Short Communication

Preliminary report: Review of adverse drug reactions (ADRs) reporting in the Malaysian elderly

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ABSTRACT

Elderly has a high risk of ADRs due to multifactorial factors. The occurrence of the ADRs can be patient-related or drug-related such as polypharmacy, impaired organ function and pharmacokinetic changes. This study aimed to review the medications and system organ function associated with ADRs in the Malaysian elderly population. Observational data were collected retrospectively from the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) database from January to December 2015. A total of 6,862 ADRs case were reported in year 2015, and 23% consisted of elderly patient (n=1328) with mean age of 68±7 years. Most of the elderly were Malays (45.5%), followed by Chinese (35.3%) and Indians 11.3%. The drug classes frequently implicated were antihypertensive agents (n=389), followed by anti-infectives (n=195) and lipid-lowering agents (n=147). The most common ADRs reported based on System Organ Class (SOC) were skin and appendages disorders (n=407), followed by body as whole (n=217) and central nervous system (CNS) (n=209). Using the Naranjo's algorithm to determine the causality of event, of the total 1,328 ADRs cases, it was found that 249 were definite, 635 were probable, and 444 were possible. This study showed that cardiovascular drugs and anti-infective agents were the drugs highly associated with the occurrence of ADRs which commonly affected CNS, respiratory and skin disorders. The highest ADRs reported in the Malaysian elderly population were skin appendages and body as whole.

1. INTRODUCTION

An increased number of medications and multiple co-morbidities put the elderly at high risk to develop ADR[1-3]. Medications are also highly used in the elderly populations generally to manage chronic diseases[4]. The medications are specifically indicated to relieve symptoms, to slow disease progression, as well as to improve quality of life. However, the safety of medications used in adult age group cannot be extrapolated towards elderly as age-related changes in pharmacokinetics and pharmacodynamics have significant clinical implication including drug-related problems in elderly population[5-7]. A 2002 meta-analysis showed that the average rate of ADRs is 4-7 times higher

in those patients over 65 years of age compared to younger patient age groups[8]. Early framework in pharmacological therapy in the elderly was developed by Gruppo Italiano Di Farmacovigilanza Nell 'Anziano' known as GIFA since 30 decade ago[9]. According to Carbonin.P, the incidence of ADR consistently increases with the age, until a patient reaches 80 years of age[10].

The prevalence of ADRs in the elderly varies, and documented ranged from 3.3% to 37%[6, 11-14]. Another systematic review reported that the mean prevalence of ADRs in the elderly was 11.0% (95% confidence interval [CI]: 5.1%–16.8%)[12, 15]. In another study, it was reported that about 63% of ADRs can be prevented from either serious or life- threatening event[16]. Study from GIFA group enable the development of the risk score to predict ADR in hospitalized patients[5]. Continuous exploratory ADRs in the elderly group has shown the importance of this issue in healthcare as it is associated with hospitalization, prolonged hospital stay and increased risk of morbidity and mortality. Hence, it is an imperative concern that needs to be explored to enhance and ensure the quality of geriatric care service in country like Malaysia. To date, there is little evidence on the incidence of reported ADRs among the elderly population in Malaysia. Therefore, the aim of this study is to review ADRs cases in the elderly reported to Malaysian Adverse Report Advisory Committee (MADRAC). The primary outcome is to determine the classes of medication that are highly associated with the occurrence of ADRs and the secondary outcome to estimate the risk and related system associated with ADRs in the Malaysian elderly.

2. MATERIALS AND METHODS

2.1. Study design

This cross-sectional study included all ADRs cases reported to MADRAC from January 2015 until December 2015. Data were retrospectively retrieved from the ADRs database at National Pharmaceutical Regulatory Agency (NPRA). Type of ADRs reported was classified into System Organ Class (SOC) according to World Health Organization (WHO) Adverse Reaction Terminology 2012[17]. In this study, medication that triggered ADRs was tabulated according to Anatomical Therapeutic Chemical (ATC) [18] classification system as recommended

by the WHO for drug utilization and SOC[17] were used to classify the ADRs category[19]. Causality assessment was evaluated using the Naranjo Algorithm[20]. All ADRs cases reported to the MADRAC from January 2015 until December 2015 who were 60 year of age and above were included in this study. Study protocol was registered with National Medical Research Registry (NMRR) and approved by the Medical Research and Ethics Committee (MREC) prior to commencement of the study. (NMRR-1662314-31833).

