Research Article

Retrospective evaluation of adverse drug reactions induced by antihypertensive treatment

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ABSTRACT

The use of cardiovascular drugs is related to the development of adverse drug reactions (ADRs) in about 24% of the patients in the Cardiovascular Care Unit. Here, we evaluated the ADRs in patients treated with antihypertensive drugs. The study was conducted in two phases: In the first phase, we performed a retrospective study on clinical records of Clinical Divisions (i.e., Internal Medicine Operative Unit and Geriatric Operative Unit) from January 1, 2012 to December 31, 2012. Moreover from January 1, 2013 to March 30, 2013 we performed a prospective study on the outpatients attending the Emergency Department (ED) of the Pugliese-Ciaccio Hospital of Catanzaro, by conducting patient interviews after their informed consent was obtained. The association between a drug and ADR was evaluated using the Naranjo scale. We recorded 72 ADRs in the Clinical Divisions and six in the ED, and these were more frequent in women. Using the Naranjo score, we showed a probable association in 92% of these reactions and a possible association in 8%. The most vulnerable age group involved in ADRs was that of the elderly patients. In conclusion, our results indicate that antihypertensive drugs may be able to induce the development of ADRs, particularly in elderly women receiving multiple drug treatment. Therefore, it is important to motivate the healthcare providers to understand their role and responsibility in the detection, management, documentation, and reporting of ADRs, as also all the essential activities for optimizing patient safety.

Key words: Adverse events, antihypertensive drugs, pharmacovigilance, prospective study, retrospective study

INTRODUCTION

Hypertension represents the most common disease in the world; up to 50 years of age it is more common in men, whereas, after this age, the incidence of BH is the same for both sexes.[1] Usually, five major classes of antihypertensive agents such as thiazide diuretics, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists and beta-blockers are used.[2]

The use of cardiovascular drugs was related to the development of adverse drug reactions (ADRs) in about 24% of the patients in the Cardiovascular Care Unit.[3] Previously, we reported that both the age of patients and the number of drugs played a role in the development of ADRs or drug — drug interactions (DDIs), with an impairment of the quality of life and an increase in healthcare costs.[4-7] Monitoring of ADRs through pharmacovigilance (PV) is useful to improve the safety of each patient. PV supports public health programs providing reliable

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and balanced information for the effective assessment of the risk-benefit profile of each drug.[8,9] In light of this, the aim of this article is to critically evaluate the ADRs in patients treated with antihypertensive drugs.

MATERIALS AND METHODS

We performed an open, non-comparative, observational study, to report the incidence of ADRs due to antihypertensive medicines, at the Pugliese-Ciaccio Hospital of Catanzaro, Italy. The study protocol was assessed and approved by the Ethics Committee of the same hospital. The study was conducted in two phases: In the first phase, we performed a retrospective study on the clinical records of Clinical Divisions (i.e., the Internal Medicine Operative Unit and the Geriatric Operative Unit) from January 1, 2012 to December 31, 2012. In the second phase, from January 1, 2013 to March 30, 2013, we performed a prospective study on the outpatients who attended the Emergency Department (ED) of the Pugliese-Ciaccio Hospital of Catanzaro, by conducting patient interviews, after their informed consent was obtained and recording the data on an ADR monitoring form, in agreement with our previous studies.[4-7] The information collected included, patient general data (initials, age, sex, height, weight), suspected ADR (brief description of the reaction, onset date vs stop date of occurrence of events, outcome of events, treatment received), suspected medication (name, indication, start date vs stop date, dose, frequency, route of administration), medical history (past vs present), concomitant medications, and any other relevant history, including the pre-existing medical conditions. All hypertensive patients, irrespective of age and sex, and patients treated with at least one antihypertensive agent, were included in the study. Patients not treated with antihypertensive agents, unconscious patients (patients depending on other people for medicine administration), and drug addicts were excluded from the study. All the data were kept confidential in respect of the national laws. The association between drug and ADR was evaluated using the Naranjo scale.[10]

