DRUGS INDUCING DIABETES MELLITUS

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INTRODUCTION

A wide variety of frequently prescribed medications are known to cause glucose intolerance and/or to precipitate overt diabetes mellitus in non-diabetic individuals or to worsen glycemic control in subjects with established diabetes mellitus. These adverse effects on glucose homeostasis are exerted by induction of insulin resistance and/or by the inhibition of insulin secretion. Since glucose intolerance is a characteristic feature of normal aging process, the development of impaired glucose tolerance or even frank diabetes mellitus is frequently observed when older patients are treated for their underlying medical disorders. Despite the rather large number of drugs known to worsen glucose tolerance, in relation to the total number of diabetics, drug induced diabetes can be considered a rare cause of diabetes. This suggests that only sub-populations of the glucose intolerant population are actually at risk and might be prospectively identified.

DRUGS INDUCING DIABETES MELLITUS

Table 1 lists a classification of drug induced diabetes mellitus based on the mechanism of diabetogenesis.

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I Drugs that cause diabetes by interfering with insulin production and secretion

(A) Pentamidine

This is an antiparasitic agent frequently used to treat infections with Pneumocystis carinii in patients with AIDS. It has been recognized that pentamidine can lead to the development of impaired glucose tolerance and overt diabetes mellitus. Higher doses of pentamidine have been associated with more severe hyperglycemia. Pentamidine appears to have a multiphasic effect on the beta cell. Initially the drug causes acute cytolysis and degranulation of beta cells with release of insulin and hypoglycemia. Later on beta cell destruction and impaired insulin release develops with the onset of hyperglycemia and even overt diabetic ketoacidosis may occur within 2-6 months in upto 20% of patients. Pentamidine mesylate has been found to be more cytotoxic than pentamidine isethione.

(B) L-Asparaginase

There are several case reports of diabetes and ketoacidosis in non-diabetic children treated with L-asparaginase. In these cases, there are very low circulating levels of insulin. L-asparaginase does not directly metabolise the insulin molecule but impairs insulin production by depleting asparagine molecule (insulin molecule contains three asparagine residues). Diabetes usually resolves when treatment is withdrawn or completed.

(C) Diphenylhydantoin

It is a commonly used anti-convulsant that is known to inhibit insulin secretion. Dilantin has been shown to inhibit both first and second phases of insulin release. It also inhibits glucose and arginine stimulated insulin secretion. Diabetes usually resolves once the medication is discontinued.

(D) Beta-blockers

Antagonists to beta adrenergic receptors (β-blockers) are commonly used medications that are known to impair insulin secretion. Beta blockers have been shown to worsen glycemic control in NIDDM patients and to impair glucose tolerance or even precipitate
overt diabetes mellitus in non-diabetic individuals. The deleterious effect of beta blockers on glucose tolerance is more pronounced with nonspecific beta antagonists like propranolol compared to beta-1 selective blockers like atenolol. The degree of lipophilicity seems to be an important determinant of the effect of beta blockers on glucose tolerance. Combination therapy with a beta blocker plus a diuretic has an additive and perhaps even a synergistic effect to cause glucose intolerance. The deleterious effect of beta blockers on glucose homeostasis is related both to their ability to inhibit insulin secretion and to induce insulin resistance. Beta blockers also inhibit insulin secretion by pancreatic islets in response to glucose, glucagon or arginine. The inhibitory effect is mediated via beta-2 receptor. This decrease in insulin secretion has been found to be associated with a decline in insulin sensitivity.

Beta blocking drugs have been associated with the development of hypoglycemia in both diabetic and non-diabetic subjects. This can be particularly severe in NIDDM patients in whom normal feedback suppression of hypoglycemia on insulin secretion is absent. The hypoglycemic action of beta blockers is mediated through an inhibition of hepatic glucose production. Beta antagonists can also produce hypoglycemic unawareness by blocking the sympathetic response to hypoglycemia.

Precautions while using Beta blockers in diabetics:

Nonselective beta blockers such as propranolol, pindolol and nadolol will block both beta-1 and beta-2 adrenergic receptors while cardioselective beta blockers block beta-2 receptors only in higher doses. These drugs are indicated in diabetes with coronary artery disease and hypertension. Beta blocking agents have assumed an important role in angina control despite potential problems in diabetics.

