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Retrospective Evaluation of Adverse Drug Reactions in a Central Hospital in Malawi

Yardlee S. Kauffman[1], Sharon E. Connor[2*], Lauren J. Jonkman[3], Tadala Himisi[4], Sandra L. Kane-Gill[5], E. Miranda Gillespie[6], and Gerald P. Douglas[7]

[1]*Assistant Professor, Clinical Pharmacy, Department of Pharmacy Practice and Pharmacy Administration Philadelphia College of Pharmacy, University of the Sciences*

[2]*Assistant Professor, Pharmacy & Therapeutics, School of Pharmacy, University of Pittsburgh*

[3]*Clinical Instructor, Pharmacy & Therapeutics, School of Pharmacy, University of Pittsburgh*

[4]*Pharmacist, Kamuzu Central Hospital*

[5]*Associate Professor, Pharmacy & Therapeutics, School of Pharmacy, University of Pittsburgh*

[6]*Internal Medicine physician, Grady Health System*

[7]*Assistant Professor, Biomedical Informatics, School of Medicine, University of Pittsburgh*

***Corresponding author**: Sharon E. Connor, PharmD, Assistant Professor, Pharmacy & Therapeutics, School of Pharmacy, University of Pittsburgh, 726 Salk Hall, 3501 Terrace Street, Pittsburgh, PA 15261. Tel: 412-648-7192; Fax: 412-624-8175; E-mail: sconnor@pitt.edu

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Abstract

Background

Few studies have reported rates of adverse drug reactions (ADRs) within low-income countries, and the resulting rates are extremely variable. Limited information exists about patterns of ADRs within African countries.

Objective

To identify the incidence and describe the types of ADRs for adult admissions to the Kamuzu Central Hospital in Lilongwe, Malawi.

Methods

In this retrospective chart review, baseline descriptive information for all patients and details surrounding any identified potential ADR were documented. Only medical charts that included both laboratory results and a medication administration record were included. An expert panel reviewed all potential ADRs for study inclusion.

Results

263 charts were reviewed and only 16% (42) met inclusion criteria. Of those 42 charts, 4 ADRs were identified. A cumulative ADR occurrence of 9.5% was observed.

Conclusions

The preliminary incidence of ADRs in Malawi appears high and requires further evaluation to identify potential causes and solutions.

Keywords Pharmacovigilance; Adverse drug reaction; Patient safety; Drug utilisation

Introduction

Adverse drug reactions (ADRs) are a significant public health concern and leading cause of death in the world [1]. Pharmacovigilance, an essential component of safe and effective drug use, allows for the prevention of ADRs, yet remains a challenge in low-income countries (LICs) [1]. While medication access is increasing in LICs, systems and resources necessary to support medication safety activities are lacking. Challenges that limit safety monitoring of medications in LICs include: poor record keeping of medication exposures and outcomes; overburdened health care systems that are unable to afford the financial cost of system implementation; poor drug control due to inadequate regulatory measures; informal drug markets which enable counterfeit and substandard medications to be sold; and use of new medications for which there is only partial knowledge of adverse events due to limited use in clinical trials [1]. These challenges are widespread in Sub-Saharan Africa (SSA), an area where knowledge about the incidence and types of adverse drug reactions (ADRs) is limited [2-4]. In Malawi, this data has not been reported. The objective of this pilot study is to identify the incidence and types of ADRs for adult admissions at the Kamuzu Central Hospital in Lilongwe, Malawi.

Methods

Study Setting and Design

A retrospective chart review was conducted at the Kamuzu Central Hospital (KCH) in Lilongwe, a tertiary referral centre for the central region of Malawi [5]. All available records meeting inclusion criteria were examined in May of 2012. Inclusion criteria included age greater or equal to 18 years and a hospital discharge date between November 2011 and April 2012. Charts were excluded from analysis if the medication administration record (MAR) and/or laboratory results were missing from the chart.

Data Collection

From each eligible chart, the following was extracted: admission diagnosis; length of stay; medications including the total number of doses administered to the patient; past medical history; laboratory results; and outcome of the hospital stay. Adverse drug reations were identified with the assistance of an ADR trigger tool [6-7], and an ADR assessment was completed if a trigger was identified. The Naranjo criteria, a published causality assessment instrument, were used to determine the potential associations between an event and drug administration [8].

Findings were validated by an experienced team of clinicians who reviewed each case collectively to determine the likelihood of each ADR. This multidisciplinary team included U.S. based clinicians who have provided clinical services at KCH and a medication safety pharmacist. The University of Pittsburgh Institutional Review Board and the National Health Sciences Research Committee of Malawi approved this study.

Results

A total of 263 charts were available for review; 42 charts were included after the application of exclusion criteria. Four ADRs were identified with a rate of 15.3 ADRs per 1,000 patient days. Three ADRs were associated with hospital admission and one was identified as a hospital-acquired ADR. A cumulative ADR occurrence of 9.5% was observed with a 7.1% incidence of ADRs leading to admission and a 2.4% incidence of inpatient ADRs.

