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Pharmacovigilance of polypharmacy and adverse drug reactions in hospitalized elderly in a university hospital in Manaus, Amazonas

Farmacovigilância de polifarmácia e reações adversas medicamentosas em idosos hospitalizados em hospital universitário de Manaus, Amazonas

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ABSTRACT

Introduction: Polypharmacy – the concomitant use of multiple (usually five or more) prescription drugs - poses exacerbated risks of adverse drug reactions (ADR) for the elderly. **Objective:** The aim of this study was to observe the prevalence of polypharmacy and the incidence of ADR in hospitalized elderly. **Method:** An observational, analytical and prospective study was performed to collect data from the medical prescriptions of selected elderly and from ADR reports. Patients were evaluated for the prevalence of polypharmacy and the incidence of ADR. **Results:** A total of 42 elderly patients were hospitalized from January to June 2018 (66.7% were female and 33.3% were male). The mean age and hospitalization time were, respectively, 73 ± 8 years and 22 ± 14 days. Polypharmacy was detected in 85.0% prescriptions, with an average of 9 medications per patient. The most frequent adverse events were hypotension (18.3%), bleeding (12.2%) and hypoglycemia (10.2%). **Conclusions:** The results reveal a high prevalence of polypharmacy in hospitalized elderly, also related to the significant incidence of ADR in this population. The role of the clinical pharmacist and the institution of drug conciliation are necessary measures to identify prescribing patterns focused on the elderly population and to propose specific strategies for the problem of polypharmacy in the elderly.

KEYWORDS: Elderly; Polypharmacy; Pharmacovigilance; Side Effects; Adverse Drug Reactions

RESUMO

Introdução: A polifarmácia – uso concomitante de cinco ou mais medicamentos – apresenta riscos exacerbados de reações adversas medicamentosas (RAM) no idoso. **Objetivo:** Esse trabalho teve como objetivo observar a ocorrência da polifarmácia e de eventos adversos relacionados a medicamentos em idosos hospitalizados. **Método:** Foi realizado um estudo observacional, analítico e prospectivo, com coleta de dados a partir das prescrições dos idosos selecionados e de notificações de RAM. Os pacientes foram avaliados quanto à prevalência de polifarmácia e à incidência de RAM. **Resultados:** Foram acompanhados 42 idosos internados na enfermaria de clínica médica de janeiro a junho de 2018, sendo 66,7% do gênero feminino e 33,3% do masculino. As médias de idade e de tempo de hospitalização foram, respectivamente, 73 ± 8 anos e 22 ± 14 dias. Foi verificada a presença de polifarmácia em 85,0% das prescrições, com média de nove medicamentos por paciente. Os eventos adversos mais frequentes foram: hipotensão arterial (18,3%), hemorragias (12,2%) e hipoglicemia (10,2%). Os resultados revelam uma alta prevalência de polifarmácia em idosos internados associada também à significativa incidência de RAM nesta população. **Conclusões:** A atuação do farmacêutico clínico e a instituição de conciliação medicamentosa são medidas necessárias para identificar os padrões de prescrições direcionadas à população idosa e propor estratégias específicas para o problema da polifarmácia no idoso.

PALAVRAS-CHAVE: Idoso; Polimedicação; Farmacovigilância; Efeitos Colaterais; Reações Adversas Relacionadas a Medicamentos

INTRODUCTION

In Brazil and worldwide, the epidemiological transition process, characterized by a decrease in morbidity and mortality rates and a consequent increase in life expectancy, has been determining an increase in the prevalence of health problems related to aging and chronic degenerative diseases[1]. According to the Brazilian Institute of Geography and Statistics (IBGE), more than 28 million people are aged 60 and over in Brazil, accounting for about 15% of the current country's population[2].

The increase in the number of senior citizens requires redesigned public health policies, especially those related to medication use, particularly because of the higher demand for health services and regular pharmacological treatment. On the other hand, the emphasis on public health policies that involve the provision of drugs within disease-specific programs exposes the elderly population to risks associated with polypharmacy and potential adverse reactions, which may result in hospitalizations and higher healthcare-related costs[3,4].

There are several definitions of polypharmacy in the literature. However, in studies that included the elderly, the most commonly used criterion is the consumption of five or more drugs concomitantly, a parameter that seems more appropriate for this age group[5,6].

An adverse drug reaction (ADR) is any response to a drug that is harmful, unintentional and occurs at standard (or recommended) dosage normally used in humans for disease prophylaxis, diagnosis, treatment or for the modification of a physiological function[7,8].

