# Hypoglycaemic Complications with Diabetes Mellitus Management

## The Predominant Adverse Drug Reaction Presenting to the Accident and Emergency Department of The University Hospital of The West Indies

M Gossell-Williams[1], J Williams-Johnson[2], L Francis[1]

***ABSTRACT***

*Evaluation of adverse drug reactions (ADRs) is important to the assessment of risk factors in an aim to ensure maximum benefits of drug therapy. This study was done to assess the types of ADRs presenting to the Accident and Emergency department (A&E) of the University Hospital of the West Indies. Admissions to the A&E associated with drugs were followed on a weekly basis for 19 weeks from October 2007 to February 2008 using the patient logbook. Medical records of patients with suspected ADRs were collected and evaluated by an Emergency Medicine Consultant of A&E to confirm the occurrence of ADRs and the suspected drug. Of the 8170 admissions to A&E, 48 (0.6%) were related to ADRs, with most occurring in females and the mean age (± standard error) was 58.9 (± 3.4) years. Drug induced hypoglycaemia accounted for 28 (56.3%) cases of ADRs and included mainly patients on insulin, with or without a sulphonylurea therapy. Most of these diabetic patients also had co-morbidities and were on multi-drug therapy (18).*

*Allergic reactions accounted for 10 (21%) of the ADR outcomes. Other drugs accounting for ADRs included cardiovascular drugs (10.4%), analgesic/anti-inflammatory medications (8.3%), drugs acting on the central nervous system (8.3%) and anti-infectives (8.3%). It is concluded that drug-induced hypoglycaemia is the major ADR presenting to the A&E of the University Hospital of the West Indies; it is a preventable ADR and therefore further investigation should evaluate possible factors attributed to the occurrences.*

**Keywords:** Adverse drug reactions, diabetes mellitus, drug-induced hypoglycaemia

# Complicaciones Hipoglicémicas en el Tratamiento de la Diabetes Mellitus

## Las Reacciones Adversas a los Medicamentos que de Manera Predominante se Presentan en la División de Accidentes y Emergencias del Hospital Universitario de West Indies

M Gossell-Williams[1], J Williams-Johnson[2], L Francis[1]

***RESUMEN***

*La evaluación de reacciones adversas a los medicamentos (RAMs) es importante a la hora de evaluar los factores de riesgo con el objeto de asegurar beneficios máximos con la terapia medicamentosa. Este estudio fue realizado con el propósito de evaluar los tipos de RAMs que se presentan en la División de Accidentes y Emergencias (DAE) del Hospital Universitario de West Indies. Los ingresos al DAE asociados con medicamentos, fueron seguidos de forma hebdomadaria por un período de 19 semanas, desde octubre de 2007 hasta febrero de 2008, usando el libro de registro de pacientes. Las historias clínicas de los pacientes sospechosos de RAMs fueron recogidas y evaluadas por un Consultante de Medicina de Emergencia del DAE con el fin de confirmar que se trataba en efecto de un caso de RAM y verificar el medicamento de sospecha. De los 8170 ingresos al DAE, 48 (0.6%) guardaban relación con RAMs, siendo el caso que la mayor parte ocurrió con hembras y la edad promedio (± error*

From: [1]Department of Basic Medical Sciences, The University of the West Indies, Kingston 7, [2]Department of Surgery, Accident and Emergency Department, University Hospital of the West Indies, Kingston 7, Jamaica, West Indies.

Correspondence: Dr M Gossell-Williams, Department of Basic Medical Sciences, Pharmacology Section, The University of the West Indies, Kingston 7, Jamaica, West Indies. Fax: (876) 977-3823, e-mail: maxine.gossell@uwimona.edu.jm

*estándar) fue 58.9 (± 3.4) años. La hipoglicemia inducida por medicamento representó 28 (56.3%) casos de RAMs e incluyó principalmente a pacientes bajo el uso de insulina, con o sin una terapia sulfonilurea. La mayoría de estos pacientes diabéticos también presentaban co-morbosidades y estaban bajo terapia multi-medicamentosa (18). Las reacciones alérgicas representan 10 (21%) de los resultados de ADR. Otros medicamentos causantes de RAMs incluyeron los medicamentos cardiovasculares (10.4%), los analgésicos/anti-inflamatorios (8.3%), los medicamentos que actúan sobre el sistema nervioso central (8.3%) y los anti-infecciosos (8.3%). Se concluye que la hipoglicemia inducida por medicamento es la RAM mayor que se presenta al DAE del Hospital Universitario de West Indies. Se trata de una RAM prevenible, y por ende las investigaciones ulteriores deben evaluar los posibles factores responsables de estas ocurrencias.*

