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# OBSERVATION ON EFFECTS OF SULFONYLUREA ON GLYCAEMIC CONTROL IN INSULIN REQUIRING DIABETICS

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## Abstract

Extrapancreatic effect of Glybenclamide was studied in insulin requiring diabetics, of whom seven were secondary sulfonylurea failure (NIDDM) and five were primary failure cases (Four J type diabetics and one young diabetic with pancreatic calculi).

All the patients were put on soluble insulin at the start of the study and were satisfactorily controlled. The mean dose of insulin requirement for ideal control was 77.6 units per day in patients of primary sulfonylurea failure and 75.57 units per day in patients of NIDDM with secondary sulfonylurea failure. An addition of 20 mg of glybenclamide in two divided doses to both the groups of patients - there was a significant fall in insulin requirement in the latter group ($P < 0.05$) inspite of insignificant fall of blood glucose. In cases of primary sulfonylurea failure the fall of insulin requirement on addition of Glybenclamide was substantial but statistically insignificant. Analysis of glycosylated Hb at this stage showed an improved status (mean $HbA_1$ -6.08 ± 0.41) from an initial value of 12.92 ± 0.80%.

On withdrawal of Glybenclamide keeping insulin dose fixed, it was found that there was rise of blood glucose in both the groups of patients suggesting extra-pancreatic effect of glybenclamide in these insulinopenic diabetics.

Results from this study emphasise the beneficial effect of a mixed regimen of antidiabetic therapy in patients of NIDDM with secondary sulfonylurea failure particularly and in those young diabetics who have high insulin requirements.

## Introduction

The mechanism of hypoglycaemic action of sulfonylurea (SU) compounds is *as yet controversial.* Both in-vivo and in-vitro observations have established that on *acute administration,* SU compounds stimulate release of insulin from B cells of the pancreas. (l, 2, 3, 4). But during prolonged therapeutic use glycaemic control may be maintained even when plasma insulin levels are no higher than pretreatment values. These and other experimental evidences strongly suggest the possibility of additional extrapancreatic mechanisms for the hypoglycaemic effect of SU compounds. Among a number of such

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actions observed in experimental set up, the following two are most likely to be operational in clinical situations :

(i) reduction of hepatic glucose output by decreasing glycogenolysis and gluconeogenesis (l, 5).

(ii) enhancing tlie effectiveness of available insulin by increasing the number of insulin receptors on target cells (1, 2). These mechanisms, of necessity, operate in the presence of endogenous insulin. *As such, there should be no reason why the same should not happen* in the presence of exogenous insulin in patients with gross insulin deficiency.

So far it is not customary to use SU compounds in combination with insulin. In practice this combination is not generally encouraged. In view of the hypothetical possibility of potentiation of action of exogenous insulin by SU compounds through their extrapancreatic action, it was decided to investigate the *clinical outcome of combined* SU and insulin therapy in patients with gross insulin deficiency. For the purpose of this study, insulin requiring diabetics were considered most suitable as they are known to be unresponsive to SU compounds and yet unlike patients of insulin dependent diabetes mellitus (Type I), do not develop ketosis inspite of inadequate control.

## Patients and Methods

(i) Selection of patients

Seven patients of NIDDM and five young insulin requiring diabetics (Four Type J and one pancreatic secondary diabetes) were taken up for study.

The cases of NIDDM, followed up at the diabetic clinic were non-responsive to SU compounds after a variable period of successful control. Ketosis resistant young diabetics included in this study were admitted and treated with a daily dose of 20 mg of glybenclamide. None of these patients was controlled with this maximal doses within three weeks of test period and hence were considered as cases of primary SU failure.

Patients were explained the possible benefits from this study and a verbal promise of cooperation was obtained from each.

After full clinical examination and evaluation, the data were recorded in a protocol. All patients were admitted either in the general medical or endocrine ward of the hospital and put on appropriate diet, served as three meals : 1/Sth of the total calories at breakfast and 2/5th each at lunch and supper.

(ii) Collection of Samples :

At the start of the study blood samples were drawn at the fasting and two hours after lunch for estimation of blood glucose by ortho-toluidine method. Patients were put on soluble insulin in three divided doses half an hour prior to each meal. Blood glucose levels were estimated every three days. Step by step, the insulin dose was increased until establishment of glycaemic control.

Control was considered satisfactory when fasting blood glucose was < 110 mg/dl and 2 hour post-prandial blood glucose < 150 mg/dl. Once control was achieved with appropriate dose of insulin, the patients were maintained on the same dose and diet.