In Brazil, about 23.0% of the population consumes 60.0% of the national production of medicines, and in this group are mainly people over 60 years old[9]. The 2006 Health, Welfare and Aging (SABE) study, conducted with 1,115 senior citizens in the city of São Paulo, found that 89.5% of them were taking some medication[6]. In other Brazilian cities, the study found that 69.1% to 85.0% of the senior citizens took more than three prescription drugs, demonstrating the high prevalence of medication consumption in this age group[3].

In comparison with the young, it is estimated that the elderly are seven times more likely to have an ADR and four times more likely to be hospitalized because of an ADR. Furthermore, ADRs may simulate geriatric syndromes or precipitate mental confusion, urinary and fecal incontinence, and falls[3]. Overall, the main risk factors for polypharmacy-related ADRs are interactions, side effects, toxicity, overdose, intolerance, and idiosyncrasy[10,11]. In elderly patients, physiological changes resulting from old age may modify drug distribution, metabolism and excretion, changing the action and concentration at the receptor site, hence justifying the higher probability of ADR in senescence[10,11].

Given the risks that accompany drug use – and polypharmacy, in particular – pharmacovigilance appears as an intervention to "detect, assess and monitor the occurrence of adverse events related to drug use, with the objective of ensuring that the benefits related to their use are greater than the risks they may cause"[8]. According to the World Health Organization (WHO), pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems[8].

In countries like the United States, pharmacovigilance plays a consolidated role in assessing the impact of medication use on the local health system. It is estimated that for every dollar spent on medication, USD 1.33 is spent on treating adverse drug events[11]. In Brazil, data on the use of multiple drugs by the elderly and their consequences for the Unified Health System (SUS) are scarce, especially regarding the prevalence of polypharmacy in populations living outside the big cities of Southern and Southeastern Brazil.

In this context of uncertainty, the present study aimed to identify the prevalence of polypharmacy and the associated incidence of ADRs in an elderly population admitted to a tertiary public university hospital in the city of Manaus, state of Amazonas.

METHOD

An observational, analytical, descriptive, prospective and quantitative study was designed, with collection of primary data from the medical records of hospitalized elderly patients and secondary data from pharmacovigilance reports of the Health and Safety Surveillance Service (SVSSP) of the Getúlio Vargas University Hospital (HUGV).

We included patients aged 60 and older, admitted to the male and female internal medicine units, from January to June 2018. These patients were followed during the hospitalization period for the presence of polypharmacy and ADRs. Exclusion criteria were the presence, at admission, of complications related to the use of drugs, delirium, chronic or acute liver and/or kidney failure.

For data collection regarding medication prescription, a standardized protocol form was filled out for the assessment of each patient included in the research. The form contained the participant's identification information (name, gender, age and medical record number), clinical data (dates of hospitalization and discharge and diagnoses) and relevant information for the research, like number and list of all drugs in use, presence of polypharmacy and description of drug groups.

The categorization of the drugs followed the classification criteria of the Anatomical Therapeutic Chemical (ATC), which distinguishes the drugs according to their performance in the various organ systems: digestive system/metabolism, blood and hematopoietic, cardiovascular system, dermatological drugs, musculoskeletal system, anti-infectious diseases,

antineoplastic/immunomodulatory agents, nervous system, respiratory tract and others[12,13].

The protocol forms were filled out after review of the medical records. Complementary data and data that were missing from the medical records were retrieved from the electronic information system of the hospital (Management Application for University Hospitals – AGHU) and bedside interviews with the patients.

After data collection, the information obtained was stored in Google Forms online database and imported by Microsoft Excel version 2013. For quantitative variables like "age" and "number of prescribed medications", simple statistical calculation was performed and the results were presented according to the format: mean (X) ± standard deviation (SD). For the "length of stay" variable, the median (in days) was calculated.

The criterion for detection of polypharmacy was the use of five or more drugs concurrently during admission or during hospitalization, according to the definition of polypharmacy most commonly used in international studies[5]. In addition to the prevalence of polypharmacy (existing cases at hospital admission and new cases detected after hospitalization) and the incidence of ADRs (new cases during follow-up), we quantified the percentage of use of potentially inappropriate medications (PIMs) for the elderly and the presence of multimorbidity.

The prescribed drugs were characterized as inappropriate or not based on the Beers-Fick criteria, according to their last update in 2015[14,15]. For the diagnosis of multimorbidity, the presence of two or more diseases was considered simultaneously, as per the WHO definition[16].

