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TREND IN THE USE OF ORAL HYPOGLYCEMIC AGENTS IN AN OUTPATIENT PHARMACY DEPARTMENT OF A TERTIARY HOSPITAL IN MALAYSIA (2003-2006)

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The last one decade has seen a tremendous reformation in oral hypoglycemic agents (OHA) utilization in clinical practice throughout the world. The trend and variation in OHA being used in Malaysia has not been sufficiently explored. This study setout to identify trends in the utilization of OHA over a 4-year period in Ipoh Hospital, a 900-bed tertiary institution in Malaysia, in an effort to expand the existing knowledge and to describe the changes observed over time. We retrospectively reviewed prescription records in the Outpatient Pharmacy Department (OPD) of the hospital from 2003 to 2006. About 12,000 prescriptions containing at least one OHA were systematically sampled and evaluated. Chinese patients had a decreasing trend in OHA usage over the study. Sulphonylurea (SU) group was found to be the most widely utilized OHA with a decreasing trend in usage over time (51.2% to 48.5%). In contrast, metformin, a biguanide (BG) agent, recorded a dramatic increase in utilization over the study period, suggesting a new trend in prescribing practices among medical practitioners (48.6% to 51.3%; p-value < 0.001). Although monotherapy was popular with metformin, the overall pattern profoundly favored combination therapy. This study also found an increasing pattern in the use of OHA with insulin rather than triple OHA therapy among practitioners. The biguanide group is gradually becoming the new reigning lord of OHA use, replacing sulphonylurea. Pattern of oral hypoglycemic use is shifting towards combination therapy, mainly dual OHA therapy and OHA-insulin therapy. In general, this study has contributed additional information regarding the epidemiology of OHA in Malaysia.

Keywords : Oral hypoglycemic agents, patterns of use, trends in therapy, Malaysia.

INTRODUCTION

Diabetes mellitus (DM) is becoming a phenomenal worry to mankind in the new millennium, evident by dramatic increase in its prevalence and incidence globally. In Malaysia, the prevalence of DM was estimated to be 2.8% and was projected to increase to 3.7% by the year 2025.[1] Type 2 DM (Non-Insulin Dependent Diabetes Mellitus, NIDDM) is the more common form of the disease, engulfing around 90% of all diabetes cases worldwide.[2] This is due to many socio-demographic factors such as increased life expectancy, high rates of obesity and changes in dietary habits.

The goals of therapy in NIDDM are to ameliorate symptoms of hyperglycemia, prevent the onset as well as slow the progression of complications, and improve quality of life. Landmark studies including the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), have emphasized on the benefits of intensive therapy in DM patients.[3-4] OHA have a prominent role in the management of NIDDM, where they play a primary defense function against hyperglycemic events in comparison to insulin therapy.[4] Traditionally in OHA therapy, sulphonylureas (SU) have always been the agents of first choice, while biguanides (BG) and alpha-glucosidase inhibitors (AG) were unpopular. The use of OHA has tremendously changed globally due to development of novel therapeutic agents and emerging clinical evidences. Particularly, the last one decade has seen a reformation in OHA utilization throughout the world.[5] Furthermore, recent investigations and revised clinical guidelines have generated a new trend among the medical community.[6-7]

Pharmacoepidemiological researches globally have revealed a deviation from the normal mantra of OHA therapy. A study conducted in Taiwan by Chang and colleagues, showed a preference in metformin use compared to SU among practitioners.[8] This was consistent with national studies in the United States (US) and the United Kingdom (UK) that also showed a decline in SU usage as well as the rise in the use of biguanides and newer agents for type 2 diabetes mellitus.[9-10] In contrast, SU still dominated the OHA realm in a South African study by Truter.[11]

In Malaysia, the Statistics on Medicines 2004 showed that sulphonylureas were the most widely used agents followed by biguanides in the management of NIDDM.[12] As the patterns in OHA use begin to change enormously around the world, it would be essential to conduct an investigation into the trends that are occurring in Malaysia. To date, studies evaluating OHA prescribing trends have not been done in Malaysia. Thus, this study is to the best of our knowledge a pioneer in exploring the trends in OHA utilization in Malaysia.

