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Gliclazide

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ABBREVIATIONS: (AGE) advanced glycation end products, (CV) cardiovascular, (ESR) electron spin resonance, (HGP) hepatic glucose production, (HPLC) high performance liquid chromatography, (NIDDM) non-insulin dependent diabetes mellitus, (ROS) reactive oxygen species, (SOD) superoxide dismutase

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ABSTRACT: Gliclazide, a sulphonylurea, is used to treat non-insulin dependent diabetes mellitus (NIDDM). Its primary mode of action is to increase insulin secretion by pancreatic β cells. It also as a variety of other effects on the cells; such as a reduction in hepatic glucose production, improved glucose turnover, a reduction in platelet aggregation and a free radical scavenging effect. This paper will explore the characteristics of gliclazide and its primary biological effects.

INTRODUCTION

The treatment for NIDDM generally focuses on the reduction of blood glucose levels. Increased blood glucose, which is caused by defective insulin secretion and decreased insulin sensitivity, is the hallmark of diabetes. There is a multitude of complications involved with this disease; kidney failure, micro- and macrovascular disease, retinopathy and atherosclerosis.

Gliclazide (1-(1-azabicyclo[3,3,0]oct-3-yl)-3-(p-toylsulphonyl)urea) is a second generation sulphonylurea drug. It is used for treatment of non-insulin dependent diabetes mellitus. Gliclazide works in several different ways, but its primary function is to increase insulin sensitivity, improve glucose clearance and reduce the amount of hepatic glucose produced. Gliclazide has also been shown to reduce platelet adhesion and aggregation, increase fibrinolysis and scavenge free radicals.

DIABETES AND FREE RADICALS

Diabetic patients have an increased level of blood glucose, but some patients also have secondary effects from the diabetes, such as poor circulation, platelet adhesion and aggregation, excess free radicals, shortage of antioxidants, heart disease, cataracts and liver and kidney problems. Most of these are caused, at least in part, by too much glucose. Excess glucose can be toxic to cells in several ways, two of which are the formation of advanced glycation end products (AGE) and free radicals such as $O_2^{\bullet -}$, $^{\bullet}OH$. Both types of products can contribute to diabetic complications. The ideal drug for diabetes treatment would be one that not only controlled the glucose levels, but also dealt with some of the complications and secondary effects of diabetes.

GLICLAZIDE

Gliclazide is available from a variety of different companies under many different brand names. The brand names and manufacturer are listed in Table I.

Table I. Brand names and manufacturers of gliclazide.

Brand Name	Manufacturer
D Clic	Grandix
Diabend	Bal Pharma
Diamicron	Serdia
Dianorm	Micro Labs
Diasafe	Sertec
Gliclaz	Khandelwal
Glidiet	Modi-Mundi
Glix	Indipharma
Glizid	Panacea
Glycigon	Aristo

Gliclazide has a molecular weight of 323.4 g / mol and is a weak acid with a pKa of 5.8 [2]. It is a second-generation sulphonylurea drug, but unlike other drugs in this family, gliclazide contains an azabicyclo-octyl ring (Figure 1). The best method for assaying gliclazide is HPLC, which is highly sensitive and specific for gliclazide. There is a radioimmunoassay for gliclazide, but it is not as specific as HPLC.

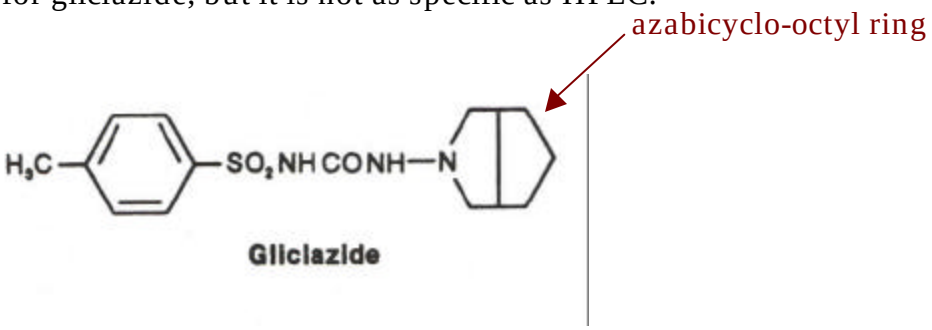

Figure 1. The structure of gliclazide [2].