**Palabras claves:** Reacciones adversas a los medicamentos, diabetes mellitus, hipoglicemia inducida por medicamento

**West Indian Med J 2010; 59 (5): 566**

## INTRODUCTION

Drugs have helped to bring improved health and longer life to human beings, but they are not without risks, as there is always the potential for adverse drug reactions. An adverse drug reaction (ADR), as defined by the World Health Organization (1), is the response to a drug which is noxious and unintended and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of a disease or for the modification of physiological functions.

Adverse drug reactions may be previously described or appear with use of the drug in the general market. They are a frequent cause of mortality and morbidity of patients worldwide (2–4), accounting for 2–7% of hospital admissions and being the fourth to sixth leading cause of death (2, 5). Additionally, worldwide trends suggest that the majority are related to the pharmacological action of the drug (Type A) and preventable, rather than being associated with some action not explained by the pharmacology of the drug (Type B) such as an allergic response and irritation of organs. Therefore, monitoring of ADRs is vital to the assessment of risk *versus* benefits of drugs, especially since pre-market clinical trials have limited assessment of drugs used in children, the elderly, as well as the impact of long term use, co-morbidities and drug interactions. While some assessment has been made of the cases of drug-related angio-edema presenting to the University Hospital of the West Indies in Jamaica (6), there is little available data on other types of ADRs. The present study aimed to examine the prevalence and trends of ADRs presenting to the Accident and Emergency department of the University Hospital of the West Indies.

## SUBJECTS AND METHODS

The study was approved by the Faculty of Medical Sciences, University of the West Indies/University Hospital of the West Indies Ethics Committee. It was a prospective, observational study conducted on patients seen at the Accident and Emergency department (A&E) of the University Hospital of the West Indies from October 2007 to February 2008 for 19 weeks.

All admissions associated with drugs were collected from the A&E patient logbook weekly and ADRs were confirmed by gathering additional information from patient medical records with the assistance of an Emergency Medicine Consultant of A&E. An assessment of whether the ADR was type A, that is, associated with the pharmacological action of the drug or type B, that is, not related to pharmacological action (*eg* allergic) (7) was also done. Information taken from patient medical records included details of drugs implicated (daily dose and route), length of ADR event, description of the ADR, abnormal laboratory test results, age and gender. Other relevant history, such as co-administered drugs and other pre-existing medical conditions were also collected. The frequency and distribution of the most common ADRs and drugs associated with ADRs were analyzed. ADRs were classified using the scale of "certain, probable, possible, unlikely, unclassified and unclassifiable" as standardized by the World Health Organization (8).

## RESULTS

During the 19 weeks of the study, 8170 patients presented to the A&E department and 48 were found to be associated with ADRs, giving a prevalence of 0.6%. There was a greater representation of females (29, 60% of the total ADRs) than males (19, 40% of ADRs, odds ratio = 1.5). The majority of the cases were associated with elderly adults (Table 1) with 29 of the cases being over the age of 60 years (mean ± standard error = 58.9 ± 3.4 yrs).

Using the World Health Organization classification, none of the ADRs were classified as "certain", because the outcome of re-challenge was not assessed. Twenty-five of the cases were classified as probable, 19 as possible and 4 were unclassifiable (Table 2).

Of the cases presented, 75% of the ADRs were type A reactions including 28 cases of hypoglycaemia, 5 cases of extrapyramidal effects, 1 case each of bradycardia, dizziness and elevated blood pressure (failure of therapy). Twelve ADRs (25%) were type B reactions, involving 2 cases of gastrointestinal irritation, 10 cases of allergic responses, most

Table 1: Distribution of the ages of the patients presenting to A&E at the University Hospital of the West Indies

| Age range/yrs | Frequency |
|---|---|
| 10–15 | 1 |
| 16–20 | 1 |
| 21–25 | 5 |
| 26–30 | 2 |
| 31–35 | 2 |
| 36–40 | 2 |
| 41–45 | 2 |
| 46–50 | 1 |
| 51–55 | 1 |
| 56–60 | 2 |
| 61–65 | 3 |
| 66–70 | 3 |
| 71–75 | 11 |
| 76–80 | 5 |
| 81–85 | 4 |
| 86–86 | 2 |
| 91–95 | 1 |
| **Total** | **48** |

being skin related allergies and one anaphylaxis, resulting in death.

