PANCREATIC INSULIN RESERVE IN RESPONSE TO GLIBENCLAMIDE

THESIS

For Partial Fulfilment of Master Degree

In

GENERAL MEDICINE

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1980

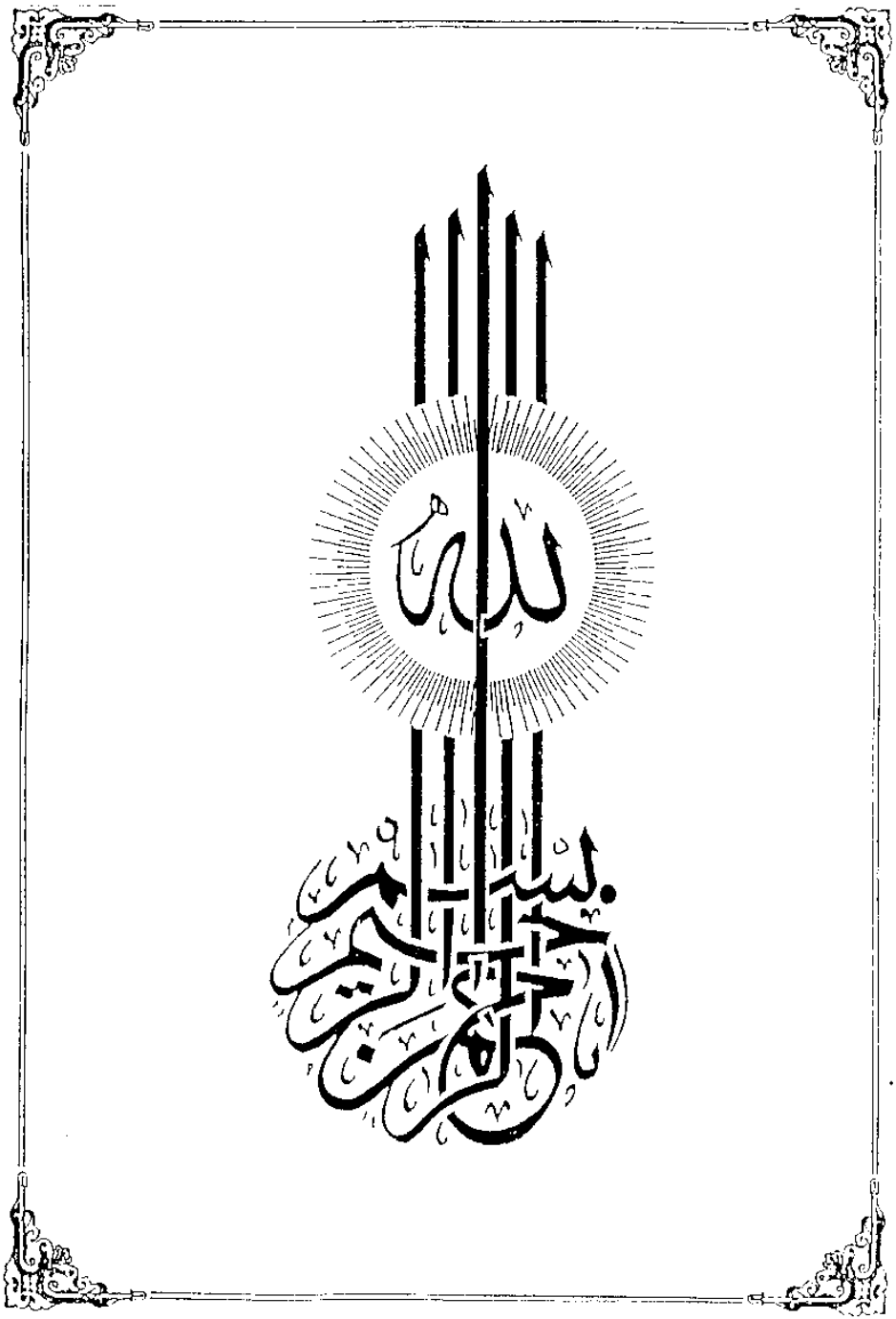
ACKNOWLEDGEMENT

I would like to express my deepest gratitude and most sincere thanks to Prof. Dr. Ahmed Ghareeb Prof. of Medicine and Head of Endocrine Unit Ain Shams University for his valuable supervision and encouragement through the whole work.