2.2. Statistical analysis

Descriptive findings were presented in percentage and mean ± standard deviation (SD), as accordingly. Logistic regression was used to evaluate the influence of these risk factors on development of ADRs. All statistical analyses were performed using Statistical Package for Social Science (SPSS) Version 21.0. A P value of < 0.05 was considered statistically significant.

3. RESULTS

The total number of reported cases of ADRs in Malaysia obtained from MADRAC for whole year of 2015 was approximately 6,862. Of the total number of reported ADRs, 23.0% of the ADRs cases involved the elderly patients (N=1,570). A number of 1328 elderly patients were included for final analyses. Of all the 1328 patients experiencing ADRs, there was a female predominance of 54.7 % (n=726). The mean age of the patients was 68.3 ± 6.7 years. Most of the study population (45.5%) were Malays (n=604), followed by Chinese (35.3%, n=469) and Indians (11.3%, n=150). In this study, ADRs causality was divided into 4 categories according to Naranjo score. However, only 3 categories were included in this study, namely definite (n=249 cases), probable (n=635 cases) and possible (n=444 cases).

Table 1 shows the most common group of medications that were highly associated with the ADRs based on pharmacological class. The most common classes of medication that were highly associated with the development of ADRs were cardiovascular drugs (n=587) which consist of antihypertensive agent (n=389) and lipid lowering agents (n=147). Among the antihypertensive agent, calcium channel blocker and ACEi were the most related group that caused ADRs with the total of cases 125 and 119,

Table 1. Classes drug causing ADRs.

Type of Medication	n	Implicated medication
Antihypertensive	389	Calcium Channel Blocker (125), ACEi (119), Beta Blocker (48). Other (97)
Anti-infective	196	Penicillin (81), Cephalosporin (35), Anti Tuberculosis (29) and Others (51)
Lipid–lowering agents	147	Simvastatin (113) Lovastatin (14) Atovarstatin (12) and Others (8
Anti-diabetic	120	Metformin(67), Gliclazide (15), Insulin (32) and Others (6)
NSAID	42	Diclofenac (24), Mefenamic acid (11), Cox-2 inhibitor (7) and Others (7)
Immunosuppression	36	Alkylating agent (10), Antimetabolite (7), Taxane derivative (10)
Anti-gout	35	Allopurinol (34) and Colchicine (1)

respectively. Meanwhile, β-lactam group specifically penicillin (n=81) and cephalosporin (n=35) were the majority of the drug among the anti-infective agents associated with the ADRs.

Classification of ADRs based on system organ class and the frequency of ADRs description with the implicated drug is shown in Table 2. The highest numbers of ADRs reported were associated with the skin and appendages disorders which contributed 30.6% (n=407) of total cases, followed by body as whole disorders (n=217, 16%), central nervous system disorders (n=209, 16%) and respiratory & thoracic disorders (153, 14%). ADRs report related to the skin and appendages disorders come from the anti-hypertensive agent used, which is 122 cases. Beside ADRs associated with dry cough (n=114, 75%) event also accompanying with the use of anti-hypertensive agent that contributed about 70 cases.

4. DISCUSSION

This study was a regional study conducted to review and analyzed the ADRs reports among the elderly Malaysian population. The main outcome measure was to determine the type of medication that cause of ADRs. The study showed that the causative drug classes were similar to other studies which reported that cardiovascular agents, antibiotic and anti-diabetic agents were responsible for two-thirds of the ADRs cases[16,21]. This clearly reflected that,

these are medications were highly prescribed and the results correlates with National Health Morbidity Survey (NHMS) report with the high prevalence of non-communicable diseases[22,23]. Among the antihypertensive agent, amlodipine (n=109) was the most common drug to cause ADRs. Majority of reported adverse reactions were edema (n=25) and dizziness (n=17), which fall under mild to moderate categories. Meanwhile, among all ACE-inhibitors (n=117), perindopril (n=108) contributed to more than three quarters of the total group associated with the adverse reaction. The most common reported side effect with the use of ACE-inhibitor was related to the dry cough.

In this study, the identified ADRs of musculoskeletal such as muscle pain and myalgia were highly associated with the use of lipid-lowering agents, specifically the statin group. Most commonly used statin among these agents was simvastatin. This findings reflected the high prevalence of hypercholesterolemia (25.2%) among the elderly[23]. Furthermore lipid-lowering agents also highly use for prevention of cardiovascular heart disease.