Participants stated their consent to participate in the study by signing the Informed Consent Form (ICF). The project was submitted to the Research Ethics Committee (CEP) of the Federal University of Amazonas (UFAM) and was approved under the opinion n. 2.275.077, of September 14, 2017.

RESULTS

Fifty-four elderly patients admitted to the internal medicine units of the HUGV were followed from January to June 2018. Of these, 12 patients were withdrawn from the study because they had acute liver and/or kidney failure (three patients), exacerbated chronic liver and/or kidney failure (eight patients), or delirium at admission (one patient), according to the exclusion criteria.

Of the 42 elderly patients eligible for follow-up, 28 (66.7%) were female and 14 (33.3%) male. The mean age of the patients was 73 ± 8 years. The elderly population analyzed had a mean length of stay of 22 ± 14 days, with the median length of stay of 18.5 days. The minimum hospitalization time observed was 6 days and the maximum time was 71 days. Most patients (35.0%) remained hospitalized for 10 to 19 days (Figure 1).

The most common clinical conditions presented by the elderly were systemic hypertension (81.0%), type 2 diabetes mellitus (33.0%), heart failure (23.0%), dementia (19.0%), bleeding disorders (14.0%), falls and/or fractures (12.0%) and arrhythmias (12.0%). Multimorbidity was found in 31 (74.0%) cases followed.

The main complaints reported by patients during hospitalization were dyspnea (40.0%), weight loss (38.0%), hyporexia/anorexia (33.0%), peripheral edema (28.0%), asthenia (24.0%), voiding disorders (24.0%), ascites (21.0%), chest pain (21.0%), constipation (21.0%), cough (16.0%), abdominal pain (14.0%), hemorrhages (14.0%) and paraesthesia (14.0%).

A total of 391 prescription drugs were recorded, with an average of 9 ± 4 medications per patient. All patients were prescribed at least one drug and one patient had a maximum of 19 different drugs prescribed. Most patients (59.5%) received between five and 12 medications during hospitalization.

Figure 2 illustrates the distribution of elderly by number of prescribed drugs.

The presence of polypharmacy was verified in 36 prescriptions analyzed, that is, a prevalence of 85.0% of polypharmacy per semester. It worth highlighting that 26 elderly patients (61.9%) were already exposed to polypharmacy at hospital admission.

Among the prescribed medications, 49 were suspended due to the occurrence of ADRs during hospitalization, which corresponded to an incidence of 12.5% of ADRs in the semester. The most frequently detected adverse events were: hypotension

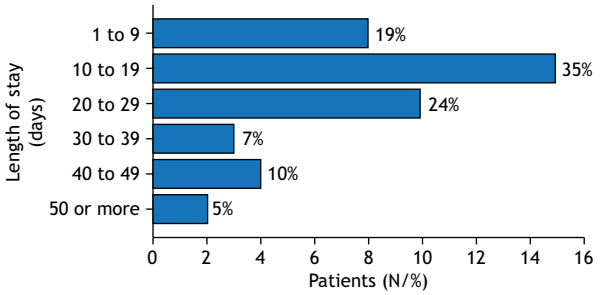

Figure 1. Distribution of hospitalized elderly patients by length of stay (days) at the Getulio Vargas University Hospital, 2018.

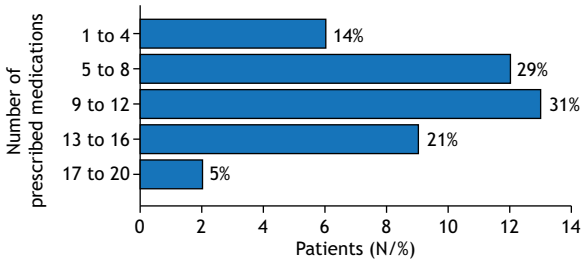

Figure 2. Distribution of hospitalized elderly patients at the Getulio Vargas University Hospital by number of prescribed medications, 2018.

(18.3%), bleeding disorders (12.2%) and episodes of hypoglycemia (10.2%) due to the use of antihypertensive, anticoagulant and oral hypoglycemic agents, respectively. Nevertheless, these adverse events are considered to be expected for such pharmacological groups[3,4,15].

The most prescribed class of drugs, according to the ATC classification, were the medications indicated for the treatment of cardiovascular diseases, with a total of 128 prescriptions (32.0%), followed by those related to the digestive tract and metabolism (Table 1).

In a secondary analysis of the data, 10.0% of the prescribed drugs were potentially inappropriate for the elderly, according to the Beers-Fick criteria, of which the most representative were also cardiovascular drugs (Table 2).

