Drug-drug Interaction-related Uncontrolled Glycemia

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**Context:** The literature of drug-drug interaction (DDI)-related uncontrolled glycemia (UCG) among outpatients with Type 2 diabetes mellitus is still limited.

**Aims:** The aim of this study is to identify the prevalence, mechanism, severity, causality, and preventability of DDI-induced UCG (HbA1c >7%) in outpatients with Type 2 diabetes.

**Settings and Design:** A cross-sectional study was conducted in Penang General Hospital.

**Methods:** A computerized system for DDI checking was used to assess the severity and mechanism of DDIs. Drug interaction probability scale was used to evaluate the likelihood of DDIs. Preventability of DDIs has been determined by the instrument of Hallas. The UCG prevalence related to DDIs was further assessed.

**Statistical Analysis Used:** SPSS 21.00 was used in this study.

**Results:** From 425 outpatients with HbA1c% test, their mean age was 58.7 ± 12.8 years. Only 225 (52.9%) cases had controlled glycemia while 200 (47.1%) cases with UCG. They had multiple comorbidities, with a mean number of 3.8 ± 2.2/patient and often prescribed with multiple medications, with a mean number of 6.33 ± 4.67/patient. It has been detected that 86 DDIs causing UCG in 46 patients (23%) with range of (1 – 4) DDIs per patient.

**Conclusion:** Nearly one-quarter of UCG was induced by DDIs; most of these DDIs are possible, and more than one-third are preventable. It was concluded that thiazide diuretics have the highest prevalence of DDI-related UCG.

**Keywords:** Diabetes mellitus, drug interaction probability scale, HbA1c, hyperglycemia

**Introduction**

There is a category of drugs that interacts and interferes with the action of diabetes medications.[1-4] Hence, it is important to monitor patients’ glucose levels carefully.[5,6] Complications of diabetes are the leading cause of morbidity and mortality in persons with diabetes.[6,8] If Type 2 diabetes patients decrease their HbA1c level by 1%, there are a 19% reduction in cataract extractions, 16% decrease in heart failure, and 43% reduction in amputation or death due to peripheral vascular disease.[9,10] Significant drug interactions and the patient harm that is associated with them are common concerns in clinical practice.[11,12]

**Aim of the study**

The current prospective observational study was conducted to investigate the prevalence, mechanism, severity, causality, and preventability of drug-drug interactions (DDIs) accounting for uncontrolled hyperglycemia development among outpatients with Type 2 diabetes at endocrine clinics and to identify the medications that are associated with DDI-related uncontrolled glycemia (UCG).

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**How to cite this article:** Hammad MA, Tangiisuran B, Kharshid AM, Abdul-Aziz N, Hassan Y, Aziz NA, et al. Drug-drug interaction-related uncontrolled glycemia. J Pharm Bioall Sci 2017;9:221-8.
METHODS

Study design and participants

The conducted prospective observational study involves outpatients with Type 2 diabetes at endocrine clinics in Penang General Hospital with confirmed UCG. According to the American Diabetes Association, UCG is defined (HbA1c >7% for patients <65 years and >8% for patients ≥65 years).[13] The study presented in this paper was conducted from July 1, 2011, to February 1, 2012. Patients younger than 18-year-old, pregnant women, outpatients with Type 1 diabetes, and patients with cancer or HIV were excluded from the study. Furthermore, newly diagnosed outpatients with Type 2 diabetes (within 6 months) and outpatients with Type 2 diabetes under lifestyle modification only were not included in this study. Figure 1 shows the flowchart of the conducted study.

Data collection

Patients’ sociodemographics, comorbidities, laboratory data, number and dose regimen of medications, and clinical characteristics were collected from patients’ records, the medical team in charge, and patients’ interviews. Other confounding factors of UCG such as patients’ noncompliance, obesity under therapeutic doses, and monotherapy were assessed and ruled out.

