Eighteen-Month Follow-up of Glipizide and Human Insulin Combination in the Treatment of Type II Diabetes Mellitus

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ABSTRACT. This study reports a follow up of 29 Type II Diabetic patients with secondary drug failure treated by a combination of Human Insulin and Glipizide. During their follow-up, Insulin therapy was instituted following discontinuation of the maximum permissible dose of sulphonylureas for variable periods of time and thereafter Glipizide was added to Insulin treatment. Their diabetic control was assessed by checking the fasting and 2hr postprandial venous blood glucose values, HbA1c, and weight changes. These results were then compared in various phases of treatment, i.e. Phase I: Oral hypoglycemic agents, Phase II: Insulin alone (mean duration 2.55 ± 1.75 years), and Phase III: Human Insulin and Glipizide combination (mean duration 1.93 ± 0.72 years).

It was found that patients in Phase III showed an overall improved glycemic control compared to Phase I and II. HbA1c, dropped to 9.11±3.25 in Phase III compared to 11.13±2.75 in Phase II and 11.45±2.07 in Phase I. There was a weight gain of 3.56±6.69 kg in Phase II as compared to a net loss of 1.14±5.93 kg in Phase III. The mean daily requirement of Insulin in Phase II of 65.19 U decreased to 49.62 U in Phase III.

No relationship was established between the initial high Body Mass Index and initial C-peptides of responders and non-responders to combination therapy.

This study highlights the value of combination therapy of Glipizide plus Human Insulin in the control of diabetes after secondary failure in Type II diabetic patients.

Introduction

Non-Insulin dependent diabetes mellitus is the most common form of diabetes in the
world. Although the major therapeutic goal in treating patients with type II is to normalize metabolic control in order to prevent various complications associated with diabetes[11], it is a common observation that control of glycaemia in a large portion of type II patients remains poor[12]. It is still debatable as to what could be the best mode of treatment of type II diabetics with secondary drug failure[13].

Insulin alone is still a recognized mode of treatment for type II diabetic patients but not without risk[4,5]. It is interesting to note that combination therapy (Oral hypoglycemic + Insulin) was tried on type II patients not very long after the discovery of Sulfonylureas but this mode of treatment did not gain general acceptance as it produced some controversial results. Recent studies with combination therapy for type II patients have shown some encouraging results[6-10].

Studies have shown that Glipizide, a second generation sulphonylurea, may show some advantages over first generation sulfonylurea drugs in patients in whom adequate glycemic control has not been achieved[11,12]. This prompted us to study Type II Diabetes Mellitus patients with secondary drug failure on combination therapy (Glipizide + Human Insulin).

Patients and Methods

Twenty nine type II diabetic patients with established secondary drug failure who were regularly attending the diabetic clinic at the King Abdulaziz University Hospital were selected for this study. Secondary drug failure was established after achieving either fasting blood glucose of above 15 mmol/l and/or 2 hr post prandial (2HrPP) blood glucose of over 20 mmol/l when these patients were on maximum permissible dose of sulfonylureas in the hospital after being kept on strict diet for an average of ten days. Body Mass Index (BMI) was calculated for each patient. Their initial fasting C-peptides were also measured. Once secondary drug failure was established, the oral hypoglycaemic drug was stopped and the patients were commenced on Human Insulin (Humulin by Lilly, Indiana, U.S.A.). The dose of insulin was adjusted accordingly and these patients were then discharged from the hospital to be followed up in the diabetic clinic.

Insulin Therapy (Phase II)

These patients were followed up at regular intervals of 4-6 weeks. At each visit, their weight was recorded. Fasting + 2 hr postprandial venous blood glucose were done and their insulin requirement was noted and adjusted accordingly. Glycosylated hemoglobin levels were checked at regular intervals. Soluble and NPH insulin combination was used in morning and evening doses.

Diet

The patients were put on isocaloric weight maintaining diet; which included 45% carbohydrates, 40% fat and 15% proteins. A registered dietician interviewed these patients at regular intervals to stress dietary management.