Gliclazide is well absorbed by the body, approximately 80% is absorbed. One dose of gliclazide has a half-life of 11-12 hours with the peak absorbance occurring at about 4-6 hours. A steady state level is reached after about 2 days of treatment. This convenient half-life allows the patient to keep a steady level of the drug in their system while only having to take the drug twice a day. The daily dose, which is given in two fractions, is generally between 40 and 80 mg at the beginning of treatment, but the dose can be increased up to 320 mg / day. Like most sulphonylureas, gliclazide binds primarily to plasma albumin (85-99%), allowing it to be distributed uniformly throughout the body [2].

Gliclazide is metabolized *via* three primary methods: oxidation of the tolyl group; hydroxylation of the azabicyclo-octyl ring; and glucuronidation [2]. There are 8 known metabolites. The majority of the drug excreted is found in the form of one of the metabolites. In contrast, approximately 90% of the drug found in the plasma is in the original, unmetabolized form.

The use of gliclazide is not suggested in patients with any of the following conditions: pregnancy, lactation, renal impairment, juvenile or brittle diabetes and diabetic ketoacidosis [10]. Gliclazide is known to cause interactions with several other drugs, such as aspirin, sulphonamides, oral anticoagulants, MAO inhibitors, barbiturates, alcohol, glucocorticoids, estrogens and several others [10].

There are few side effects caused by the use of gliclazide, and most are mild. Some of the common side effects are gastrointestinal problems (nausea, diarrhea, pain, constipation), dermatological disturbances (rash, flushing, erythema), lightheadedness, headaches and dizziness [8,10]. One of the important problems to watch for is hypoglycemia. Hypoglycemia is caused by not enough glucose, and it can be just as dangerous as an excess of glucose. Since gliclazide is designed to increase glucose clearance, it is possible for it to work too efficiently, thereby causing hypoglycemia. This side effect can be avoided by carefully monitoring blood glucose, especially at the beginning of treatment, and following a diabetic mean plan that includes small snacks between meals to keep the blood sugar stable.

BIOLOGICAL EFFECTS

Glucose and gliclazide stimulate insulin release in a similar manner. Glucose increases the concentration of ATP in the cell, which then inhibits the action of the K^+ ATP channel. This causes a depolarization of the cell membrane, inducing the Ca^{2+} channel to open. Gliclazide acts by binding to the β cell sulphonylurea receptor. This binding subsequently blocks the K^+ efflux which in turn activates the voltage-dependent Ca^{2+} channels. Glucose and gliclazide may also cause a direct increase in the Ca^{2+} flow. This increase in intracellular calcium acts as a second messenger. Calcium,

acting as a second messenger, can induce phosphorylation of the proteins involved in insulin release (Figure 2).

