Factors Influencing Utilization of Different Types of Sulphonylureas Amongst Type 2 Diabetes Patients

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SUMMARY. Sulphonylureas (SUs) are commonly prescribed in Malaysia and also worldwide. However, very limited information is available on their pattern of use and appropriateness of its utilization. Age, concurrent use of drugs such as beta blocker, salicylate and frusemide and also renal impairment were found to have influence on the selection of different types of SUs.

INTRODUCTION

In Malaysia, majority of diabetes mellitus cases are type 2 diabetes mellitus (T2DM). This is a direct extension from the fact that in 1997, 97% of all cases of diabetes mellitus are T2DM 1. The oral drugs used for the treatment of T2DM are known as oral hypoglycemic agents (OHAs). The most frequently prescribed OHAs are SUs. In the Malaysian Statistics on Medicine 2004, SUs makes up to more than 60% of all OHAs prescribed 2.

The individual SU agents differs in terms of their cost, tolerability, pharmacokinetic profiles and extrapancreatic effects, thus, it is important to identify factors that influence the prescribing pattern of SUs in order to ensure optimal utilization of the drugs 3. As SUs are widely used for T2DM in Malaysia, appropriate utilization of these agents will lead to better diabetes care to the patients and at the same time ensure a more cost-effective usage of SUs in the country. This is important as the cost burden in diabetes mellitus in 2004 was as high as RM 39 million, where gliclazide alone costed RM 16.5 million in the same year in Malaysia 2.

Although foreign data are available for the comparison between the individual SU agents, there are limited studies conducted to evaluate the choice of SUs when making clinical decisions 4. In Malaysia, there is no data on factors that determine the prescribing pattern of SUs. In addition, there are lacks of studies that evaluate the appropriateness of utilization of SUs. Therefore, this study aims to investigate the utilization of different types of SUs among the type 2 diabetics.

This retrospective observational study was conducted in the University Malaya Medical Centre (UMMC) in the year 2006. This study consisted of all adult type 2 diabetics who had received or was currently receiving glibenclamide, gliclazide or glipizide.

METHODOLOGY

Study Procedures

This study was conducted upon obtaining approval from the UMMC Ethical Committee. A total of 14,824 Registration Number (R/N) of patients prescribed with glibenclamide, gliclazide or glipizide from January to December 2006 was generated using the Pharmacy Information System (PIS). Systematic sampling was conducted with every 50th patient included as the study sample. Out of that, a total of 356 patients were
identified via this sampling. However, only medical records for 334 (93.8 %) subjects were successfully retrieved from the Medical Records Office. Thus, the final sum of subjects which were included in this study were 334 subjects (N = 334).

The following Inclusion and Exclusion criteria were considered. **Inclusion Criteria:** (1) Patients with T2DM, (2) Patients who were prescribed with glibenclamide, gliclazide or glipizide, either currently or previously as a monotherapy or in combination with other antidiabetic medications, (3) Adult patients aged 18 years old and above. **Exclusion Criteria:** (1) Patients with other than T2DM, (2) Patients aged less than 18 years old, (3) Patients who never received glibenclamide, gliclazide or glipizide, (4) Patients who had serious psychiatric illness where there were indications that compliance with diabetic treatment may be severely compromised.

**Statistical Techniques**

All the data extracted were analyzed using the Statistical Package for the Social Sciences (SPSS) Software version 15.0. All continuous data were tested for normality using the Kolmogorov-Smirnov test. Results which were normally distributed were expressed as mean ± standard deviation and those that were not normally distributed were presented as median (range of minimum and maximum value). Pearson Chi Square test was used to analyze categorical data. When the expected cell count for >20 % was less than 5, Fisher’s Exact Test was used. In this study, statistical significance was assumed at p < 0.05.

**Data Analysis**

Currently there was no guideline to evaluate the appropriateness of utilization of different types of SUs. Therefore, for the purpose of this study, the criteria for evaluation were based on the collection of established literature. Utilization of glibenclamide, glipizide and gliclazide was considered inappropriate when used in the presence of absolute contraindication(s) (referred to Table 1).

As for glibenclamide, utilization will be considered inappropriate when prescribed in the presence of any factor(s) as below in Table 2. The list of non-selective beta blockers considered were those available in UMMC 7.

When SUs were prescribed without any of the factor(s) stated in the tables above, their utilization was considered to be appropriate.

**RESULTS**

A total of 334 (93.8 %) patients were included in this study. Females made up the majority (about 60 %) of the subjects. The most common ethnic group encountered was the Indian (40 %), followed by the Chinese (32 %).

<table>
<thead>
<tr>
<th>Inappropriate utilization</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolutely contraindicated</td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>Diabetic coma</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity towards sulpha drugs</td>
</tr>
</tbody>
</table>

**Table 1.** Inappropriate utilization of glibenclamide, gliclazide and glipizide. Adapted from: Lacy et al. 5 and Wong 6.