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METHODS

Study design and population

This was a cross-sectional study that retrospectively reviewed prescriptions from the Outpatient Pharmacy Department (OPD) of Hospital Ipoh, a 900-bed tertiary-care referral hospital in the State of Perak in Peninsular Malaysia. Permission to conduct the study was obtained from the State and hospital ethics committees. Targeted data for the study were prescriptions available at the OPD from the year 2003 to 2006 containing one or more OHA. A randomized systematic sampling method was used, whereby diabetic prescriptions that satisfied the study criteria were identified from the main study population (sampling frame). Outpatients who were 21 years and older with at least one OHA claim in the prescriptions were picked for sampling. Subsequently, for every 2 diabetic prescriptions fulfilling the criteria, one was randomly picked to be utilized in the study.

Data collection

Relevant data were extracted and recorded from eligible prescriptions using a data collection form. The documentation involved demographic characteristics, pattern of drug use (drug, dose, frequency, duration) and trends in treatment modality (monotherapy vs. polytherapy and types of combinations).

Statistical analysis

The data collected were analyzed using SPSS version 12.0 (SPSS Inc., Chicago, IL) and Microsoft Excel. Continuous data were presented as mean values + standard deviation while categorical data were presented as percentages. Descriptive statistics were used to analyze the data and results were represented in tabular form or graphically. Cross tabulation using ÷ ^{2}tests were used to evaluate the pattern of drug use. The level of significance (*p*-value) was set at = 0.05.

TABLE – 1 Demographic characteristics of outpatients' prescriptions for oha at a tertiary hospital in peninsular Malaysia (2003-2006)

Characteristic	2003	2004	2005	2006	*p*-value
Gender					
-Male	1502 (50.6)	1473 (49.1)	1453 (48.5)	1382 (46.0)	0.0014 (S)
-Female	1498 (49.4)	1527 (50.9)	1547 (51.5)	1619 (54.0)	
Mean age	56.95 ± 11.69	56.65 ± 11.86	57.39 ± 11.97	56.98 ± 11.91	<0.001(S)
Race					
-Malay	1038 (34.6%)	1053 (35.1%)	1071 (35.7%)	1083 (36.1%)	< 0.001 (S)
-Chinese	954 (31.8%)	928 (30.9%)	910 (30.3%)	890 (29.6%)	
-Indian	861 (28.7%)	799 (26.6%)	893 (29.8%)	865 (28.8%)	
-Others	147 (4.9%)	222 (7.4%)	126 (4.2%)	165 (4.9%)	

S = Significant

TABLE – 2 Trends in the usage of oha among outpatients receiving oral anti-diabetic prescriptions at a tertiary hospital in Peninsular Malatsia (2003-2006)

Agent	2003	2004	2005	2006	*p*-value
Sulphonylureas (SU)					
-Glibenclamide	2222 (47.5%)	2216 (47.4%)	2140 (45.9%)	2100 (44.8%)	<0.001(S)
-Gliclazide	177 (3.7%)	179 (3.8%)	188 (4.0%)	174 (3.7%)	0.0801(NS)
Biguanides (BG)					
-Metformin	2277 (48.6%)	2275 (48.6%)	2311 (49.6%)	2413 (51.3%)	<0.001 (S)
Alpha-glucosidase Inhibitor (AGI)					
-Acarbose	10 (0.2%)	16 (0.2%)	14 (0.5%)	13 (0.2%)	0.622(NS)
Total	4680 (100%)	4692 (100%)	4653 (100%)	4700 (100%)	

S = Significant; NS = Not Significant

RESULTS

A total of 12,000 prescriptions were randomly selected for this study, averaging to around 3000 prescriptions for each study year. Women receiving OHA prescriptions registered a steady increase throughout the study period. In terms of ethnic differences, the Malays recorded the highest proportion of OHA prescription claims and some increase from 34.6% in 2003 to 36.1% in 2006. In contrast, their Chinese counterparts had some degree of decline in OHA prescriptions claims during the 4-year period. **Table-1** provides a summary of the demographic data obtained from the prescriptions.

