Glycaemic Control And Cost Analysis When Changing From Gliclazide Co-Administered With Metformin To Pre-Combined Glibenclamide-Metformin Tablets In Type 2 Diabetes Mellitus

P C Lim, BPharm(Hons)*, S L Lim, FRCP, Oiyammaal C, MClinPharm***

*Pharmacy Department, Penang Hospital, Jalan Residensi, 10990 Penang, Malaysia, **Medical Department, Penang Hospital, Jalan Residensi, 10990 Penang, Malaysia

SUMMARY

Type-2 diabetes mellitus (T2DM) patients who were on gliclazide co-administered with metformin were changed to pre-combined glibenclamide-metformin tablets in the Endocrine Clinic, Penang Hospital. We conducted a retrospective study to evaluate the differences in glycaemic control and treatment cost following the change. Eighty patients (60% females) with a mean age of 55 years old were studied. Mean glycosylated haemoglobin (HbA1c) reduction was -0.92% (p<0.01) and -0.83% (p<0.01) after three and six months respectively. Patients with baseline HbA1c ≥8% had greater reduction in mean HbA1c (-1.36%) after six months. The treatment cost per month was reduced by 45% at 3 months (p<0.01)) and 44% at 6 months (p<0.01). The change to pre-combined glibenclamide-metformin tablets resulted in significant improvement in glycaemia and reduction in treatment cost

KEY WORDS:
Glibenclamide-metformin, Gliclazide co-administered with metformin, Glycosylated haemoglobin, Cost-effective

INTRODUCTION

Type 2 diabetes is caused by two major metabolic defects namely insulin resistance and reduction in insulin secretion secondary to progressive decline in pancreatic ß-cell function. Insulin resistance reduces glucose uptake and increases hepatic glucose output leading to increase glucose load. Compensatory hyperinsulinemia to maintain normal glycaemia causes exhaustion of ß-cell resulting in ß-cell dysfunction and hyperglycaemia [1,2]. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated 50% loss of ß-cell function and 60% reduction of normal insulin sensitivity at the time of diagnosis of type 2 diabetes mellitus[3].

Poorly controlled diabetes is associated with macrovascular (myocardial infarction) and microvascular (retinopathy and nephropathy) complications. Therefore, intensive glycaemic control is important in decreasing the microvascular risk, risk of myocardial infarction and death from any cause [4]. UKPDS showed that only 25% of patients maintained target glycaemic control of less than 7% over nine years follow-up period with monotherapy of either insulin, sulphonylurea or metformin [5] suggesting that majority of patients require multiple therapies to achieve target glycaemic control.

Thus, combination therapy is more effective in the treatment of type 2 diabetes especially combination of agents that target insulin resistance and insulin deficiency. The most commonly used combination oral antidiabetic agents are metformin (insulin sensitizer) plus sulphonylurea (insulin secretagogue) [1]. Study by Hermann et al., demonstrated better glycaemic control with combination therapy of metformin and glibenclamide as compared to treatment with metformin or glibenclamide alone [6]. Interestingly, retrospective cohort study by Blonde *et al.*, showed that lower dose of glibenclamide-metformin combination tablet (Glucovance®) provided a significant greater reduction in glycosylated haemoglobin (HbA1c) than glibenclamide co-administered with metformin [7].

Pre-combined glibenclamide-metformin tablets (Glucovance®, Merck) have been available in the Malaysia Ministry of Health drug formulary since 2007. The prices of glibenclamide/metformin (Glucovance®) 2.5/500mg and 5.0/500mg are cheaper compared to gliclazide (generic, Pharmaniaga) co-administered with metformin (generic, Pharmaniaga) [8]. Since then, some patients who were on gliclazide co-administered with metformin were changed to glibenclamide-metformin tablets in the Endocrine Clinic, Penang Hospital, Malaysia. Retrospective studies had demonstrated that pre-combined glibenclamide-metformin tablets provided a significant greater reduction in HbA1c than sulphonylurea co-administered with metformin [7,9]. However, there is no literature on the glycaemic control and cost of oral antidiabetic agents in type 2 diabetes patients when gliclazide co-administered with metformin were changed to pre-combined glibenclamide/metform tablets.

The objective of our study was to evaluate the differences in glycaemic control and cost of oral antidiabetic agents when gliclazide co-administered with metformin patients were changed to pre-combined glibenclamide-metformin tablets.