Combination Therapy (Phase III: Human Insulin + Glipizide)

Combination therapy was discussed with the patients and those who consented
were commenced on combination therapy of Human Insulin and Gipipizde (Minidab, Farmatolia Carlo Erba, Italy). Initial dose of Gipipizde was 5 mg tds before meals. Doses of Insulin and Gipipizde were adjusted thereafter depending upon individual responses. These patients were then followed up in the diabetic clinic with weight, fasting and 2HrPP venous blood glucose; Insulin and Gipipizde doses recorded on each clinic visit. Glycosylated hemoglobin levels were checked at regular intervals. Insulin, Gipipizde and insulin syringes were provided by the hospital.

Plasma glucose was estimated by glucose analyzer (Beckman Fullerton CA) with specific enzymatic assay. Glycosylated haemoglobin (HbA1c) was estimated using affinity chromatography column. Data were collected and statistically analysed using the SPSS package.

Results

The twenty nine patients included 10 men and 19 women with an average age of 48.5 years having had Diabetes for a mean period of 7.65 years.

**Phase I (On oral Hypoglycemics alone)**

Mean values of the last 3 months before being labelled as secondary drug failure were as follows:

- Fasting blood glucose ......................... 14.29 ± 5.18 mmol/l
- 2hr post prandial venous B. Glucose .......... 19.02 ± 5.14 mmol/l
- HbA1c ........................................... 11.45 ± 2.07 %
- Mean Initial Fasting C-peptides .................. 3.25 ng/ml
- Mean calculated BMI for Males ................. 26.36.
(Obesity considered when Men BMI >27, Women BMI >25)[13].

**Phase II and Phase III**

Average duration of Phase II was 2.55 ± 1.75 years and that of Phase III was 1.93 ± 0.72 years.

**Metabolic Control**

The mean random blood glucose (Mean of FBS±2HrPP) in Phase II was 12.28±2.67 and for Phase III the mean RBS was 12.87±2.42 (P <0.975). For HbA1c, the mean for Phase II was 11.13±2.75 and for Phase III was 9.11±3.25 (P <0.004).

There was a marginal improvement in the metabolic control in Phase III.

**Weight Changes**

There was a net loss of 1.14±5.93 kg when patients were treated with combination therapy as compared to weight gain of 3.66±6.69 kg on insulin therapy alone.

Table 1 compares the changes in weight in Phase II and Phase III. It was also noticed that the maximum weight loss occurred in 12-18 months follow up period.
### TABLE 1. Comparison of insulin requirement and weight changes between phase II and III

<table>
<thead>
<tr>
<th></th>
<th>Weight (kg) (Mean ± SD)</th>
<th>Total Daily Dose of Insulin (Units) (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II (n = 26)</td>
<td>3.66 ± 6.69</td>
<td>55.19</td>
</tr>
<tr>
<td>Phase III (n = 29)</td>
<td>– 1.14 ± 5.39</td>
<td>49.62</td>
</tr>
<tr>
<td>Phase III 1st 6 months</td>
<td>0.41 ± 2.39</td>
<td>52.36</td>
</tr>
<tr>
<td>Phase III 6-12 months</td>
<td>– 0.52 ± 2.23</td>
<td>52.67</td>
</tr>
<tr>
<td>Phase III 12-18 months</td>
<td>– 1.22 ± 3.17</td>
<td>43.85</td>
</tr>
</tbody>
</table>

Phase II and Phase III Insulin P value = 0.030.
Phase II and Phase III Weight changes P value = 0.012.

**Insulin Changes**

When patients were kept on insulin therapy alone, there was a progressive increase in insulin requirement, which is consistent with observations elsewhere[14]. Whereas on Combination therapy, there was a decrease in daily insulin requirement. It was again noticed that maximum decrease in insulin requirement was seen during the 12-18 months follow up period (Table 1).

**Responders vs Non-responders to Combination Therapy**

Fifteen (51.7%) patients showed an overall improvement in metabolic control, and there was a net weight loss while on combination therapy along with a decrease in their daily insulin requirement (Table 2).

