the risk of hypoglycaemia.

3. Combinations of Biguanides and Sulphonylureas

Combination therapy is useful when one group of drug fail to give adequate response. This is because the mechanisms of action are complimentary. However adverse events are additive and it is particularly dangerous to combine these drugs in patients with significant renal, hepatic or cardiovascular disease.

Fixed dose combination of above have drawback of dosage adjustment and titration with individual drugs.

4. α -Glucosidase Inhibitors

- α - glucosidase inhibitors (e.g. acarbose), act at the gut epithelium, to reduce glucose absorption by inhibiting the β -glycosidase enzymes.
- α - glucosidase inhibitors decrease postprandial glucose surge. They do not cause hypoglycaemia.
- They are useful particularly in those with normal fasting glucose levels and raised postprandial glucose levels. They can have synergistic effects when used with metformin and sulphonylureas. They may also be used in combination with insulin.

Dosage of Acarbose

Initial dose	50 mg/day and increase only in the absence of gastrointestinal symptoms
Usual dose	5-100 mg during main meals

General Use of OHA in Diabetes

- For **non-obese patients** who could not be controlled on diet and exercise, sulphonylureas such as glicazied, glipizide, glibenclamide should be

started. Diet and exercise must be re-emphasized. Sulphonylureas can be combined with metformin and/or acarbose to improve control if indicated.

- For **obese patients** who could not be controlled on diet and exercise, metformin is the drug of choice. Acarbose is an acceptable alternative as first line therapy. For those who still could not be controlled on metformin and/or acarbose, sulphonylurea, such as glibenclamide or glipizide or glicazide can be started. Diet and exercise must be re-emphasized.
- In **elderly non-obese subjects**, a sulphonylurea can be started but long acting drugs are to be avoided. The patient should be monitored for renal impairment. Targets for control are less stringent because of increased risk of hypoglycaemia but metformin is to be avoided. Acarbose can be safely used. If diabetes is still not well controlled, insulin may be started.

OHA Failure:

Unsatisfactory glycaemic control is a common problem in people with Type 2 diabetes treated with oral agents. It is a condition in which an individual does not respond adequately / satisfactorily to therapy with OHAs.

PRIMARY FAILURE:

About one third of unselected Type 2 patients fail to respond to sulphonylurea within one month of initiation of therapy and are referred to as primary failures.

SECONDARY FAILURE:

Of the patients that initially achieve satisfactory glycemic control, about 5 to 10% go on to develop secondary failure each year, so that after 10 years only about half of the patients continue to have satisfactory response. From the preliminary data of the UKPD study, it appears that by the sixth year approximately 50% of patients randomized to sulphonylurea needed supplemental insulin to maintain adequate control.

How Common?

Percent with OHA failure after 10 years duration of Type 2 diabetes

Lean	47%
Overweight	23%
Obese	13%

Diagnosing OHA Failure

Clinically, following parameters can be of great relevance in diagnosing OHA failure;

1. Inadequate/deteriorating blood glucose control. The objective to be pursued on this front is:

Fasting blood glucose	< 140 mg/100ml
PP blood glucose	< 180 mg/100ml

2. Inadequate improvement in the classical signs and symptoms of diabetes viz., polydipsia, polyuria, polyphagin and fatigue.
3. Weight loss accompanied by rising blood glucose and recurrent infections.
4. High and increasing number of tablets with inadequate control; especially exceeding two to two and a half tablets in case of commonly used OHAs.

Poor performance on the above parameters indicate the necessity to review the entire therapy and one of the therapeutic alternatives to be considered at this point of time is initiation of insulin therapy as insulin has the advantage of always working.