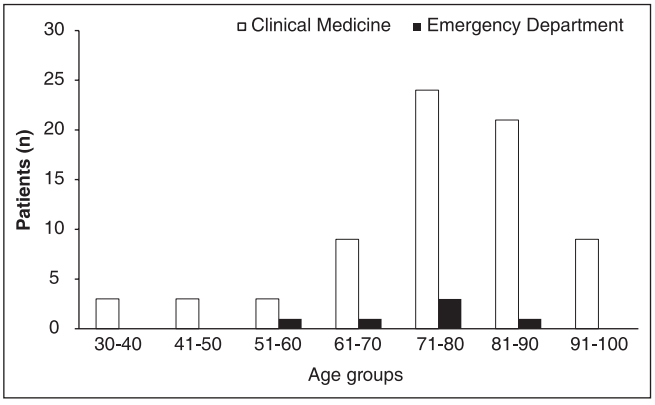

Figure 1: Age distribution of patients developing an adverse drug reaction (n = 78)

RESULTS

During the study period, 3,400 clinical records were evaluated and 15,360 prescriptions were analyzed. Moreover, 10,112 patients were admitted to the ED and 24,268 prescriptions were studied. Our analysis showed that 2,900 patients of the Clinical Divisions (85.3%; 1885 women and 1015 men) and 141 patients of ED (1.4%; 62 women and 79 men) received a treatment with antihypertensive drugs. We recorded 72 ADRs in the Clinical Divisions (2.11%) and six in the ED (0.06%), and these were more frequent in women (68%). Using the Naranjo score, we showed a probable association in 92% of these reactions and a possible association in 8%. The most vulnerable age group involved in ADRs was that of the elderly patients [Figure 1]. Patients with ADRs received a mean of eight drugs compared to those not experiencing ADRs (mean of four drugs). The antihypertensive drugs most frequently involved in ADRs were furosemide (21%) and carvedilol (12.5%) [Table 1], while the most frequently reported ADRs were hypotension (29%) and hyponatremia (12.8%) [Figure 2]. Finally, 21%

Table 1: Antihypertensive drugs involved in the development of adverse drug reactions

Drugs	Number	%
Furosemide	16	20.51282
Carvedilol	10	12.82051
Bisoprolol	6	7.692308
Amlodipine	5	6.410256
Spironolattone	5	6.410256
Enalapril	4	5.128205
Ramipril	4	5.128205
Nicardipine	4	5.128205
Metaprolol	4	5.128205
Torasemide	3	3.846154
Perindopril+Amlodipine	4	5.128205
Losartan+Hydrochlorothiazide	4	5.128205
Telmisartan+Hydrochlorothiazide	3	3.846154
Furosemide+Ramipril	3	3.846154
Ramipril+Bisoprolol+Spironolactone	3	3.846154

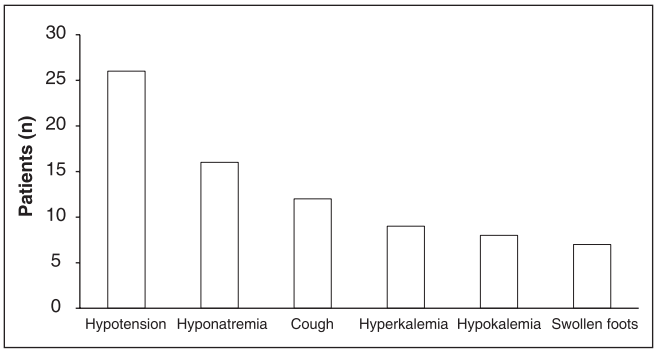

Figure 2: Adverse drug reactions recorded in patients taking antihypertensive drugs

of the ADRs were classified as serious, while in 86% of the patients who developed ADRs, withdrawal of the suspected drug led to a full resolution.

