Research article

Adverse drug reactions and associated factors in a cohort of Sri Lankan patients with non-communicable chronic diseases

Shanika L.G.T[1,2*], Jayamanne S[2.3], Coombes J[4], Coombes I[5], Wijekoon C.N.[6]

[1]Department of Allied Health Sciences, Faculty of Medical Sciences, University of Sri Jayewardenepura, [2]South Asian Clinical Toxicology Research Collaboration, Sri Lanka, [3]Faculty of Medicine, University of Kelaniya, Sri Lanka, [4]School of Pharmacy, Pharmacy Department, University of Queensland, Princess Alexandra Hospital, Australia, [5]Pharmacy Department, School of Royal Brisbane Hospital, University of Queensland, Australia, [6]Department of Pharmacology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka.

* Corresponding author: thushani@sjp.ac.lk

Abstract

Introduction and objectives: Adverse drug reactions (ADRs) are a major problem in drug utilization. Objective of this study was to describe the incidence, nature and the factors associated with ADRs in a cohort of Sri Lankan patients with non-communicable chronic diseases (NCCDs).

Methods: This study includes observational data from a cohort of patients recruited to a controlled trial, where no difference was observed between the intervention and control arms with regard to the incidence of ADRs. In-patients with NCCDs were recruited. All ADRs that occurred during the index hospital admission and the 6-month period following discharge were detected by active surveillance. Details were recorded using ADR reporting form, developed based on the publication of Clinical Center, Pharmacy Department, National Institute of Health.

Results: 715 patients were studied. 50.3% were females. Mean age was 58.3±15.4 years; 35.4% were elderly (aged ≥65years). 45.6% had diabetes. Mean number of medicines per patient was 6.11±2.97. 154 (21.5%) ADRs [33(4.6%) during index hospital admission; 121(16.9%) during 6- months period following discharge] were detected involving 112 (15.7%) patients. 51.9% (80/154) of them were potentially avoidable. 47% (73/154) of ADRs were Serious Adverse Events (SAEs). Incidence of ADRs was not significantly different between males and females (males=21.1%; females=21.9%,; (p = 0.79). ADRs were more common in elderly than in non-elderly (34% vs 14.7%, p<0.001) and in those who were on ≥5 drugs than in those who were on <5 drugs (25.9% vs 12.7%, p<0.001). ADRs were more common among those with diabetes than among those without diabetes (28.5% vs 15.6%, p<0.001).

Conclusion: Incidence of ADRs were frequent in the study population. Some factors associated with a higher incidence of ADRs were age ≥65 years, ≥5drugs in the prescription and presence of diabetes. Among patients with NCCDs, these special patient groups need more attention to minimize ADRs.

Keywords: Drug related problems, Sri Lanka

Introduction

Hospitalization, morbidity and mortality due to adverse drug reactions (ADRs) is a significant health problem which may have a great impact on health care cost. The WHO defined an ADR as a "response to a drug that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of

physiologic function".[1]Several classifications are available for ADRs. ADRs can be divided into five types; Type A (expected reactions, based on the pharmacologic properties and dose dependent), Type B (idiosyncratic and unexpected reactions, dose independent), Type C (reactions are chronic effects related to long-term drug use), Type D (reactions are delayed drug effects) and finally Type E (reactions occurring due to abrupt withdrawal of chronic therapy).[2]

Every year more than 770,000 people are injured or die in hospitals in the world due to ADRs and estimated cost for the management of ADRs is about $5.6 million per hospital.[3] According to Lazarou et al. fatal ADRs were the sixth leading cause of death in USA in 1994.[4] However, 30% to 60% of reported ADRs could have been prevented.[4] Research studies on post- discharge adverse drug events had estimated that 11%-23% of general medical patients experienced adverse events during post- discharge period.[5, 6]

Underreporting is the main problem linked with ADRs worldwide. In Sri Lanka, the Department of Pharmacology, Faculty of Medicine in University of Colombo has become a member in the WHO collaboration center for ADR monitoring. However, the number of ADR cases received per year is not satisfactory. [7] This result may not mean that patients in Sri Lanka experience very few ADRs in their medication use process. It is more likely to be due to lack of motivation among health care workers, fear of 'shame and blame', logistic reasons such as time restrictions, as well as lack of resources to promote and facilitate the ADR monitoring and reporting system in the country.