Identification of drug-drug interaction-related uncontrolled glycemia

DDIs for each patient medication were investigated by the primary researcher, a clinical pharmacist. In this study, the definition of DDI by introduced Tatro (2010)[14] was applied. Tatro’s description states that DDIs represents; the pharmacologic or clinical response to the administration of a medicine combination is different from that anticipated from the remarkable effects of the two drugs when given alone. Clinically significant drug interactions, which may induce potential harm to the patients, can be resulted from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties.[15]

A computerized system has been used in this study for DDI checking such as UpToDate, Lexicomp,[16] drugs.com,[17] and Micromedex and Medscape[18] drug interaction checkers to assess and confirm the mechanism, severity, and significance of drug interactions. The DDI identification in this study relies mainly on Lexicomp and drugs.com, drug, interaction checkers which provide the references in addition to the evidence of literature review for each DDI. Thus, the DDI-related hyperglycemia was identified. Mechanism of DDIs is classified as pharmacodynamic or pharmacokinetic. The severity of DDIs was classified into major, moderate, and minor. Major represents a severely clinically significant DDI and that patient should not use the combinations if the risk of the interaction is more than the benefit. Moderate DDI is categorized under moderately clinically significant and that the combination can be given with certain conditions only; otherwise, co-administration should be bypassed. Minor DDI is classified as minimally clinically significant. Where instructions to the health-care providers in such case are to decrease harm; include estimating the potential risk and considering an alternative medicine, taking steps to avoid the interaction damage, and establishing a monitoring plan. The principal investigator of this study has determined and investigated the DDIs while other researchers have reviewed all the findings for agreement and correction.

Assessment of causality and preventability of drug-drug interaction-related uncontrolled glycemia

Drug interaction probability scale (DIPS) proposed by Horn et al.[19] was followed to evaluate the likelihood
of DDI. UCG prevalence related to DDIs was then examined. The DIPS was modified from Naranjo et al. scale[20] to meet the requirements of DIPS. It was developed to provide a guide for evaluating drug interaction causation in a particular patient. It is intended to be used to help practitioners in the evaluation of drug interaction-related adverse events. DIPS follows a series of questions related to the potential drug interaction to determine a probability score which is classified to highly probable, probable, possible and doubtful DDI.

The preventability of DDI-related UCG was assessed based on the method proposed by Hallas et al.,[21] where each DDI was classified into definitely preventable, possibly preventable, or nonpreventable.[22] In the analysis of this study, the final assessment of DDI-related UCG is reported as either preventable or nonpreventable. Figure 2 shows the identification and classification of the DDIs.

**Statistical analysis**

Descriptive analyses were performed, and categorical variables were described by frequencies and percentages. Continuous variables were documented by means and standard deviations or range. Chi-square test was performed for the categorical data, and Student’s t-test was used to compare the continuous data. The variables for multicollinearity were assessed determining the variance inflation factors and value of standard errors to prevent any strong correlation between the variables. Independent predictors of DDI-related UCG were described using a logistic regression analysis, which was modified for gender, age, and any other variables that were significant. In this study, variables were selected according to their clinical and statistical significance (described thoroughly in Steyerberg et al.’s study[23]), and overfitting was prevented by assigning the maximum number of variables entered in multivariate regression as one variable for every eight DDI events (which was also followed in Vittinghoff and McCulloch[24]). The statistical software packages followed were SPSS 21.00 (SPSS Inc., Chicago, IL, USA). A two-sided $P < 0.05$ was considered to be statically significant.

**Ethical approval**

This study was approved by National Institute of Health in Malaysia, Clinical Research Centre at Penang General Hospital, and Malaysian Ministry of Health and Ethics Committee. The approved unique National Medical Research Register (NMRR) registration ID is NMRR-11-407-8807.[23]

**Results**

It was observed that among 720 outpatients with Type 2 diabetes who were scanned for HbA1c% test, only 425 (59%) of them had HbA1c% test in the past 3 months while the rest 295 (41%) outpatients had not. Among 425 with HbA1c% test, only 225 (52.9%) outpatients had controlled glycemia.

The remaining 200 patients with UCG were included in the study. Their mean age was 58.7 ± 12.8 years. Approximately half of the patients were male, 101 (50.5%). From 200 UCG patients, 88 (44%) were Chinese, 56 (28%) were Malay, 52 (26%) were Indian, and only 4 (2%) patients were from other ethnicities. UCG patients in this study had multiple comorbidities, with a mean number of 3.8 ± 2.2/patient. Patients in this study were often prescribed with multiple medications, with mean number of 6.33 ± 4.67/patient.

