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Adverse drug reactions at a university hospital in Brazil

Reações adversas a medicamentos em um hospital universitário no Brasil

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Abstract
The aim of this study is to characterize the patients and the ADR notified to a Pharmacovigilance Center at a university hospital in Brazil. The ADR rate in hospitalized patients is 10% to 20% and the frequency of hospitalization due to ADR is 0,5% to 6,5%. The ADRs contribute to the increase of length in hospitalization and costs. Patient's exposures have an increase in the rate of mortality, although about 60% to 80% could be prevented. A descriptive study carried at a university hospital in Northeast of Brazil, where all the spontaneous notifications were analyzed during two years. For the process of notification of ADR suspicions, WHO definition was used. After receiving the notification, ADR suspicions were analyzed and the causality assessment was done by CFV staff members, using three different algorithms, and classified according to severity and type. Seventy eight ADR suspicions were spontaneously notified. The female gender represented 55% of cases. Black and mulatto races represented 70%. The most frequent organ and system affected was the skin. Medicines most frequently involved in ADR were anti-infectious agents followed by anti-parasitic agents. The causality assessment shows that the frequency of certain and probable ADRs were around 55%. ADRs severity was moderate in 41%, although more than 60% of all ADRs could be prevented. ADRs are a major problem and measures must be adopted to minimize them.
Keywords: Pharmacovigilance – Adverse drug reactions – Medicines – Side effects.

Resumo
O objetivo deste trabalho foi caracterizar os pacientes e as reações adversas a medicamentos (RAMs) notificadas ao Centro de Farmacovigilância de um hospital universitário no Brasil. Sabe-se que a taxa de RAM em pacientes hospitalizados é de 10% a 20% e que a frequência de hospitalização por RAM é de 0,5% a 6,5%. As RAMs contribuem para o aumento do tempo de internação e dos custos em saúde. Os pacientes expostos às RAMs têm uma taxa de mortalidade aumentada, embora cerca de 60% a 80% sejam passíveis de prevenir. Um estudo descritivo foi conduzido em um hospital universitário do Nordeste do Brasil, onde todas as notificações espontâneas foram analisadas durante um período de dois anos. Para o processo de notificação das suspeitas de RAM, foi utilizada a definição de reação da OMS. Após o recebimento das notificações, as relações de causalidade das suspeitas de RAM, foram analisadas pelos membros do CFV, com o uso de três algoritmos diferentes, e também classificadas de acordo com a gravidade e tipo. Setenta e oito suspeitas de RAM foram notificadas espontaneamente. O gênero feminino representou 55% dos casos. A raça mulata e a negra representaram 70%. O órgão e sistema mais frequentemente afetado foi a pele, tendo os anti-infecciosos e antiparasitários como principais desencadeadores. Na análise da relação causal, as reações certas e prováveis representaram cerca de 55%. As RAMs foram moderadas em 41% dos casos, embora mais de 60% fossem passíveis de prevenir, portanto evitáveis. As RAMs são um grande problema, e medidas devem ser adotadas para minimizá-las.
Palavras-chave: *Farmacovigilância – Reações adversas – Medicamentos – Efeitos dversos.*

INTRODUCTION

The adverse reactions to drugs (ADRs) are commons health problems that affect the population. Studies indicate that the ADR rate in hospitalized patients ranges from 10 to 20% [1,2]. It is also estimated that the frequency of hospital admissions caused by ADRs ranges from 0.5% to 6,5%[1,3,4]. The patients exposed to ADRs have an increased mortality rate, varying from 0.01 to 0.1 %[1]. In 1998, Lazarou, Pomeranz and Corey carried out a meta-analysis, where the severe and fatal adverse reactions were the fourth cause of mortality in the United States, losing out only to ischaemic heart diseases, cancers and stroke[5]. The adverse reactions also contribute to the increase in length of hospitalization and account for 5.5% to 9% of health care costs [6,7,8], although nearly 60% to 80% are considered preventable, therefore avoidable [1,6].

The lack of knowledge of the morbidity and mortality profile related to ADRs and the patients exposed to these reactions in Brazil and at the hospital studied justify studies that can contribute to preventive actions in Pharmacovigilance. The aim of this study was to characterize patients and ADRs notified spontaneously to the Pharmacovigilance Center (CFV) of a University Hospital.