Sri Lanka is a developing country with a high burden of non-communicable chronic diseases (NCCDs) accounting for a large number of hospital admissions.[8] The patients with NCCDs need to be on long term medications, most often lifelong therapy, and thus comprise a group of patients most vulnerable to experience ADRs.

Objective of this study was to describe the incidence, nature and factors associated with ADRs in a cohort of Sri Lankan patients with NCCDs.

Methods

Study design and setting

A prospective hospital based descriptive study including observational data from a cohort of patients recruited to a controlled trial, where no difference was observed between the intervention and control arms with regard to the incidence of ADRs (Control - 71/356, 20.0% vs. Intervention - 83/361, 23.0%; P=0.320) was conducted. It was conducted over a thirteen month period, in the University Medical Unit of a tertiary care hospital in Sri Lanka. The University Medical Unit consisted of two wards – a female and a male ward accommodating approximately 55 and 65 patients, respectively.

Study participants

Patients admitted to the study unit with defined NCCDs who needed long-term treatment and follow-up were included in the study. According to WHO, NCCDs were defined as disease conditions which are not contagious and that of long duration and slow progression.[9] Examples include cardiovascular diseases (hypertension, ischaemic heartisease, heart failure, arrhythmias), neurological diseases (stroke, peripheral neuropathy), metabolic disorders (diabetes mellitus, hyperlipidemia, thyroid disorders), gastro-intestinal disorders (chronic pancreatitis, liver disorders, inflammatory bowel disease), chronic renal diseases, chronic respiratory diseases (chronic obstructive pulmonary disease, bronchial asthma, interstitial lung disease), genitourinary diseases (chronic kidney disease, glomerulonephritis, bladder outflow obstruction, benign prostatic hyperplasia), musculoskeletal diseases (osteoporosis, osteoarthritis, rheumatoid arthritis) and autoimmune diseases (systemic lupus erythematosus, connective tissue disorders, vasculitis).

Patients who were admitted to the University Medical Unit for acute care but were receiving routine long term treatment from other medical units, patients with poor cognition with no caregiver to manage medicines, and patients with communication difficulties were excluded. The participants re-admitted during the study period were not re-recruited as new subjects.

The study participants were systematically selected by an independent medical officer using the admission register in the wards as the sampling frame. In each ward the first 10 patients who had been admitted during the previous 24 hour period were selected and reviewed for inclusion and exclusion criteria. The first five eligible patients were recruited for the study. When five eligible patients could not be found within the first 10 patients in the admission register the next 10 admissions were reviewed.

ADR detection

During the hospital stay, all ADRs were detected by active surveillance by intensive monitoring using hospital records and patient interviews. The reference sources used were the British National Formulary (BNF) 65 and/or Australian Medicines Handbook (AMH). The ADRs were confirmed after discussing with a senior clinical pharmacologist. Active surveillance of post-discharge ADRs was carried out via monthly telephone interviews up to six months after discharge in all patients. In both phases the active surveillance and data collection was done by a trained B.Pharm graduate. The graduate was trained for 1 year period for ADR detection by a senior clinical pharmacologist, physician and a team of clinical pharmacist. Details were recorded using an ADR reporting form which was developed based on the publication of Clinical Center Pharmacy Department National Institutes of Health.[10]

All reported ADRs were further classified into to Serious Adverse Events (SAEs) depending on the severity of ADRs. According to the National Institutes of Health SAEs are defined as those causing death, causing a life threatening event, causing disability/ incapacity, causing admission to hospital or causing congenital deformity or carcinogenicity.[10]

Data analysis

Data were entered into SPSS.21.0 (IBM Corporation, Armonk, NY). Data cleaning was carried out by a different investigator to assure the quality of entered data. The identified discrepancies were resolved after discussing with a senior clinical pharmacologist. Descriptive statistics were shown as frequencies and means with standard deviations. For categorical data, the proportions were compared from MINITAB version 14. P values less than 0.05 ($P < 0.05$) were considered to be statistically significant.