These drugs must be used cautiously in patients with diabetes. Cardiac failure due to coronary artery disease, hypertensive heart disease and cardiomyopathy is frequent in diabetic population. Beta blockers by depressing the myocardial contractility further may precipitate overt heart failure in patients with borderline myocardial reserve.

Catecholamine release associated with hypoglycemia accounts for some of the symptoms of hypoglycemia. Because of this, there has been some resistance to use beta blockers in diabetic patients for fear that hypoglycemia symptoms may be masked. Although some hypoglycemic symptoms may be blunted in the occasional patient following beta blockers, this rarely produces a problem. However the diabetic patients who are treated with these drugs must be warned that symptoms of hypoglycaemia may be diminished.

A further caution for the use of beta blockers in the diabetic patient is the potential for aggravating peripheral vascular disease. This can occur through blockade of beta2 mediated vasodilatory responses.

Although beta adrenergic blocking agents have the potential to produce several adverse effects in diabetic patients, serious problems are infrequently reported. The difference between non-selective and cardioselective beta blockers should be considered when these drugs are used to treat diabetic patients.

(E) Diazoxide

Parenteral diazoxide inhibits insulin secretion and there are reports of ketoacidosis in non-diabetic patients treated with multiple intravenous doses of diazoxide. Mechanism is not known, but is reversible on discontinuing the drug.

II Drugs that cause diabetes by reducing effectiveness of insulin in regulating metabolism

(A) Steroids

Glucocorticoids such as hydrocortisone, demethasone and prednisolone may induce diabetes. These drugs are used in a wide variety of disorders and in a wide range of doses. Glucocorticoid induced hyperglycemia can be detected even within hours of administration of the steroid. Glucocorticoids encourage the breakdown of stored protein and fat stores which cause an increased stream of free fatty acids and branched amino acids to the liver. Steroids also induce increased cellular concentration of gluconeogenic enzymes. The result of increased amount of substrate for gluconeogenesis and increased amounts of hepatic enzymatic activity for gluconeogenesis is increased hepatic glucose output. Glucose uptake by fat and muscle is reduced due to insulin resistance and direct steroid effects. Glucocorticoid therapy is a challenge to endogenous insulin secretion and those who have limited pancreatic beta cell reserves may become diabetic.

Oral contraceptives are steroid combinations that are known to increase average glucose concentration in patients with and without diabetes by decreasing insulin sensitivity.

(B) Beta agonists

Ironically both beta agonists and antagonists have been implicated in causing diabetes, albeit through dif-
ferent mechanisms. There is abundant evidence to indicate that beta agonists cause hyperglycemia especially in the later stages of pregnancy. There have been case reports of diabetic ketoacidosis after the infusion of beta-2 agonists and IDDM patients appear to be especially prone to the hyperglycemic effects of these agents because they lack the endogenous insulin secretory capacity to counteract the increase in plasma glucose concentration.

Mechanisms by which beta agonists cause hyperglycemia seem to be multiple. Firstly they stimulate the release of glucose by the liver. They also induce peripheral insulin resistance. Other effects include increase in plasma glucagon following beta-2 agonists and increase in lipolysis. The diabetogenic effect shows a dose-response relationship and oral route of administration may be more diabetogenic than the subcutaneous route of administration with this drug.

(C) Growth Hormone

Growth hormone is a member of the counter regulatory system that is being widely used in varying conditions like short stature. Growth hormone causes insulin resistance at a cellular site after the binding of insulin to its receptor. In the natural example of growth hormone excess namely acromegaly, diabetes occurs in about 20% to 30% of the patients. It is likely that growth hormone therapy will cause diabetes in susceptible persons and that the number of reported cases will increase if growth hormone therapy is extended to other patient groups.

III Drugs that act on both insulin secretion and insulin sensitivity

(A) Diuretics

It is well recognised that diuretic usage is associated with the development of impaired glucose metabolism. Shortly after their institution in 1950’s it became quite clear that many hypertensive patients who were treated with thiazide diuretics developed impaired glucose tolerance or overt diabetes mellitus. Some studies suggest that there is a 28% increase in fasting plasma glucose concentrations and a 45% increase in 2 hour post glucose load concentrations in patients treated with thiazide diuretics.

Apart from thiazides, other diuretics including loop diuretics have also been shown to increase fasting plasma glucose and impair oral glucose concentration. Loop diuretics along with thiazides have been implicated in the precipitation of hyperosmolar hyperglycemic non-ketotic coma.

