

Secondary failure to OHA: Etiology and management possibilities

C. M. Batra

ABSTRACT

A widely accepted definition of secondary drug failure is lacking. Secondary drug failure to oral hypoglycemic agents results either because of patient related causes (improper diet, obesity, lack of exercise, lack of knowledge and stress), or due to a defect in the 'stimulus secretion system' of the beta cells and an impaired glucose metabolism. Islet cell antibody studies have identified a new subgroup of NIDDM patients, named 'latent Type I Diabetes' by Group (1). Efficient management possibilities include diet and weight reduction, exercise and in some, insulin treatment.

INTRODUCTION

Secondary failure to oral hypoglycemic agents is defined as a good initial response to oral agents (at least one month) with decreasing effectiveness and eventual failure.

The incidence of secondary drug failure, as published in literature is 0.3% to 30%. A major reason for this discrepancy is the lack of a widely accepted definition of secondary drug failure. Differences in the cut-off level of plasma glucose defining secondary failure and differences in the time period required for a good initial response to treatment are responsible for the wide variation.

The causes of secondary drug failure to oral hypoglycemic agents can be divided into two main groups: the patient factors and disease related factors.

The patient related factors are an improper diet, obesity, lack of exercise, lack of knowledge of diabetes and stress. These factors are well known.

The disease related factors are complex. In order to understand them, we need to go into the pathogenesis of NIDDM. NIDDM is a defect in the 'stimulus secretion system' of beta cells in the interaction between gastrointestinal system and liver and at the cellular level.

The insulin secretion in response to glucose is

frequently but not invariably deficient. The basal insulin secretion is normal and milder degrees of glucose intolerance can be associated with normal or even supernormal insulin response to glucose. Insulin resistance is the hallmark of NIDDM and is located both in the liver and peripheral tissues (mainly the muscle). Hepatic resistance is present in the form of inappropriately high glucose production in the fasting state and non-suppressibility after meals. Peripheral resistance manifests as deficient glucose uptake following glucose ingestion, due to decreased glucose uptake by muscle after exposure to endogenous or exogenous insulin and reduced clearance of plasma glucose in the fasting state. At the cellular level, there is a decreased binding of insulin to its receptors. There is also a significant post-receptor defect.

ISLET CELL AUTO-ANTIBODY STUDIES IN NIDDM:

Islet cell antibody studies have identified a new subgroup of NIDDM patients who are predominantly female, normal to slightly underweight and have a high frequency of other organ specific antibodies. They are islet cell antibody positive. This subgroup has an excess of HLA-DR3 and HLA-DR4, and have a more severely impaired beta cell function as compared to islet cell antibody negative NIDDM patients. Group has named this subgroup as 'latent type I diabetes (1). It has been shown that a large number of these patients develop secondary failure to oral hypoglycemic agents when compared to the small fraction of islet cell antibody negative patients. Irvine (2) first reported islet cell antibody positivity in 11.2% of diabetics on oral hypoglycemic agents within 3 months of diagnosis. DiMario (5) found 16% newly diagnosed NIDDM patients positive for islet cell antibodies.

DISEASE FACTORS IN SECONDARY DRUG FAILURE:

1. Beta cell function-Endogenous insulin reserve as measured in C-peptide response to a test meal is reduced in patients developing secondary drug failure. Thus the fasting blood glucose is higher and rises to higher peak values after a meal.

From: Department of Endocrinology, Batra Hospital, New Delhi.

2. Glucose Metabolism-The basal rates of hepatic glucose production are higher in patients of secondary drug failure compared to responders. Insulin stimulated glucose metabolism is significantly reduced in patients of secondary drug failure. The defect is mainly in the non-oxidative pathway.
3. The net lipid oxidation, protein oxidation and energy expenditure do not differ in patients of secondary drug failure and responders.

To summarise, the patients with secondary failure to oral hypoglycemic agents are characterized by the following:

- I. An impaired C-peptide response to a meal
- II. An enhanced basal rate of hepatic glucose production which is insufficiently suppressed by insulin and
- III. Impaired storage of glucose as glycogen.

MANAGEMENT POSSIBILITIES:

1. Diet and weight reduction: Weight loss has been shown to enhance insulin action. A twenty pound weight loss leads to a doubling of insulin action in obese patients with normal or impaired glucose tolerance. Studies have shown that starvation diets and surgical bypass procedures have produced a remarkable decrease in insulin resistance.
2. Exercise: There is indirect evidence that physical training will enhance insulin action in diabetic patients. The ability of exercise to potentiate the action of insulin has been documented in normal rats and it appears that insulin stimulated uptake is enhanced in muscles of exercise-trained animals.
3. Insulin: By definition, NIDDM patients are not absolutely insulin dependent but yet there is a substantial number of NIDDM patients who require insulin to control hyperglycemia. One report has suggested that in vivo insulin action can be returned to normal levels in at least some insulin-treated patients with NIDDM. However the majority of patients treated with insulin remained insulin resistant. Thus, accumulating evidence suggests that insulin therapy of NIDDM patients may be under-taken with amount of exogenous insulin that would lead to circulating plasma insulin greatly in excess of that which exists in normal persons. The potential side effects of this requires consideration. Thus insulin alone as a therapy for patients of secondary drug failure should be restricted to patients who are lean,

underweight, who are having weight loss, who are islet cell antibody positive and those who have an absent serum insulin in response to a test meal.

4. Insulin and sulfonylurea drugs: Sulfonylureas, besides increasing insulin production by beta cells, have extrapancreatic effects like increasing binding of insulin to its receptor and at the post-receptor level. The discovery of these extra-pancreatic effects justify the combination of insulin and sulfonylureas for patients of secondary drug failure. The combination is recommended in obese patients who have very high insulin requirements, who have insulin resistance and whose C-peptide response is still present.
5. Sulfonylurea with Metformin: The addition of metformin potentiates the action of sulfonylurea drugs because metformin has, besides the actions of sulfonylurea drugs, effects of reducing intestinal glucose absorption, decreased gluconeogenesis, increased glycolysis and increased uptake of glucose. The combination is most effective in patients who are obese, whose main problem is insulin resistance and whose C-peptide response is still present. There should be no contraindications of biguanide therapy like renal, hepatic are cardiac diseases.

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