This article was accepted: 4 November 2011
Corresponding Author: Shueh Lin Lim, Penang Hospital, Medical Department, Jalan Residensi, Georgetown, Penang 10990 Malaysia
Email: shepsll@yahoo.com

MATERIALS AND METHODS

A retrospective cross-sectional study on patients who were changed to pre-combined glibenclamide-metformin tablets (Glucovance®, Merck) from gliclazide (generic, Pharmaniaga) co-administered with metformin (generic, Pharmaniaga) from September 2008 to December 2009. This study was approved by the Medical Research Ethics Committee, Ministry of Health, Malaysia.

This study included type 2 diabetes patients aged 18 years old and above who received treatment in the Endocrine Clinic, Penang Hospital, Malaysia. Penang Hospital is a tertiary public hospital. Patients who were currently treated with pre-combined glibenclamide-metformin combination (Glucovance®, Merck) and previously on gliclazide (generic, Pharmaniaga) co-administered with metformin (generic, Pharmaniaga) for more than six months were included. Data of patients who had baseline glycosylated haemoglobin (HbA1c) within 30 days prior to switching to pre-combined glibenclamide-metformin tablets and HbA1c value three- and six- month after switching were captured.

Patients were excluded if new antidiabetic agents or insulin were added or if the dose of antidiabetic agents (other than pre-combined glibenclamide-metformin tablets) was titrated. Medical records of patients that met the inclusion criteria were reviewed and the data was collected using a standard data collection form. Information about patients' demographics, weight, medication regimens and laboratory parameters, baseline HbA1c, HbA1c value after three- and six-month of switching, fasting blood glucose (FBG) at baseline, three- and six- month after switching was captured.

In addition, data on medication dose and number of tablets per month were collected. The costs of pre-combined glibenclamide-metformin tablets and gliclazide co-administered with metformin were calculated base on the dose and number of tablets per month. The prices of glibenclamide/metformin 2.5/500mg and 5.0/500mg are RM0.09 and RM0.11 per tablet respectively. The price of gliclazide is RM0.14 per tablet and metformin RM0.04 per tablet [8].

The primary outcome was mean difference in HbA1c after three- and six- month of the change. Secondary outcomes included difference in HbA1c in patients with baseline HbA1c ≥ 8%, cost of treatment per month, fasting blood glucose (FBG) and weight change.

Data were analyzed using PASW® version 18 (formerly known as SPSS). The paired t-test was used to analyze the difference of normally distributed data. If the data was not normally distributed, the Wilcoxon signed-rank test was used. Results were statistically significant if the p value was <0.05.

RESULTS

A total of 180 patients were changed to pre-combined glibenclamide-metformin tablets from September 2008 to December 2009. Eighty patient records (44%) met the inclusion criteria. 100 patient records (56%) were excluded with majority patients on other oral antidiabetic agent other than gliclazide co-administered with metformin. Demographics of these patients were shown in Table I.

The mean baseline, three- and six-month after the change to pre-combined glibenclamide-metformin tablets outcome measures are shown in Table II. The mean HbA1c reduced significantly after three-month, -0.92% (p<0.001) and maintained until six-month, -0.83 % (p=0.001). There was greater HbA1c reduction in patients with baseline HbA1c 8% or more after three- and six-month, -1.32% and -1.36% respectively (Figure 1). However, there were no significant differences in fasting blood glucose after three and six months.

The monthly cost of oral antidiabetic agents also reduced significantly after the change to pre-combined glibenclamide-metformin tablets as compared to gliclazide co-administered with metformin. The treatment cost reduced by 45% (p<0.001) and 44% (p<0.001) monthly after three- and six-month. Even though there was reduction in patient weight after three and six months, the reductions were not significant.

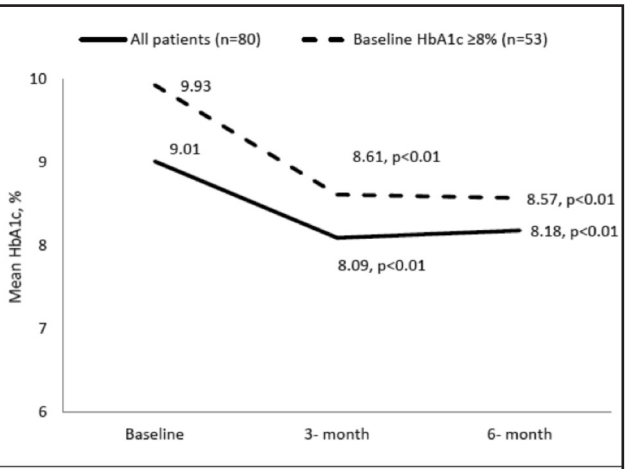
Table I: Patient Demographics

Demographics	Number of patients (%), n=80
Age (y)	55.43 (SD=9.78)
Duration of type 2 diabetes mellitus (y)	11.63 (SD=7.03)
Gender	
Male	32 (40.0)
Female	48 (60.0)
Race or ethnicity	
Malay	34 (42.5)
Chinese	29 (36.2)
Indian	17 (21.2)