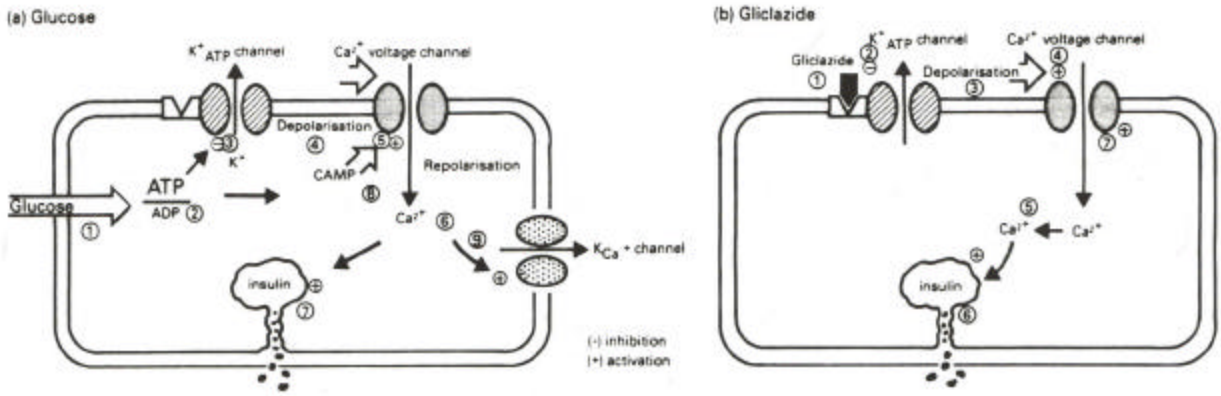

Figure 2. The effect of glucose and gliclazide on insulin secretion. Glucose and gliclazide both depolarize the cell membrane, thereby causing the activation of the voltage-gated Ca2+ channel. Ca2+ ions then act as a second messenger, causing phosphorylation of proteins involved in insulin secretion.

Basal hepatic glucose production was not affected by gliclazide, but insulin-stimulated HGP was reduced by 31-85% through gliclazide treatment. It does not appear to be cause an increase in insulin levels, in either the basal or insulin-stimulated state [8]. In both *in vitro* and *in vivo* studies, gliclazide appeared to have no direct effect on the cell's insulin receptors. Gliclazide appears to allow the cell's insulin sensitivity to revert back to normal, *via* an unknown mechanism.

Gliclazide enhances glucose uptake and clearance by approximately 50% [2]. This effect on glucose levels is comparable to other sulphonylureas and oral hypoglycaemic agents. It also seems to inhibit the gluconeogenesis process and cause an increase in the amount of fructose-2,6-bisphosphatase available to the cell, which increases the amount of glycolysis occurring. Both of these processes, gluconeogenesis and glycolysis, act to decrease the amount of glucose available to the cell.

Diabetic patients have been shown to have platelets with increased adhesiveness and aggregation, increased concentrations of thromboxane A_2, platelet factor 4 and β-thromboglobulin [8]. Increase in platelet aggregation can cause a variety of effects: vasoconstriction, anoxia, ROS, atherosclerotic plaques, retinopathy, nephropathy and CV disease. Gliclazide is able to reduce the increase in platelet adhesiveness and

aggregation, it has also been shown to reduce the release of platelet factors. Gliclazide causes a reduction in anoxia, reperfusion damage and ROS, while increasing fibrinolysis and basement membrane thickness. Figure 1 details some of the haemobiological actions of gliclazide. The net effect of these actions is a reduction in the risk of atherosclerosis.

