

## Potential Impairment of Hypoglycemic Control Associated with Drug Interactions: A Look at Closer Management Needs for Diabetes Mellitus

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### Abstract

**Objectives:** One of the main adverse drug reactions presenting to emergency departments is drug induced hypoglycemia in diabetes mellitus patients. The aim of this study was to determine factors, other than lack of compliance with dietary requirements that could be increasing the risk of hypoglycemia among these patients.

**Methods:** A prospective, observational study was conducted from September 2009 to January 2010 collecting information on all diabetes mellitus patients confirmed to be experiencing hypoglycemia presenting to the Accident and Emergency Department of The University Hospital of the West Indies. Data collected included name of drug implicated and co-administered drug information. Compliance with drug therapy was confirmed. Pubmed search conducted identified peered review papers providing evidence of drug interactions established to increase risk of hypoglycemia.

**Results:** Eighteen patients were identified for the time period. Most patients (72.2%) were 65 years and older and most (66.7%) were also taking co-administered drugs. A total of 37 combinations in 12 of the patients known to potentiate hypoglycemia were identified. These included aspirin (13 cases), angiotensin converting enzyme inhibitors (12 cases) and beta-adrenoreceptor blockers (6 cases).

**Conclusions:** Most of the patients presenting with drug induced hypoglycemia were at increased risk of experiencing this adverse event from their prescribed drug combinations. Therefore drug induced hypoglycemia in patients on antidiabetic therapy may not only be associated with non-compliance and patient assessment should review the risk of the combination to the maintenance of glycaemic control.

**The significant finding of the study:** Most of the diabetes mellitus patients presenting with drug induced hypoglycemia (66.7%) were on drug combinations with increased risk of this adverse drug reaction. This study provides evidence of a need for physicians to have easy access to drug interaction information that can facilitate assessment of risk to glycaemic control in diabetic mellitus patients.

**Keywords:** Adverse drug reaction; Antidiabetic; Drug interactions hypoglycemia

### Introduction

Hypoglycemia in patients with diabetes mellitus is a common occurrence and has been established to negatively impact their quality of life [1]. It may be as a result of the hypoglycemic drug therapy and is usually related to noncompliance issues, such as inadequate food intake. It is also well established that the risk of hypoglycemia among patients with diabetes mellitus is increased with the presence of other comorbidities, as well as concomitant administration of other drug therapy. Drug interactions that increase the risk of hypoglycemia can be through pharmacokinetic mechanisms, such as inhibition of drug metabolism or through pharmacodynamic mechanisms, such as increase  $\beta$ -cell function; the impact of these interactions may require dose adjustments [2].

Previous reports from the Accident and Emergency Department (AED) of the University Hospital of the West Indies identified hypoglycemic episodes as the most common adverse drug reaction presenting to the Department [3], thus highlighting a need for further assessment of the possible causes. This report was therefore aimed at identifying possible drug combinations that may account for hypoglycemic episodes in diabetes mellitus patients presenting to the AED.

### Methods

A prospective, observational study was conducted in patients seen at the AED of the University of the West Indies.

Hospital from September 2009 to January 2010. AED logbook was the source of identification of all diabetes mellitus patients experiencing hypoglycemia and one senior consultant evaluated the patient medical records to help confirm presentation was associated with drug-induced hypoglycemia, as well as to confirm compliance with drug dosage instructions. The study protocol was approved by the UHWI/UWI/FMS Ethics Committee.

Data collected from the logbook, supported by patient docket included age, gender; name of drug implicated in the hypoglycemic episode and co-administered drug information. Direct patient communication was performed where necessary.

PubMed search identified peered review papers providing evidence of drug interactions established to increase risk of hypoglycemia in persons with diabetes mellitus [4-11]. This information facilitated

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	Drug	Frequency
<b>Antidiabetics</b>	Acarbose	1
	Glibenclamide	4
	Gliclazide	4
	Glimepiride	1
	Glipizide	2
	Glyburide	3
	Insulin	6
	Metformin	12
<b>Cardiovascular</b>	Aspirin	6
	Atenolol	1
	Captopril	1
	Carvedilol	2
	Digoxin	1
	Enalapril	5
	Frusemide	5
	Hydrochlorothiazide	2
	Hydralazine	2
	Lisonopril	2
	Nifedipine	1
	Pentoxifylline	2
	Propranolol	1
	Simvastatin	1
	Slow K	2
Spiroglactone	1	
<b>CNS</b>	Benzotropine	1
	Chlorpromazine	1
	Haloperidol	1
<b>Others</b>	Bropheniramine	1
	Calcium supplements	2
	Daflon	3
	Indomethacin	1
	Iron supplements	2
	Ranitidine	2
	Vitamin C	1
	Total	83

**Table 1:** List of drug taken by patients at the time of presentation to AED.

descriptive analysis of drug combinations among these patients that can increase their risk of hypoglycemia.

