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Original Research Article

Efficacy of Some Combination Regimens of Oral Hypoglycaemic Agents in Type 2 Diabetes Mellitus Patients

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Abstract

Purpose: *To examine the efficacy of selected oral hypoglycaemic agent (OHA) regimens in a small group of patients receiving such treatment.*
Methods: *This was a retrospective, observational study that involved patients who had been diagnosed with type 2 diabetes mellitus and undergoing routine follow-up at a teaching hospital. By reviewing patients' medical records, changes in fasting blood glucose (FPG) and glycated haemoglobin (HbA1c) levels induced by several OHA cobmination regimens were documented. Target FPG and HbA1c were defined as 4.4 - 6.1 mmol/L and 6.5 %, respectively.*
Results: *Based on the medical records of 156 patients reviewed, the combination of metformin and gliclazide was the most commonly prescribed regimen (63.46 %). The use of gliclazide + rosiglitazone + acarbose produced the greatest reduction in FPG and HbA1c (-4.80 mmol/L and - 4.20 %, respectively), but the number of patients receiving this combination was too small to allow definitive conclusions to be made. More patients in the triple OHA group were able to achieve the desired glycaemic control than those in the dual OHA group (FPG, 44.44 % versus 41.18 %; HbA1c, 52.94 % versus 47.06 %), highlighting the important benefits conferred by the use of multiple OHAs.*
Conclusion: *The efficacy of various OHA combinations varies, and adding a third drug to a dual-agent regimen further reduces FPG and HbA1c levels. Though gliclazide + rosiglitazone + acarbose produces the greatest reduction in FPG and HbA1c levels, larger studies are required to confirm these findings.*

Keywords: *Type 2 diabetes mellitus, Oral hypoglycaemic agents, Fasting plasma glucose (FPG), Glycated haemoglobin (HbA1c), Combination therapy, Gliclazide, Rosiglitazone, Acarbose*

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INTRODUCTION

Oral hypoglycaemic agents (OHAs) represent an important treatment option for type 2 diabetes mellitus (DM). Several classes of OHAs are available, namely thiazolidinediones (TZDs), insulin secretagogues [sulphonylureas (SUs) and non-SUs], biguanides and α-glucosidase inhibitors. Each of the OHA classes exerts its hypoglycaemic effect via a different mode of action. When used alone, metformin, second-generation SUs and TZDs were found to be comparable with respect to their efficacy in reducing the glycated haemoglobin (HbA1c) levels [1].

The major limitation of OHA monotherapy is a loss of effectiveness over time, necessitating addition of another OHA or switch to insulin therapy [2]. Where the first OHA at maximum dosage does not achieve the desired glycaemic control, a second OHA from a different class is usually added. The most common combination regimens are a SU plus metformin, a SU plus a

TZD (for metformin-intolerant patients), or metformin plus a TZD (for patients with peripheral insulin resistance). When taken in combination, OHAs produce additive therapeutic effects by simultaneously targeting different glucose utilisation pathways in vivo [3, 4]. Combination OHA therapy is also preferable over insulin, the use of which is often complicated by compliance issues [4]. Recognising the indispensable role of combined OHAs in type 2 DM, we set out to assess the efficacy of different OHA combination regimens in a small group of patients receiving such treatment.

EXPERIMENTAL

Subject recruitment

The study was retrospective and observational in design and was conducted from February 2010 to September 2010, involving patients who had been diagnosed with type 2 DM and undergoing routine follow-up at the Endocrine Clinic, Hospital Universiti Kebangsaan Malaysia. Study subjects were identified from the electronic documentation system at the hospital pharmacy, according to the following inclusion criteria: the subject must be diagnosed with type 2 DM, aged at least 18 years, and were being treated with OHAs; those who were prescribed with insulin or were pregnant, or whose medical records were incomplete were excluded. At the time of study implementation, no ethical approval was required as there was no direct contact with the patients; only the medical records were reviewed.