The trend in OHA usage over the 4-year study period is shown in **Table-2**. SU as a class was the most widely used OHA in this study, accounting for about 50% of the total prescriptions in each study year. Glibenclamide, a second generation SU, stands out to be the second most widely used single agent amongst the OHA prescriptions. However, a decline of about 3% had occurred from 2003 to 2006. Notably, there was no statistically significant difference in the pattern of gliclazide use during the study period. Metformin, a BG was the most widely utilized OHA with a total of more than 2000 prescription claims per year. It also recorded an increasing trend over the study period. Acarbose, an AGI, demonstrated the same fate as gliclazide with no significant changes in use and was the least used OHA among outpatients receiving oral anti-diabetic prescriptions.

Therapeutic pattern (mono vs. polytherapy) in the use of OHA is shown in Figure 1. Generally, polytherapy constituted more than half of the total OHA prescriptions for each study year. The monotherapy category was largely dominated by glibenclamide, as demonstrated in Figure 2, but a significant downward trend was identified with this SU agent whereby usage declined from 51.5% in 2003 to 41.7% in 2006. However, this trend was in contrast to the pattern seen in metformin monotherapy, which recorded a significant increase of about 11% over the 4 year period. Gliclazide remained without major changes and had very low usage as a monotherapy among the selected outpatient prescriptions. Combination therapy, as stated earlier (Fig. 1) was the primary modality observed among the outpatient prescriptions and dual therapy was the most utilized combination, accounting for more than half of the total OHA prescriptions annually. In the realm of dual therapy as illustrated in Fig. 3, the trend was dominated solely by BG-SU group, particularly metformin with glibenclamide. This combination represented more than 80% of the OHA dual combination prescriptions for each study year. Triple OHA therapy was not a very popular regimen and had a significant 50% decrease from 2003 to 2006. Most remarkably, insulin-OHA combination was more widely used as tertiary therapy compared to triple OHA therapy. The most widely used triple OHA therapy was metformin, glibenclamide and acarbose while the most popular insulin-OHA therapy was metformin-glibenclamide with insulin. Between the year 2003 to 2005, there was a steady rise in proportion of prescriptions for insulin-OHA therapy which peaked in 2005 to 4.5% of the total combination therapy prescriptions.

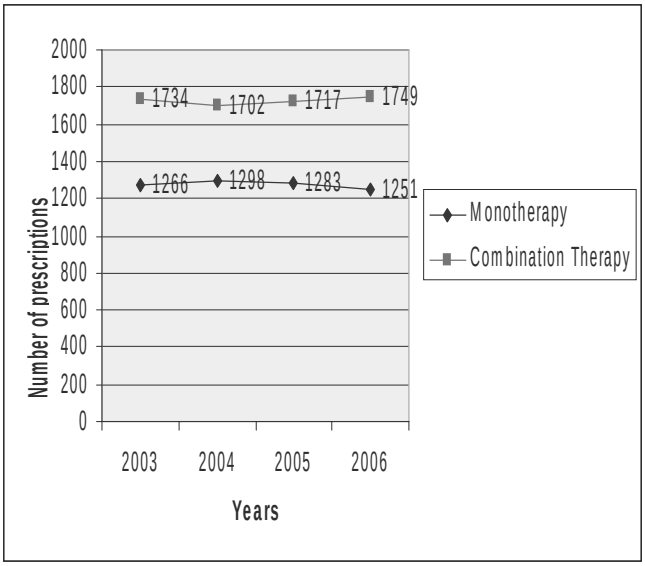

FIGURE - 1 Trends in therapy modalities for niddm amongst outpatients receiving oral anti-diabetic prescriptions at a tertiary hospital in peninsular Malatsia (2003-2006)