It was observed that the length of hospitalization had a slight trend toward positive correlation with the number of prescribed drugs and, consequently, with the presence of polypharmacy. The mean of potentially inappropriate medications prescribed to the elderly correlated directly with polypharmacy (Figures 3 and 4).

DISCUSSION

The choice of a drug-based therapy for an elderly patient should be careful and consider the metabolic changes resulting from old age. The worldwide trend of prescribing multiple drugs to the elderly is increasing and is associated with several types of adverse events[17,18,19,20].

A recent European study using data from the SHARE Cohort, conducted in 18 countries across the continent, found polypharmacy indices in elderly Europeans ranging from 26.0% in Switzerland to 40.0% in the Czech Republic[21]. Another cohort conducted in Sweden has shown an expected trend toward increasing the percentage of polypharmacy as the Swedish population ages, with rates of 27.0% in 1988, 54.0% in 2001 and 65.0% in 2006[22].

In Brazil, a recent population-based survey in the city of Florianópolis, state of Santa Catarina, found a prevalence of polypharmacy in the elderly of 32.0% (95% CI 29.8-34.3), with a 3.8 mean of drug use in the 30 days before the interviews (ranging from 0 to 28)[17]. The variables associated with polypharmacy were female gender, old age (70 to 79 years, 95% CI 1.15-1.68; 80 years or older, 95% CI 1.22-2.02), negatively self-assessed health, medical appointment in the last 3 months and hospitalization in the last 6 months[17].

Table 1. Classes of drugs prescribed for hospitalized elderly patients at the Getulio Vargas University Hospital, 2018.

Drug class (ATC Classification)	N	%
Cardiovascular system	128	32.7
Digestive tract and metabolism	81	20.7
Blood and hematopoietic organs	67	17.1
Nervous system	54	13.8
Anti-infectives for systemic use	27	6.9
Musculoskeletal system	16	4.1
Genitourinary system	9	2.3
Respiratory system	6	1.6
Sensory organs	3	0.8
Total	391	100.0

ATC: Anatomical Therapeutic Chemical

Table 2. Distribution of potentially inappropriate medications prescribed to the elderly during hospitalization at the Getulio Vargas University Hospital, according to pharmacological group, 2018.

Pharmacological group	Medication	N	%
Cardiovascular system	Furosemide	8	20.5
	Digoxin	4	10.2
	Propranolol	3	7.6
Digestive tract and metabolism	Omprazole	7	17.9
	Mineral oil	3	7.6
	Glibenclamide	2	5.1
	Metoclopramide	2	5.1
	Dexametazone	1	2.5
Blood and hematopoietic organs	Enoxaparin	1	2.5
	Warfarin	1	2.5
Nervous system	Amitriptyline	2	5.1
	Clonazepam	2	5.1
	Haloperidol	2	5.1
	Alprazolam	1	2.5
Total		39	100.0

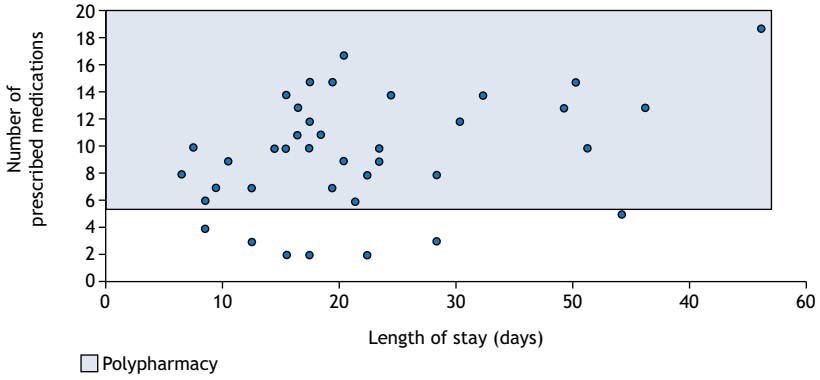

Figure 3. Relationship between length of stay and presence of polypharmacy in the elderly hospitalized at the Getulio Vargas University Hospital, 2018.

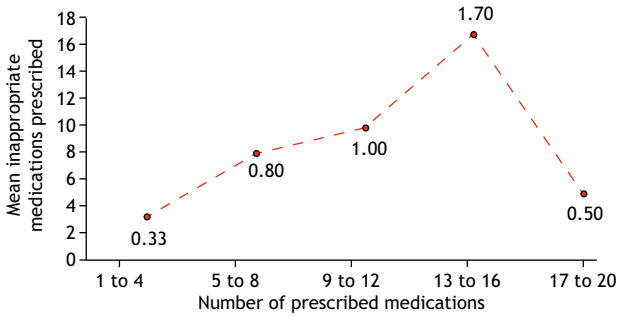

Figure 4. Relationship between the number of prescribed medications/polypharmacy and the mean number of inappropriate medications prescribed to the elderly admitted to the Getulio Vargas University Hospital, 2018.