### TABLE 2. Comparison of phase II and III in 15 patients (51.71%) with overall improvement in monitoring criteria.

<table>
<thead>
<tr>
<th></th>
<th>Phase II (N = 15) (Mean ± SD)</th>
<th>Phase III (N = 15) (Mean ± SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBS (mmol/l) (Mean of FBS + 2HPP)</td>
<td>13.11 ± 2.46</td>
<td>12.12 ± 2.04</td>
<td>0.020</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>11.26 ± 2.14</td>
<td>9.15 ± 2.81</td>
<td>0.071</td>
</tr>
<tr>
<td>Weight changes (kg)</td>
<td>7.33 ± 6.23</td>
<td>–2.87 ± 6.45</td>
<td>0.003</td>
</tr>
<tr>
<td>Insulin changes (Units)</td>
<td>73.80 ± 36.75</td>
<td>59.47 ± 39.66</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Five (17.2%) patients demonstrated a statistically significant weight loss on combination therapy without showing much improvement in their metabolic control (Table 3). They also had a marginal decrease in their daily insulin requirement but this decrease was not statistically significant (Table 1).
Table 3. Comparison of phase II and III in 5 patients (17.2%) with improvement in weight and metabolic control.

<table>
<thead>
<tr>
<th></th>
<th>Phase II (N = 5) (Mean ± SD)</th>
<th>Phase III (N = 5) (Mean ± SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBS (mmol/l) (Mean of FBS + 2HrPP)</td>
<td>12.32 ± 2.14</td>
<td>14.22 ± 3.16</td>
<td>0.034</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>11.50 ± 4.61</td>
<td>10.00 ± 6.02</td>
<td>0.360</td>
</tr>
<tr>
<td>Weight changes (kg)</td>
<td>4.40 ± 1.67</td>
<td>-0.20 ± 2.36</td>
<td>0.005</td>
</tr>
<tr>
<td>Insulin changes (Units)</td>
<td>71.60 ± 25.52</td>
<td>69.20 ± 29.55</td>
<td>0.654</td>
</tr>
</tbody>
</table>

Another group of 5 (17.2%) patients showed an improvement in their metabolic control when on combination therapy (not statistically significant) with an increase in weight on combination therapy (Table 4).

Table 4. Comparison of phase II and III in 5 patients (17.2%) showing only partial improvement in weight and metabolic control.

<table>
<thead>
<tr>
<th></th>
<th>Phase II (N = 5) (Mean ± SD)</th>
<th>Phase III (N = 5) (Mean ± SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBS (mmol/l) (Mean of FBS + 2HrPP)</td>
<td>13.52 ± 3.46</td>
<td>11.14 ± 9.92</td>
<td>0.264</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.35 ± 2.05</td>
<td>7.40 ± 3.21</td>
<td>0.405</td>
</tr>
<tr>
<td>Weight changes (kg)</td>
<td>-3.20 ± 6.67</td>
<td>3.20 ± 3.96</td>
<td>0.247</td>
</tr>
<tr>
<td>Insulin changes (Units)</td>
<td>49.20 ± 15.91</td>
<td>45.20 ± 14.41</td>
<td>0.497</td>
</tr>
</tbody>
</table>

Four (13.7%) patients showed no improvement on combination therapy. There was no improvement in their blood glucose values (P = 0.068) and their weight increased (P = 0.146) along with an increase in their daily insulin requirement on combination therapy (P = 0.777).

Discussion

It is estimated that between 1-5% of patients with Type II Diabetes mellitus will develop primary or secondary drug failure[3]. Diet, drug non-compliance and intercurrent illness account for a percentage of these drug failures. Long-term management of this group remains controversial and generally unsatisfactory.

Diet, with exercise aimed at achieving ideal body weight and maintaining it, is disappointingly successful only in a small percentage of this group, however, it remains an important part of any management plan.