Table 2: Causality assessment using WHO classification

| **Suspected Drug group** | **Causality** | | |
|---|---|---|---|
| | **Probable** | **Possible** | **Unclassifiable** |
| Hypoglycaemic | 14 | 14 | 0 |
| Cardiovascular | 2 | 3 | 0 |
| Analgesic/Anti-inflammatory | 3 | 0 | 1 |
| Central nervous system | 2 | 1 | 0 |
| Anti-infective | 2 | 1 | 2 |
| Anti-ulcer | 1 | 0 | 0 |
| Anti-tussive | 1 | 0 | 0 |
| Undertermined | 0 | 0 | 1 |
| **Total** | **25** | **19** | **4** |

Patients being treated with anti-diabetic drugs represented most of the cases presented (28 or 56.3% of the cases) and the majority of these diabetic patients (22 out of 28) were adults over the age of 60 years. The hypoglycaemia was mainly associated with insulin only therapy (12 cases), followed by oral hypoglycaemic drugs (OHA, 12 cases) and 4 related to insulin plus OHA combination. The presenting complaints of all diabetic patients were the result of the induced hypoglycaemic state and records of 13 patients

Table 3: ADRs associated with hypoglycaemic drugs presenting to A&E at the University Hospital of the West Indies over the 19 weeks of the study. The co-morbidities and additional drug therapy are also given

| **Suspected Drug Class and % of total ADRs** | **Individual drugs** | **Adverse effects** | **Co-morbidities/Other drug therapy** |
|---|---|---|---|
| Hypoglycaemic 56.3% | Glyburide | hypoglycaemia (1) | hypertension managed with Trihexyphenidyl |
| | Glicazide | hypoglycaemia (1) | stroke, hypertension, hysterectomy(*drug history not given*) |
| | Glibenclamide | hypoglycaemia (6) | hypertensive-drug history not available (3), hypertension and Parkinson's disease (1; *drug history not given*) |
| | Glibenclamide + Metformin + Acarbose | hypoglycaemia:disoriented (1) | hypertension managed with Enalapril |
| | Insulin 70/30 | hypoglycaemia (8), | hypertension managed with Trihexyphenidyl (1), hypertension (3; *drug history not given*) bipolar disorder (1), myasthenia gravis (1) |
| | | hypoglycaemia:disoriented (1) | |
| | | hypoglycaemia:unresponsive (1) | |
| | | hypoglycaemia:coma (1) | hypertension + end stage renal disease (*drug history not given*) |
| | Insulin 70/30 + Gliclazide | hypoglycaemia:unresponsive (1) | |
| | Insulin 70/30 + Metformin | hypoglycaemia (2) | hypertension managed with Atenolol +Enalapril (1) |
| | Insulin 70/30 + Metformin + Glyburide | hypoglycaemia (1) | |
| | Insulin NPH + soluble | hypoglycaemia (1) | |
| | Metformin + Glibenclamide | hypoglycaemia (1) | hypertension + chronic renal failure (*drug history not given*) |
| | Metformin + Glyburide | hypoglycaemia (1) | hypertension managed with Enalapril |
| | Rosiglitazone + Metformin + Gliclazide | hypoglycaemia (1) | hypertension (*drug history not given*) |

documented them as being compliant with their drug regimen (2 reported non-compliance, 7 had no notes on compliance). The doses of the drugs involved in each case were determined to be in the therapeutic dose range. The majority of diabetic patients also had other complications ranging from cardiovascular diseases (with and without renal failure 16) to myasthenia gravis (1) and parkinsonism (1) but specific details related to these co-morbidities, including information on drug therapy were not completely documented in patients' case notes (Table 3).

Cardiovascular drugs accounted for 10.4% of the total ADRs (Table 4). Drugs with action on the central nervous system, analgesics/anti-inflammatory drugs and anti-infectives accounted for 8.3% each of the total ADRs. Antitussive and anti-ulcer drugs each accounted for 2.1% of the total ADRs while there was another 2.1% in which the drug associated with the ADRs was undetermined because of the involvement of more than one drug and the nature of the ADR. Of the 20 patients comprising these other groups, good compliance with therapy was confirmed for 16 cases, poor compliance was determined for one and compliance information was missing for 2 cases.

