STUDY OF THE EFFECTS OF VERAPAMIL ON THE SERUM GLUCOSE AND INSULIN LEVELS OF NORMAL AND HYPERTENSIVE SUBJECTS

RIAZ NASIM, HIDAYAT HUSSAIN KHAN, IHTESHAMUL HAQ, ABDUL QAYUM AND ABDUL WADOOD.

Department of Pharmacology, Department of Physiology and Department of Pharmacy, Khyber Medical College, Peshawar, Allama Iqbal Medical College, Lahore and University of Peshawar.

SUMMARY

The influence of verapamil on the levels of fasting serum glucose and insulin was evaluated in twenty normal subjects, and thirty patients suffering from mild to moderate hypertension. The levels of glucose and insulin were determined in both the groups, before and after the oral administration of verapamil (80mg t.i.d.). In normal subjects the values of glucose and insulin were 85.0 ± 9.8mg/dl and 9.8 ± 4.8/uU/ml before and 84.0 ± 9.5mg/dl and 9.0 ± 4.5/uU/ml after verapamil treatment. In the hypertensive subjects these values were 90.0 ± 12.4mg/dl and 9.8 ± 5.6/uU/ml before and 91.0 ± 15.0mg/dl and 9.1 ± 5.3/uU/ml after administration of verapamil. The differences in the control and test values were statistically not significant. It is concluded that verapamil does not produce a significant effect on the fasting serum glucose and insulin levels of both normotensive and hypertensive individuals of Pakistan population, when given in therapeutic doses and for a short duration of time.

INTRODUCTION

The observation that the initiation of insulin secretion was due to the accumulation of Calcium in the beta cells of the pancreas and that Calcium entered the beta cells, at least in part, via voltage-operated Calcium channels, which were opened following depolarization of the beta cell membrane, secondary to a reduction of Potassium permeability¹. This has prompted research workers to study the effects of the calcium channel blocker Verapamil on the release of insulin from the beta cells of the pancreas, and its subsequent effects on the blood glucose level of the experimental animals or human subjects. A variety of experimental procedures have been designed for studying these effects on isolated beta cells of the pancreas from laboratory animals (in-vitro experiments) and on intact laboratory animals and human beings, and it has been found that verapamil (and other Calcium channel blockers) can effectively block the glucose-induced insulin release from the isolated beta cells of the pancreas¹.

Although some studies on experimental animals and human beings (in-vivo experiments) suggest that verapamil (and other related drugs) may reduce the insulin response to a glucose load and impair glucose tolerance,¹ other investigations suggest that the oral administration of verapamil, in haemodynamically active doses, does not interfere with insulin release or serum glucose levels¹. It has also been observed that verapamil does not produce a significant effect on glucose induced release of insulin in concentrations which are sufficient to produce a significant fall in the
blood glucose pressure of rats. The present work was undertaken to test the validity of the above mentioned contradictory findings in normal and hypertensive human subjects. Since no such studies have been carried out in Pakistan, this study will also help in arriving at useful conclusions, as far as the effects of verapamil on the blood glucose and the insulin levels of Pakistan subjects are concerned.

MATERIALS AND METHODS

A) Selection of Subjects

Fifty subjects were included in this study. They were divided in the following two groups.

i. Normal Subjects:

Twenty healthy subjects (12 women and 8 men, aged between 34 and 65 years) entered the trial after taking informed consent from them. They included the doctors residing at King Edward Medical College, Hostel, Lahore, and patients visiting the Centre of the Pakistan Medical Research Council (PMRC), at Fatima Jinnah Medical College and Ganga Ram Hospital, Lahore for minor illnesses, but having no evidence of debilitating disease or hypertension.

ii. Hypertensive Subjects:

The patients in this group were having essential hypertension and were screened carefully from registered and newly diagnosed cases at Hypertension Clinic, of the Centre of Pakistan Medical Research Council (PMRC) at Fatima Jinnah Medical College, and Ganga Ram Hospital, Lahore. Thirty hypertensive out-patients (17 women, and 13 men, aged between 35 and 65 years) were included in this group after taking informed consent from them. This group included the patients having systolic blood pressure equal to or greater than 160 mm Hg and/or diastolic blood pressure between 95 and 115 mm Hg. The term mild to moderate hypertension is used to denote this range of blood pressure. The selection of the patients was such that monotherapy with verapamil could be initiated to avoid different problems associated with multiple drug therapy. Patients who were newly diagnosed or were off treatment for 2 weeks were included in this study. The patients who had history of angina, myocardial infarction, secondary or malignant arterial hypertension, heart failure and cerebro-vascular accidents were excluded from the trial. Women who were pregnant or lactating were also excluded.

B) Experimental Procedures

i. Serum Glucose Estimation

The serum glucose estimation was done by GOD/PAP method (calorimetric method without deproteinization). The kit was provided by Randox Laboratories Limited, Kremlin, Co. Antrim, N. Ireland (Cat.No.GL 365).

ii. Serum Insulin Estimation

Serum insulin estimation was done by enzyme-linked immunosorbent assay (Elisa principle). The kit used was that manuf-

TABLE - I

COMPARISON OF THE MEAN VALUES (+ SD) OF GLUCOSE LEVEL IN NORMAL (GROUP - A) AND HYPERTENSIVE (GROUP - B) SUBJECTS BEFORE AND AFTER THE ADMINISTRATION OF VERAPAMIL.