Table II: Changes in glycaemic control, cost of oral antidiabetic agents and weight

Outcome measures	Baseline	3-month after the switch			6-month after the switch		
		3-month	Mean difference	p-value	6-month	Mean difference	p-value
HbA1c (%)	9.01±0.22	8.09±0.21	-0.92	<0.001*	8.18±0.16	-0.83	0.001*
FBG (mmol/l)	8.47±0.51	7.83±0.46	-0.64	0.236*	7.55±0.50	-0.92	0.134+
Cost of oral antidiabetic agents/ month (RM)	18.85±0.49	10.35±0.18	-8.50	<0.001+	10.63±0.16	-8.22	<0.001+
Weight (kg)	71.61±1.62	71.39±1.60	-0.22	0.354+	70.63±1.82	-0.98	0.149+

Data are mean±SD. *paired t-test. +Wilcoxon signed-rank test



Metformin (mg/day)	1950.0	1925.0	1937.5
Gliclazide (mg/day)	270.5	-	-
Glibenclamide (mg/day)	-	9.9	10.3

Fig. 1: Difference in Mean HbA1c.

DISCUSSION

This study is the first to demonstrate that the change to pre-combined glibenclamide-metformin tablets from gliclazide co-administered with metformin improved HbA1c as well as monthly cost of oral antidiabetic agents significantly. The mean HbA1c reduced by 0.9% in all patients after three months and maintained until six months. In patients with baseline HbA1c ≥8%, the reduction of mean HbA1c was more prominent, -1.3%. This finding was similar to retrospective study by Duckworth *et al*. that demonstrated a 1.3% reduction in mean HbA1c in patients with baseline HbA1c ≥8% when change from glipizide or glibenclamide co-administered with metformin to pre-combined glibenclamide-metformin tablets [9].

UKPDS has proven that every 1% reduction of HbA1c is associated with a 37% risk reduction of microvascular complications and 14% risk reduction of myocardial infarction [10]. With the 1.3% reduction in mean HbA1c in patients with baseline HbA1c ≥8%, the change to pre-combined glibenclamide-metformin tablets had an important impact on microvascular and cardiovascular endpoints. The change may improve these patients' quality of life.

Moreover, this study also demonstrated that lower doses of pre-combined glibenclamide-metformin tablets (10mg/day of glibenclamide vs. 270mg/day of gliclazide) were sufficient to further reduce the HbA1c when change from gliclazide co-administered with metformin. Double blind randomized study by Baba *et al.*, reported 40mg of gliclazide had similar potency with 2.5mg of glibenclamide [11]. In a multicentre, randomized, three-arm, double blind trial by Garber *et al.,* lower doses of glibenclamide-metformin tablets provided superior glycaemic control over monotherapy with either metformin or glibenclamide alone when diet and exercise failed. In addition, lower doses of glibenclamide-metformin tablets were well tolerated and had significantly lower incidence of gastrointestinal side effects (32%) as compared with metformin monotherapy (43%) [12]. Lower doses of pre-combined glibenclamide-metformin tablets enable further upward dosage titration in future management and thus, allowing a delay in introduction of third oral antidiabetic agents or insulin. Addition of third agent may increase the treatment cost of type 2 diabetes. The finding also suggests that lower doses of pre-combined glibenclamide-metformin tablets may be the choice of treatment when combination therapy is needed in patients who do not achieve their treatment target of HbA1c <7% with metformin and lifestyle changes as recommended by American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) treatment guideline [13]. In Malaysia, this combination tablet may be the choice of treatment for patients with HbA1c of 8% to 10% as stated in the Ministry of Health Clinical Practice Guidelines [14].

Even though there was a significant reduction of HbA1c in this study, the reduction of fasting blood glucose was not significant. Therefore, the reduction in HbA1c may be contributed by better post prandial glycaemic control when change to pre-combined glibenclamide-metformin tablets. This may be attributed to the unique pre-combined glibenclamide-metformin tablets formulation whereby controlled range of particle sizes of glibenclamide contained within a freely-soluble metformin matrix [15]. In a randomized crossover trial by Donahue et al., the difference in particle sizes of glibenclamide in the pre-combined tablets resulted in two-fold amount of glibenclamide delivers within the first 3 hours of dosing [16]. As a result, pre-combined glibenclamide-metformin tablets may contribute to better post prandial glycaemic control as compared to gliclazide co-administered with metformin.