## DISCUSSION

This is the first study to evaluate the prevalence of ADRs presenting to the A&E department of the University Hospital of the West Indies. The report showed that 6 out of every 1000 patients presenting to A&E were likely to be experiencing complications to normal drug therapeutic doses. The study also found that the patient presenting to A&E with an ADR was more likely to be elderly; a finding that is consistent with advance age being an established risk factor for the occurrence of ADRs (9–11).

Causality assessment resulted in ADRs being classified mainly as probable. None of the patients' casefiles indicated use of herbal preparations which is known to be a highly prevalent practice in Jamaican culture and patients do not willingly discuss this practice with their physicians (12–13). Herbal preparations are also associated with ADRs (14) and

Table 4: ADRs associated with other drug classes (20 of 48 cases) presenting to A&E at the University Hospital of the West Indies over the 19 weeks of the study. The co-morbidities and additional drug therapy are also given.

| Suspected Drug Class and % of total ADRs | Individual drugs | Adverse effects | Co-morbidities/Other drug therapy |
|---|---|---|---|
| Cardiovascular 10.4% | Atenolol | Allergy:angioedma (1) | |
| | Digoxin | Bradycardia (1) | |
| | Enalapril | Allergy: angioedema (1) | |
| | Hydrocholothiazide | Allergy: itching (1) | Benign positional vertigo |
| | Hydrocholothiazide | Elevated blood pressure (1) | Also taking carbamazepine/atenolol/ nifedipine/lovostatin |
| Anti-infectives 10.4% | Amoxycillin | Allergy:weals (1) | |
| | Amoxycillin+ Clavulanic acid + Metronidazole | Allergy: anaphylaxis and death (1) | |
| | Doxycycline + Metronidazole | Allergy:specifics not noted (1) | |
| | Doxycycline + Metronidazole + Norfloxacin | Allergy:papular rash (1) | |
| | Terbinafine | Allergy:papular rash (1) | |
| Analgesic/Anti-inflammatory 8.3% | Acetaminophen | Chest tightness (1) | |
| | Acetaminophen + Diclofenac | Allergy: papular rash (1) | |
| | Diclofenac | Gastritis/Vomiting (1) | |
| | Etoricoxib | Gastritis/Vomiting (1) | |
| Central Nervous System 8.3% | Haloperidol | Extrapyramidal effects (1) | |
| | Haloperidol + Benztropine | Extrapyramidal effects (1) | |
| | Risperidone | Extrapyramidal effects (1) | |
| Anti-ulcer 2.1% | Ranitidine | Extrapyramidal effects (1) | |
| Anti-tussive 2.1% | Guaifenesin | Extrapyramidal effects (1) | |
| Undertermined 2.1% | Salbutamol +Cetirizine | Dizziness (1) | Hypertension managed with Methyldopa |

therefore use with prescribed medications could change classification from "probable" to "possible". This therefore limits confidence in causality assessment, as patients may not have provided this information.

Interestingly, more than fifty per cent of ADR cases were diabetic patients experiencing hypoglycaemia associated with their drug therapy. In Italy and Spain, drug induced hypoglycaemia is ranked as the fourth leading cause of ADRs presenting to emergency rooms, accounting for less than 10% of the cases (15–16). This difference in proportions could be due to differences in patient admission procedures between hospitals. For example, in the Italian study, allergic skin reactions were recorded as the more common emergency room ADR presentation than hypoglycaemia; however, for the hospital involved in this study, patients with allergic skin reactions would more likely present to the Casualty Division of the hospital and therefore not form part of data from the A&E department.

This study also found that the majority of the hypoglycaemic episodes involved insulin therapy. This is consistent with other studies out of the United States of America and Hong Kong, showing a higher risk of hypoglycaemia in insulin users (17–20). Drug induced hypoglycaemia is characterized as a type A adverse drug reaction and therefore is preventable. It is well established that along with advancing age, co-morbidities and multi-drug use increase the risk of hypoglycaemia. For example, concomitant administration of non-selective beta blockers or angiotensin converting enzyme inhibitors can increase the risk of hypoglycaemia in patients with diabetes mellitus and co-administration of anti-diabetic drugs may require dose adjustments (21). Therefore, assessment of preventability becomes important in order to determine what adjustments could be made to obviate re-occurrence.

The evaluation of preventability of ADRs according to the methods described by Schumock (22) and Winterstein (23) depends on an evaluation of appropriateness of drug dose and route, in relation to patient factors (age, weight, disease state and compliance to therapy). It also requires evaluating whether there is need for therapeutic dose monitoring, information of previous problems with drug exposure and possible involvement of medication error. Some of these factors, such as blood concentration of drugs, patient history of previous ADRs and severity of co-morbid states could not be determined from patient case-notes and therefore no assessment was made of the preventability of the ADRs.

