A Comparative Study of Three different Commercial brands of Glibenclamide Preparations

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Abstract
This study aimed to assess the efficacy and the serum levels of three commercial brands of glibenclamide on diabetic patients.

The design of study was case control and triple blind study of the serum level and the hypoglycemic efficacy of three commercial brands of glibenclamide on ninety patients with diabetes mellitus.

The study was performed at AL-Wafa Center for the treatment of Diabetes mellitus and at Nenava Factory for Pharmaceuticals, during the period from August 2002 to February 2003.

Ninety patients with Diabetes mellitus, 48 female and 42 male patients, and their ages ranging from 31 to 80 years and the mean were 54.07 years.

To compare the three brands of glibenclamide and to test their hypoglycemic effect, Analysis of variance (ANOVA) test were utilized. Furthermore to determine which one of them is the most statistically significant Duncan's Multiple Range Test were utilized.

To determine which one of them has the highest serum level in two hours, the analysis of variance for the three samples was used.

The analysis of variance indicates that there were statistically significance differences between the three groups. The calculated (F) is larger than the tabulated (F) at the level of 0.05 and at 0.01 level.

Duncan's Multiple Range Test indicates that the GLIBESYN brand is the most potent hypoglycemic brand among them. For the serum level of the three brands, the analysis of variance indicates that there was no statistically significant difference between the serum levels of the three brands.

This study ascertains the need of wide range of determination of the efficacy of the other hypoglycemic drugs. The High Performance Liquid Chromatography with fluorescence detection (HPLC) is very easy and very sensitive test and should be used more regularly.
Introduction

Glibenclamide is a potent second generation sulphonylurea, oral hypoglycemic agent. It lowers blood glucose concentration in diabetic and non-diabetic patients by stimulating the release of insulin from the functioning beta cells of the pancreas. It leads to insulin secretion in rhythm with the meals. Furthermore, it leads to reduction of basal hepatic glucose production, enhancement of peripheral insulin action and increases tissue sensitivity to insulin [1]. It also exerts a direct inhibitory effect on glucagon production through the alpha cells of the pancreas and increases the release of somatostatin, these two actions exert minor hypoglycemic effect.

Glibenclamide is readily absorbed (approximately 85-90%) from the gastrointestinal tract after oral administration. Food does not appear to affect the rate and extent of absorption of glibenclamide and this is more clear with gliclazide although some prefer to give glibenclamide half an hour before meal [2,3].

After oral administration of 5mg of glibenclamide, peak serum concentrations are reached in 2 hours or less(1.3-1.4 hours) [4], and some time up to 6 hours and within 24hours the concentration falls, with a half-life of nearly(2.6±0.75 h)[3]. Accumulation of glibenclamide is not observed after repeated doses with no build up of the drug level in the tissues. Approximately 50% of the dose is excreted in urine and 50% via the bile into the faeces. To monitor the bioavailability of glibenclamide High performance liquid chromatographic (HPLC) methods have been developed. The sensitivity and easy sample processing make the HPLC with fluorescence detection is suitable for monitoring the bioavailability of glibenclamide [5,6,7].

The aim of this study is to determine the efficacy and the best hypoglycemic effect achieved in the first two hours after taking 5mg of glibenclamide of the three tested commercial brands of glibenclamide i.e. GLIBIL5(GLIBIL5:AIKMA Made In Jordan)or SAMACLAMIDE-5(S.D .I Iraq)or GLIBESYN(GLIBESYN MEDOCHEMIE LTD-CYPRUS). Furthermore is to determine the bioavailability of each brand in the first two hours after taken 5mg of glibenclamide, by testing the serum level of each type by using the High performance liquid chromatography with fluorescence detection (HPLC) method.

Patient and Methods

At Al-Wafa Center for the treatment of diabetes mellitus we studied ninety patients with diabetes mellitus during the period from August 2002 to February2003; all of them were on oral 5mg Glibenclamide therapy. The sample include 48 female and42 male patients with their age distribution as shown in the table (1). The ninety patients further subdivided into three equal groups, thirty patients each, all of them agreed to be included in the study. All the patients consult AL-Wafa center for follow-up while they were fasting and with no treatment for the pretest 24hours as usually done during their monthly consultation. Sample of blood for fasting blood sugar (FBS) were taken from each patient, and every one of them received immediately 5mg Glibenclamide of either GLIBIL5 or SAMACLAMIDE-5 or GLIBESYN commercial brand. Each patient were told to have breakfast after they gave the blood for fasting
blood sugar and they had taken 5mg glibenclamide, and to call back to the clinic in two hours time to receive free treatment for one month and to give another sample of blood for random blood sugar (RBS) and blood sample for serum level of glibenclamide.

All the fasting blood sugar measurements were carried out at the Al-Wafa Center for the treatment of diabetes mellitus, while the measurements of the sample for random blood sugar and blood sample for serum level of glibenclamide were carried out at Nenava Factory for Pharmaceuticals. The laboratory personals of Nenava Factory for Pharmaceuticals have no idea about the type of treatment that the patients were taken; they received the blood samples with the names of the patients only. The glibenclamide tablets were supplied by one of the authors who have the key of the three groups. All the treatments given to each group of patients were belonging to the same batch and to one of the manufacturing companies. These batches were all examined by the Quality Control Measures Committee of the Ministry of Health of IRAQ and passed the test as safe and works properly before they were introduced for the consumers use.