A description of each identified ADR is shown in (Table 1). The first case was a hospital-acquired ADR involving bleeding secondary to anticoagulants and was classified as a probable ADR. The other three cases were classified as possible ADRs, each possibly contributing to the hospital admission.

Discussion

In this study, an overall ADR incidence rate of 9.5% was observed. Three of the events occurred prior to admission suggesting challenges in monitoring chronic medications in the outpatient setting. A retrospective review of 15,548 patient records conducted in eight low- and middle- income countries illustrated ADR incidence ranging from 2.5% to 18.4% per country [3]. Studies conducted in Uganda and South Africa identified that 4.5% and 6.3% of patients, respectively, were admitted to a hospital with suspected ADRs and 1.5% and 6.3% of patients, respectively, developed an ADR during hospitalization [2,4]. Data from this study are consistent with the published literature in Africa.

Case #1 was related to the use of intravenous heparin and was the only hospital acquired ADR identified. Clinicians may find heparin management challenging since it is not included in the Malawi treatment guidelines [9] and clotting tests are not available at KCH. Cases #2 and #3 were related to antiretroviral therapy for HIV. First-line treatment of HIV in Malawi includes the antiretrovirals (ARV), nevirapine, lamivudine, and stavudine. Although anaemia (Case #2) is not generally linked with stavudine use, post-marketing reports have described cases [10]. The incidence of side effects especially lactic acidosis (Case #3) seems to be higher in African nations, likely due to the use of stavudine as first-line therapy [9]. In both cases, the patients' underlying conditions likely contributed to hospital admission, though it is possible that ARVs contributed to their presentation. If so, changes in first-line ARV therapy would be needed to prevent and minimise future events from occurring. Lastly, Case #4 was related to metronidazole use in a patient with a history of side effects during prior use.

In only one case (Case #3) did the treating medical team document the possible ADR at the time of the event? Clinician training focused on ADR identification in hospitalised patients is needed, especially when ADRs mirror the presentation of other common endemic diseases (e.g. HIV, malaria) [11]. Underreporting of ADRs is a common phenomenon across all health care settings; reported reasons for underreporting are due to lack of knowledge between drugs and suspected ADRs, unfamiliarity with pharmacovigilance reporting systems, and lack of interest or time to report ADRs [12-14]. Reducing the burden of this problem is not unsolvable. Other members of the health care team such as pharmacists have a key role in identifying and reporting ADRs [15-17]. Furthermore, electronic systems that flag ADRs using information from the record streamline the process of identifying ADRs [18] (e.g. a system flags elevated potassium as a potential ADR due to spironolactone). These strategies have improved identification and reporting rates of ADRs; however for countries where hospital technology is either outdated or nonexistent, performing a thorough work-up to narrow a differential diagnosis is often not an option.

Study Limitations

In this setting, incomplete records significantly reduced the sample size, preventing a reliable and robust estimate of ADRs. Determining the actual ADR incidence was challenging because a standardized method for storing patient records does not exist. Only 263 records could be located for the six-month study period though the number of admissions and discharges was likely higher during this time [5]. Finally, inadequate access to diagnostic testing also leads to uncertainties in diagnosis and ADR identification. The authors' believe the incidence of ADRs is higher than the rate reported in this study due to inadequate chart documentation and limited drug monitoring. If progress notes were thorough and laboratory results readily available, it is likely more ADRs would have been identified. Future prospective studies may be able to overcome some of these limitations as some information is discussed during patient care rounds but is rarely documented in the paper chart.

	Case description	Likelihood of ADR based on clinician review
Hospital-acquired ADR	Case #1: A 38yo male was admitted to KCH with symptoms of a painful and swollen right leg, shortness of breath, abdominal pain, and vomiting. He was diagnosed with deep vein thrombosis + potential pulmonary embolism. He was started on heparin 15,000 units intravenously every 12 hours, aspirin (dose not documented), and warfarin 2mg daily. One Day 2 of his hospital stay, he complained of abdominal pain. Patient was started on ceftriaxone IV 2g daily for abdominal pain of unknown cause. Aspirin was stopped and heparin and warfarin were continued. On Day 4, the patient developed hematochezia. Bleeding was attributed to heparin use and exacerbated by potential underlying peptic ulcer disease. Vitamin K 10mg was administered intramuscularly and bleeding resolved. Hemoglobin was measured to be 7.5 g/dL. INR monitoring was ordered, but lab results were not included in the chart. Patient was discharged on Day 11. Discharge medications, if any, were not recorded.	Probable ADR: *bleeding secondary to anticoagulants or underlying disease* (Naranjo = 4)
Pre-admission ADR	**Case #2:** A 22yo male was admitted to KCH for anemia. Patient reported symptoms of paleness and general weakness for a "long time" and had been transfused several times since 2009 - cause was not identified. This patient received an antiretroviral treatment (ART) regimen of stavudine, lamivudine, and nevirapine for three years. No other chronic medications or problems were reported. The patient received a blood transfusion after discovery of a hemoglobin of 2.8 g/dL. He was discharged on his previous ART regimen, ferrous sulfate, and folic acid.	Possible ADR: *anemia secondary to stavudine or underlying disease* (Naranjo = 3)
	Case #3: A 42yo male with history of HIV presented to KCH with fevers and general body weakness. He was empirically treated for cryptococcal mengingitis upon admission with oral fluconazole. He received ART for two weeks prior to admission with stavudine, lamivudine, and nevirapine. Lactic acidosis was also suspected as a probable cause of symptoms and ART was held. A lactate level was measured and revealed an elevated level of 4.9 mmol/L (ref range 0.5-2.2 mmol/L). Cryptococcal meningitis was confirmed with a positive India Ink test. Treatment plan to begin intravenous amphotericin B and blood transfusions was recommended. Patient status declined as he refused to eat and refused oral medications. The patient died on Day 5.	Possible ADR: *elevated lactate secondary to stavudine or underlying disease* (Naranjo = 3)
	Case #4: A 44yo female with a history of vomiting for 3 Days, watery diarrhea for 4 Days, and heart palpitations for one Day was admitted to KCH. She received ciprofloxacin, metronidazole, and diclofenac at an outpatient clinic prior to admission. Suspected indication for treatment is unknown. Patient reported a history of gastrointestinal upset (vomiting, diarrhea) with prior administration of metronidazole. The patient has a history of HIV and was receiving ART regimen of tenofovir, lamivudine, and efavirenz. The duration of ART is unknown. A CBC and serum lactate were ordered and the patient was started on ceftriaxone 2g IV daily and promethazine 25mg IV as needed. The patient was discharged on Day 2 with an order for ciprofloxacin 500mg twice daily for 5 Days and an oral rehydration solution packet.	Possible ADR *Gastrointestinal distress secondary to metronidazole or other condition* (Naranjo = 4)