MATERIAL AND METHODS

A descriptive study of all spontaneously notified ADRs, in a public University Hospital of the city of Salvador, Bahia, in the northeast of Brazil was conducted between 2005 and 2006. This hospital, with 389 beds, consisting of a hospital unit, an ambulatory center and

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a pediatric center attending several medical specialties. Since 2001, CFV is directly subordinated to the Hospital Risk Management and linked to the National Health Surveillance Agency (ANVISA), through the Sentinel Hospitals Project. The staff consists of a coordinating physician, a vice-coordinating and teaching pharmacist, two pharmacists and a trainee. CFV also relies on consulting members for specific issues of medical specialties.

Data collection

This study included inpatients and outpatients attended at the Hospital, that presented a suspicious ADR and that has been notified spontaneously to CFV. Daily revisions of medical prescriptions were carried out in an attempt to identify trails of ADRs, thus helping maintaining the flow of notifications. The ADR WHO definition was used for the notification process and the securing of adverse reaction suspicions: "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[9]

Following receipt of the suspected ADR, the causality assessment was carried out. The patients were categorized as having an adverse reaction when the causes of the reaction would be consistent with the profile of adverse effect known for that medicine, through searches in databases (MEDLINE® and LILACS), in the existence of plausible temporal relationship with the beginning of the treatment, following appropriate research and when other causes could be excluded, and if after suspension or decrease of the dosage of the suspected medicine an improvement or disappearance of the reaction occurs.

In the weekly clinical sessions, all the causality assessment process was analyzed by CFV's staff, with a subsequent on-line forwarding of ADRs to ANVISA.

Description of variables

All the reactions were characterized in accordance with the variables contained in the ADR suspicion notification card (yellow card), which was the instrument used for data collection, as well as those found in the review of literature with reference to the patient, medicine and ADR.

The variables related to patients were gender, age and race. The international terminology of the World Health Organization - *WHO –ART*[10] - was used for the description of organs and affected systems by ADRs, and the causing medicines were classified in accordance with the Anatomical-Therapeutic-Chemical Classification Index (ATC)[11] in this analysis.

The causality assessment of ADRs was established by the algorithms of Naranjo, Busto e Sellers [12], WHO [13] and European Union[13]. The severity was established according to Pearson[14] criteria, and, finally, ADRs were classified in accordance with the type as per Rawlins and Thompson[15] criteria.

Data was reviewed and launched in a database built in the SPSS ® for Windows ® PC version 10.0 software[16], with a descriptive analysis of simple frequency to determine every event being carried out.

Ethical aspect

The study was approved by the Research Ethics Committee of the Federal University of Bahia. Possible conflicts of interest: there are none.

RESULTS

Seventy eight yellow cards were sent spontaneously to CFV, corresponding to 122 reactions. The frequency of patients with one ADR was nearly 72% (56/78) and two ADR corresponding 15% (12/78). The average age was 40.89 ± 21.81 years, and the median 44. Table 1 describes the general characteristics of the patients.

In accordance with the origin of the notification, cases were classified as out-patients cases 45.9% (56/122) and in-patients cases 54.1% (66/122). In in-patients cases, 65.2% (43/66) were Medical Clinical, 25.8% (17/66) Pediatric, 7.5% (5/66) Intensive Care and 1.5% (1/66) Surgical Clinical.

The average total number of prescribed drugs was 4.02 ± 2.18, being the average medicines of concomitant use as 2.56 ± 2.12. In 73% (89/122) of the cases, only one medicine was suspected to have triggered the reaction. Patients with 3 or more prescribed drugs were the ones that more developed reactions. Table 2 describes the frequency of affected organs systems and the therapeutic classes involved in each reaction.

The 122 cases had their causality relation evaluated and results of this evaluation are shown in Table 3.

The treatment of ADRs was stratified on 03 groups: suspension of the medicine suspect and introduction of treatment for reaction in 55.7% (68/122), only suspension of the medicine suspicion 32.8% (40/122) and the reaction untreated amounted to 11.5% (14/122).

ADRs were classified into mild, moderate, severe and lethal in 33.6% (41/122), 41% (50/122), 23.8% (29/122) and 1.6% (2/122), respectively, according to the severity.

According to Type, 66.4% (81/122) of the ADRs were classified as A and 33.6% (41/122) as B.

The severity of adverse reactions and rate of mortality appear in Table 4.

The health professionals responsible for the spontaneous notification were the physicians with 56,6% (69/122), pharmacists with 41% (50/122) and nurses with 2,5% (3/122).

DISCUSSION AND CONCLUSION

In this work, the majority of the population studied was concentrated in the intermediary age range of 20-59 years, similar to the data found in the study led by Pearson and collaborators [14], where 58% of the cases

Table 1. General characteristics of patients observed during the period January 2005 to December 2006.

