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PHARMACODYNAMICS OF METFORMIN IN DETARIUM GUM MUCOADHESIVE FORMULATION

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ABSTRACT

The pharmacodynamic effects of metformin in a mucoadhesive delivery system of detarium gum are presented. The gum compacts alone without the drug showed blood glucose lowering capacity. The combinations showed marked antidiabetic effect in streptozotocin-induced diabetic rat models.

Key words: *pharmacodynamics, metformin, detarium gum, mucoadhesive*

INTRODUCTION

The use of various combinations of antidiabetic agents in the management of diabetes is a common practice in clinical medicine.[1-3] This is used to achieve stable blood glucose level, reduce toxicity and possibly increase dosage intervals. Metformin is a biguanide antidiabetic with no hypoglycaemic activity.[4] The drug is one of the mainstays in the management of type 2 non-insulin dependent diabetes mellitus (NIDDM). Its use as an antiaging drug has been pointed out.[5] The use of the drug in the treatment of diabetes is sometimes limited because it is known to precipitate hyperlactataemia with resultant lactic acidosis. This is dose dependent and hence any combination that will reduce the dose while maintaining therapeutic equivalence is encouraged.

Detarium gum is a polysaccharide extracted from the seeds of *Detarium microcarpum* (Fam. Malvaceae). The seeds are often used among natives as soup thickener. The gum is known to reduce blood glucose level as many gelling agents do.[6] The effect of compacts of this gum containing metformin on blood glucose level is presented in this study.

Materials and Methods

MATERIALS

The following materials were used as purchased from their commercial sources. Acetone(Riedel de Haen), sodium metabisulphite (BDH Chemicals), metformin (Sigma), streptozotocin (Wako Pure Chemicals), and phenobarbitone sodium (Sigma). Detarium gum was obtained from a batch processed in our laboratory.[7]

ANIMALS

Male Wistar rats having a mean weight of 160 ± 12 gm were used for the studies. The rats were kept under standard laboratory conditions, fed with standard meal before use and acclimatized in the new laboratory condition for two weeks prior to experimentation.

Methods

Induction of diabetes

Diabetes was induced using streptozotocin. The drug was dissolved in 0.1 M citrate buffer (pH 4.5). A total quantity of 60mg/kg body weight of the streptozotocin was administered to the rats intraperitoneally. After four days of streptozotocin administration, the animals were checked for diabetes induction based on weight loss and

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serum glucose level. Before determination of the blood glucose level, the animals were fasted for 18 h with free access to water.

PREPARATION OF DETARIUM GUM

The detarium seeds were purchased locally from Nsukka market. The seeds were heated at 100°C in an oven (Gallenkamp) for 6h to remove the cracked seed coats. The heating also denatures some auto-oxidation enhancing enzymes, which are present in many seeds that contain polyphenols. The resultant cotyledons of the detarium seeds were pulverized using a hammer mill. The powdered material was dispersed in water and allowed to hydrate. The hydrated mucilaginous material was passed through a calico and the resultant filtrate was desolvated-using acetone. The resulting wooly white precipitate was collected on a Buchner funnel by means of suction by a vacuum pump. The resultant material was dried in a vacuum desiccator to prevent darkening as a result of auto-oxidation. The dried material was powdered using an end runner mill and stored in well-stoppered containers until used.

COMPRESSION OF THE TABLETS

One hundred and fifty flat-faced tablets were compressed using a hand press (Shimadzu Pressure Apparatus, model SS-P10A) at a pressure of 0.15-ton force. The tablets were 14 mm in diameter and 1.25 mm thick. The dimensions were measured using micrometer screw gauge (model ìmate, Sony Magnescale, Inc.) The tablets contained 200 mg of metformin. A batch was also prepared without any metformin for the purpose of comparison.

EVALUATION OF PHARMACODYNAMIC EFFECTS

All the studies were carried out according to the World Health Organization Guidelines on the Use of Laboratory Animals, 1982.

The study was carried out invasively. Using surgical materials the stomach of the rats were opened after anesthesia with phenobarbitone sodium (50 mg/ml given as 0.1 ml/kg body weight of the rats). Similarly, the jugular veins of the rats were carefully exposed, and the initial blood glucose level was determined at time zero. A piece of the tablet containing 150 mg/kg of metformin was carefully placed in the duodenum using a pair of forceps and sealed with glue. The abdominal portion of the rats as well as the areas around the jugular vein were kept from drying by means of a cotton wool soaked in normal saline. At predetermined time intervals 0.3 ml of the blood was withdrawn and analyzed for glucose content using a test kit (Glu B, Wako).