Clinical measurements

The following clinical data were documented using a questionnaire designed for this study: patient demographics, smoking status, alcohol consumption history, co-morbidities, past medication history, OHA regimens, and laboratory measurements, namely fasting plasma glucose (FPG) and HbA1c levels. Target glycaemic control was defined as a FPG of 4.4-6.1 mmol/L and a HbA1c level < 6.5 % [5]. Changes in FPG or HbA1c levels were calculated based on the values documented before and after treatment initiation.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as counts (%). Independent T-test was used to compare different OHA combinations by the achieved FPG and HbA1c levels. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Science (SPSS) version 16.0.

RESULTS

The medical records of a total of 156 patients, of whom 91 (58.33 %) were female and 65 (41.67 %) were male, were examined in this study (Table 1). These patients represented an aged population having a long history of type 2 DM, with the mean disease duration and the mean age being 12.41 ± 6.22 years and 60.79 ± 12.73 years, respectively. Seventy-four (47.43 %) subjects were of Malay descent; whereas 56 (35.90 %) identified as Chinese and 26 (16.67 %) as Indian. The majority of the patients were overweight (63, 40.38 %) and were found to have multiple co-morbidities (146, 93.59 %). Low rates of active smoking and alchohol consumption were noted, with only 29 (18.59 %) subjects identified as smokers and 21 (13.46 %) subjects found to be regularly consuming alcohol.

As illustrated in Figure 1, the two most common OHA combinations were metformin plus gliclazide (99, 63.46 %), and metformin, gliclazide plus rosiglitazone (44, 28.21 %). The combination of metformin, rosiglitazone plus acarbose was infrequent and only one patient (0.64 %) was prescribed with such a regimen. Gliclazide, rosiglitazone plus acarbose induced the greatest reductions in FPG and HbA1c levels, namely - 4.80 mmol/L and - 4.20 %, respectively (Figures 2 and 3); but this regimen was rarely prescribed [given to only two patients (1.28 %)]. Analysis by independent T-test revealed that combined gliclazide, rosiglitazone and acarbose was significantly better than metformin plus gliclazide ($p = 0.043$) in regards to FPG control; but comparison with other regimens was not statistically significant. Similarly, gliclazide, rosiglitazone plus acarbose was found to produce significantly greater reductions in HbA1c levels when compared with metformin plus gliclazide, metformin, gliclazide plus rosiglitazone, or metformin, gliclazide plus acarbose ($p = 0.001$, $p = 0.022$ and $p = 0.008$, respectively). Intriguingly, the use of metformin, rosiglitazone plus acarbose resulted in an FPG increase of 0.70 mmol/L, but a paradoxical, marginal HbA1c reduction of - 0.40 %.

Subsequently, we determined the proportions of patients who achieved FPG or HbA1c target when receiving dual or triple OHA therapy. As shown in Figures 4(a) and (b), more patients in the triple therapy group were able to achieve

FPG or HbA1c target than those treated with dual OHA therapy (FPG, 44.44 % versus 41.18 %; HbA1c, 52.94 % versus 47.06 %).

Table 1: Patient demographics and medical history

Demographic variable	Number of patients (N=156)	(%)
Gender		
Male	65	41.67
Female	91	58.33
Age group (mean age = 60.79 ± 12.73)		
20-44 years	18	11.54
45-64 years	75	48.08
≥ 65 years	63	40.38
Race		
Malay	74	47.43
Chinese	56	35.90
Indian	26	16.67
Body Mass Index (BMI)		
Underweight	4	2.56
Normal	44	28.21
Overweight	63	40.38
Obesity	45	28.85
Co-morbidity		
DM + Hypertension	29	18.59
DM + Hyperlipidaemia	24	15.38
DM + Hypertension + Hyperlipidaemia	93	59.62
DM only	10	6.41
Smoking		
Yes	29	18.59
No	127	81.41
Consuming alcohol		
Yes	21	13.46
No	135	86.54
Disease duration (years, mean=12.4 ± 6.2)		
1 – 5	12	7.69
6 – 10	64	41.03
11 – 15	46	29.49
16 – 20	12	7.69
21 – 25	16	10.25
26 – 30	6	3.85