Ethics

Ethical approval was received from the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka (Ref. No. P 12/01/2012).

Written informed consent was obtained from each patient, or their relative (for patients who were unablet to give consent in their index admission), in their own language. The purpose of the trial, the voluntary nature of the consent and the ability of participants to withhold the consent without any effect on their medical care were clearly explained before obtaining consent.

Results

715 patients were studied. 50.3% were females. The mean age of the sample was 57.8 years (SD -14.84 years). There were 253 (35.4%) elderly (65 years of age or above) patients.[11,12] Mean number of medicines per patient was 6.11±2.97. The demographic and the other characteristics of the study sample are shown in Table 1. Out of 715, a total of 112 (15.7%) patients experienced at least one ADR either during their index hospital admission or during the 6-month post-discharge follow-up

period. Altogether, 154 ADRs were detected. Of them, 33 ADRs occurred during index hospital admission and 121 occurred during the 6-month follow-up period. The median ADR per patient was 1.0 [1-2]. Out of 154 ADRs, 73 (47%) were classified as SAEs. Different categories of SAEs observed are shown in Table 2.

More than one medication was responsible for some reported ADRs. A total of 188 medications were responsible for the 154 ADRs. ISMN and insulin caused the greatest proportion of ADRs in the study sample. The most common causes for re-hospitalization due to ADRs were hypoglycemia due to anti-diabetic drugs (17/46), bleeding due to warfarin (14/46) and hypotension due to anti-hypertensives (6/46). The rate of ADR related hospital re-admission was 6.4% (46/715). 51.9% (80/154) of the detected ADRs were potentially avoidable. The offending drug was stopped in only 57.6% (19/33) of the ADRs that occurred during index admission.

Table 1: Demographic and the other characteristics of the study sample

Parameter	Frequency
Gender	
Men	49.7%
Women	50.3%
Age	
<65 years	64.6%
≥65 years	35.4%
Number of medicines	
<5	33.1%
≥5	66.9%
Non-communicable diseases	
Hypertension	48.5%
Diabetes mellitus	45.3%
Ischemic heart disease	29.4%
Chronic respiratory diseases	19.2%
Liver and gastrointestinal diseases	16.4%
Epilepsy	5.2%
Chronic kidney diseases	4.6%
Haematological diseases	4.3%
Stroke	3.5%
Musculoskeletal diseases	3.4%
Autoimmune diseases	2.7%

Factors associated with ADRs

Incidence of ADRs in men and women were 21.1% and 21.9%, respectively ($p = 0.79$). ADRs were more common in elderly than in non-elderly (34% vs 14.7%, $p<0.001$) and in those who were on ≥5 drugs than in those who were on <5 drugs (25.9% vs 12.7%, $p<0.001$). ADRs were more common among those with diabetes than among those without diabetes (28.5% vs 15.6%, $p<0.001$).

Table 2: Percentage of Serious Adverse Events (SAEs)

SAE category	Percentage
Life threatening	17.8% (13/73)
Hospitalization	63% (46/73)
Disability / Incapacity	19.2% (14/73)

Discussion

In this study we observed that about one sixth of the patients who were admitted to the study unit with NCCDs, experienced one or more ADRs during the index hospital admission and the 6-month period following the discharge. Almost half of these ADRs were SAEs. A significant percentage of life threatening ADRs were detected. Furthermore, ADRs caused a significant number of re-hospitalization. All these findings suggest that ADRs add to the morbidity of the patients with NCCDs in the study setting and probably contribute to increased healthcare costs too.