DISCUSSION

This was a descriptive study through prescriptions evaluation, detailing on the epidemiology of OHA in Hospital Ipoh, Malaysia. Three main groups of OHA comprising of the sulphonylureas (SU), biguanides (BG) and alpha-glucosidase inhibitors (AGI) were identified and pattern of their usage were evaluated. The demographic data in this study showed that there was an increasing trend of female patients receiving OHA prescriptions, which was consistent with studies indicating that diabetes has higher prevalence in women.[13] The findings for ethnicity showed that Malays constituted the highest group of patients with diabetes having a consistent increase by year. This was an interesting finding because Ipoh is a city mainly dominated by Chinese, followed by the Malays. In contrast, the number of Chinese patients receiving OHA prescriptions was declining by the year. It is well known that ethnic differences occur in the prevalence of diabetes mellitus and also in development of its complications. In a study

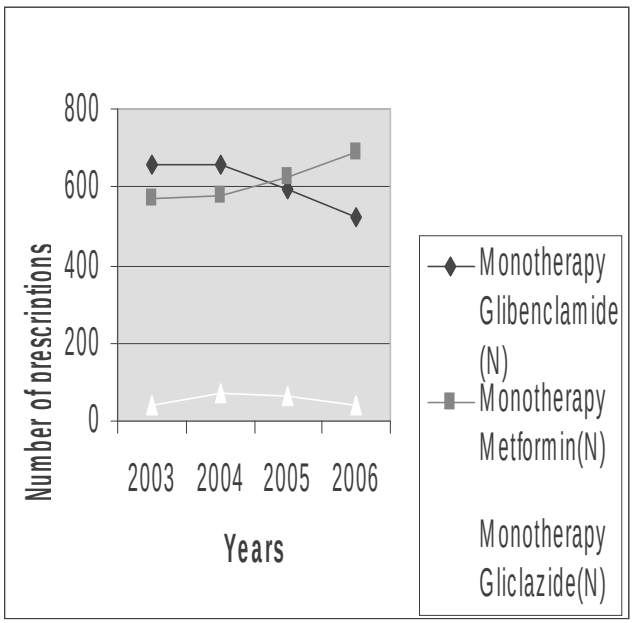

FIGURE - 2 Trends in monotherapy of oral hypoglycemic agents for out patients receiving oral prescriptions at a tertiary hospital in Peninsular Malatsia (2003-2006)

by Ismail *et al.*, good diabetic control was obtained with the Chinese compared to the Indians and the Malays in peninsular Malaysia.[14] It is believed that the ethic differences observed through the prescription patterns could be due to socio-demographic differences and genetic factors. Socio-demographic factors and inherent cultures such as lack of awareness and knowledge of diseases combined with unhealthy lifestyle can lead to poor glycemic control. Genetic factors relate to the difference in the insulin sensitivity between races that may affect glucose levels.[15-16]

Furthermore, the study disclosed a downward trend for sulphonylurea usage, particularly for glibenclamide, in the four-year period. This finding was further augmented by the decline in glibenclamide monotherapy as shown in Figure 2. Both these results suggest a new unconventional trend that threatens the monopoly and position of SU as the cornerstone of OHA in NIDDM treatment. This unprecedented conversion could be due to increasing number of obese patients in major cities in Malaysia; SU are generally not recommended in this population due to the incidence of weight gain.[17] Furthermore, the emergence and benefits of using novel anti-diabetic agents in non-obese patients could be another cause of decreased SU usage seen in this study. Insulin sensitizers such as metformin and thiazolidiones are becoming more famous with practitioners around the world.[18-19] The changes in SU usage can also be attributed to arising clinical evidence demonstrating the new-found hazards of secretagogues. Studies showed that SU use increases the risk of cardiovascular dysfunction and prolonged hypoglycemia, which causes possible qualms of SU therapy among practitioners.[20-22]