Introduction of Insulin therapy alone aimed at achieving normoglycaemia, is generally associated with an increase in body weight; this can ultimately worsen peripheral insulin resistance and adversely affect metabolic control; apart from its other inherent potential complications. The overall weight gain in our study highlights the problem and the rate of weight gain would have been higher if more vigorous Insulin therapy was employed to achieve normoglycaemia in the group.
Few studies have looked into long-term results of combination therapy with insulin and 2nd generation sulfonylureas\textsuperscript{15}, although it has a sound theoretical base. Glipizide has been shown to offer better results compared to first generation sulfonylureas because it stimulates an increase in fasting plasma insulin levels and post prandial insulin activity\textsuperscript{12}. Combination of sulfonylureas, addition of biguanides, cyclic Insulin therapy, Insulin therapy alone, and combination therapy with insulin and sulfonylureas\textsuperscript{16} have been tried with variable results. Success rates clearly reflect the difficulties encountered by the managing physicians, in attempting to achieve normoglycaemia, improve overall metabolic control, and delay or prevent the well-known complications of the disease.

It is evident from our study that the initial starting BMI and Fasting C-peptide levels do not correlate with the degree of response to such combination therapy. There remains a group of patients where possible dietary indiscretion plays an important role, and their management with insulin therapy alone or combination therapy remains highly unsatisfactory.

In conclusion, Combination therapy with Glipizide and Human Insulin may offer some advantages over insulin therapy alone in Type II diabetes mellitus patients with secondary drug failures. Further long-term studies are needed to clarify better selectivity of patients for this line of management.

Reference

\textsuperscript{[4]} Steiner G. Hyperglycemia and Carbohydrate intolerance. Interrelations and therapeutic implications. Am J Cardiol 1986; 57: 27G-30G.
\textsuperscript{[5]} Stout RW. Overview of the association between insulin and atherosclerosis. Metabolism 1985; 34 (Suppl 1): 7-12.
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(Received 29/05/1990; accepted 30/09/1990)
منحة علاج النمط الثاني من الداء السكري بالجليبيزيد وإنسولين الإنسان لفترة 18 شهرًا

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المستخلص: ناقشنا هذه المقالة نتائج 39 من مرضى النمط الثاني من داء السكري تم علاجهم بالإنسولين والجيليبيد، بعده فشل ثائي للعلاج الدوائي. وقد حررت إضافة الإنسولين خلال المتابعة بعد إيقاف الجرعة القصوى المسموح بها من البوريا السلفونيلوفة لفترات متفاوتة، وبعد ذلك أضيف الجلبيزيد إلى العلاج بالإنسولين.

وكان تقييم التحكم في السكر كي يقيس مقدار الجلوكوز في الدم الوريدي صيامًا بعد الأكل بساعتين، وكذلك قياس التغيرات في الوزن، والهيموجلوبين السكري (HbA1c) بعد ذلك، تمّت مقارنة مقدار السكر في النهاية المكتشفة في الدراسات بين (1) مرحلة العلاج بدون معالجة للسكير واستباملي (2) مرحلة العلاج بالإنسولين (3) مرحلة العلاج بالإنسولين والجيليبدء (متوسط استمرارها 11.93 سنة).

النحو: تسجيل عامة في ضغط السكر لدى مرضى النمط الثالث، مع ارتفاع مرضى المريضين في المرحلة الأولى والثانية، إذ انخفض الهيموجلوبين السكري (HbA1c) في هذه المرحلة إلى 11.14% (متوسطه 11.14% في المرحلة الثانية) مقارنةً بـ 11.17% في المرحلة الثانية، ورغم ذلك فإن في المرحلة الثالثة، بلغ متوسطها 7.9% هم. كما ظهرت زيادة في الوزن في المرحلة الثالثة، بلغ متوسطها 5.43% (متوسط الاستمرار في المرحلة الثالثة 5.43 وزن). وقد بلغ متوسط الحالة البدنية للإنسولين في المرحلة الثانية، وحده 0.19، وحده في المرحلة الثالثة، وحده 0.19، وحده 0.19.

ولنثبت أن السكر لدى المرضى في مرضى النمط الثاني من داء السكري، تحتوي على نسب متوسطية من البوريا السلفونيلوفة، ونستخدم هذا الجلبيزيد.

إن هذه الدراسة توضح قيمة المتابعة المركزية للإنسولين والجيليبيد في التحكم في الداء السكري، بعد الفشل الثاني للعلاج الدوائي لدى المصابين بالنمط الثاني من هذا المرض.