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EVALUATION OF ANTIDIABETIC EFFECTS OF CHLORPROPAMIDS IN THE PRESENCE OF ASPIRIN

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ABSTRACT

The present work has been done in an attempt to evaluate the hypoglycemic effect of Chlorpropamide in the presence of aspirin. Diabetiogenic effect of Alloxan was utilized which produced an Insulin-Dependent Diabetic State in the animals. Diabetic animals were given oral Chlorpropamide (100 mg/kg body weight) and it was seen that the drug reduced the blood sugar values although not to a significant level. Later the animals were given aspirin (30 mg/kg body weight) alongwith the daily dose of Chlorpropamide and a more significant reduction of blood sugar level took place.

Introduction

Important changes in drug distribution can arise from competition between drugs for protein-binding sites in plasma. Certain groups *of* drugs seem to share a limited number of common binding sites, and one drug can displace another, sometimes with dramatic consequences. The more tenaciously bound drugs can displace less firmly bound ones from binding sites and thus cause shifts in plasma concentration.

Tolbutamide is an example of such drugs, its free concentrations can be increased significantly in the presence of effective competitors such as many of the non steroidal anti-inflammatory agents.

Asp[i]rin is perhaps the most important synthetic drug in the whole field of medicine and because of it's polyfunctional behaviour, it is often used by the patients in various conditions.

The key point in the situation, just described, is that both sulfonylureas and aspirin are acidic, and protein bound. Aspirin has high airfinity for plasma albumin and competes with the sulfonlurea hypoglycemic drugs for binding sites. The result is that more than often hypoglycemic drug becomes free and hence active.

The aim of the present study is to evaluate the effect of chlorpropamide in the presence of aspirin as this combination drugs is quite frequent in the diabetic patients.

Material and Methods

The animals used were healthy rabbits of either sex weighing 1.3-1.7 kg and feed ad libitum on green leaves of same variety. Blood samples for the assay of blood sugar were obtained by bleeding the marginal ear vein of the animals into a heparinized pippet. Blood sugar was assayed by 0-Toluidene method by Martial et. al. (1969). The alloxan diabetes was produced in animals by the method of Hammouda (1966). Alloxan monolyorate* was injected intravenously with a 27 gauge needle in a dose of 200 mg/kg in 4 divided doses/over a period of 24 hours. Alloxan was dissolved in isotonic saline to make a 3% solution immediately before injection. After aloxan, the animals were allowed to drink a concentrated glucose solution upto the time when required complete diabetic state was reached. Chlorpropamide and Aspro tablets were supplied by Pfizer Laboratories Ltd** and Aspro-Nicholos*** respectively.

For assaying serum chlorpropamide in the presence of Aspirin the method supplied by M/S. Pfizer Laboratories was slightly modified. Blood samples were held at room temperature for a period of two hours to ensure complete hydrolysis of Aspirin to salicylic acid. Blood serum after acidification with 2 ml 0.07 M Phosphoric acid solution was shaken with 20 ml chloroform. Salicylic acid was removed from chloroform layer and treated further for the determination of serum chlorpropamide.

Experimental

I. *Effect of aspirin* on the *glucose tolerance* test *in normal animals:*

Animals used in this series were tested for 12 hrs. before the start of the experiment. Glucose was administered orally in 3 mg/kg dose by a stomach tube as a 10% solution. After a normal glucose tolerance test the animals were given a minimum daily dose of 400 mg of aspirin over a period of about 2 weeks and a second glucose tolerance test was per-formed thereafter. In order to avoid gastric irritation an antacid was given twice a week. Figure 1 shows the response of normal animals to GTT before and after the aspirin treatment. A considerable reduction was observed in the normal values of glycemic curve after aspirin treatment.

II. *Effect of chlorpropamide* in alloxan-diabetic animals:

Chlorpropamide in doses of 100 mg/kg was administered orally to a group of eight alloxan-diabetic animals for 4 consecutive days in the first medication period. Figure 2 represents the results that were obtained on the 4th day of chlorpropamide treatment in the diabetic animals. It was seen that the drug did slightly affect the diabetic state of animals. However, reduction in the blood sugar level was not significant.