The blood level of the glibenclamide was measured two hours after the drug and breakfast was given to each patient by using the High performance Liquid Chromatography with fluorescence detection (HPLC). All the measures including the FBS, RBS and HPLC were recorded after the key was disclosed, and the three groups were separated according to the brand of manufacturing company.

Statistics
To compare the three brands of glibenclamide and to test their hypoglycemic effect Analysis of variance (ANOVA) test were utilized. Furthermore to determine which of them is the most statistically significant Duncan’s Multiple Range Test were utilized.

To determine which one of the three brands has the highest serum level after two hours, the analysis of variance for the three samples was used.

Results
Ninety patients with their age range from 34-74 years, 48 female and 42 male patients distributed in the three groups as in table (1&2).

Analysis of variance test were utilized to compare the hypoglycemic effect of the three commercial preparations of glibenclamide as shown in table (3) , the ANOVA test indicates that there were statistically significant differences between the three groups.

The value of the calculated (F) was 5.53 and by comparing it with the tabulated (F) at freedom degree of (2,87) at 0.05 which is equal to 3.15 and at level 0.01 the tabulated (F) were equal to 4.98 and so the calculated (F) is larger than the tabulated (F) at the level of 0.05 and at 0.01 level).

Duncan’s Multiple Range Test were utilized to determine which one of the three brands is the most statistically significant, this test indicates that the GLIBESYN brand is the most statistically significant in its hypoglycemic effects among the three brands.

To test the serum level among the three brands, the analysis of variance for the three variables (commercial preparations) were utilized which indicates as in table (4) that SAMACLAMIDE-5 brand have the highest serum level followed by GLIBIL5 brand and GLIBESYN brand were the lowest, but the there were no statistically significant difference between the serum level of the three brands, as the calculated (F) were 3.15, and at the level of 0.01 its value is 4.98.
Discussion

This study was conducted because the Ministry of health of Iraq during the period (2000-2003) imported so many brands of hypoglycemic drugs mostly from cheap brands and of unknown manufacturers. Furthermore there were a wide spread rumors among Iraqi physicians indicating that most of these drugs were not working properly. This study tested the brands which were commonly used in the Iraqi Ministry of health hospitals and the government clinics which deal with chronic ill patients with long standing diabetes mellitus.

This study indicates that the GLIBESYN brand was the most potent in lowering blood sugar during the tested period followed by the Samaclamid-5 brand and the Glibil5 were the lowest. These hypoglycemic effects were measured two hours after meal and 5mg of glibenclamide orally. The hypoglycemic potency of glibenclamide is reported to be directly related to the starting blood sugar level, the higher the blood sugar level the greater is the decline from the original reading [8].

Furthermore the serum level of the three brands as tested by using the High performance Liquid Chromatography with fluorescence detection (HPLC) at the Nenava Factory for Pharmaceuticals indicates that the SAMACLAMIDE-5 brand have the highest serum level followed by GLIBIL5 brand and GLIBESYN brand were the lowest, but there were no statistically significant difference between the serum level of the three brands.

In reviewing the literatures, there were a very few studies dealt with glibenclamide in the same line, like the comparative study of two glibenclamide preparation carried out by Walid A.Al-Turak and his co authors in comparing Glibil5 and Daonil this study indicates that there were no much difference between the two brands in the hypoglycemic effects or the serum level[9]. Another study carried out in Jordan by El-sayed YM and his co-authors were they evaluate the in vitro dissolution as well as the pharmacokinetic and pharmacodynamic properties of Daonil and Glucomid. There were no statistically significant difference between the two products with respect to their peak serum concentrations, Furthermore, the two products were not found significantly different in the extent of absorption as indicated by the area under serum concentration-time curve[11].

The results of previous two studies are more or less in agreement with our results and especially in respect to the serum level. Furthermore this study is probably the first in Mosul or probably in IRAQ in using the High performance Liquid Chromatography with fluorescence detection (HPLC) for the determination of the serum level of glibenclamide in diabetics.

Conclusion

This limited study is probably a call for wide range of determination of the efficacy of the other hypoglycemic drugs imported to IRAQ and especially so in the absence of the quality control measures. The High performance Liquid Chromatography with fluorescence detection (HPLC) is very easy and very sensitive test and should be used more regularly in order to have more smooth control of diabetes mellitus.

References

3-Coppack SW,Lant AF,McIntosh CS,Rodgers AV.,Br J Clin Pharmacol., 1990, 29,6, 673.

Table 1: Age distribution of patients

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<th>Groups</th>
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<th>61----70</th>
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Table 2: The distribution of patient according to the Groups

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<tr>
<th>Groups</th>
<th>SAMACLAMIDE-5</th>
<th>GLIBESYN</th>
<th>GLIBIL5</th>
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<tr>
<td>Male</td>
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<td>15</td>
<td>15</td>
<td>42</td>
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<tr>
<td>female</td>
<td>18</td>
<td>15</td>
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Table 3: One-way Analysis of variance (ANOVA)

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<td>4779</td>
<td>5.53</td>
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<td>Error</td>
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<td>75190</td>
<td>864</td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
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<td>84748</td>
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Table 4: Analysis of variance (ANOVA)

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<td>Factor</td>
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HPLC Graph of the serum level of the three brands of glibinclamide, the level ranging from (0-6mg/5000)

i  SAMACLAMIDE-5 SDI
5  GLIBESYN MEDOCHEMIE LTD-Cyprus
g  GLIBIL5: AIKMA Jordan