<table>
<thead>
<tr>
<th>Inappropriate utilization</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of risk factor(s) that promote the development of hypoglycemia</td>
<td>Elderly (65 years old and above)</td>
</tr>
<tr>
<td></td>
<td>Renal impairment (glomerulonephritis, chronic nephritis, nephrosclerosis, nephropathy, uremia, creatinine clearance less than 50 ml/min, or as stated in the case notes)</td>
</tr>
<tr>
<td></td>
<td>Polypharmacy (more than 5 concurrent medications, not including other antidiabetics)</td>
</tr>
<tr>
<td></td>
<td>SU-potentiating agent(s) (salicylates, anti-thyroids, warfarin)</td>
</tr>
<tr>
<td></td>
<td>Non-selective beta blockers: carvedilol, labetolol and propanolol at any doses atenolol (more than 100 mg daily), bisoprolol (more than 10 mg daily) and metoprolol (more than 100 mg daily) where they loses selectivity.</td>
</tr>
</tbody>
</table>

**Table 2.** Inappropriate utilization of glibenclamide. Adapted from: Lacy et al. 5, Wong 6, and Staa et al. 8.
Hypertension was found to be the most common co-morbidity with 231 in 334 subjects (69.2%). On the other hand, the two leading concurrent medications used were beta blockers and salicylates, both with 132 and 130 subjects, or 39.5% and 38.9%, respectively.

**Pattern of Use of SUs**
Gliclazide was the most popular SU encountered in UMMC, where it made up to more than 50% of SUs prescribed, followed by glibenclamide (44.0%) and glipizide (5.7%).

**Significant factors associated with selection of SUs**

**Age**
Ninety subjects or approximately 60% of patients on glibenclamide were non elderly. This trend was similarly found in gliclazide, where 106 subjects or about 63% were also non elderly. However in glipizide, this was reversed since more than 68% were elderly subjects. When examined, the association between elderly and non elderly patients with different SUs was significant (\( p = 0.028 \)).

**Concurrent Medications**
The concurrent uses of 3 medications were associated with the prescription of SUs. These were beta blockers (\( p = 0.007 \)), frusemide (\( p = 0.015 \)) and salicylates (\( p < 0.000 \)). The concurrent use of beta blockers, salicylates and frusemide were highest with glipizide as compared to gliclazide and glibenclamide. The exact percentages are shown below.

**Renal Impairment**
There was significant difference in patients with renal impairment and the selection of SUs (\( p = 0.022 \)). The use of glibenclamide and gliclazide in patients with renal impairment were low. On the other hand, use of glipizide in renal impairment was approximately 4 times higher at 21.1%.

<table>
<thead>
<tr>
<th>Agent</th>
<th>n</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glibenclamide</td>
<td>147</td>
<td>7 (4.8%)</td>
<td>140 (95.2%)</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>168</td>
<td>10 (6.0%)</td>
<td>158 (94.0%)</td>
</tr>
<tr>
<td>Glipizide</td>
<td>19</td>
<td>4 (21.1%)</td>
<td>15 (78.9%)</td>
</tr>
</tbody>
</table>

Table 3. Usage of SUs with renal impairment. Data are reported as number of patients. Chi Square = 7.643; df = 2; \( p = 0.022 \).

**Utilization of SUs**

**Presence of Absolute Contraindication(s) Towards SUs**
Out of 334 subjects, none was found to have any absolute contraindication(s) towards SUs. As a result, the utilization of SUs was deemed to be appropriate.

**Utilization of Glibenclamide**
Utilization was assessed according to the presence of factors listed in Table 2. The main factor that contributed to the inappropriate utilization of glibenclamide was elderly, followed by concurrent use of salicylates and non-selective beta blockers (Table 4).

**DISCUSSION**
We discovered that gliclazide was most popular in UMMC, followed by glibenclamide. In contrast, glipizide only constituted a small percentage of use. However, the national report on medicine use in Malaysia in 2004 found that glibenclamide was still the most popular choice of SU at 68.5%, while the uses of relatively newer agents such as gliclazide and glipizide were only of 26.7% and 0.5%, respectively. Cheng et al. reported similar pattern of use in Taiwan.

High utilization of gliclazide in UMMC might reflect the current trend to support its use over glibenclamide. Usage of gliclazide was increasing worldwide because it has similar effectiveness in glucose control as compared to glibenclamide. Furthermore, it is associated with lower incidence of hypoglycaemia 10 as well as lower incidence of failure after long term therapy 11. In addition, there is also new evidence claiming that it also helped in reducing platelet aggregation 2.