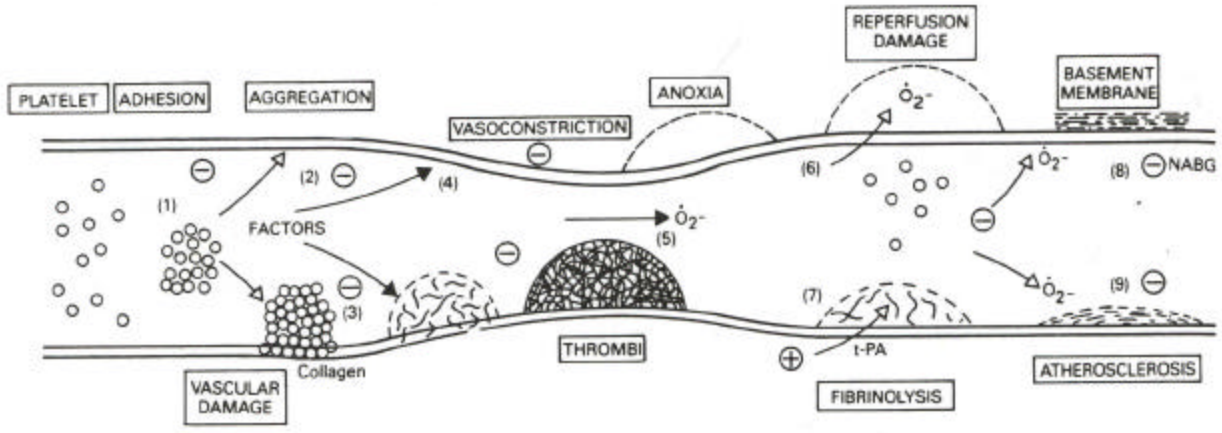

Figure 3. Hemobiological effects of gliclazide. Gliclazide causes a reduction in platelet adhesion and platelet factors, which in turn decrease platelet aggregation, vasoconstriction and vascular permeability. This allows oxygen flow to increase, reducing anoxia and reperfusion damage caused by free radicals. It also stimulates tissue plasminogen activator, which increases fibrinolysis and basement membrane thickness [2]. (+) increases, (-) decreases

Gliclazide has been shown to cause a significant reduction in free radicals. In *in vitro* studies, gliclazide performs as a free radical scavenger. Gliclazide is able to scavenge $O_2^{\bullet-}$, $^{\bullet}OH$ and $^{\bullet}NO$ [7]. The concentration required for its scavenging ability, 0.5 to 5 mg/L, can be achieved in the plasma with the normal therapeutic dose. It has also been shown that the amount of lipid peroxides in the cell is decreased and the activity of superoxide dismutase is increased (Figure 4).

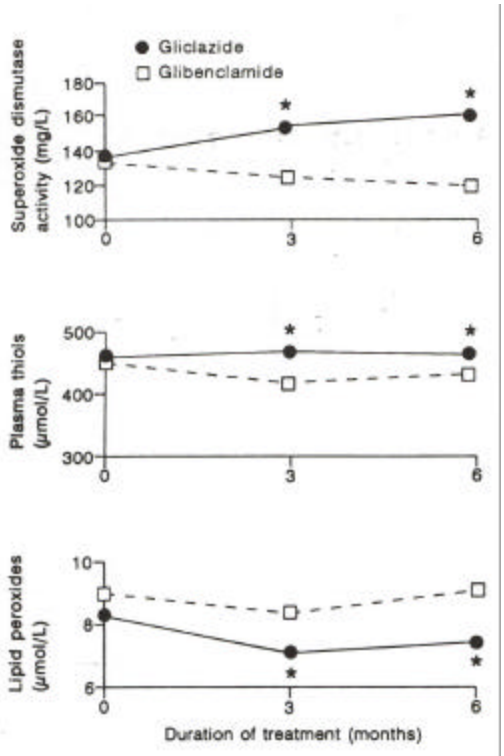

Figure 4. Comparison of gliclazide and glibenclamide's effect on various

In vitro studies were done to test gliclazide's radical scavenging ability. ESR was the means used to monitor the amount of radicals present (Figure 5). Gliclazide's ability to scavenge superoxide is considerably less than that of vitamin C, it's activity has been estimated at 0.18 ± 0.08 SOD equivalent units / mg [7].