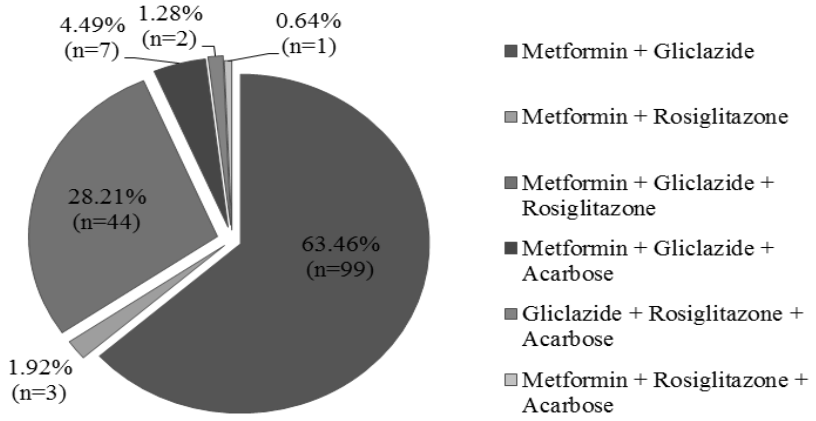
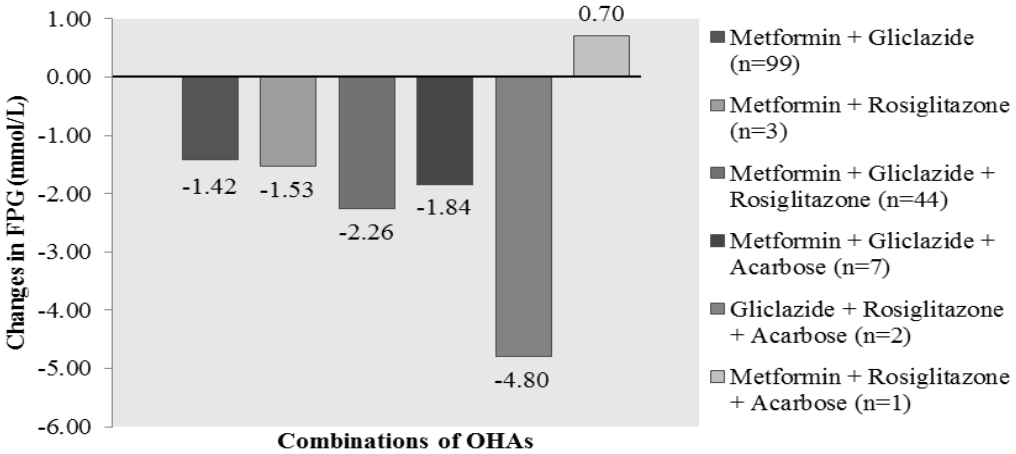
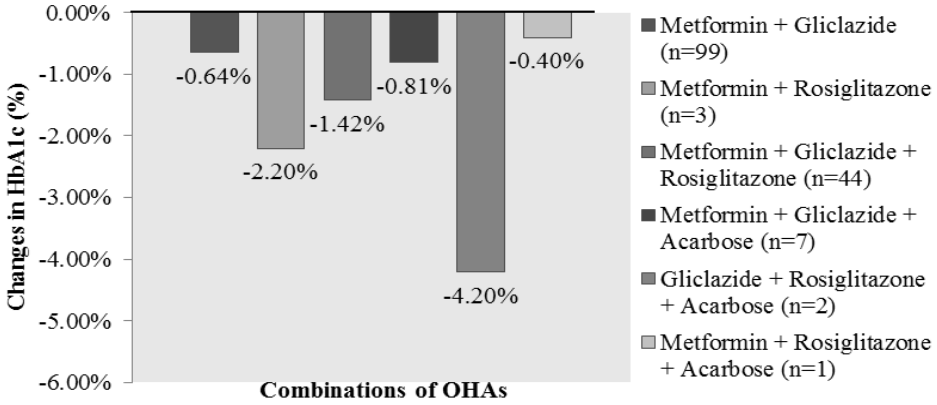