I wish to excpress my sincere appreciation to Dr. Hussein El-Sayed El-Damassy Assistant Prof. of General Medicine in Endocrine Unit Ain Shams University for giving me the broad outlines of such subject and for his close supervision throughout the whole of this study. His constant advice and constructive creticism are beyond achknowledgement.

I would like to express my thanks to Dr. Elham Ez El din Islam Lecturer of General Medicine in Endocrine Unit Ain Shams University for her help, advice and revision of this work.

I also wish to express my thanks to Mr. Nabil Mitry and Mr. Magdy Abass and Miss Nadia El-Wardani for their role in the Laboratory Assessment of the blood samples.



C O N T E N T S

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INTRODUCTION

I N T R O D U C T I O N

Glibenclamide was introduced in 1967 and was the first of the so-called second-generation sulphonylureas. It brings together research workers from Germany and abroad. The drug is better known by its designation HB 419.

Recognition of the beta-cytotropic effect of sulphonylureas has brought the physiology, normal and abnormal of the islet cells into the clear light.

The therapeutic use of sulphonylureas was confined to maturity onset diabetics who constitute the overwhelming majority of diabetic patients. Now it is known that these patients are capable of intrinsic insulin production. However, their insulin production is ineffective simply because the islets no longer respond to the physiological stimulus, namely an increase in blood sugar. With the aid of sulphonylurea derivatives, it seems to be possible to overcome this unresponsiveness of insulin secretion.

After adminstration of these drugs, all diabetics still capable of intrinsic insulin production mobilize their insulin reserve (Pfeiffer, E.F.1969).

A dose of few milligrams of glibenclamide is enough to produce the same hypoglycaemic effect as 1,000 or 1,500 mg. tolbutamide (Bhatia, S.K. et al., 1970).

This can be demonstrated on islet slices in vitro (Hinz, M. et al. 1969). From the therapeutic point of view, this fact means that the body will be exposed to minimal quantities of the chemical agent. The antigenic power of glibenclamide must be extremely small. Glibenclamide seems in fact to be the best tolerated of all drugs of this group and to have the lowest risk of allergic or toxic side effects. (Jackson W.P.U. et al. 1969).

The hypoglycaemic action of glibenclamide persists longer than that of tolbutamide. There are differences between the insulin and blood sugar curves after doses of the old or of the new sulphonylurea derivatives (Clarke, B.F. et al., 1975).

The possibility that these substances may have effects outside the pancreas must be considered. They may reach compartments of the beta cells not opened up by tolbutamide and other drugs of this group.

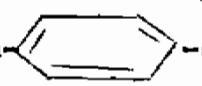
Time will tell whether the superiority of glibenclamide demonstrated in pharmacological and pharmacodynamic investigations, is in fact borne out by clinical studies. However there is no doubt that glibenclamide will give diabetes research and treatment an impetus which will be welcomed by all concerned- doctors, patients and scientists alike.

REVIEW OF LITERATURE

C H E M I S T R Y

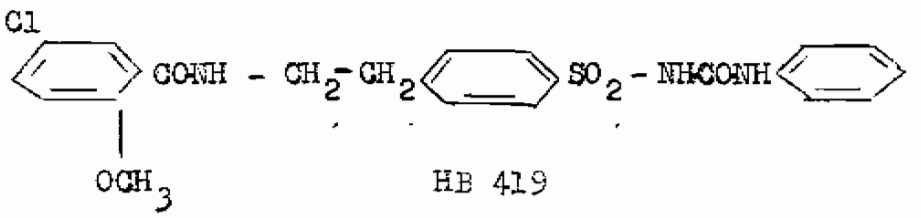
After the development of the oral antidiabetic agents carbutamide and tolubtamide by Farbwerke Hoechest and Boeringer Mannheium. Various similar compounds were synthesized by other workers. The most important drugs commerically available are chlorpropamide, acetohexamide, tolazamide and glycodiazine.

The collaboration between Hoechst and Boehringer continued with the aim of developing new oral antidiabeties with greater potency, longer duration of action and fewer side effects. In the course of these investigations some 8,000 compounds were synthesized, 6,000 of which proved to have hypoglycaemic effects on pharmacological testing. The relationships between chemical structure and pharmacological action which were worked out in the course of these studies led to the synthesis of drugs which displayed superior qualities in animal experiments and in human subjects.