**Factors significantly associated with selection of SUs**

**Age**
Age had a positive association with the se-

In UMMC, more than 68% of glipizide users were elderly in contrast with less than 40% with glibenclamide and gliclazide \( (p = 0.028) \). Thus, prescribers might prefer using glipizide in elderly patients. This was in line with current evidence that supported the use of glipizide in elderly as it has a shorter half life and is associated with a theoretical lower risk of hypoglycaemia but with the same efficacy \(^{12}\). This is especially convenient in those 80 years old and above \(^{13}\). In addition, glibenclamide is avoided in elderly patients due to its long action \(^{14}\).

As for gliclazide, the result of its use in the elderly was similar to a study by Cheng \( et al. \)^{9}. It comprised similar percentage of elderly patients as glibenclamide (more than 66%). However, these authors found that there was no association between age and selection of Sul and they 9 explained that this might be caused by long clinical experience with glibenclamide which encouraged its use in the elderly population. The different findings might also be due to the fact that Cheng \( et al. \)^{9} specifically studied a subgroup of diabetic patients with hypertension.

### Concurrent medications

The issue of concurrent use of medications with SulS, especially glibenclamide is a major consideration for the selection of SulS. Drug interactions with glibenclamide had been reported to increase the odds of being admitted to the hospital due to hypoglycemia by as much as 6 times \(^{15}\).

In this study, concurrent use of beta blockers was found to be associated with the prescribing of SulS. Use of beta blockers was significantly higher with gliclazide and glipizide in comparison with glibenclamide \( (p = 0.007) \). This indicated that prescribers tried to avoid using the longer acting-Su such as glibenclamide with beta blockers.

All beta blockers can increase the incidence of hypoglycaemia \(^{16}\) as it can attenuate the autonomic response towards hypoglycemia via beta receptor blockage. Non-selective beta blockers also delay the recovery of hypoglycemic events by inhibiting glycogenolysis \(^{17}\). Thus, it will increase the risk for the development of prolonged and severe hypoglycaemia \(^{18}\).

There was also significant difference in the pattern of use of SulS in regard to salicylates \( (p = 0.000) \). For concurrent use of salicylates, the preferred Sul was glipizide (52.6%), followed closely by gliclazide (49.4%). Glibenclamide was the least preferred with only approximately 25%. Prescribers might avoid the use of glibenclamide concurrently with salicylates as it might potentiate the action of Sul, thus leading to more frequent precipitation of hypoglycemic events \(^8\,^{16}\).

Similarly, there was positive association between frusemide and choice of SulS. Again the distribution was higher for glipizide, followed by gliclazide and lowest in glibenclamide \( (p = 0.015) \). Frusemide is a SU-antagonizing drug since it reduces the hypoglycemic action of SulS. Concurrent use of frusemide and SulS was reported to lower the incidence of hypoglycemia by rate ratio of 0.73 \(^8\). This did not explain why frusemide was a factor to be considered during the selection of SulS, moreover, no literature that evaluates this factor was found during the literature review. Thus, the reason why physicians

### Table 4: Factors leading to inappropriate utilization of glibenclamide.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Subjects on Glibenclamide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
</tr>
<tr>
<td>Elderly</td>
<td>57 (38.8)</td>
</tr>
<tr>
<td>#Non-selective Beta Blockers</td>
<td>28 (19.0)</td>
</tr>
</tbody>
</table>

**SU-potentiating Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylates</td>
<td>37 (25.2)</td>
<td>110 (74.8)</td>
</tr>
<tr>
<td>Anti-thyroids</td>
<td>10 (6.8)</td>
<td>146 (99.3)</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>13 (9.0)</td>
<td>135 (91.4)</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>7 (4.8)</td>
<td>140 (95.2)</td>
</tr>
</tbody>
</table>

\(^*\)Total percentage was more than 100% as one subject might have more than one factor. \(^\#\)Non-selective beta blockers - inclusive of all non selective agents (carvedilol, labetolol and propanolol) as well as selective agents, which, at higher doses lose their selectivity (atenolol more than 100 mg daily, bisoprolol more than 10mg daily and metoprolol more than 100 mg daily).
preferred to prescribed glipizide and gliclazide in patients using frusemide was unclear and should be subjected to further investigation.

Renal Impairment

In this study, significant difference was detected between renal impairment and choice of SUs (p = 0.022). The use of glipizide in renal impairment patients was the highest (more than 20%). Selection of glipizide in renally impaired patients was more appropriate as only a small percentage of glipizide is excreted unchanged in the urine and it has no active metabolite. In comparison, it is better to avoid the prescription of glibenclamide which should not be used in patients with creatinine level less than 50 ml/min. This is because a substantial percentage of glibenclamide and its active metabolite are excreted renally, thus they might accumulate in renal insufficiency.

CONCLUSION

Factors influenced the prescription of different types of SUs were age of the patient, concurrent use of medications (salicylate, beta blocker and frusemide) and presence of renal impairment.

REFERENCES