Furthermore, the use of pre-combined glibenclamide-metformin tablets may improve patients' compliance as it is more convenient with less pill burden. This is well supported by previous study whereby patients' compliance significantly improved by 16% when switched to a single combination tablet from polytherapy [17]. Improvement in compliance may contribute to better glycaemic control.

Importantly, change to pre-combined glibenclamide-metformin tablets resulted in cost saving of oral hypoglycaemic agents by about 45% monthly. This finding suggests that pre-combined glibenclamide-metformin tablets provide a cheaper and more effective alternative. The more convenient and cost-effective glibenclamide-metformin tablets have attributed to the increase in the usage by about two-fold from year 2006 to year 2007 [18].

Finally, this is a retrospective study and patients' sample is small. In addition, important information like incidence of adverse effect and hospitalization related to diabetes are unknown. However, the intention of this study was to show the cost effectiveness and glycemic outcome of the pre-combined glibenclamide-metformin tablets. The study gives us some insight into a potential cheaper and effective

treatment option. The ideal is to perform a prospective, randomized, parallel-group study to compare pre-combined glibenclamide-metformin tablets and gliclazide co-administered with metformin which we hope to embark in the future.

CONCLUSION

The change of gliclazide and metformin tablets to the lower doses of pre-combined glibenclamide-metformin tablets improved glycaemic control significantly in type 2 diabetes mellitus patients and the improvement was more prominent in patients with baseline HbA1c ≥8%. In addition, the significant reduction in the treatment cost suggests the use of pre-combined glibenclamide-metformin tablets as a cheaper effective alternative. The findings may have impact on policy making whereby the pre-combined glibenclamide-metformin tablets can be used in appropriate patients and reduced the cost of treatment of type 2 diabetes.

ACKNOWLEDGEMENT

We thank Director General of Health, Malaysia for the permission to publish this paper.

REFERENCES

1. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 1999;131: 281-303.
2. Kahn S. The importance of the ß-cell in the pathogenesis of type 2 diabetes mellitus. Am J med. 2000; 108(suppl 6a): 9S-14S.
3. U.K. Prospective Diabetes Study Group. Overview of 6 years' therapy of type II diabetes: a progressive disease (UKPDS 16). Diabetes 1995; 44(11): 1249-58.
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008 Oct 9; 359(15): 1577-89.
5. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA. 1999 Jun 2; 281(21): 2005-12.
6. Hermann LS, Scherstén B, Bitzén PO, Kjellström T, Lindgärde F, Melander A. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care 1994 Oct; 17(10): 1100-9
7. Blonde L, Wogen J, Kreilick C, Seymour AA. Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide co-administered with metformin. Diabetes Obes Metab. 2003 Nov; 5(6): 424-31.
8. A report of Pharmaceutical Services Division, Ministry of Health Malaysia. Private sector medicines retail price list 2011 (2nd Ed). 2010 Oct.: 210-4.
9. Duckworth W, Marcelli M, Padden M, *et al*. Improvements in glycemic control in type 2 diabetes patients switched from sulfonylurea coadministered with metformin to glyburide-metformin tablets. J Manag Care Pharm. 2003 May-Jun;9(3): 256-62.
10. U.K. Prospective Diabetes Study Group. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12; 321(7258): 405-12
11. Baba S, Nakagawa S, Takebe K, et al. Comparison of gliclazide and glibenclamide treatment in non-insulindependent diabetes. Tohoku J Exp Med 1983; 141 (Suppl.): 693-706.
12. Garber AJ, Donovan DS Jr, Dandona P, Bruce S, Park JS. Efficacy of glyburide/metformin tablets compared with initial monotherapy in type 2 diabetes. J Clin Endocrinol Metab. 2003 Aug; 88(8): 3598-604.
13. Nathan DM, Buse JB, Davidson MB *et al*. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009 Jan; 32(1): 193-203.
14. Ministry of Health Malaysia. Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus (4th Ed). 2009 May.
15. Howlett H, Porte F, Allavoine T, Kuhn T, Nicholson G. The development of an oral antidiabetic combination tablet: design, evaluation and clinical benefits for patients with type 2 diabetes.Curr Med Res Opin. 2003; 19(3): 218-25.
16. Donahue SR, Turner KC, Patel S. Pharmacokinetics and pharmacodynamics of glyburide/metformin tablets (Glucovance) versus equivalent doses of glyburide and metformin in patients with type 2 diabetes. Clin Pharmacokinet. 2002; 41(15): 1301-9.
17. Melikian C, White TJ, Vanderplas A, Dezii CM, Chang E. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther. 2002 Mar; 24(3): 460-7.
18. A publication of Pharmaceutical Services Division and Clinical Research Centre, Ministry of Health Malaysia. Malaysian statistics on medicine 2007. 2010 Oct: 21-4.