The relationship between polypharmacy and age and, consequently, the increased risk of ADRs in the elderly is well established and the correlation of ADRs with old age is significant, at least in some clinical conditions[18,23]. The prevalence of ADRs in the elderly in Indian hospitals, for example, ranged from 5.9% to 6.9%[23]. A 2016 integrative review analyzed 47 papers that addressed the topic and demonstrated the frequent occurrence of ADRs in the elderly, although it did not perform a quantitative analysis of the incidence or prevalence of ADRs[24].

In the present study, the high prevalence of polypharmacy found in patients admitted to a tertiary public hospital, that is, 85.0% per semester in 2018, with a mean of 9 ± 4 drugs per patient, is compatible with data from Brazilian and international literature. It is also directly correlated with ADRs and inappropriate drug associations[17,18,19,20,21]. The incidence of 12.5% of ADRs in the semester can be considered equally high.

The predominance of drugs for the cardiovascular system prescribed to the elderly evidenced in this study, whether appropriate or not, possibly reflects the epidemiology of cardiovascular diseases. In addition to having a high prevalence in the general population, these diseases tend to become more frequent as the mean age of the population increases, as is the case of the studied sample of patients[25].

Among the PIMs prescribed to the elderly, there were routine-use drugs, like furosemide and omeprazole. However, in this group of patients, even these drugs should be used with caution, always considering their risk-benefit ratio. Nevertheless, since information on PIMs in the elderly is poorly disseminated, it is likely that prescribers would in fact ignore the harmful potential of these drugs and the prescription of PIMs (or maintenance thereof) was made without proper adjustment or replacement in view of the risk.

Although the research was based on the definition of polypharmacy found in previous publications on polypharmacy in the elderly, that is, concomitant use of five or more drugs, there is no consensus in the literature on the minimum amount of drugs that will determine this diagnosis[5]. Therefore, if broader criteria were considered (two or more drugs, for example), the prevalence of polypharmacy found in this study could be higher and even include almost all subjects of the research.

Furthermore, the profile of the patients observed was characterized by the predominance of multimorbidity, detected in 75.0% of patients, another condition admittedly associated with aging[16]. That is, the complexity of clinical problems and the consequent need for multiple therapies and longer hospitalization may have been determinant for these patients' high vulnerability to polypharmacy, as well as for the incidence of life-threatening ADRs (hypotension and hemorrhages), evidenced in the follow-up.

It is possible that the setting in which the research was conducted (tertiary teaching hospital with pharmacovigilance system in place) determined a selection bias for more severe patients or more complex pathologies, as well as for a higher diagnosis of clinical outcomes. However, it is reasonable to extend these findings to elderly patients hospitalized in general hospitals where, in addition to the risk of polypharmacy and ADRs actually occurring, these conditions may not be detected due to the lack of continuing health surveillance actions.

This evidence underscores the importance of better assessment of drug-based therapies for hospitalized elderly patients, including measures of drug reconciliation between continuous home-use and hospital-use drugs. The establishment of pharmacovigilance of drugs prescribed to hospitalized elderly patients, especially in cases of multiple associations, is fundamental for the design of individualized therapeutic plans and to avoid complications arising from the inappropriate prescription of drugs to this vulnerable population.

CONCLUSIONS

The results of this study have shown a high prevalence of polypharmacy when compared to other Brazilian and international studies, and a significant incidence of ADRs in the elderly admitted to a university hospital in the city of Manaus, Amazonas. Analysis of data on the use of potentially inappropriate medications for the elderly and the presence of multimorbidity also suggests a significant frequency of both.

It is necessary to identify the patterns of prescriptions made for the hospitalized elderly population in order to propose specific strategies to address polypharmacy in the elderly. In this sense, the role of the clinical pharmacist is fundamental to determine the proper drug conciliation and individualized drug dosing regimen, according to the specific pharmacodynamic and pharmacokinetic parameters of this population profile.

The rational use of medications in the elderly should be compulsorily encouraged in the various categories of hospital care, in order to optimize the care provided to elderly patients and reduce adverse events resulting from inadequate drug-based therapies.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.