The study further revealed that the utilization of metformin increased over time, especially in terms of monotherapy. This trend was consistent with the patterns reported in the US, Taiwan and England.[8-10] The escalation in metformin use sparks deep interest in the reasons for the acute popularity. Although increase in prevalence of patients with obesity was an important factor to contemplate at this juncture, it is believed that other beneficial properties of metformin play a prominent role and have to be considered. The conventional cardiovascular disease (CVD) risk factors most commonly seen in patients with type 2 diabetes include hyperglycemia, elevated triglyceride (TG) and low high-density lipoprotein (HDL) cholesterol concentrations. Emerging clinical evidences have shown concurrent decrease in these risk factors for patients on metformin therapy.[19,23-24] It is easily deducible that metformin stands out to be a primary OHA with cardio-protective effects.[25] The clinical evidence of metformin superiority over the other agents has significantly contributed in the rise of metformin use as evidence-sensitive practitioners are aware of such current developments. Furthermore, studies have concluded that metformin was as efficacious in normal and overweight individuals as it was in those who were obese.[26] This is elucidated by the newly revised guidelines that recommend metformin as a first line therapy in all patients as opposed to the earlier obese patient limitation.[6-7] It is believed that these evidence-based guidelines have an impact on the prescribing patterns in this hospital setting and possibly the country in general.

It is worthwhile to mention that changes in acarbose utilization for the 4 year period were not statistically significant. Patients with diabetes attending our hospital can have their prescriptions filled either at the OPD or the specialized Diabetes Clinic, depending on where they attend their follow-up. Acarbose has formulary restrictions in most Malaysian health institutions and can only be prescribed by or with authorization from relevant medical specialist. Hence, we presumed that a substantial amount of acarbose was dispensed at the Diabetes Clinic; thus the data were unavailable for our research which focused on OPD prescriptions only. Nonetheless, our study found that the most widely used regimen was 50mg twice daily and most of the time it was given as a combination therapy. This dosing regimen was in accordance with standard acarbose dosing guidelines.[7]

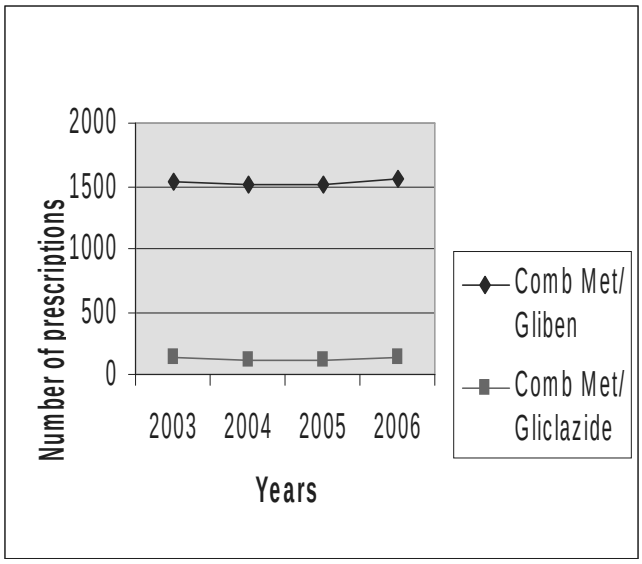

FIGURE - 3 Pattern of dual therapy of oral hypoglycemic agents for outpatients receiving oral anti-diabetic prescriptions at a tertiary hospital in Peninsular Malatsia (2003-2006)

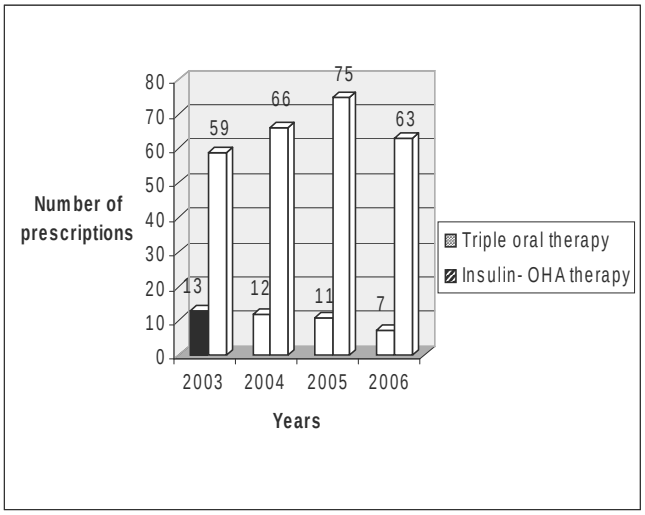

FIGURE - 4 Triple oha therapy in comparison with insulin- oha therapy for outpatients receiving oral anti-diabetic prescriptions at a tertiary hospital in Peninsular Malatsia (2003-2006)

