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EFFECTIVENESS OF RECTAL INSULIN SUPPOSITORIES CONTAINING SODIUM CHOLATE IN NORMAL AND INSULIN DEPENDENT DIABETIC SUBJECTS

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ABSTRACT

The effectiveness of 100-U porcine insulin suppository containing 5% sodium cholate was examined in 3 normal volunteers (controls) and 15 diabetics. The hypoglycaemic response, in controls, started at 15 min, peaked at 30 min and returned to the initial level after 45 min, while in diabetics, started at 15 min, peaked at 120 min and persisted for the duration of the study (150 min).The maximum percent reduction in plasma glucose was found to be significantly greater in controls than in diabetics, while the AUC for percent glucose reduction was greater in diabetics than in controls. This was accompanied by a significant rise in serum insulin in controls than in diabetics. The serum

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insulin peaked at 15 min and remained above the initial value for 45 and 120 min, post administration, in controls and diabetics, respectively. Thus, rectal insulin could be considered as alternative to existing therapies.

INTRODUCTION

Parenteral administration of insulin is associated with many risks, reactions at the sites of injection, psychological stress, costs and inconvenience, also, handicapped and geriatrics are even unable to self administer injections safely. However, insulin as a peptide substance, cannot be administered orally, probably due to its large molecular weight and to its degradation by proteolytic enzymes[1].

To alleviate these problems a great effort has been directed to develop a non oral dosage form of insulin. Rectal delivery of insulin seems to be a reasonable choice, unfortunately, insulin is not absorbed from the rectum more efficiently than from the small intestine. This problem could be solved by coadministration of absorption promoters[2-7].

The objective of this study was to investigate rectal insulin efficacy in insulin dependent diabetics and normal volunteers using rectal suppositories containing 5% sodium cholate as an absorption promoter. The pharmacokinetics of rectal insulin and possible side effects were also traced.

MATERIALS

Procine MC insulin was a gift from Novo (Bagsvaerd, Denmark). All other materials were of analytical reagent grade.

METHODS

Human Subjects

Fifteen insulin dependent diabetic patients and 3 normal subjects participated in this study. Their age ranged from 14 to 70 years and their weights were within 15% of ideal weights. Their diabetes history ranged from 1 month to 18 years. No insulin was taken by any subject on the day prior to testing.

Preparation of Suppositories

2 g suppositories were prepared adopting the fusion method. A pH adjusting material was added to the base (Witepsol H_{15}) to keep the pH in the alkaline side.

Sampling and Estimation

Blood samples were withdrawn at 0, 15, 30, 45, 60, 90 and 120 min and occasionally at 150 min and divided into two tubes, one for estimation of plasma glucose using the glucose oxidase method, while the other for estimation of serum insulin by radioimmuno assay.

Statistical Evaluation

The data were computed in an IBM Computer-Basic. The data were expressed as the mean±standard error. Statistical analysis for comparative data between two means was done using the t-test of significance.

RESULTS

Fig. (1) obviates that, plasma glucose concentration in diabetics showed a gradual decrease from an initial value of 334.9±28.04 mg/dl to a value of 202.7±32 mg/dl at 120 min. This gradual decrease was

