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Pharmacological study of the glibenclamide and glimeperide mixed ligands and their zinc complexes

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ABSTRACT

Present Communication deals with the preliminary study fo the comparison of hypoglycemic activity of two mixed sulphonyl urea. i.e. Glibenclamide (5-chloro-N-(4- N-cyclohexyl carbonyl) sulfamoyl] phenethy] 2-methoxybenzamide (L1) adn Glimeperide (3-ethyl-4-methyl-N-(4-[N-(1r,4r)-4-methylcyclohexl carbamoyl) sulfamoyl] phenethyl)-2-oxo-2, 5-dihydro-1-H-pyrrole-1-Carboxamide (L_2) in equal proportion with zinc - complex of these mixed drugs result reveals that the ternary (L_1ML_2) complex of these drugs with zinc gives surprising results.

Key words: Pharmacological study, Mixed ligands, metal complexes.

INTRODUCTION

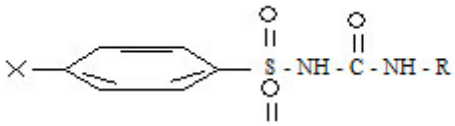
In recent times zinc - insulin has been successively used as an antidabetic agent To avoid daily pricks of insulin injections. the use of oral antidabetics have increased in recent years.

It is well established fact that a compound or a complex which is to be recommended as a drug of utility must be capable of easy absorption and excretion. it is also essential that neither the substance. it self nor the metallic products there should exercise toxicity or any adverse side effect to the patient.

For this purpose it becomes imperative that following facts must be ascertained for any substance of potential to be used as a drug.

1. Must not product toxic effects.
2. Particles size must be of the order of about 5-8 microns for easy absorption.
3. LD50 causing 50% mortality.
4. Bacteriostatic tests, where necessary, such tests should be carried out on animals such as rabbit, rat and dogs, when a substance has given satisfactory results for the above tests then only it may be tried on monkeys and men.

However the oral hypoglycemic activity of Chloropropamide. tolbutamide (mixed ligands) and their copper complexes observed by Iqbal et-al[1] and oral hypoglycemic activity of sulphonamide isopropyl thiadiazole obseved by janbon et-al[2] was followed by hypoglycemic activity of an antibacterial compound carbutamdie by frank and fuchas[3]. There after Glibenclamide (1) and Glimeperide (ii) being less toxic than other sulphonyl ureas and were previously well recognized.



$X = C_{10}H_{17}N_2O_2$ $R = C_6H_{11}$ → Glimeperide
$X = C_9H_8NO_2Cl$ $R = C_6H_{11}$ → Glibenclamide

It is necessary to find out toxicity. LD_{50} and animal tests on the metal complex of oral antidiabetic[456] Iqbal and Co-workers[7.8.9] have carried out preliminary pharmacological work for asessing the hypoglycemic activity of Glibenclamide and Glimeperide and compared it with its zinc complex. the results were satisfactory, the hypoglycemic activity was carried out on young dog of approximate 3.5 to 4.5 kg body weight.

MATERIAL AND METHODS

In present work a similar attempt have been taken by way of comparing the result of Hypoglycemic activity of mixed drugs i.e. Glibenclamide and Glimeperide compared to their zinc complex i.e. 1:1:1 (L_1ML_2)

Glibenclamide - Zn-Glimeperide complex synthesized and its structure was confirmed by analysis and I.R. spectroscopy.

Young dogs approximate body weight 3-4 kg were kept in laboratory conditions for three days. during this period milk and bread at 10.00 am. was given as diet and from the fourth day blood sugar was estimated at 11.00am. which indicated as a first day of the experiment.

Glibenclamide and Glimeperide 50mg (each 25mg) were given orally with small piece of chicken to the young dogs at 10.00 am. These after blood sugar was estimated at 12 pm. and 1.00 pm. The dog was kept on normal diet i.e. bread and milk for three days.

Allowing the blood sugar returning to normal after which 50mg of Glibenclamide - Zn - Glimeperide complex was given orally at 10.05 am. and the blood sugar level (BSL) estimated by ortho - toluidine method (Mono step)10.11.12 calorimetrically and the result are recorded in the table 1 and 2.