We detected 86 DDIs with UCG in 46 patients with a mean number of 1.9/patient (range 1–4 drug interactions). Investigators identified at least one-drug interactions in 46 patients (23%). One drug interaction has been detected for every 14 drug exposures. The major category was diuretics 79% (hydrochlorothiazide 58.1%, furosemide 13.9%, spironolactone 4.6%, and chlorothiazide 2.40%), followed by salbutamol (9.2%) and cortisones (5.8%) as presented in Tables 1 and 2 that show the details of the 86 DDIs with UCG and their medications, respectively.

Using DIPS, it was found that 77.9% of DDIs were possible DDIs (DIPS score: 2–4) and 22.1% were probable DDIs (DIPS score: 5–8). Most of the DDIs...
mechanisms were pharmacodynamic mechanism 84 (97.7%), and only 2 (2.3%) were the pharmacokinetic

DIPS: Drug interaction probability scale

### Table 1: Details of drug-drug interactions with uncontrolled glycaemia (n=86)

| Drug interaction                  | n (%) | DIPS   | Mechanism     | Severity | Preventability |
|-----------------------------------|-------|--------|---------------|----------|----------------|
| Hydrochlorothiazide-metformin     | 28 (32.5) | Probable | Pharmacodynamic | Moderate | Preventable    |
| Hydrochlorothiazide-gliclazide    | 19 (22.1) | Possible | Pharmacodynamic | Moderate | Preventable    |
| Furosemide-gliclazide             | 11 (12.7) | Possible | Pharmacodynamic | Moderate | Preventable    |
| Salbutamol-gliclazide             | 4 (4.6)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |
| Salbutamol-metformin              | 4 (4.6)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |
| Spirinolactone-metformin          | 4 (4.6)   | Probable | Pharmacodynamic | Moderate | Preventable    |
| Cortisones-gliclazide             | 2 (2.3)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |
| Cortisones-metformin              | 2 (2.3)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |
| Hydrochlorothiazide-insulins      | 2 (2.3)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |
| Acarbose-metformin                | 1 (1.2)   | Probable | Pharmacokinetic | Minor    | Preventable    |
| Chlorothiazide-gliclazide         | 1 (1.2)   | Possible | Pharmacodynamic | Moderate | Preventable    |
| Chlorothiazide-metformin          | 1 (1.2)   | Probable | Pharmacodynamic | Moderate | Preventable    |
| Cortisones-insulins               | 1 (1.2)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |
| Furosemide-acarbose               | 1 (1.2)   | Possible | Pharmacodynamic | Moderate | Preventable    |
| Hydrochlorothiazide-glibenclamide | 1 (1.2)   | Possible | Pharmacodynamic | Moderate | Preventable    |
| Levothyroxine-glyburide           | 1 (1.2)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |
| Levothyroxine-metformin           | 1 (1.2)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |
| Phenytoint-gliclazide             | 1 (1.2)   | Probable | Pharmacokinetic | Moderate | Nonpreventable |
| Risperidone-metformin             | 1 (1.2)   | Probable | Pharmacodynamic | Moderate | Nonpreventable |

### Table 2: Medications with uncontrolled glycaemia secondary to drugs interactions (n=86)

| Medicine          | n (%)      |
|-------------------|------------|
| Hydrochlorothiazide | 50 (58.1)  |
| Furosemide         | 12 (13.9)  |
| Salbutamol         | 8 (9.2)    |
| Cortisones         | 5 (5.8)    |
| Spirinolactone     | 4 (4.6)    |
| Chlorothiazide     | 2 (2.4)    |
| Levothyroxine      | 2 (2.4)    |
| Acarbose           | 1 (1.2)    |
| Phenytion          | 1 (1.2)    |
| Risperidone        | 1 (1.2)    |