Table 1: Adverse drug reaction (ADR) case descriptions

Conclusions

Since so little has been published regarding ADRs in Malawi, it is the authors' opinion that sharing this information is a vital first step. While there are multiple limitations to this initial evaluation, leading to a less than optimal sample size, the data show that ADRs are indeed occurring and begins to shed light on this important problem. This work highlights the need for more pharmacovigilance activities in low-income countries and the challenges associated with that work. This pilot project lays the groundwork for follow-up, prospective studies to identify the true, and likely greater, incidence of ADRs in this setting.

Conflicts of Interest

None to Disclose

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References

1 http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf

2 Tumwikirize WA, Ogwal-Okeng JW, Vernby A, Anokbonggo WW, Gustafsson LL, et al. (2011) Adverse drug reactions in patients admitted on internal medicine wards in a district and regional hospital in Uganda. Afr Health Sci 11: 72-78.

3 Wilson RM, Michel P, Olsen S, Gibberd RW, Vincent C, et al. (2012) Patient safety in developing countries: retrospective estimation of scale and nature of harm to patients in hospital. BMJ 344: e832.

4 Mehta U, Durrheim DN, Blockman M, Kredo T, Gounden R, et al. (2008) Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. Br J Clin Pharmacol 65: 396-406.

5 Hoffman M, Mofolo I, Salima C, Hoffman I, Zadrozny S, et al. (2012) Utilization of family members to provide hospital care in Malawi: the role of Hospital Guardians. Malawi Med J 24: 74-78.

6 Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, et al. (1998) Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. J Am Med Inform Assoc 5: 305-314.

7 Handler SM, Altman RL, Perera S, Hanlon JT, Studenski SA, et al. (2007) A systematic review of the performance characteristics of clinical event monitor signals used to detect adverse drug events in the hospital setting. J Am Med Inform Assoc 14: 451-458.

8 Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, et al. (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30: 239-245.

9 http://apps.who.int/medicinedocs/documents/s18801en/s18801en.pdf

10 http://packageinserts.bms.com/pi/pi_zerit.pdf

11 www.who.int/hiv/ARV-guidelines.pdf.

12 Stoynova V, Getov IN, Naseva EK, Lebanova HV, Grigorov EE (2013) Physicians' knowledge and attitude towards adverse event reporting system and result to intervention--randomized nested trial among Bulgarian physicians. Med Glas (Zenica) 10: 365-372.

13 Lopez-Gonzalez E, Herdeiro MT, Figueiras A (2009) Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf 32: 19-31.

14 Oshikoya KA, Awobusuyi JO (2009) Perceptions of doctors to adverse drug reaction reporting in a teaching hospital in Lagos, Nigeria. BMC Clin Pharmacol 11: 14.

15 Jiang SP, Chen J, Zhang XG, Lu XY, Zhao QW (2014) Implementation of pharmacists' interventions and assessment of medication errors in an intensive care unit of a Chinese tertiary hospital. Ther Clin Risk Manag 10: 861-866.

16 Leone R, Moretti U, D'Incau P, Conforti A, Margro L, et al. (2013) Effect of pharmacist involvement on patient reporting of adverse drug reactions: first Italian study. Drug Saf 36: 267-276.

17 Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA (2003) Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. Arch Intern Med 163: 2014-2018.

18 Park MY, Yoon D, Lee K, Kang SY, Park I, et al. (2011) Novel algorithm for detection of adverse drug reaction signals using a hospital electronic medical record database. Pharmacoepidemiol Drug Saf 20: 598-607.