In conclusion, the role of an emergency room should not only be to manage emergency cases effectively, but also to assess trends and practices associated with occurrences. There may be a need to design specific protocols for the collection and management of ADRs. The A&E department should be most concerned about the implications of the number of cases of drug induced hypoglycaemia. Consideration should be given to the design of specific protocols to accommodate adequate data collection that will facilitate causality assessment and reduce the risk of occurrences.

## REFERENCES


1. World Health Organization. Safety of Medicines. A guide to detecting and reporting adverse drug reactions. Why health professionals need to take action. Geneva World Health Organization 2002.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1982; **79:** 1200–5.
3. Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a south Indian hospital – their severity and cost involved. Pharmacoepidemiol Drug Saf 2003; **12:** 687–92.
4. Patel H, Bell D, Molokhia M, Srishanmuganathan J, Patel M, Car J et al. Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998–2005. BMC Clin Pharmacol 2007; **25:** 9.
5. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. BMJ 1998; **316:** 1295–8.
6. Williams-Johnson JA, Hemmings S, Williams EW, Channer G, McDonald AH. Six years experience of angioedema at the University Hospital of the West Indies. West Indian Med J 2007; **56:** 278–81.
7. Meyboom R, Egberts A, Edwards I, Hekster Y, de Koning FH, Gribnau FW. Principles of signal detection in pharmacovigilance. Drug Saf 1997; **16:** 355–65.
8. Edwards IR and Beriella C. Harmonization in Pharmacovigilance. Drug Saf. 1994; **10:** 93–102.
9. von Euler M, Eliasson E, Ohlén G, Bergman U. Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization. Pharmacoepidemiol Drug Saf 2006; **15:** 179–84.
10. Mjörndal T, Boman MD, Hägg S, Bäckström M, Wiholm BE, Wahlin A et al. Adverse drug reactions as a cause for admissions to a department of internal medicine. Pharmacoepidemiol Drug Saf 2002; **11:** 65–72.
11. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. Br J Clin Pharmacol 2004; **57:** 121–6.
12. Connell P, McKevitt C, Wolfe C. Strategies to manage hypertension: a qualitative study with Black, Caribbean, patients. Br J Gen Pract 2005; **55:** 357–61.
13. Delgoda R, Ellington C, Barrett S, Gordon N, Clarke N, Younger N. The practice of polypharmacy involving herbal and prescription medicines in the treatment of diabetes mellitus, hypertension, and gastrointestinal disorders, in Jamaica. West Indian Med J 2004; **53:** 400–5.
14. Ulbricht C, Chao W, Costa D, Rusie-Seamon E, Weissner W, Woods J. Clinical evidence of herb-drug interactions: a systematic review by the natural standard research collaboration. Curr Drug Metab 2008; **9:** 1063–120.
15. Zanocchi M, Tibaldi V, Amati D, Francisetti F, Martinelli E, Gonella M. Adverse drug reactions as cause of visit to the emergency department: incidence, features and outcomes. Recenti Prog Med 2006; **97:** 381–8. [Abstract].
16. Machado-Alba JE, Moncada-Escobar JC. Adverse drug reactions in patients attending in emergency service. Rev Salud Publica (Bogota). 2006; **8:** 200–8 [Abstract].
17. Ginde AA, Pallin DJ, Camargo CA Jr. Hospitalization and discharge education of emergency department patients with hypoglycemia. Diabetes Educ 2008; **34:** 683–91.
18. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med 1997; **157:** 1681–6.
19. Chan TY. Estimates on the incidence of antidiabetic drug-induced severe hypoglycaemia in Hong Kong. Pharmacoepidemiol Drug Saf 1998; **7:** 411–4.
20. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W et al. DARTS/MEMO Collaboration. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a

population-based study of health service resource use. Diabetes Care 2003; **26:** 1176–80.
21. Chelliah A, Burge MR. Hypoglycaemia in elderly patients with diabetes mellitus: causes and strategies for prevention. Drugs Aging 2004; **21:** 511–30.
22. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hospital Pharmacy 1992; **27:** 538.
23. Winterstein AG, Hatton RC, Gonzalez-Rothi R, Johns TE, Segal R. Identifying clinically significant preventable adverse drug events through a hospital's database of adverse drug reaction reports. Am J Health-system Pharm 2002, **59:** 1742–9.