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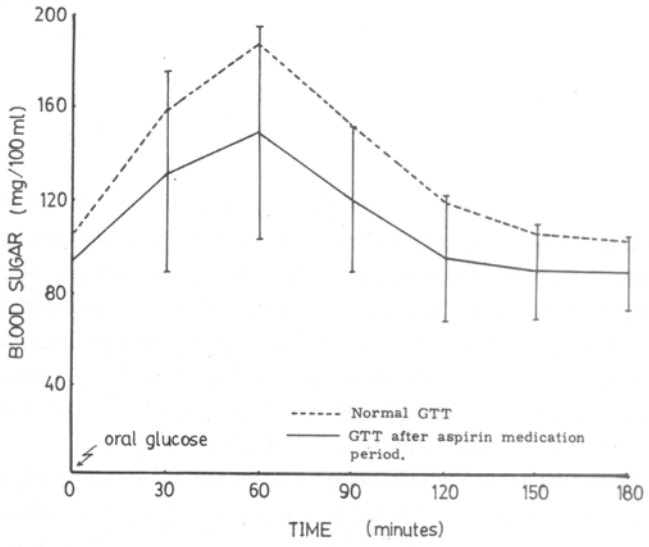

Fig. 1: Glucose tolerance test after aspirin medication in a group of eight animals over a period of 3 hours.

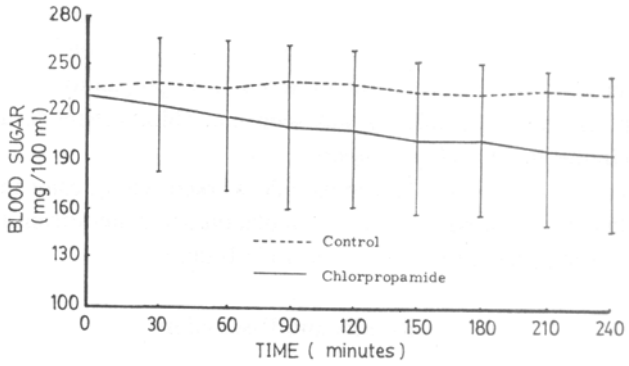

Fig. 2: Blood sugar level in a group of eight alloxandiabetic animals on the 4th day of oral chlarpsapamide (100 mg/kg. body weight) over a period of 4 hours.

III. *Effect of aspirin-chlorpropamide combination on the blood sugar level of alloxan-diabetic animals:*

After a rest period of 4 weeks, when the drug administered in the first medication period was completely eliminated from the animal bodies, a second medication period was initiated as part III of the experimental work. To a group of eight alloxan-diabetic animals 30 mg/kg aspirin and 100 mg/kg chlorpropamide was administered orally for 4 consecutive days. Figure 3 shows the results of the 4th day of this combined therapy. It is seen that immediately after the administration of drugs blood sugar values started falling. Maximum fall was observed at 150 minutes after which the blood sugar values started rising but it did not reach back to initial values even after 4 hrs.

Results show that aspirin acted synergistically and increased the hypoglycemic effect of chlorpropamide. The period of 0 to 150 minutes was the period when aspirin was giving "Push" to the hypoglycemic drug. Maximum pancreatic stimulation took place during this period and a marked reduction in the blood sugar was observed.

IV. *Effect of aspirin on serum chlorprpamide:*

Two groups of four animals from each medication period were chosen to observe the effect of aspirin on serum chlorpropamide. All animals received 100 mg/kg oral dose of chlorpropamide in the first medication period while in the second 30 mg/kg aspirin was also administered orally. Figure 4 shows serum chlorpropamide at different sampling times for both medication periods. It was seen that chlorpropamide attained maximum concentration in the blood at about 2 hours.

In the presence of aspirin, chlorpropamide worked with greater intensity in this period and resulted in increased pancreatic stimulation and a significant reduction of blood sugar was observed as has already been shown in Figure 3.

