

USE OF DIAZOXIDE FOR THE TREATMENT OF METABOLIC SYNDROME AND DIABETES COMPLICATIONS

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a novel treatment for metabolic syndrome and resulting complications, such as obesity, hypertension, hyperlipidemia, hyperinsulinemia and impaired glucose tolerance. In addition, it concerns the use of diazoxide for the treatment of syndrome-X and resulting complications, as well as diabetic complications.

Oral diazoxide (7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-diazoxide) is a nondiuretic congener of the thiazide diuretics which inhibits insulin release from the pancreas (ref. 1). Diazoxide was originally developed for the treatment of hypertension. One of the adverse affects of diazoxide was found to be hyperglycemia, which proved useful in the treatment of hypoglycemia. The hyperglycemia caused by diazoxide is usually transitory and is due to decreased insulin secretion and decreased peripheral utilization of glucose (ref. 2). Diazoxide is now used primarily for the treatment of hypoglycemia due to hyperinsulinism, associated with conditions such as inoperable islet cell adenoma or carcinoma (ref. 3). The drug is currently marketed in the U.S. under the tradename Proglycem.

Syndrome-X is a metabolic syndrome. The term syndrome-X was given by Reaven et al describing a condition characterized by central obesity, and metabolic manifestations including resistance to insulin stimulated glucose uptake, hyperinsulinemia, glucose intolerance (not necessarily diabetes), increased level of very low density lipoprotein triglyceride (VLDL), decreased level of high density lipoprotein cholesterol (HDL) concentrations and hypertension (refs. 4, 5). Each of these characteristic features are considered to be risk factors for development of atherosclerosis and other 'old age' diseases. It is believed that syndrome-X is caused by insulin resistance, but no treatment is available at present.

U.S. Pat. No. 5,284,845 discloses the use of oral diazoxide for the normalization of blood glucose and insulin levels in disorders of hyperinsulinemia and diabetes.

However, the background art does not suggest the use of diazoxide for the treatment of syndrome-X, nor for diabetes complications.

No treatment is available for syndrome-X and thus there is a widely recognized need for a drug such as is described in the present invention which is effective in the possible prevention and treatment of syndrome-X and diabetes complications.

SUMMARY OF THE INVENTION

The present invention provides a drug for the treatment of metabolic syndrome, related complications and diabetes complications. Preferably, the present invention provides diazoxide to inhibit the release of insulin and proinsulin, lower weight, reduce levels of circulating cholesterol and triglycerides, lower blood pressure and prevent and reverse diabetic complications in subjects with a metabolic syndrome such as syndrome-X, or with diabetes complications.

According to the teachings of the present invention there is provided in a first embodiment a method for treating syndrome-X and resulting complications in a subject, comprising the step of administering to the subject, a pharmaceutically effective amount of diazoxide.

In a preferred embodiment the complication is selected from the group consisting of central obesity, hyperlipidemia, hyperinsulinemia, hypertension and impaired glucose tolerance.

In a preferred embodiment the pharmaceutically effective amount is from about 4 mg/kg to about 15 mg/kg.

In a preferred embodiment the pharmaceutically effective amount is from about 5 mg/kg to about 8 mg/kg.

In a preferred embodiment the diazoxide is provided in a tablet form.

In a preferred embodiment the diazoxide is provided in an intravenous form.

In a preferred embodiment the preferred route of administration is oral.

In a preferred embodiment the diazoxide is administered until endogenous insulin levels are lowered.

In a preferred embodiment exogenous insulin must be administered.

In a preferred embodiment the diazoxide decreases proinsulin levels.

In a second embodiment, the present invention provides a method for prophylactic treatment of syndrome-X in a subject, comprising the step of administering to the subject a pharmaceutically effective amount of diazoxide.

In a third embodiment, the present invention provides a method for reducing the release of insulin and proinsulin in a subject with syndrome-X, comprising the step of administering to the subject a pharmaceutically effective amount of diazoxide.

In a preferred embodiment the method for reducing the release of insulin and proinsulin in a subject with syndrome-X, further comprises the step of administering exogenous insulin.

In a fourth embodiment, the present invention provides a method for reducing weight in a subject with syndrome-X, comprising the step of administering to the subject a pharmaceutically effective amount of diazoxide.

In a fifth embodiment the present invention provides a method for reducing the levels of circulating cholesterol and triglycerides in a subject with syndrome-X, comprising the step of administering to the subject a pharmaceutically effective amount of diazoxide.

In a sixth embodiment, the present invention provides a method for lowering blood pressure in a subject with syndrome-X, comprising the step of administering to the subject a pharmaceutically effective amount of diazoxide.

In a seventh embodiment, the present invention provides a method for treating a diabetic complication in a subject, comprising the step of administering to the subject, a pharmaceutically effective amount of diazoxide.

In a preferred embodiment in a method for treating a diabetic complication in a subject, the diabetic complication is selected from the group consisting of complications of adult-onset diabetes, syndrome-X and other metabolic disorder.

In a preferred embodiment in a method for treating a diabetic complication in a subject, the complication is high proinsulin levels.

In a preferred embodiment in a method for treating a diabetic complication in a subject, the pharmaceutically effective amount of diazoxide is increasing doses of diazoxide until endogenous insulin levels are lowered with ketonuria necessitating exogenous insulin administration appears.

In an eighth embodiment, the present invention provides a method for causing insulin sensitization in a subject,