After three consecutive blood sugar estimations were within the range of satisfactory control, glybenclamide was given to the patients, 10 mg each prior to breakfast and night meals. While the patients were on this schedule, care was taken to monitor the hypoglycaemic effect. Insulin dose was reduced step by step either when the patient complained of repeated hypoglycaemic symptoms or when blood sugar fell below 70 mg/dl at fasting or 100 mg/dl at 2 hr. P.P.

After a follow up period of 3 months, the reduction in dose of insulin on addition of glybenclamide was calculated. Thereafter Glybenclamide was totally withdrawn. Blood glucose was estimated every three days for the next fifteen days.

Glycosylated haemoglobin ($HbA_1$) was estimated by the colorimetric method at three points during the study : first at inclusion in the study and subsequently at the second and third month of achievement of satisfactory control.

## Results

Age, sex, duration of diabetes and body mass index in both groups of patients studied is shown in Table-I.

**Table l**

**General information on subjects**

| | | SU Primary failure group | SU Secondary failure group |
|---|---|---|---|
| Age in Years | = Mean | 25.6 | 43.4 |
| | = Range | 21.35 | 22-57 |
| Sex | =Mean | 5 | 4 |
| | = Female | 0 | 3 |
| Duration of Diabetes in yrs. | = Mean | 3.5 | 5.7 |
| | = Range | 3.5 | 2.15 |
| B.M.I. | = Mean | 13.76 | 17.24 |
| | = S. D. | ± 1.73 | ± 2.94 |

su=Sulfonylures compounds.

**Table 2**

**Insulin requirement for glycaemic control when given alone and in combination with SU (20 mg of glybenclamide)**

| Group | | Primary SU failure | | | Secondary SU failure | |
|---|---|---|---|---|---|---|
| Phases | Mean Blood glucose in mg/dl ±SD | | Mean Insulin dose Units/day ±SD | Mean Blood glucose in mg/dl ±SD | | Insulin dose units/day (mean & S.D.) |
| Pre-treatment | Fasting | 253±47.22 | — | Fasting | 278±73.13 | — |
| | Two hr. PP | 308±44.38 | | Two hr. PP | 365±76.48 | |
| During control with insulin | Fasting | 86±12.72 | 77.6±40 | Fasting | 94.1±10.62 | 75.57±19.20 |
| | Two hr. PP | 129±5.98 | | Two hr. PP | 148.4±17.01 | |
| During control with insulin +S.U. | Fasting | 92.4±5.54 | 60.4±12.14 | Fasting | 102±12.74 | 54.16±12.18 |
| | Two hr. PP | 141.2±7.29 | | Two hr. PP | 144.6±11.91 | |
| On withdrawal of SU | Fasting | 122±5.58 | 60.4±12.14 | Fasting | 128±11.74 | 54.16±12.18 |
| | Two hr. PP | 167±8.62 | | Two hr. PP | 168±128.14 | |

SU=Sulfonylurea

Details of blood glucose profile and insulin requirement during insulin therapy and a mixed regimen of glybenclamide and insulin are depicted in Table-2.

Analysis of significance of differences in blood glucose and insulin requirement in both groups is presented in Table-3.

Mean glycosylated haemoglobin of all the patients on entry to the study was 12.96 ± 80%. After very stringent control with mixed regimen of insulin and glybenclamide it was reduced to 6.08 ± .41 % at the end of 2nd month and 6.68 ± .97% at the end of 3rd month.

Clinical hypoglycaemia was experienced in 8 of 12 cases when patients were on insulin and glybenclamide after a varying period of 2-6 weeks.

**Table 3**
**Significance of difference in blood glucose and insulin requirement**

| Categories | | | | Primary SU failure | | Secondary SU failure |
|---|---|---|---|---|---|---|
| Regimens | Fasting blood glucose | 2 Hr. PP blood glucose | Insulin require-ment | Fasting blood glucose | 2 Hr. PP blood glucose | Insulin require-ment |
| Insulin alone Vs Insulin+SU | P>0.1 | P<0.05* | P>0.1 | P>0.1 | P>0.1 | P<0.05* |
| Insulin+SU Vs Insulin alone (SU withdrawn) | P<0.01* | P<0.01* | - | P<0.01* | P<0.01* | - |

SU = Sulfonylurea
*Significant.