### Table 3: Drug interaction probability, mechanisms, and severity of 86 drug interactions

| Variable                  | n (%) |
|---------------------------|-------|
| Drug interaction probability |       |
| Possible                  | 67 (77.9) |
| Probable                  | 19 (22.1) |
| Mechanism                 |       |
| Pharmacodynamic           | 84 (97.7) |
| Pharmacokinetic           | 2 (2.3)   |
| Preventability            |       |
| Nonpreventable            | 54 (62.8) |
| Preventable               | 32 (37.2) |
| Severity                  |       |
| Minor                     | 1 (1.2)   |
| Moderate                  | 85 (98.8) |

mechanism. Most of the DDIs-related UCG cases have a moderate significance of 98.8%, and only 1.2% has a minor significance. Furthermore, 37.2% from these DDIs are preventable, and 62.8% are nonpreventable as shown in Table 3 that presents the drug interaction probability, mechanisms, and severity of the mentioned 86 drug interactions.

According to multivariate logistic regression, there is no association relation between the number of medications and DDI-related UCG incidence (P value 0.112). Furthermore, there is no association relationship of DDIs incidence with the comorbidity number (Charlson et al. index\(^{26}\)) (P = 0.131) as shown in Table 4 that presents the of DDIs’ predictors.

### Table 4: Predicators of drug-drug interactions

| Variable            | Crude OR (95% CI) | Adjusted OR (95% CI) | P   |
|---------------------|-------------------|----------------------|-----|
| Age                 | 1.04 (0.98-1.05)  | 1.03 (.98-1.05)      | 0.399|
| Gender              | 1.29 (0.71-2.62)  | 1.08 (0.56-2.15)     | 0.864|
| Medication number   | 1.18 (0.91-1.35)  | 1.13 (0.83-1.28)     | 0.112|
| Comorbidity number  | 0.85 (0.66-1.13)  | 0.79 (0.61-1.05)     | 0.131|

OR: Odds ratio, CI: Confidence interval

### Discussion

This study evaluates the hyperglycemic effect of DDIs which lead to UCG in outpatients with Type 2 diabetes. Most of the previous studies have discussed the hypoglycemic effect of drug interactions of hypoglycemic agents\(^{27-30}\)
In a study by McDonnell and Jacobs, which is conducted over 1 year, 158 adverse drug reactions (ADRs) were directly related to hospital admission, which supports findings of the study was presented in this paper. The relationship of these admissions to drug use was determined to be probable or highly probable in 154 (97.4%) of these cases. From this category, 96 (62.3%) of the events were considered potentially preventable, with 23 (24%) were considered as severe to life-threatening. Characteristics accompanied with these ADRs include documentation of a toxic drug concentration or abnormal laboratory value of (80%); the inadequate monitoring of a patient’s drug therapy is (67%). While it was revealed that inappropriate is a dose (51%), patient noncompliance is (33%), DDIs is (26%) which tallies with the findings of the current study (23%), contraindication to treatment is (3%), and reported allergy is (1%). These ADRs lead to 595 hospital days, with a mean length of stay of 6.1 days.[31,32]

In a more recent study conducted by Strandell and Wahlin, the characteristics of problematic drug combinations that result in adverse reactions were analyzed. Drug combinations that are most frequently suspected as interacting in VigBase were determined for their interaction mechanism(s). In this group of the database, there was a prominent (40%) portion of drug combinations with pharmacodynamic mechanisms being additive pharmacological effects. While 25% of the drug interactions had a pharmacokinetic mechanism which is mainly the inhibition of hepatic cytochrome P450 (CYP) enzymes, 19% the mechanism were not yet illustrated, and 16% had both pharmacodynamic and pharmacokinetic mechanisms.[33] In the study was presented in this paper, the mechanism of interaction was mainly pharmacodynamic mechanism.

The finding of the study was presented in this article agrees with another review by Strandell et al. where it was stated that spontaneous reporting systems are still the cornerstone of the early identification of previously unknown ADRs. However, a significant proportion of ADRs are known and preventable, and they are often due to the co-administration of medications known to interact.[34] In a meta-analysis study by Hakkarainen et al., data were analyzed from 16 original studies on outpatients with 48797 emergency visits. Among adult outpatients, 2.0% (95% confidence interval [CI]: 1.2%–3.2%) had preventable ADRs and 52% (95% CI: 42%–62%) of these identified adverse drug events were preventable. This meta-analysis has confirmed that preventable ADRs are a significant burden to health care among adult outpatients. Among outpatients approximately half of ADRs are preventable, reporting that further evidence on prevention strategies is required.[35–37]