## Results

The period of the study identified 18 diabetes mellitus patients (9 males, 9 females) presenting to AED with hypoglycemia. The mean age ( $\pm$  standard deviation) was  $68.8 \pm 18.1$  years with 13 patients (72.2%) being 65 years and older. All patients confirmed compliance with prescribed regimen.

Table 1 lists all the prescription drugs the patients were currently taking; sulphonylureas were the most common antidiabetic drugs. Most of the patients (16 of 18, 88.9%) were also taking drug prescribed for other comorbidities.

In total there were 104 pairs of drug combination involving one antidiabetic drug and a drug for another indication.

There were 12 patients (66.7%) taking drugs known to potentiate

hypoglycemia when combined with antidiabetic drug. Table 2 lists the combinations which have been established to increase potential risk of hypoglycemia. The total number of potential drug interactions with increase risk of hypoglycemia was 37 of the 104 pairs (35.5%) with the co-administration of aspirin presenting as the most common offending drug (13 of 37).

## Discussion

Maintaining glycemic control without inducing episodes of hypoglycemia is critical in reducing progressive complication with diabetes mellitus, including the risk of cardiovascular disease and death [12-15]. It was previously established that hypoglycemia was the most commonly presenting drug related complication to AED at University Hospital of the West Indies [3] and therefore required further investigation of the possible risk factors that could be pre-disposing diabetes mellitus patients to this complication, as well as intervention to improve patient management.

Most of diabetes mellitus patients admitted to AED with hypoglycemic symptoms during the time period followed were elderly, a factor well known to increase the risk of hypoglycemia [16] and also highlighted by the clinical guidelines for management of diabetes mellitus patients adopted by the Caribbean Health Research Council (CHRC) (<http://www.chrc-caribbean.org/files/Pocket%20Diabetes%20Guidelines%20-%20Pocket%20Edition.pdf>).

Most were also taking drugs prescribed for other conditions and thus were predisposed to likely drug interactions. Using drug interactions based on previous reports from review of clinical studies and an understanding of pharmacologic mechanisms of the drugs involved, thirty seven combinations were identified as being able to potentiate hypoglycemia. These included beta receptor blockers (e.g. propranolol), aspirin, indomethacin and angiotensin converting enzyme inhibitors (enalapril, lisonopril, and captopril). The mechanism associated with the increase hypoglycemic potential of the drug combinations include stimulating secretion of insulin (reported with aspirin and indomethacin), blocking adrenergic mediated glycogenolysis (reported with beta-blockers), displacing sulphonylureas from plasma proteins

Drug combinations	Sulphonyl-ureas	Insulin	Metformin	Total	Interaction likely to facilitate hypoglycemia
Aspirin	7	1	5	13	Promotes insulin secretion and sulphonylurea availability [7,8,11].
Captopril	0	1	1	2	Promotes sensitivity to insulin [5,7,11].
Enalapril	3	0	3	6	
Lisinopril	4	0	2	6	
Carvedilol	3	0	1	4	Inhibit the adrenergic response to hypoglycemia [5,9,11].
Propranolol	1	0	1	2	
Indomethacin	1	0	1	2	Promotes insulin secretion and sulphonylurea availability [7,11].
Ranitidine	2	0	0	2	Increases the bioavailability of sulphonylureas [4, 10].
Total potential drug induced hypoglycemia	21	2	15	37	

**Table 2:** Drug combinations known to increase risk of hypoglycemia which combined with antidiabetic drugs. Values in columns represent number of patients in study taking individual combinations and the mechanism of the increased risk.

(reported with aspirin and indomethacin) and increasing the oral bioavailability of sulphonylureas through inhibition of metabolism (reported with ranitidine) [4-11].

Using the drug interaction checker available at [www.drugs.com](http://www.drugs.com), except for the combination of metformin with aspirin or indomethacin, all other drug combinations were classified as interactions that were moderately clinically significant (defined as combination that should be avoided and used only under special circumstances).

Therefore, consideration must be given to the clinical implications of drug combinations that are known to have added risk of drug induced hypoglycemia when patients present to AED with this complication.

The data collected from this study did not include a full assessment of other risk factors that could have predisposed patients to hypoglycemia, such as non-compliance with dietary guides. While none of the patients reported non-compliance with medication regimen, the researchers did not attempt to check the written instructions provided with medication.

This is the first study to further examine the profile of the patients presenting with hypoglycemic episodes to AED.

## Conclusions

The findings support a need for patient assessment to include whether drug combinations require more vigilant monitoring or adjustment to prevent hypoglycemic episodes. Interventions should include educating patients about measures to ensure glycemic control, as previous studies out of the United Kingdom have confirmed the benefit of patient education to clinical outcomes [17,18]. It is also important to ensure information on compromising drug interactions is easily accessible to physicians in AED, as this will facilitate better assessment of patient risk of hypoglycemia and appropriate adjustment of regimen.

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## Disclosure

There is no conflict of interest to disclose.

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