Results and Discussion

These results clearly demonstrate that aspirin like other salicylates can increase the blood chlorpropamide levels by itself, potentiating and producing a some what additive effect (Martin 1978). The sliding of blood sugar to lower values took place much more earlier in the second medication period of combined therapy with aspirin and chlorpropamide than it was in the lust medication period when chlorpropamide was given alone. Results explain that aspirin having more affinity for the binding sites pre-vented the hypoglycemic drug chlorpropamide from being bound and much of the later was thrown in the blood in an active un-bouned form. Thus in the presence of aspirin blood sugar was reduced much more significantly than m its absence, however, all animals did not get back to their normal sugar levels due to insufficient response from destroyed beta cells and diminished insulin secretion.

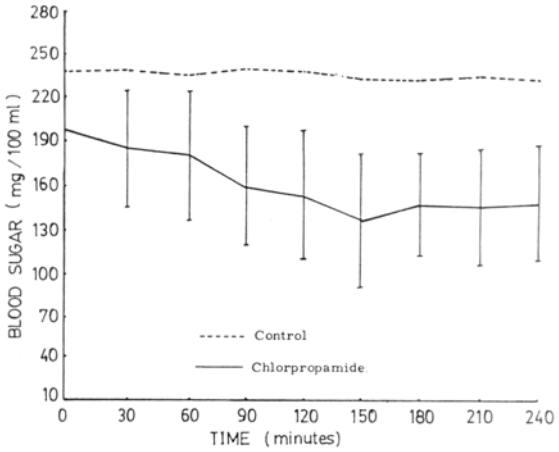

Fig. 3: Blood sugar level in a group of eight allxandiabetic animals on the 4th day of oral chlorpropamide (100 mg/kg. body weight) and aspirin (30mgkg body weight) over a period of 4 hours.

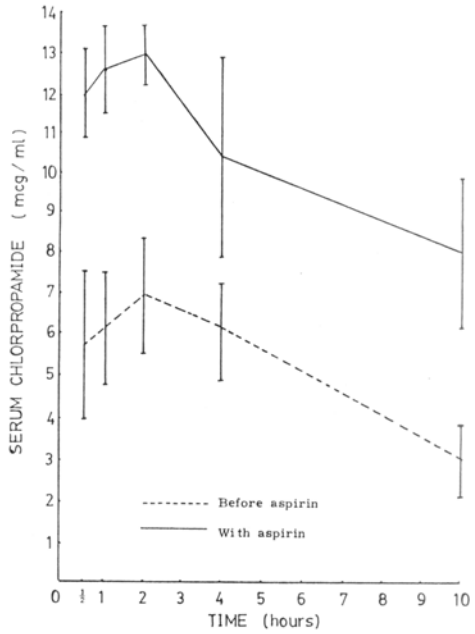

Fig. 4: Serum chlorpropamide in a group of four alloxandiabetic animals on the 4th dazy of Chlcpropamide (100 mg/kg body weighs) and aspirin (30 mg/kg body weight) over a period of 10 hours.

The potentiating time i.e., 0-150 minutes upto which aspirin forced chlorporpamide ended as the former was being excreted. The blood sugar was getting lowered along with reduction in pancreatic stimulation. Chlorporpamide in the blood probably equilibrated itself with the binding sites, as such increased concentration of scrum chlorpropamide in the presence of aspirin does indicate a type of drag interaction. Figure 4 indicates that even after the time when aspirin is supposed to have been excreted and its potentiating effect on chlorpropamide diminished, the chlorpropamide level in combined therapy with aspirin does not decline and does not reach nearer to the other curve when chlorpropamide was given alone even at 101h hour of blood sampling. This effect can be due to:

a. The fact that excretion of chlorpropamide was probably affected due to disturbance in the renal system of animals.
b. Delay in the chlorpropamide metablism in the presence of aspirin might be there.
c. The fact that aspirin and chlorpropamide being acidic a competition for the excretory system might have occurred.

The situation also seems to confirm that chlorpropamide may increase salicylate blood levels as mentioned by (Martin 1978), increased salicylate level may have affected the drug by any one of the factors given above.

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