Another important result of anti-infective agent was found to be developing risk of skin and appendages disorders, hematologic disorders, and liver disorder. A few studies identified anti-infective agent as being commonly implicated to the same adverse reaction either in young or older adult[24,25]. It has

Table 2. Classifications of ADRs by System Organ Class (SOC)

Classification of ADRs	n	Description of ADRs	Implicated medication
Skin and Appendages disorders	407	Pruritus (19%), urticarial (17%) and itching (16%)	Anti-infective (122), antihypertensive (67) analgesic (43)
Body as whole disorders	217	Edema 57%, fatigue and lethargy (19%) dress syndrome 8%	Antihypertensive (31), lipid-lowerng agents (19), anti-diabetic (7)
CNS	209	Headache (28%), Dizziness (23%), Giddiness (23%)	Antihypertensive(109) lipid-lowerng agents (30), anti-diabetic (14)
Respiratory & thoracic disorders	153	Dry cough (75%) , SOB (13%) dyspnoea (4%)	Antihypertensive (70), lipid-lowering agents(16), anti-diabetic (15)
Gastrointestinal	124	Nausea (22%), Abdominal discomfort (18%), diarrhoea (13%)	Antihypertensive (32), anti-diabetic (24)

also been reported that anti-infective agents are one of the most common drugs highly associated with the ADRs among the elderly[26,27]. Thus presentation of adverse reaction, with close monitoring and special precaution is important especially during periods of acute ill-health stage among the elderly patient.

The use of anti-diabetic agent was found to develop adverse reaction to the CNS disorder such as dizziness and giddiness. It's known as part of hypoglycemic symptom which commonly affected this group of people. Gastrointestinal effect such as nausea, abdominal discomfort and vomiting were frequently reported related to anti-diabetic use. In addition, a few reported cases of insulin associated to the rash and urticarial (n=21). On the other hand, one unexpected case of blurred vision was reported due to metformin. This effect is very rare and difficult to differentiate from the secondary complication of diabetic. However, blurred vision can be explained as an effect to the extraocular muscle paresis and optic neuritis[28].

Almost a quarter (n=317; 23.87%) of the study population were reported to have received polypharmacy and reported to experience ADRs. In this study, polypharmacy is considered a concurrent use of five and more medication at a time as defined by WHO. The maximum number of medication prescribed to the patient detected in this study was 10 medications (n=45). However almost half (n=537; 40.4%) of the cases were with only single prescription. As known, in real life situation, it is quite rare for an elderly patient to be prescribed with a single medication as they were known to have multiple co-morbidity[29]. This is self-voluntary ADRs reporting system by healthcare provider in Malaysia, with some lack of clinical information that may contribute to incomplete data.

5. CONCLUSIONS

Noticeably, cardiovascular and anti-infective agents commonly prescribed in the elderly were highly associated to ADRs reported compared to other class of medications. Prominently antihypertensive agents were highly associated to the risk of CNS disorder and respiratory disorders. Meanwhile the most common ADRs reported based on SOC category were skin and appendages, body as whole and CNS disorders. Further investigations are needed to identify the patient-related risk factors associated to the ADRs in the elderly patients.

REFERENCES

1. Hedna K, Hakkarainen KM, Gyllensten H, Jnsson AK, Petzold M, Hgg S. Potentially inappropriate prescribing and adverse drug reactions in the elderly: a population-based study. Eur J Clin Pharmacol. 2015;71(12):1525-33.
2. Brahma DK, Wahlang JB, Marak MD, Sangma M. Adverse drug reactions in the elderly. J Pharmacol Pharmacother. 2013;4(2):91-4.
3. Dormann H, Sonst A, Müller F. Adverse drug events in older patients admitted as an emergency: the role of potentially inappropriate medication in elderly people (PRISCUS). Dtsch Arztebl Int. 2013;110(13):213-9.
4. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. Br J Clin Pharmacol. 2004;57(2):121-6.
5. Petrovic M, Tangiisuran B, Rajkumar C, Van-Der CT, Onder G. Predicting the risk of adverse drug reactions in older inpatients: external validation of the GerontoNet ADR risk score using the CRIME cohort. Drugs Aging. 2016.
6. Pedros C, Formiga F, Corbella X, Arnau JM. Adverse drug reactions leading to urgent hospital admission in an elderly population: prevalence and main features. Eur J Clin Pharmacol. 2016;72(2):219-26.
7. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - The elderly. Br J Clin Pharmacol. 2015;80(4):796-807.
8. Beijer HJM, De BCJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci. 2002;24(2):46-54.
9. Carosella L, Pahor M, Pedone C, Zuccala G, Manto A, Carbonin P. Pharmacosurveillance in hospitalized patients in Italy: Study design of the "Gruppo Italiano di Farmacovigilanza nell"Anziano' (GIFA). Pharmacol Res. 1999;40(3):287-95.
10. Carbonin P, Pahor M, Bernabei R. Is age an independent risk factor of adverse drug reactions in