Figure 1: Frequencies of different OHA regimens (N=156)



Gliclazide + rosiglitazone + acarbose versus metformin + gliclazide; $p = 0.043$
Gliclazide + rosiglitazone + acarbose versus metformin + rosiglitazone; $p = 0.120$
Gliclazide + rosiglitazone + acarbose versus metformin + gliclazide + rosiglitazone; $p = 0.229$
Gliclazide + rosiglitazone + acarbose versus metformin + gliclazide + acarbose; $p = 0.245$

Figure 2: Changes in FPG levels by different OHA combinations



Gliclazide + rosiglitazone + acarbose versus metformin + gliclazide; p = 0.001
Gliclazide + rosiglitazone + acarbose versus metformin + rosiglitazone; p=0.169
Gliclazide + rosiglitazone + acarbose versus metformin + gliclazide + rosiglitazone; p=0.022
Gliclazide + rosiglitazone + acarbose versus metformin + gliclazide + acarbose; p=0.008

Figure 3: Changes in HbA1c levels by different OHA combinations

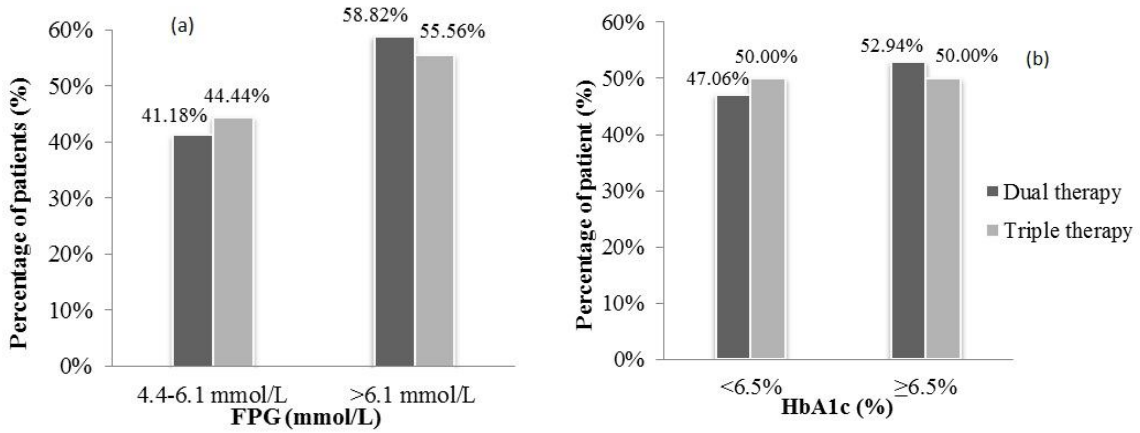


Figure 4: Proportion of patients achieving FPG (a) or HbA1c (b) target following dual or triple OHA therapy

DISCUSSION

In the present study, the medical records of 156 patients who had been diagnosed with type 2 DM and receiving combined OHAs regimens were reviewed. Metformin plus gliclazide (63.46 %) was the most commonly prescribed regimen for type 2 DM, consistent with the findings of other studies [6,7]. Indeed, metformin is recommended by International Diabetes Federation as the first-line monotherapy for type 2 DM. When the use of metformin alone fails to achieve normoglycaemia, addition of a SU is appropriate [8]. Combining different agents produces additive effects which are beneficial for certain patients [9].