**Furosemide and thiazide ↔ acarbose, insulin, and sulfonylureas drug interactions**

These are possible, moderate, pharmacodynamic, and preventable drugs interactions. Certain drugs, including thiazides and other diuretics, may diminish the efficacy of oral hypoglycemic agents and insulin. These drugs can cause hyperglycemia, glucose intolerance, new-onset diabetes mellitus, and exacerbation of preexisting diabetes as they may interfere with blood glucose control.[38,39] Close monitoring of glycemic control is required if the patient co-administered these drugs with antidiabetic medications. Likewise, patients should be monitored for hypoglycemia when the physician stops or patient withdraws these medicines from their therapeutic regimen. Dose modification of the hypoglycemic agent may be required. These DDIs are preventable in the case of furosemide by substituting object drug by metformin and decreasing the dose of furosemide. However, the interactions of thiazides with sulfonylureas or insulin are nonpreventable when patients cannot use metformin due to renal impairment or that metformin was contraindicated.[40,41]

**Thiazide and spironolactone ↔ metformin drug interactions**

These are probable with moderate significance, pharmacodynamic, and preventable drugs interactions. Diuretic-induced renal impairment and dehydration may increase the risk of lactic acidosis in patients who are concomitantly taking metformin. Furthermore, thiazides and other diuretics may interfere with glucose control by causing hyperglycemia, glucose intolerance, new-onset diabetes mellitus, and exacerbation of preexisting diabetes. A close clinical monitoring is needed if diuretics are co-administered with antidiabetic drugs. The patients should be advised to monitor their blood glucose and to promptly communicate their doctor when experiencing possible signs and symptoms of lactic acidosis (such as abdominal upset, hyperventilation, irregular heartbeat, malaise, respiratory distress, and somnolence) or loss of glycemic control. Furthermore, dosage regimen correction of metformin might be needed. Likewise, if the patient stops diuretics from the therapeutic regimen, the patient should be observed for hypoglycemia. These interactions are preventable by substituting the participate drug (thiazide by furosemide) or substituting metformin by sulfonylureas in the case of spironolactone drug interactions with metformin.[42,43]

**Corticosteroids, levothyroxine, risperidone, and salbutamol interactions with hypoglycemic agents**

All these drug interactions with hypoglycemic drugs were probable of moderate significance.
Relationship between number of drug interactions and the numbers of comorbidities and medications

From the current prospective observational study, it was found that there is no significant relation between the numbers of drug interactions inducing UCG and comorbidities numbers and/or number of medications for each patient. However, it was noticed that the number of drug interactions depends on the type of comorbidity and/or medication.

To explain these findings, some examples in the context of the facts, recommendations, and justifications presented in the online database are provided in the following. Outpatients with Type 2 diabetes had hypertension and treated with metformin, acarbose, and hydrochlorothiazide. While another outpatient with Type 2 diabetes had hypertension, dyslipidemia, ischemic heart diseases, and treated with metformin, atorvastatin, perindopril, aspirin, insulin, metoprolol, isosorbide dinitrate, and ranitidine. From previous examples, the first model patient has had only two diseases and had used only three medications and had three drug interactions that led to UCG. While, in the second example, the patient has had four conditions and had used eight drugs and had no drug interactions that can result in UCG.

**Limitation**

The prospective observational study was presented in this paper covers only the outpatients at endocrine clinics and does not account for DDI-related UCG of outpatients with Type 2 diabetes in the other clinics, and time is limited for the period of study.

**Conclusion**

Patients with Type 2 diabetes mellitus are at high risk of developing DDI-related UCG. Nearly one-quarter of UCG is induced by drug interactions. The majority of these drug interactions are possible and more than one-third is preventable. Thiazides have the highest prevalence of DDI-related UCG. The prevalence of DDI-related UCG depends on the type of medications and comorbidities, and on the other hand, it does not rely on the number of drugs or comorbidities.

**Acknowledgment**

We introduce our special thanks to all staff at the clinics of endocrinology, department of pharmacy and laboratory team in Penang General Hospital, for their kind support and help in facilitating this study.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.
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