## Discussion

The possible potentiating effect of SU compounds on action of insulin on the target cells has been explored by several groups of workers. While Reavan[6] showed a partial restoration of number of functioning insulin receptors on circulating monocytes of patients with NIDDM, Feiglos and Levovitx[7] demonstrated an increase in number of hepatic plasma membrane insulin receptors in normal mice on glipzizide therapy.

The present study was taken up to ascertain whether SU therapy in insulin requiring patients will be of any benefit in terms of control of hyperglycaemia. It was presumed

that both groups of patients included have very low residual B cell function. The first group which were cases of 'O' type and PSD did not respond to SU therapy over a period of three weeks. Plasma insulin, basal and in response to glucose and SU in these categories of diabetes have been estimated by us and were found to be lows. Patients of secondary failure are cases of NIDDM on SU compounds for long periods. Complete refractoriness to the highest dose of oral drugs suggested very low residual B cell function in these patients.

Both the groups of patients were lean and had severe diabetes (Table 1 & 2). All the patients with primary SU failure and one with secondary failure were young. Mean insulin requirement was high in both groups. On addition of glybenclamide symptoms of mild to moderate hypoglycaemia were experienced by 8 patients after varied period of 2 to 6 weeks. In three others a gradual falling trend of blood glucose was noticed, thereby suggesting potentiation of effects of insulin. Mean glycosylated Haemoglobin ($HbA_1$) which was 12.92 ± 0.80% before treatment came down to 6.68 ± 0.97% in the last month of combined treatment, confirming excellent control.

Thus there was definite evidence of fall in insulin requirement in both groups of patients on addition of glybenclamide. In the primary failure group (consisting of 5 patients), the fall from 77.6 ± 17.4 to 60.4 ± 12.14 units/day was, although substantial, not statistically significant ($P > 0.1$). Fasting blood glucose levels during two regimes were similar ($P < 0.1$), but mean postprandial blood sugar was significantly higher ($P < 0.05$) during combined therapy. In view of this, it will be difficult to conclude that combination of glybenclamide with insulin is of therapeutic benefit in patients with primary SU failure. But there was significant rise ($P < 0.01$) in the mean blood sugar levels following withdrawal of glybenclamide without alteration of insulin (Table 2 & 3). This inconsistency in the result (in our observation) may be due to the small number of patients studied.

On the other hand the patients with secondary SU failure had decreased insulin requirement on addition of glybenclamide (mean 75.57 ± 19.20 to 54.16 ± 12.18 units) which is statistically significant ($P < 0.05$), while there was no significant difference in mean blood sugar levels. Further, the rise in blood sugar following withdrawal of glybenclamide was significant ($P < 0.01$).

More work is necessary to establish that the addition of SU to insulin could in general improve and stabilise glycaemic control. Results from the present study indicate the usefulness of combined therapy in patients of NIDDM with secondary SU failure, particularly in those who have high insulin requirements.

## References

1. Barnes, A.J., Garbien, KJT; Crowley, M.F. and Bloom, A. Effect of short and long term chlorpropamide treatment on insulin release and blood glucose : Lancet 1974, 2 : 1139-1142.

2. Hetch, A., Gershberg, H., Hulse, M. Effect of chlorpropamide treatment on insulin secretion in diabetics : its relationship to hypoglycaemic effect: Metabolism 1973 22 : 723-733.

3. Mutch, W.G. and Stower, J.M. Reversible mild diabetes in children after treatment with chlorpropamide. Lancet 1980, 1 : 1158-1161.

4. Ward, E. A., Ward, G. M. and Turner, R. C. Effect of sulfonylurea on insulin secretion and glucose control in insulin treated Diabetes. British Medical Journal 1981, 278-283.

5. James, D., Best. Roman, G., Judze Witsch Michel, A., Pfeifer James, C., Beard Jeffrey, B., Halter and Daniel Porte, Jr. Effect of chronic sulfonylurea therapy in hepatic glucose production in NIDDM. Diabetes 1982, 31 : 333-338.

6. Reaven, G. and Dray, J. Effect of chlorpropamide on serum glucose and immunoreactive insulin concentration in patients with maturity onset diabetes mellitus,. Diabetes 1967, 16 : 487-492.

7. Libovitz, H. and Feirgles M. Sulfonylurea drug mechanism of antidiabetic action and therapeutic usefulness. Diabetic care 1980, 29 : 488-494.

8. Tripathy, B.B., Samal, K.C., Murty V.K., Mishra, P.K. and Parida, R.K. Insulin response to sulfonylurea in Diabetes mellitus. Jr. Assoc. Phys. India 1984, 1 : 411-416.