DISCUSSION

In the present study, we have documented that antihypertensive drugs are able to induce the development of ADRs in about 3% of the treated patients. The previous article has documented that ADRs, during the treatment with cardiovascular drugs, are particularly more frequent in women.[3] In the present article, we have documented a higher percentage of women experiencing ADRs in comparison to men (49 vs. 23), but this is related to the higher number of women enrolled in this observation (1947 women vs. 1094 men). Therefore, considering the incidences of ADRs we have recorded, there is no significant difference between the two groups.

In agreement with the previous studies,[4-7,11] we have detected the highest percentage of ADRs in patients >61 years, who have also been receiving multiple therapies. This high percentage is probably underestimated, because in older adults it may be difficult to recognize an ADR, as it can mimic some features of their age-related disease.[12] Therefore, in elderly patients multiple therapies need to be discouraged, as these enhance the probability of ADRs, due to drug—drug interactions. Usually drug treatment in hospitalized patients involves ACE inhibitors or angiotensin receptor antagonists, although patients with mild-to-moderate hypertension and no renal impairment respond well to lower doses of diuretics.[13] In particular, loop diuretics are usually indicated in patients with renal failure, resistant hypertension or heart failure, although their use may be related to the development of ADRs (e.g., hypotension and hypokalemia). In agreement with the previous literature,[14] we have observed that furosemide is most frequently involved in ADRs and its use is related to the development of hypotension and hypokalemia. Many of these ADRs result from either primary or secondary pharmacological action. Therefore, during treatment with furosemide, regular monitoring of the serum levels of sodium, potassium, and creatinine is suggested, particularly in patients with high risk for electrolyte imbalance or in the presence of liquid loss (i.e., vomiting, diarrhea, or heavy sweating). Previous observational studies have documented that furosemide is able to induce and increase mortality[15] particularly when the daily dose is 50 mg.[16] In our study, we have not found any significant increase in mortality after furosemide treatment, probably because furosemide was administered at a lower dosage (25 mg), every two or three days. Higher dosages of furosemide (1-3 g daily) may be associated with ototoxicity,[17,18] although we have failed to describe it. However, this effect may be related to other factors, such as, patient characteristics, co-prescribed drugs, and genetic variability.

Drug—drug interactions (DDIs) represent a common problem during drug administration.[19-21] In particular it has been reported that the inhibition of the organic anion uptake (hOAT1, hOAT2, hOAT3, and hOAT4) may be related to the development of ADRs.[4,22] In our study we have not recorded the development of any ADRs related to DDIs.

The current recommendations reflect the findings from hypertension trials on patients with myocardial infarction and congestive heart failure, who reported better cardiovascular outcomes in patients receiving these drugs, including a lower risk of death. It is widely assumed that beta-blockers also prevent first episodes of cardiovascular events.[23] Carvedilol is a nonselective beta-blocker with vasodilatory effects that are thought to be due to its ability to concurrently block both alpha- and beta-receptors.[24] In our study, we have documented that carvedilol induced ADRs in nine patients, commonly bradycardia. The Naranjo score indicated a probable relationship between antihypertensive drugs and ADRs in 92% of the patients, although due to the Ethics Agreement, we were unable to perform a re-challenge. It is important to underline that this study has several limitations. One important limitation, in particular, is represented by the under-reporting of suspected ADRs, as previously reported.[25,26] Another limitation is represented by the type of study. In fact during a retrospective study, data are recorded from the clinical records, therefore, information concerning the characteristics of each patient is not well-described. In this context it is not possible to perform a statistical analysis, considering the role of comorbidity or genetics in the development of ADRs. In conclusion, our results indicate that antihypertensive drugs may be able to induce the development of ADRs, particularly in the elderly. Therefore, it is important to motivate the healthcare providers to understand their role and responsibility in the detection, management, documentation, and reporting of ADRs, as also all the essential activities for optimizing patient safety.

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