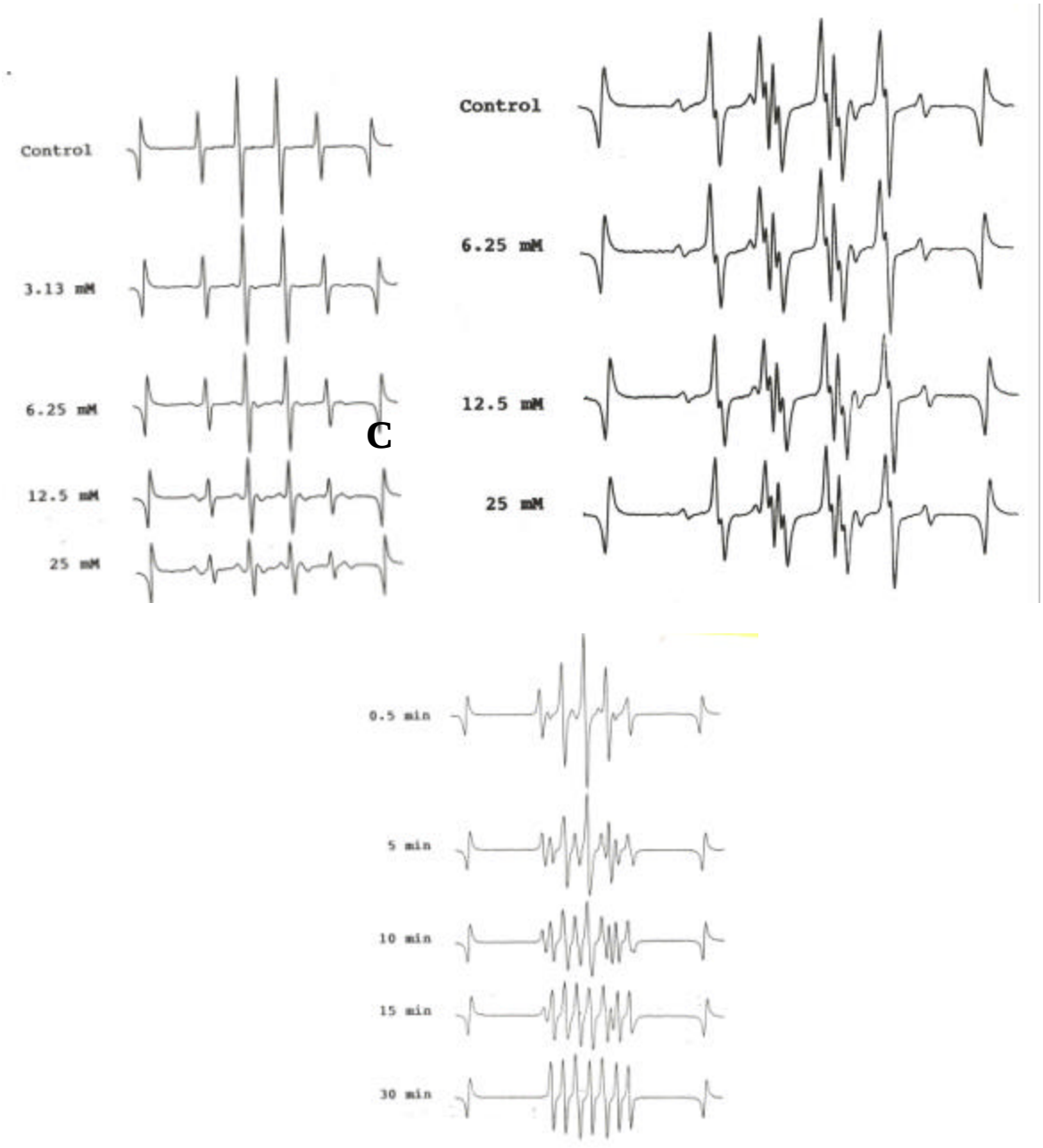

Figure 5. ESR spectra. The ESR spectra of gliclazide with a) hydroxyl radical, b) superoxide radical and c) nitric oxide [7].

It is a fairly capable scavenger of the hydroxyl radical, with its activity estimated at 0.18 ± 0.06 EPC-K_1 equivalent (μmol / mg). Gliclazide is also an effective scavenger of nitric oxide, an estimate of its scavenging ability has not been made. Gliclazide's scavenging ability may have a secondary effect of reducing protein glycation and AGE formation. This has not been proven to date though. The actual mechanism of gliclazide's scavenging ability is not known at present, but I believe it will be shown to involve its azabicyclo-octyl ring, because it is gliclazide's unique feature. No other sulphonylureas are free radical scavengers, and none contain this distinct moiety.

CONCLUSION

Gliclazide does a good job of controlling glucose levels through a variety of paths. It utilizes different methods of increasing glucose disposal, while simultaneously decreasing glucose production to accomplish this overall reduction. The maintenance of the proper blood sugar level is highly important for diabetic patients, but even with good glucose control, diabetic patients still suffer from a variety of complications. Gliclazide may not address all of these complications, but it is able to improve several secondary effects of diabetes, such as platelet aggregation and free radical levels.

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