As diabetes further progresses, functional decline in beta-cells is usually apparent and the need for combination therapy is unavoidable. Therefore, combination modalities have become an integral part of diabetes management, whereby most patients are eventually started on this mode of therapy. This explains the reason why polytherapy predominates over monotherapy with a proportion of more than 55% (Fig. 1). The basic rationale of combination therapy is to provide additive effects with different mechanisms of action and to allow employment of lower doses for the disease management. Subsequently, this provides better safety profile for patients.[27] In this study, three main types of combination therapies were observed including dual OHA, triple OHA and insulin-OHA.

Conventionally, a combination of dual therapy is used when monotherapy is no longer able to achieve adequate glucose control. A plethora of evidences has outlined the indisputable fact that for certain OHA, combination therapy is better than using high dose monotherapy regimen to treat patients.[27-29] In terms of dual OHA therapy, the most widely used combination in our hospital setting was that of metformin and glibenclamide, which represented around 85% of dual therapy combinations. The dual combination therapy trend seen here was also similar to the ones found in other countries.[8,9,11] The wide acceptance of this modality of treatment was probably due to its proven efficacy and cost-benefit. Metformin and glibenclamide possess different mechanisms of action that compliment each other and the combination was associated with low drug utilization costs.[29-30] These essential factors make this combination the desired treatment of dual therapy among practitioners.

Trends in other parts of the world have shown an increase in triple OHA therapy and also the emergence of quadruple OHA therapy.[9-10] An increase of nearly nine-fold use of triple oral therapy was observed in Taiwan.[8] But these modalities depend on the physician's judgment and the patient's acceptance of the therapy. When a patient has failed to attain glycemic control with dual therapy, then triple therapy or OHA-Insulin therapy may be warranted. Although practitioners in certain countries prefer the triple oral therapy, the practitioners in this hospital seem to be more inclined to the alternative insulin-OHA therapy. Our findings showed that triple oral therapy consisted of only about 1.5% of the patients receiving combination therapy for each study year while insulin-OHA treatment was around 6.5%. The insulin-OHA treatment was completely dominated by SU and biguanide agents. The efficacy of this therapy has been well established by many studies. One such study reported by Tong and colleagues that showed that the use of this modality was essential in improving metabolic control in type 2 DM patients who have secondary drug failure.[31] So far there is no concrete trial comparing efficacy of triple oral therapy with insulin-OHA therapy.[32] The practitioner's judgment plays a vital role in deciding which modality to use in patients. Patients with worrying underlying factors such as renal failure and liver failure might be refrained from taking triple oral therapy.[33] Apart from these, some practitioners believe that eventually patients would need insulin therapy as the function of beta cells begins to decline completely. So, it is perceived that initiating insulin therapy benefits the patient in the long term effect because it can reduce the burden of the beta cells.[34-36]

CONCLUSION

Overall, the emergence of novel therapeutic agents and new clinical evidences in the management of DM has initiated a revolution in OHA use among practitioners. Metformin is gradually replacing sulphonylurea as the first line agent in oral-hypoglycemic therapy among practitioners in Hospital Ipoh, Malaysia. The prescribing trend is moving towards combination therapy, particularly dual therapy and OHA-insulin therapy. The actual reasons and rationale for the observed trends in this study may need further exploration. Perhaps, this study might have expanded our current knowledge on OHA utilization pattern and in general contributed additional information regarding the epidemiology of OHA in Malaysia.

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