hospitalized medical patients? J Am Geriatr Soc. 1991;39:1093-9.

11. Ventura MT, Laddaga R, Cavallera P. Adverse drug reactions as the cause of emergency department admission: focus on the elderly. Immunopharmacol Immunotoxicol. 2010;32(11):426-9.

12. Alhawassi TM, Krass I, Bajorek B V, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging. 2014;9:2079-86.

13. O'Connor MN, Gallagher P, Byrne S, O'Mahony D. Adverse drug reactions in older patients during hospitalisation: are they predictable? Age Ageing. 2012;41(6):771-6.

14. Nair NP, Chalmers L, Connolly M. Prediction of hospitalization due to adverse drug reactions in elderly community-dwelling patients (The PADR-EC score). PLoS One. 2016;11(10):e0165757.

15. Li L, @bullet C, Tangiisuran B. Evaluation of potentially inappropriate medications among older residents of Malaysian nursing homes. Int J Clin Pharm. 2012;34:596-603.

16. Tangiisuran B, Davies JG, Wright JE, Rajkumar C. Adverse Drug Reactions in a Population of Hospitalized Very Elderly Patients. Drugs Aging. 2012;29(8):669-79.

17. World Health Organization. Introductory Guide MedRA version 14.0 :2011 March. Available from: https://www.medra.org/sites/default/files/guidance/file/intguide 2011;(March).

18. World Health WHO Collaborating Centre for Drug Statistics Methodology. [document on the internet.] Guidelines for ATC Classification and DDD Assignment 16th edition [updated december 2012; cited January 2013]. Available from : http://www.whocc.no/filearchive/publications/.

19. Malaysian Adverse Drug Reaction Advisory Committee (MADRAC). Annual report t of the Malaysian Adverse Drug Reactions Advisory . Madrac Committee; 2012.

20. Naranjo CA, Busto U, Sellers EM. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.

21. Trivalle C, Cartier T, Verny C. Identifying and preventing adverse drug events in elderly hospitalised patients: A randomised trial of a program to reduce adverse drug effects. J Nutr Heal Aging. 2010;14(1):57-61.

22. Amal NM, Paramesarvathy R, Tee GH, Gurpreet K, Karuthan C. Prevalence of chronic illness and health seeking behaviour in Malaysian population: results from the third National Health Morbidity Survey (NHMS III) 2006. Med J Malaysia. 2011;66(1):36-41.

23. National Health and Morbidity Survey 2015 (NHMS 2015). Vol. II: Non-Communicable diseases, risk factors & other health problems. Institute for Public Health Vol. II; 2015.

24. Gholami K, Parsa S, Shalviri G, Sharifzadeh M, Assasi N. Anti-infectives-induced adverse drug reactions in hospitalized patients. Pharmacoepidemiol Drug Saf. 2005;14(7):501-6.

25. Thompson JW, Jacobs RF. Adverse Effects of Newer Cephalosporins: an update. Drug Saf. 1993;9(2):132-42.

26. Ahmed B, Nanji K, Mujeeb R, Patel MJ. Effects of polypharmacy on adverse drug reactions among geriatric outpatients at a tertiary care hospital in karachi: a prospective cohort study. PLoS One. 2014;9(11): e112133.

27. Harugeri A, Parthasarathi G, Ramesh M, Guido S, Basavanagowdappa H. Frequency and nature of adverse drug reactions in elderly in-patients of two Indian medical college hospitals. J Postgrad Med. 2011;57(3):189-95.

28. Wren VQ. Ocular and visual side effects clinically relevant toxicology and patient. J Behav Optom. 2000;11(6):149-57.

29. Petrovic, Mirko T, Van DC. Adverse drug reactions in older people: detection and prevention. Drugs Aging. 2012;29(6):453-62.