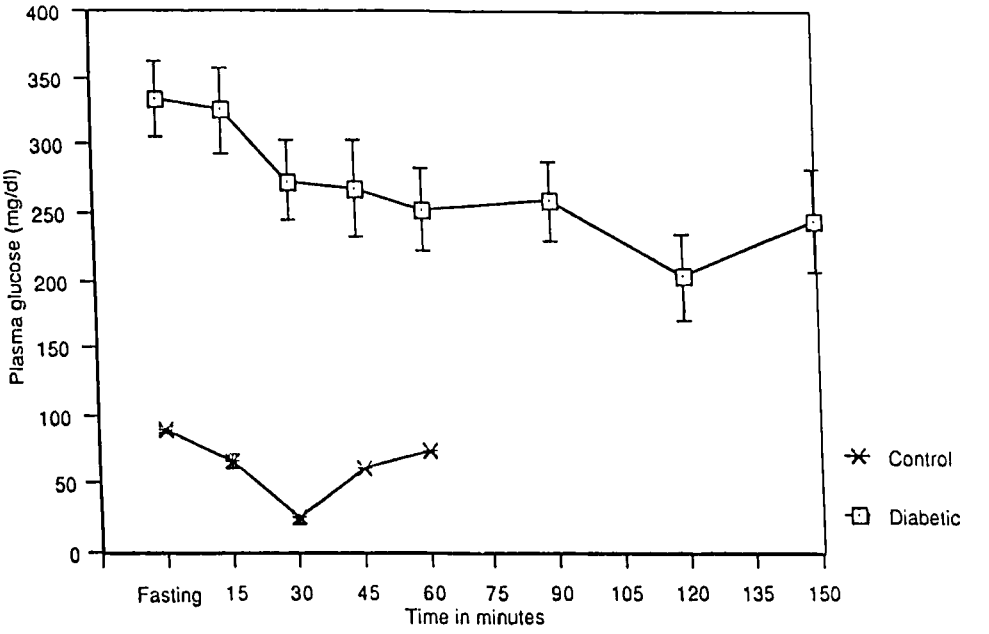

FIGURE 1
The effect of insulin suppositories on plasma glucose in diabetics and controls.

statistically significant from 60 min ($p<0.05$) to 120 min ($p<0.01$). This decrease was followed by an increase to reach 245.4±38.28 mg/dl at 150 min which was still non significantly less than the initial value ($p>0.05$).

In controls, plasma glucose showed a highly significant decrease ($p<0.01$) from a value of 89.33±3.53 mg/dl to 24.33±4.69 mg/dl at 30 min, then increased to a value slightly lower than the initial one at 60 min in only one subject as the other subjects suffered from severe hypoglycaemia and the test was terminated for them.

Fig. (2) demonstrates that, serum insulin concentration, in diabetics, showed a significant rapid increase ($p<0.05$) from an initial value of 106.9±37.52

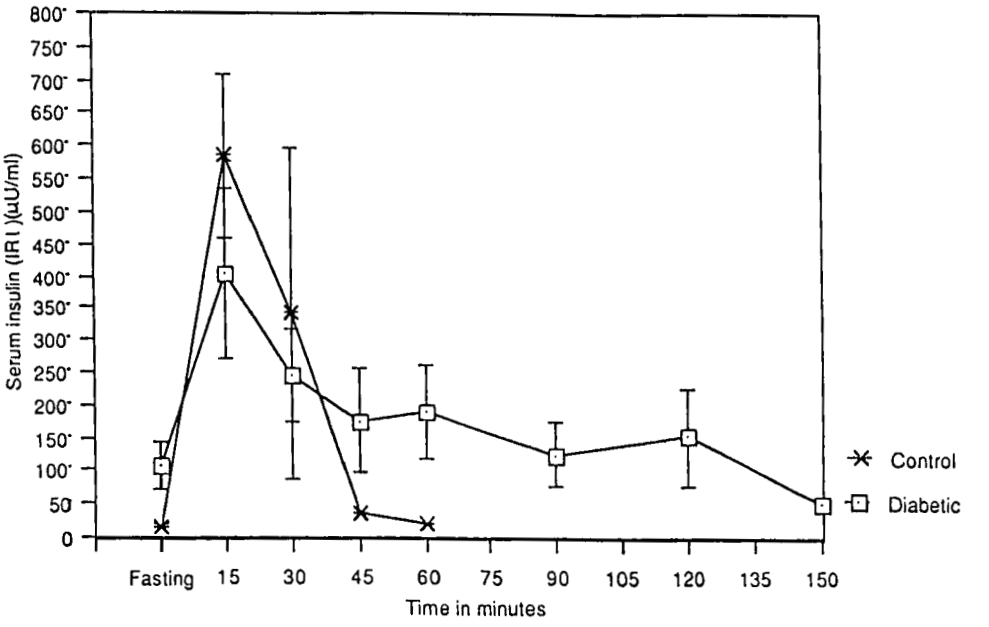

FIGURE 2
The effect of insulin suppositories on serum insulin in diabetics and controls.

mu/ml to a peak value of 403±132.41 mu/ml after 15 min. This was followed by non significant decline to 151.4±74.34 mu/ml at 120 min and to 49.12±7.23 mu/ml at 150 min ($p>0.05$).