<table>
<thead>
<tr>
<th>Group</th>
<th>Glucose level (mg/dl)</th>
<th>P. Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Test</td>
</tr>
<tr>
<td>A</td>
<td>85.0\pm 9.8</td>
<td>84.0\pm 9.5</td>
</tr>
<tr>
<td></td>
<td>(20)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>90.0\pm 12.4</td>
<td>91.0\pm 15.0</td>
</tr>
<tr>
<td></td>
<td>(30)</td>
<td></td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the number of subjects.
RESULTS

Glucose Levels

In normal subjects the values of glucose ranged between 72-110mg/dl before and 72-112mg/dl after verapamil therapy. In hypertensive subjects these values were 72-110mg/dl and 74-116mg/dl respectively. The mean ± S.D. values in the case of normal subjects were 85.0±9.8mg/dl for untreated group and 84.0±9.5mg/dl for the treated group. The mean ± S.D. values in hypertensive subjects were 90.0±12.4mg/dl for untreated group and 91.0±15.0mg/dl for the treated group. The comparison of these values indicates that the differences between the untreated and treated groups are not statistically significant (Table-1, Fig.1).

Insulin Levels

In normal subjects the values of fasting serum insulin ranged between 2-18uU/ml before medication, and 2-18uU/ml after medication. In the hypertensive subjects the values were in the range of 1-20uU/ml and 2-20uU/ml respectively.

The mean ± S.D. values in the case of experiments on normal subjects were 9.8±4.8uU/ml for the untreated group, and 9.0±4.5uU/ml after treatment with verapamil. In hypertensive subjects these values were 9.8±5.6uU/ml before and 9.1±5.3uU/ml after treatment with verapamil. The comparison of these values indicates that the differences between the untreated and treated groups are not statistically significant (Table-II, Fig.2).

<table>
<thead>
<tr>
<th>Group</th>
<th>Insulin Level (uU/ml)</th>
<th>P. Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Test</td>
</tr>
<tr>
<td>A (20)</td>
<td>9.8±4.8</td>
<td>9.0±4.5</td>
</tr>
<tr>
<td>B (30)</td>
<td>9.8±5.6</td>
<td>9.1±5.3</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the number of subjects.
DISCUSSION

The range of fasting serum glucose level was 72-110mg/dl in normal and 72-110mg/dl in hypertensive subjects. Similarly the range of fasting insulin levels was 2-18uU/ml in normal and 1-20uU/ml in hypertensive subjects. The survey of literature indicates that these values are in normal range.

There was no significant difference between the mean values of fasting serum glucose before and after medication, in the normal as well as hypertensive subjects.

These results are in accordance with the results obtained by Semple et al, Vincenzi et al, Rojmark and Anderson and Lethトンen et al. These workers studied the short and long term effects of verapamil in normal and hypertensive subjects, and found insignificant change in the serum glucose concentrations.

There was no significant difference between the mean values of fasting serum insulin before and after medication, in normal as well as hypertensive subjects. Thus, the results obtained in the present work are in accordance with those of Shamooh et al, who studied the effects of verapamil (320mg/day for 2 weeks) on glucose induced insulin secretion in hypertensive subjects, and found that verapamil treatment did not produce a significant change in the plasma insulin levels. Almost similar findings have been reported by Semple et al and Rojmark et al. On the other hand, Enyeart et al reported a prominent fall in the level of insulin in female patient after an inadvertent overdose and DeMarinimis and Barbarino reported significant fall of insulin in patients suffering from islet cell tumour, insulinoma. The results obtained in the present study are thus not in accordance with their observations. This may be because of the fact, that the patients reported by these workers had either consumed a dose which was very large (2.4g) compared to the dose (80mg t.i.d) used in the study under discussion, or they were secreting more than normal insulin.

Semple et al studied the effect of verapamil on glucose induced release of insulin on the beta cells of the islets of Langerhans of pancreas of rats in vitro, and found that it produced a prominent inhibitory effect on the glucose induced release. They then performed experiments on intact rats, to see whether verapamil could produce similar effects in vivo also, and observed that it could not produce
inhibitory effect on glucose induced release in intact rats, in doses which could produce a significant fall in blood pressure. These workers determined the relative concentration of verapamil in the blood of the rats, and observed that the concentration of verapamil in the blood was less than the concentration in-vitro experiments. They, therefore, postulated that the cardiovascular system of an intact animal was more sensitive to the calcium channel blocking effect of verapamil as compared to the beta cells of pancreas.

These findings lead us to the conclusion, that in those cases where the insulin content of the pancreas in more than normal (i.e. insulinoma⁹,¹⁵; whereas in individuals with apparently normal pancreas, such as Pakistan subjects in the present study, this effect is either not produced, or this effect may appear after administering comparatively larger doses⁸,¹³,⁹ or when the drug is administered for a comparatively longer period¹³.

REFERENCES