Above values were obtained after giving the Dog's normal diet+GLB/GLP at 9.15 a.m. The dogs were kept on normal diet without drugs for three days.

Colorimetric estimation of % of blood sugar level by Glucose, GOD-POD method (Glucose oxidase - peroxidase (GOD - POD) method).

Principle

$$\text{D-Glucose} + O_2 \xrightarrow{\text{GOD}} \text{D-Gluconic acid} + H_2O_2$$

$$H_2O_2 + \text{4-AAP} + \text{P-Hydroxy benzoic acid Sodium} + H_3O^+ \xrightarrow{\text{POD}} \text{Quinone imine} + 5H_2O_2 +$$

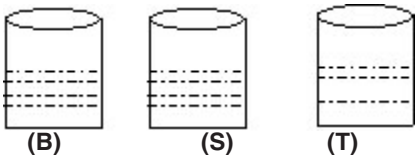
Glucose in presence of GOD oxidised to form D-Gluconic acid and H_2O_2. Thus from react with 4-aminoantipyrine to form red quinoneimine. Quinoneimine thus forms is pink color complex the intensity of which indicates the amount of sugar present in given specimen.

Requriement

Enyzme powder buffer solution (diluent) glucose standard (100mg%)

Preparation of Glucose working solutions

Mix 1 vails of reagent to 1 in a bottle (50ml) of the reagent to diluent utility of solution in 45 days from the date of preparation.



Working Solutions	1 ml.	1ml.	1ml.
		10µl Glucose standard	10µl Blood serum

Test procedure

Take 3 clean and dry test tube. test tube label as blank (B), Standard (S) Test (T) Blank solution is any for the selting of photo colorimeter.

Mix and incubate at 370°C for 10 min. or keep at room temperature for 20 min. Take optical density (OD) of standard and test. Using green filter against blank to set zero and absorbance of reagent blank at 270 nm.

Table 2: Comparison of hypoglycemic activity of Glibenclamide and Glimeperide with their zinc complex

Days of taking blood sample	Drug dose and time	Diet	Time	Glucose estimated in mg/dl 9.00 a.m	11.00a.m	1.00 p.m.
Day Ist	Nill	Milk & Bread	11.00 am	104	104	103
Day 2nd	Nill	Milk & Bread	11.00 am	97.4	97.5	97.0
Day3rd	Nill	Milk & Bread	11.00 am	84.6	85.6	85.4
Day 4th	Nill	Milk & Bread	11.00 am	82.6	82.8	82.6
Day 5th	Nill	Milk & Bread	11.00 am	87.6	87.8	87.4
Day 6th	GLB/GLP	Fasting	11.00 am	84.4	53.4*	44.7*
Above values were obtained after giving the Dog's normal diet+GLB/GLP at 9.15 a.m. The dogs were kept on normal diet without drugs for three days						
Days 10th	GLB-Zn-GLB complex 50mg		fasting	11.00 a.m.	86.2	51.4 42.8

Calculations were made using following formula

$$\text{Blood sugar level (mg\%) (mg/d)} = \frac{OD(T)}{OD(S)} \times \text{Standard(100\%)}$$

RESULTS AND DICUSSION

Before the first day of taking blood sample for glucose estimation Dog's were kept on normal diet (milk and bread)for three days. Table 2 indicates that the dogs were acclimatized for laboratory conditions with in three days and these after the blood sugar level (BSL) was daily estimated at 9.00a.m. before meals. the average values of all the five days were carried out i.e. 104, 97,4,84,6,4,87.6 mg/dl blood for five days On the day 6th GLB+GLP 50 mg was given at 9.00 a.m. and blood sugar (BSL) level were estimated at 11.10 a.m. and 1.00 pm and the results were recorded in table 2.

The similar process was applied to young male dogs for estimating blood sugar level (BSL) by way of giving orally GLB-Zn-GLP complex in ratio to taking 50 mg/kg body weight. Before performing the experiment of oral administration of mixed ligand complex. The animals were kept for normal diet for three days in order to maintain their normal blood sugar level (BSL).

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