Triafterene, a potassium sparing diuretic has been implicated in the causation of diabetes. Interestingly indapamide has been reported to have no significant adverse effects on glucose tolerance.

It has been shown that there is impaired glucose tolerance despite a two fold increase in plasma insulin response during an oral GTT indicating impairment in insulin sensitivity. Several studies have shown that thiazide administration can lead to impaired insulin secretion. In some patients, the defect in insulin secretion after thiazide treatment can be related to the presence of hypokalemia. Insulin secretion quantitated with hyperglycemic clamp technique, declined by 25% and the decrease in insulin response correlated well with the severity of total body potassium depletion and the degree of hypokalemia. Potassium repletion has been shown to reverse thiazide induced hyperglycemia in several studies.

Use of diuretics in diabetic patients:

Thiazide diuretics are often effective before the onset of azotemia and in the early azotemic phase of nephropathy and should be considered if there is evidence of fluid overload. While thiazides worsen glucose tolerance in NIDDM patients, this complication is usually not observed in patients with IDDM. Should hyperglycaemia be associated with diuretic induced hypokalemia, potassium supplementation or the addition of a potassium sparing diuretic such as spironolactone or triamterene will generally reverse the abnormality.

Potassium sparing diuretics like spironolactone or triamterene and amiloride should not be used in patients with nephropathy and also in patients with hypaldosteronism, as they may precipitate severe hyperkalemia with associated cardiac arrhythmias.

(B) Cyclosporine

Cyclosporine is a fungal metabolite that is extensively used as an immunosupressant in organ transplant programs. But therapy with cyclosporine has been found by various studies to cause impaired glucose tolerance or diabetes mellitus in 13-47% of renal transplant patients treated with cyclosporine. Mechanisms of cyclosporine induced glucose intolerance appears to be related to a combination of defects in insulin secretion and peripheral tissue sensitivity to insulin. A direct toxic effect of cyclosporine on islet cell function has also been implicated. Cyclosporine has also been shown to inhibit the stimulatory action of oral sulphonylurea agents on insulin secretion.
This compound is a macrolide used for immunosuppression that is more potent that cyclosporine. It also has a similar effect on carbohydrate metabolism but fewer trials have been conducted.

IV Drugs that induce diabetes independent of insulin

(A) Nicotinic acid

This is an effective therapy for dyslipidemia. Nicotinic acid therapy is however associated with increased levels of blood glucose in both diabetic and non-diabetic patients and uncontrolled hyperglycemia is a frequent reason for discontinuing therapy. Mechanism of nicotinic acid induced hyperglycemia is an increase in hepatic blood glucose output due to enhanced gluconeogenesis, secondary to rebound increase in flow of free fatty acids (FFA) to the liver.

(B) Total parenteral nutrition (TPN)

TPN in the intensive care and non-intensive care settings is frequently associated with significant elevation in blood glucose concentrations. No large studies have been conducted in this regard but the physician must monitor these patients for the development of diabetes.

(C) Miscellaneous drugs

Aspirin has a biphasic response on glucose tolerance. In low doses, glucose tolerance improves and hypoglycemia may occur secondary to stimulation of insulin secretion. In higher doses, aspirin impairs insulin sensitivity by uncoupling oxidative phosphorylation which may lead to a decline in glucose tolerance.

Phenothiazines have long been implicated in the development of impaired glucose tolerance. The most commonly cited offender in this class of drugs is chlorpromazine. It is thought to impair glucose tolerance by inhibition of insulin secretion.

A number of other drugs including librium, dapsone, indomethacin, theophyllin, cimetidine and nalidixic acid have been implicated in the development of glucose intolerance.

SUMMARY

Drug induced diabetes occurs due to a variety of drugs and mechanisms. Considering the vast number of diabetics in this country and also the wide variety of drugs prescribed for diabetic as well as non-diabetic patients especially the elderly, the entity of drug induced diabetes does not appear to be very common. This suggests that an underlying and often unsuspected abnormality probably increases the risk of developing diabetes mellitus. Sulphonylureas which act primarily by enhancing insulin secretion, would not be an effective therapeutic modality for countering drug induced diabetes. In case the drug has to be continued, insulin therapy is the most efficacious approach. The new thiazolidinedione drugs such as troglitazone which increase insulin sensitivity in patient with glucose intolerance and diabetes, may be very useful in cases where insulin resistance has resulted in diabetes.

REFERENCES