In controls, serum insulin concentration showed a highly significant increase ($p<0.01$) from 16.73±2.17 mu/ml to 585.4±124.5 mu/ml after 15 min. This was followed by a non significant ($p>0.05$) rapid decline to 340±255 mu/ml at 30 min. The test for two subjects was stopped at this point due to development of severe hypoglycaemia. For the third subject, serum insulin decreased to reach around its basal value at 60 min.

Fig. (3) shows the relation between plasma glucose and serum insulin in diabetic patients. Serum insulin

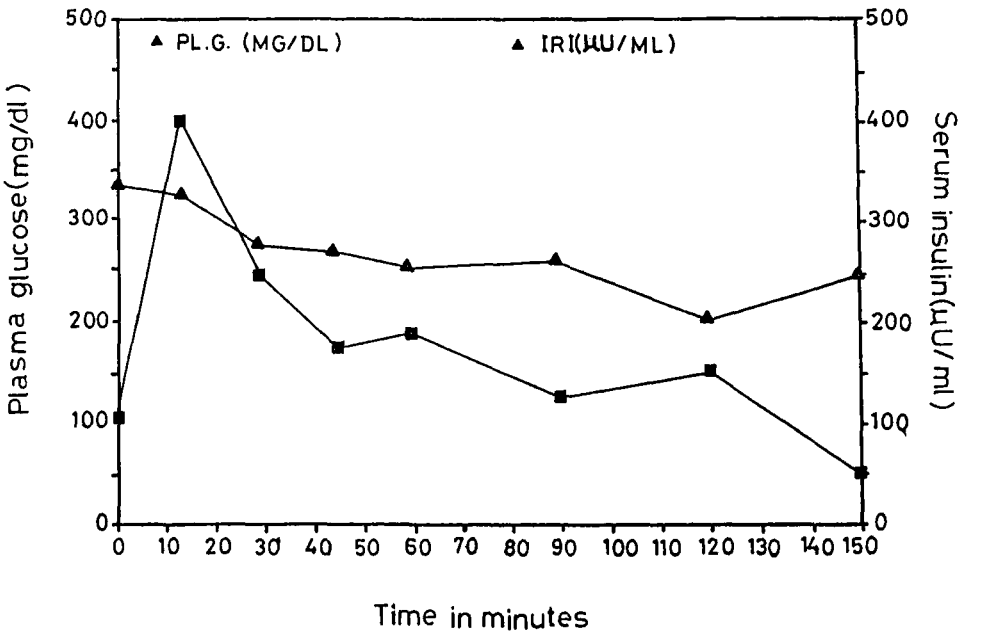

FIGURE 3
The effect of insulin suppositories on plasma glucose and serum insulin in diabetic patients.

was found to peak at 15 min, thus, showing a gap of 45 and 105 min before a significant decrease ($p<0.05$) in plasma glucose was traced at 60 and 120 min.

It was also observed that serum insulin maintained a non significant higher level ($p>0.05$) than the initial one by about 82 mu/ml from 45-120 min. This was followed by a rapid decline in serum insulin accompanied by a rapid rise in plasma glucose 120-150 min post administration.

In controls, Fig. (4) shows a gradual decline in plasma glucose to reach a significant minimum level ($p<0.01$) at 30 min which is 15 min latter than the serum insulin peak. The latter is rapidly declined to reach a value, at 30 min, which was non significantly