Literature survey found one published study from Sri Lanka describing ADRs, which determined the ADR related hospital admissions in a pediatric population. According to the study 0.16% of hospital admissions were due to ADRs.[13] We cannot compare our results with these findings as the study populations are different and the studied outcomes are also different. However, our findings are compatible with findings of some other studies conducted in the world.[14, 15] A study in United Kingdom (UK) showed that 1 in 5 patients were re- admitted to hospitals over

one year after their index admission due to an ADR[16] which is higher than what we observed. Another study conducted among an elderly population in Australia reported that repeat ADR-related hospitalizations were constantly increased from 1980-2003 and accounted 30.3% of all ADRs by 2003.[17]

Table 3: Example of different categories of Serious Adverse Events (SAEs)

Type of SAE	Case
Life threatening	A 53-year old man was diagnosed with ST elevation myocardial infarction (STEMI) during the index hospital admission. At 7.20 p.m. streptokinase infusion was started. After 40 minutes (at 8.00 p.m.) the patient developed itching and wheezing which was diagnosed as anaphylaxis to streptokinase.
Hospitalization	A 73-year old man was prescribed warfarin 10 mg once daily for dilated cardiomyopathy during his index admission. One month later his international normalized ratio (INR) was 10.8 and he had been admitted to the hospital to manage the condition.
Disability / Incapacity	A 60 year old woman was on five medications causing hypotension (atenolol 25 mg once daily, Isosorbide mononitrate (ISMN) 30 mg twice daily, frusemide 40 mg once daily, carvedilol 3.125 mg twice daily and captopril 12.5 mg three times daily). Her blood pressure was 90/50 mmHg for three consecutive days. Her medication regimen is inappropriate as she was on 2 beta-blockers. This multiple medication regimen caused dizziness which interfered with her daily activities.

More than half of the ADRs detected in our study were avoidable. The majority of ADRs that required re-hospitalization were caused by widely used medications such as anti-diabetic agents, anti-hypertensive agents and warfarin, causing hypoglycaemia, hypotension and bleeding, respectively. Most of these ADRs could have been prevented with optimization of medication management. These findings are consistent with studies from other parts of the world.[16-18]

ADRs were more common among elderly, those with diabetes and those who were receiving ≥ 5 medications. Similar findings have been reported in previous studies from different countries.[19-21] Higher incidence of ADRs among those who were receiving ≥5 medications highlights the importance of avoiding polypharmacy. Inadequate communication between the prescriber and/or pharmacist and the patient, leading to poor patient awareness about medication administration and adverse effects is also a likely cause for the high incidence of ADRs in the study population.

The findings of this study are important to alert the health professionals about the magnitude and the nature of this important health care problem and to stimulate them towards the rational use of medicines. Furthermore, it alerts our health care system to find potential avenues to minimize the occurrence of ADRs. Active participation of clinical pharmacists in medication management of patients has been identified as one such method.[22]

There are some limitation in this study. Firstly, the post-discharge ADR surveillance was done via telephone interviews and the obtained data were based on the self-reported responses by the patients or care givers. An objective assessment would have been more desirable, however the study team had to resort

to this method due to logistic limitations. The other limitation applies to data collection during the index-hospital admission. Even though the ADR surveillance in some patients was based on hospital notes as well as direct patient interviews, in about half of the sample these data are based on hospital notes alone. As inadequate recording is an inherent characteristic of hospital notes [22, 23] the actual figures for ADRs during the index hospital admission may be higher than what we found.

Conclusion

Incidence of ADRs was frequent in this cohort of patients with NCCDs. A large proportion of them were SAEs. The majority of ADRs that required re-hospitalization were caused by widely used medicines and were potentially avoidable. Some factors associated with a higher incidence of ADRs were age ≥65years, ≥5drugs in the prescription and presence of diabetes. Among patients with NCCDs, these special patient groups need more attention to minimize ADRs. Finally, the findings of this study highlight the need for improving rational use of medicines in Sri Lankan hospital setting.

Acknowledgements

We would like to thank South Asian Clinical Toxicology Research Collaboration (Australian NHMRC Grant 630650) for the funding. We also thank Ms. N Mamunuwa and Ms.V Pathiraja for the support given in data collection, Dr. Buddika Wijayawickrama for doing the sample selection, the staff of the University Medical Unit of the study hospital and the patients who participated in the study for their cooperation.