Reasons for OHA Failure

DISEASE RELATED:

- Progressive deterioration of Beta cell function (natural history of Type 2 diabetes)
- Increased insulin resistance (secondary to weight gain)

THERAPY RELATED:

- Inappropriate regimen
- Other medications especially corticosteroids, thiazide diuretics

PATIENT RELATED

- Non-adherence with medication, diet or exercise
- Inappropriate diet
- Lack of exercise

- Infections
- Concomitant endocrine problem, e.g., thyroid disease, Cushing's syndrome and acromegaly
- Concomitant medical problem
- Stress
- Change in lifestyle

Management of OHA Failure

- Over a period of time, in substantial number of patients, there is a progressive cell failure, hence, type 2 diabetes is considered as an evolutionary disorder and its management over the years cannot and should not be static.
- Establish diagnosis by excluding or correcting remediable factors
 - Intercurrent problems
 - Other medications e.g. thiazide diuretics, short term corticosteroids
 - Compliance
- Encourage dietary improvement
- Re-education and consider/review self monitoring of blood glucose
- Maximize use and dose of oral agents
- If these measures fail to achieve blood glucose targets insulin therapy is usually indicated.

Summary

Type 2 diabetes mellitus is the most common form of diabetes. It is characterized by three basic pathophysiologic abnormalities including impaired pancreatic insulin secretion; peripheral insulin resistance, primarily at liver and muscle tissue; and excessive hepatic glucose production. Due to its insidious onset and lack of dramatic symptoms the disease often remains undiagnosed for many years and patients have existing complications at presentation. Hence Type 2 diabetes merits aggressive pharmacological intervention to attain and to

maintain good metabolic control. A common sequence of therapy in Type 2 diabetes starts with diet and exercise followed by drug therapy.

When used judiciously and selectively, oral hypoglycaemic agents have a major role in achieving good metabolic control. When failure to respond to optimum dose of OHA (either primary or secondary OHA failure), insulin will be needed for glycaemic control.

Patients with Type 2 diabetes often need insulin to control hyperglycaemia either at presentation due to the severity of hyperglycaemia or during periods of stress, surgery, infection, pregnancy and labour; as well as during other medical problems such as myocardial infarction, cerebrovascular disease, hyperosmolar coma or acute painful diabetic neuropathy.

Suggested Readings

1. Dan KG Anderson, Long-term glycaemic control relates to mortality in type II diabetes, *Diabetes Care*, Vol 18, No. 12, December 1995, page 1534.
2. U K Prospective Diabetes study Group, U K Prospective diabetes Study 15, *Diabetes* Vol 44, November 1995, page 1254.
3. Consensus statement. The pharmacological treatment of hyperglycaemia in NIDDM; *Diabetes Care*, Vol. 18, No. 11, November 1995, page 1511-1517.
4. Robert C Turner, Insulin use in NIDDM, *Diabetes Care*, Vol 13, No. 9, September 1990, page 1015.
5. U K Prospective diabetes Study Group, U K Prospective Diabetes Study 16, *Diabetes*, Vol 44, November 1995, page 1256.
6. Heine R J, Insulin treatment of NIDDM, *Bailliere's clinical endocrinology and metabolism*, Vol 2, No., May 1988, page 47.
7. Melander A, Bitzen P-O, Faber O, and Groop L. Sulphonylurea anti-diabetic drugs. *Drugs*. 1989; 37:58-72.
8. DeFronzo RA, Goodman AM et al. Efficacy of metformin in patients with NIDDM. *New Engl. J Med*. 1995; 9:541.

Oral Hypoglycemic Agents: Experts Opinion

Dr. Sudhir Tripathi

Secondary OHA Failure is probably under reported. A large proportion of patients on submaximal/maximal doses of OHA are not adequately controlled. They need to switch over to insulin for better control as time goes on.

Mumbai

Dr. Uday Phadke

Even if patient selection is appropriate, 20% patients fail to respond of OHAs initially and another 5-10% lose their response every year. Due to the progressive pancreatic exhaustion that occurs in DM, only a few will continue to respond adequately to OHA's after DM has been present for a decade or longer.

Pune

Dr. Bipin K. Sethi

An inevitable feature considering the progressive nature of the beta cell dysfunction, the factor which is the prime determinant of response to success of OHA's.

Hyderabad

Dr. P. V. Rao

Physicians tend to experiment with several permutations and combinations of OHA's and do not recognize secondary OHA failure at the earliest.

Hyderabad