They differ from the available preparations in that, the radicles in R-alkylen-  -SO_2 NHCONH-- (alkyl) are linked to the phenylsulphonyl residue by an alkylene bridge. Systemic modification of the acylaminoalkyl

residue (R-NH-CO-) resulted in the synthesis of N-4-(2-benzamidoethyl) phenylsulphonyl-N-cyclohexylurea. Attachment of various groups to the benzoyl residue of this compound showed that the introduction of chlorine at a siutable position prolonged its action while the introduction of a methyl group impaired a definite increase in potency (Weber, H. et al., 1969).

Combination of both these procedures led to the outstanding compound N-4-2-(5-chloro-2-methoxybenzamido) phenylsulphonyl-N-cyclohexylurea, which was evaluated under the designation HB 419.



HB 419

Glibenclamide is a stable, crystalline, odourless, colourless compound.

ABSORPTION, METABOLISM AND EXCRETION OF GLIBENCLAMIDE

Gastro-intestinal absorption:

The comparison of the initial concentration after oral and intravenous application, of glibenclamide following correction for dose difference by Christ, O.E et al., 1969 , showed that an absorption rate of 43 per cent. Since elimination can only proceed after metabolism of glibenclamide, absorption rate can be calculated from the quantity of unchanged glibenclamide excepted with stools; this results is 46 per cent. Measuring urinary excretion after intravenous and oral application constitutes a third method of calculation. This procedure results in 45 percent absorption rate.

Studies with C^{14}-labelled glibenclamide was undertaken by (Anderson, J. et al., 1970), to determine the nature of the metabolism of glibenclamide in diabetic patients and compaired with the data on the non diabetic subjects as obtained by Christ. O.E. et al., 1969 . The peak plasma radioactivity occured between 2-6 hours which is a wider range than that reported in healthy volunteers where the peak activity was never after 4 hours. This

could be due to altered absorption characteristics, and it is interesting that the greatest delay in reaching maximum plasma and urine activity occured in diabetics complicated by cardiac and hepatic disease.

Metabolism:

Christ O.E. et al., (1969) found that in man there are three metabolites M_1, M_2 and M_6. M_1 is the principal metabolite. It is found in the serum, urine and faeces. It has been identified as a derivative of glibenclamide hydroxylated at the trans position of the cyclohexyl ring. M_2 was found in smaller amounts in the serum and also present in urine and faeces. It is hydroxylated in the same ring but in the 3-cis position. M_6 found only in minute amounts in urine has not yet been identified.

Excretion:

Glibenclamide which has been absorbed from the intestine or given intravenously is excreted only in the metabolised form. The intact drug found in the faeces has not been absorbed. About 40% of the oral dose of glibenclamide can be recovered from urine over the 48 hours period after administration, which probably indicate that a similar

proportion is abosrbed from the gut, and little appear to be retained in the body. Because glibenclamide is excreted in urine this leads to caution in its use in patients with renal impairment, who might be expected to retain both drug and metabolities with resultant higher plasma level and the risk of prolonged hypoglycaemia.

For actual clinical application of glibenclamide the following in noticed by Christ O.E. (1969):

1. Approximately 50 per cent of the compound is absorbed after oral administration.
2. Glibenclamide does not pass through the entero-hepatic cycle.
3. The measured half life periods and the calculated dose relations do not suggest accumulation.
4. Absorbed glibenclamide is completely metabolised.
5. The metabolites in their actual concentration have no essential hypoglycaemic effect. They are quickly and completely eliminated.

MECHANISM OF ACTION

Glibenclamide has a high potency relative to all other sulphanylureas and it is up to thousand times as active as tolbutamide on a milligram for milligram basis. (Schmidt, F.H. 1969). This difference is difficult to explain from an examination of the structural formula of the two compounds and there is at present no evidence that the extent of their plasma protein-binding or ability to enter the tissues differ sufficiently to provide a satisfactory explanation. Glibenclamide acts in the same manner as the other sulphonylureas-that is by stimulating pancreatic beta cells to release insulin (Strek O.V. 1969). Thus it is unlikely to exert any effect in people without pancreatic function (whether as a result of pancreatectomy or of chronic pancreatic disease). This has been confirmed by Pfaff. W. et al., (1969) in animals rendered diabetic by the administration of alloxan, in which glibenclamide failed to reduce blood sugar. Further evidence that glibenclamide increases the secretion of insulin from pancreatic beta cells come from the observation that action potentials in isolated mouse islet cells may be produced by sulphonylurea compounds including glibenclamide and that these potentials are