References

1. World Health Organization, Technical Report No 498: International Drug Monitoring, The Role of National Centres. 1972, The Institute Geneva.
2. Walker R and Whittlesea C. Clinical Pharmacy and Therapeutics. 5th ed. 2012.
3. Agency for Healthcare Research and Quality, Reducing and preventing adverse drug events to decrease hospital costs. Research in Action. 2001(1 http://www.ahrq.gov/qual/aderia/aderia.htm.).
4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalised patients: a meta-analysis of prospective studies. JAMA. 1998. 279: p. 1200 - 5.
5. Forster AJ, Clark HD, Menard A et al. Adverse events among medical patients after discharge from hospital. CMAJ. 2004. 170(3): p. 345-9.
6. Forster AJ, Murff HJ, Peterson JF et al. Adverse drug events occurring following hospital discharge. J Gen Intern Med. 2006. 20(4): p. 317-23.
7. Munasinghe TMJ. Adverse drug reactions: monitoring, reporting and prevention. CMJ. 2014. 47(1).
8. nnual Health Bulletin, Medical Statistics Unit. 2013, Ministry of Health, Sri Lanka.
9. World Health Organisation, Noncommunicable diseases. WHO, Geneva, Switzerland, 2015; http://www.who.int/mediacentre/factsheets/fs355/en/ (accessed on 6/6/2016)
10. Chamberlain C. Clinical Analysis of Adverse Drug Reactions. Clinical Center Pharmacy Department National Institutes of Health. 2011.
11. World Health Organisation. Definition of an older or elderly person. WHO, Geneva, Switzerland. 2010. http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html (accessed 6/6/2016).
12. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly". Geriatrics & gerontology international. 2006;6(3):149-158. doi:10.1111/j.1447- 0594.2006.00341.x
13. Lamabadusuriya SP and Githanjall Sathiadas. Adverse drug reactions in children requiring hospital admission. CMJ, 2003. 48: p. 86-7.
14. Lepori V, Perren A, Marone C. Adverse

internal medicine drug effects at hospital admission. Schweiz Med Wochenschr, 1999. 129(24), 915-922.
15. Dormann H, Neubert A, Criegee- Rieck M et al. Readmissions and adverse drug reactions in internal medicine: the economic impact. J Intern Med. 2004. 255: p. 653-63.
16. Davies EC, Green CF, Mottram DR et al. Emergency re-admissions to hospital due to adverse drug reactions within 1 year of the index admission. BJCP. 2010. 70(5): p. 749-55.
17. Zhang M, Holman CD, Preen DB et al. Repeat adverse drug reactions causing hospitalization in older Australians: a population-based longitudinal study 1980-2003. BJCP. 2007. 63(2): p. 163-70.
18. Budnitz DS, Lovegrove MC, Shehab N et al. Emergency Hospitalizations for Adverse Drug Events in Older Americans. N Engl J Med. 2011. 365(21): p. 2002-2012.
19. Field TS, Gurwitz JH, Avorn J. Risk factors for adverse drug events among nursing home residents. Arch Intern Med, 2001. 161: p. 1629– 1634.
20. Hohl CM, Dankoff J, Colacone A et al. Polypharmacy, adverse drug- related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med. 2001. 38: p. 666–671.
21. Camargo AL, Cardoso Ferreira MB, Heineck I. Adverse drug reactions: a cohort study in internal medicine units at a university hospital. Eur J Clin Pharmacol. 2006. 62(2): p. 143-149.
22. Kaboli PJ, Hoth AB, McClimon BJ et al. Clinical pharmacists and inpatient medical care: a systematic review. Arch Intern Med. 2006. 166(9): p. 955–64.
23. Cox JL, Zitner D, Courtney KD et al. Undocumented patient information: an impediment to quality of care. Am J Med. 2003. 114: p. 211–216