The most frequently used triple therapy was metformin, gliclazide plus rosiglitazone (28.21 %). Adding a TZD to a SU plus metformin conferred additional glucose-lowering benefits which are comparable to those of insulin use. Furthermore, the addition of a TZD has the potential to stabilize or improve beta-cell function, and reduce adverse cardiac risk [10, 11]. In our study, patients who received those OHA combination regimens made up a major proportion (> 90 %) of the study population, showing that most physicians did adhere to evidence-based guidelines when prescribing OHAs. It is noteworthy that metformin, rosiglitazone plus acarbose was the least favoured combination, being given to only one patient. This is probably because concurrent administration of metformin and acarbose could lead to excessive gastrointestinal side effects and thus would not be tolerable [12].

Overall, the mean changes in FPG and HbA1c values were varied and inconsistent for the OHA combinations examined. A decrease in FPG did not always translate into a corresponding HbA1c reduction. This is particularly true with metformin, rosiglitazone plus acarbose. Use of this combination resulted in a small increase in FPG of 0.70 mmol/L, but a slight decrease in HbA1c (-0.40 %). Only one patient was prescribed with this combination. Therefore, it is likely that the discrepancy was due to patient-related factors such as non-compliance with the prescribed treatment or non-adherence to dietary restrictions.

The use of gliclazide, rosiglitazone plus acarbose produced the greatest reductions in FPG and HbA1c values. But, statistical significance was not consistently attained when comparison was made against other drug combinations. This OHA combination was found to be significantly better than metformin plus gliclazide in reducing FPG; and the following regimens in reducing HbA1c levels: metformin plus gliclazide, metformin, gliclazide plus rosiglitazone, and metformin, gliclazide plus acarbose. However, because the number of patients prescribed with gliclazide, rosiglitazone plus acarbose is too small (2, 1.28 %), the statistical significance is dubious. Acarbose is generally considered less potent than other OHAs; hence, its additive effect to an existing dual-agent regimen should have been less substantial. Larger studies are required to confirm our findings. Until then, gliclazide, rosiglitazone plus acarbose cannot be recommended as the preferred triple OHA therapy.

Triple OHAs were found to be better than dual-agent regimens in regards to the proportions of patients achieving the target FPG and HbA1c levels (FPG, 44.44 % versus 41.18 %; HbA1c, 52.94 % versus 47.06 %). Nonetheless, the overall glycaemic control with both treatment schemes was not satisfactory, with non-optimal treatment outcome being documented for 40-50 % of the patients. More importantly, physicians seemed to refrain from prescribing triple OHAs, despite the fact that a substantial number of patients failed to achieve the desired glycaemic goals. This is probably due to practical considerations such as difficulty in adhering to a complex regimen. Given the progressive nature of type 2 DM, introducing triple-agent combination at lower baseline HbA1c levels could potentially increase the proportion of patients attaining and sustaining the target HbA1c level (7 %) [13]. The benefits conferred by triple therapy have been reported in other studies [10,13]. Triple oral antidiabetic therapy was proven to be an effective long-term treatment for patients with type 2 diabetes [14].

Limitations of the study

The main limitation of this study is that of sample size. For several OHA combinations, the number of patients was too small to allow definitive conclusions to be made. Also, the dosage of individual OHAs was not accounted for, and this might have influenced changes in FPG or HbA1c. The authos were also unable to examine patient-related confounding factors, particularly adherence to prescribed regimens due to the retrospective nature of the study.

CONCLUSION

The combination of metformin and gliclazide is the most commonly prescribed OHA therapy for type 2 DM patients being treated at the Endocrine Clinic, Hospital Universiti Kebangsaan

Malaysia. The efficacy of different OHA combinations varies, and adding a third drug to a dual-agent regimen further reduces FPG and HbA1c levels. Although gliclazide + rosiglitazone + acarbose produces the greatest reduction in FPG and HbA1c levels, larger studies are required to confirm these findings. Despite some limitations, the results of this study provide some clues to the design of future studies that would aim to assess the efficacy of dual or triple OHAs therapy in type 2 DM.

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