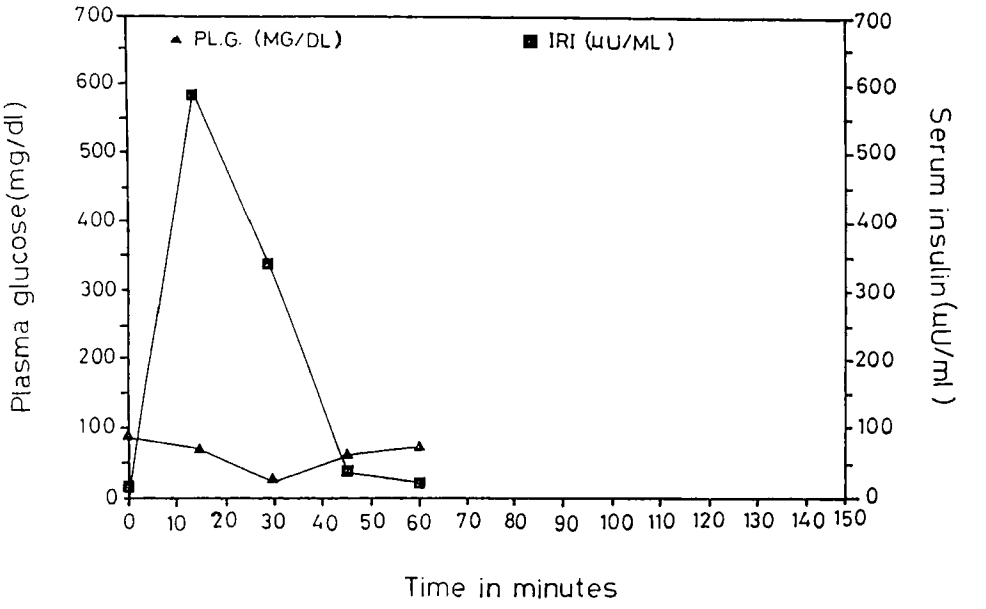

FIGURE 4
The effect of insulin suppositories on plasma glucose and and serum insulin in controls.

higher ($p>0.05$) than the initial value. For the control readings taken after 30 min, the serum insulin declined to reach a value around its basal value. This was accompanied by a gradual increase in plasma glucose to reach a value close to the initial value at 60 min.

DISCUSSION

It has been reported that portal insulin delivery is important in normalizing both glycaemia and insulinaemia postprandially[8-10]. Thus, rectal insulin suppositories could control the postprandial glycaemia in a more physiologic manner than conventional insulin therapy, because substantial amounts of insulin absorbed rectally enters directly into the liver which is the locus of highest insulin utilization.

In this work, rectal insulin administration resulted in a prompt increase in serum insulin levels in all subjects. This rise was definitely due to absorption of insulin into systemic circulation. The endogenous insulin was not affected because all subjects were fasting with no glycaemic stimulus during testing.

The peak of insulin was reached within 15 min post administration and maintained for 90 min in diabetics and 45 min in controls. There was a late rise in serum insulin starting from 90 to 120 min in diabetics. This may be due to entrapment of some insulin in sodium cholate micelles or a delayed release of insulin from the suppository[11]. This mode of insulin absorption is unique when compared to other parenteral routes, as porcine crystalline insulin when administered to controls through I.V., I.M. and S.C. routes, resulted in peak serum insulin 2, 50-60 and 120-180 min, respectively[12].

The rapid return of serum insulin, after 45-60 min, to its initial value in controls can be explained by the combined release of epinephrine and glucagon and by the result of insulin induced hypoglycaemia as expected for normal glucose counterregulation[13]. On the other hand, the persistence of higher levels of insulin in diabetics (120 min) can be either due to a decreased degradation rate and/or clearance of insulin due to diabetic nephritic complications[14].

The respective lag periods of 15 and 105 min between the peak of serum insulin and the maximum reduction in plasma glucose, in controls and diabetics, can be explained in the light of De Fronzo and Tobin[15] conclusion as the time required for the dynamics of insulin distribution from plasma to tissues via capillary membrane. The explanation of the marked difference in the duration of insulin hypoglycaemic response in

diabetics versus controls is still obscure, however, Dixon et al[16] suggested that insulin bound to insulin antibodies in type I patients acts as a depot store, thus prolonging its hypoglycaemic effect. Furthermore, the decreased degradation rate and/or clearance of insulin in diabetics may provide an added explanation of such prolonged hypoglycaemic response. Thus, our study, in humans, obviates the effectiveness of rectal insulin delivery and strongly support the proposition that rectal suppositories can be a viable alternative to the existing therapies, especially suitable for meal-time administration.

The suppositories were well tolerated and accepted by all diabetics and controls except only one patient complained of urgency of defecation and mild anal irritation.

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