Analysis of blood glucose level

Calibration curve

This was prepared using standard test kits (Glu B, Wako). A standard curve was plotted using standard solutions II and I. The standard solutions were appropriately diluted and 1 ml of glucose test reagent was added. Similarly, 2 ml of water was added and vortex-mixed using a minishaker (model MSII KA Works, Inc) for 10 secs. The resulting solution was incubated at 37°C for 20 min and analyzed spectrophotometrically at 505 nm using UV 1600 spectrophotometer (Shimadzu). The resulting data was used to plot a standard curve.

DETERMINATION OF SERUM GLUCOSE LEVEL

This was done using glucose test kits. A 0.3 ml of blood sample was withdrawn from the rats and allowed to stand for 40 min. After this, it was centrifuged at a speed of 1200 rpm at 4°C for 70 secs in a Kubota centrifuge (model 1720). The clear serum above the residue was collected using 200 µl Drummond pipettes and refrigerated. A 20-µl aliquot of the serum was further collected and treated with the glucose reagent (1 ml), mixed with 2 ml of deionized water and vortexed for 10 secs. The resulting purple coloured solution was incubated in a water bath at 37°C for 20 min and assayed spectrophotometrically. The concentration of the glucose in the solution was extrapolated from the standard curve. Four rats were used for each experiment and the data shown is the mean of four observations.

RESULTS

The results are presented in tables 1 and 2, and in Figure 1.

Table 1. Changes in the body weight and serum glucose levels of the rats.

	Before administration of streptozotocin	4 days after administration of streptozotocin
Body weight (gm)	430.31± 28.57	351.24 ± 33.3
Serum glucose level (mg/dl)	182.14 ± 22.41	552.25 ± 29.25

Table 2. *The AUEC (Area under the effects Vs concentration time curve) of the preparations.*

Material	AUEC*
Normal saline	485.82
150 mg metformin in aqueous solution	1000.61
150 mg metformin / 100 mg detarium gum	1259.91

* Determined using WinHARMONY programme[12]

DISCUSSION

The weight and serum glucose levels of the rats are shown in Table 1. The table indicates that there was a fall in the body weight of the rats and a sharp rise in the serum glucose level. This is indicative that diabetes was induced as in an earlier study.[8]

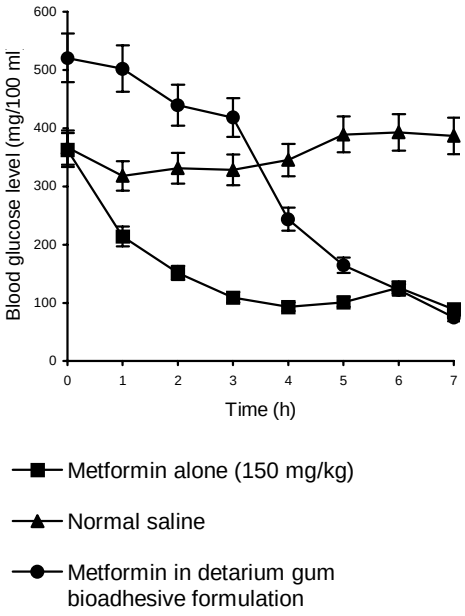

Figure 1. Blood glucose lowering property of the mucoadhesive tablets

Glucose levels above 180 mg/dl may be taken as diabetic in heavy rats like those used in this study especially as the animals were fasted for 18 h with access to water only. The weight loss is due largely to the diabetes but to a smaller extent to the fasting as well.

Fig. 1 shows the blood glucose lowering property of the mucoadhesive tablets. The 150 mg/kg of the drug in 100 mg/kg of the detarium showed a more marked decrease in serum glucose level. This is more clearly shown in Table 2.

Detarium gum as with many other gums, is known to possess mucoadhesive property.[9] This means that in the stomach environment the gum swells after absorbing water and adheres to the stomach wall. The gum has also been shown to possess glucose-lowering property.[10]

Detarium gum has been shown to form a non-digestible gel in the stomach thus preventing glucose resorption after food digestion.[10] This may also affect the level of digestive enzyme secretion. This effect on the entero-insular axis[6] may be responsible for the higher depression of blood glucose level of the mucoadhesive tablet of metformin/detarium gum.

This finding is significant because detarium gum is a food additive. Apart from this, the gum has been evaluated for use in bread making.[11] This may result in bread for diabetics. There is also the possibility of food-drug interactions when the gum is used in food concomitantly with other ant-diabetic drugs. This calls for further research on the uses of this material with other oral hypoglycaemic agents.

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