Variable	n/N - (%)
Gender	
Female	67/122 (54,9)
Age Range	
Up to 19 years	22/122 (18)
20 to 39 years	34/122 (27,0)
40 to 59 years	42/122 (34,4)
+60 years	24/122 (19,7)
Race	
White	26/122 (21,3)
Mulatto	44/122 (36,1)
Black	41/122 (33,6)
Other	11/122 (9)

Table 2. Frequency of the affected organs and systems and therapeutic classes involved in the reactions observed during the period January 2005 to December 2006.

Affected Organs and Systems	n/N (%)	Therapeutic Classes (n)
Skin and Related	36/122 (29,5)	Antibiotic (18), antiretroviral (9) antiparasitic (3), corticosteroid (2), antituberculostatic (2), antineoplastic (2)
Central and Peripheral Nervous System	25/122 (20,5)	Antiretroviral (12), anticholinesterases (4) antibiotic (3), antipsychotic (3), anticoagulant (1), dopaminergic agonist (1) and antituberculostatic (1)
Liver and Gallbladder	10/122 (8,2)	Antituberculostatic (5), antiparasitic (3), antifungic (1) and nutritional complex (1)
General State	9/122 (7,4)	Antiretroviral (3), antiparasitic(3), analgesic (1), analgesic opioid (1) and antihypertensive (1)
Respiratory System	8/122 (6,6)	Antibiotic (2), antineoplastic (2), antiretroviral (2), antiparasitic (1) and corticosteroid (1)
Gastrointestinal Tract	7/122 (5,7)	Antiretroviral (3), antituberculostatic (2), antiparasitic (1) and anticholinesterases (1)
Skeletal Musculature	6/122 (4,9)	Antiretroviral (3), antibiotic(1), antihyperlipemiant (1) and antineoplastic(1)
Metabolism and Nutrition	6/122 (4,9)	Antiretroviral(3), antiparasitic (2) and corticosteroid (1)
Autonomous Nervous System	4/122 (3,3)	Antiretroviral(4)
Urinary System	4/122 (3,3)	Antiparasitic (3) and antineoplastic (1)
Blood Cells	2/122 (1,6)	Antiretroviral (1) and antineoplastic (1)
Oropharynx	2/122 (1,6)	Antiretroviral(1) and corticosteroid (1)
Cardiovascular	2/122 (1,6)	Antibiotic (1) and cardiac glycoside (1)
Psychiatric	1/122 (0,8)	Corticosteroid (1)

were in the 20-64 years age range. The average age found was 40.9 years, in which the age ranges corresponding to the ages extremes (up to 19 years and above 60 years) resulted in 37.7% of the cases being considered as risk factor for the development of ADR, as per literature data. In the study carried out by Bordet and collaborators [7], there was an increase of 1.5% in the rate of reactions proportional to age for young patients and up to 60 years, and of 2.9% in patients with 60 years or more. Pirmohamed and collaborators [1], in a study of review on adverse reactions to drugs found in the elderly patients a tendency to develop ADR. Davies and collaborators [2], conducted a study where the average age of the group of patients with a reaction was higher than the average of the group of patients without a reaction. It is worth pointing out that the life expectancy of the Brazilian population is relatively low, which would possibly explain the low frequency detected in elderly

Table 3. ADRs causality frequency according to WHO, Naranjo and European Union algorithms during the period January 2005 to December 2006.

Variable	n/N (%)
WHO Algorithm	
Certain	49/122 (40,2)
Probable	22/122 (18)
Possible	40/122 (32,8)
Improbable	9/122 (7,4)
Conditional	2/122 (1,6)
Naranjo Algorithm	
Defined	13/122(10,7)
Probable	55/122(45,1)
Possible	41/122(33,6)
Doubtful	13/122(10,7)
European Union Algorithm	
A	69/122(56,6)
B	43/122(35,2)
O	10/122(8,2)

Table 4. Severity frequency and rate mortality, observed during the period January 2005 to December 2006.

Variable	n/N - (%)
Severity	
Light	41/122 (33,6)
Moderate	50/122 (41)
Severe	29/122 (23,8)
Lethal	2/122 (1,6)
Life Risk	
Yes	21/122 (17,2)
No	101/122 (82,8)
Death	
Yes	4/122 (3,3)
No	118/122 (96,7)
Adjusted	4/21(19)

patients, as observed in the stratification of the age ranges.

The female gender was the most affected by ADRs. The largest frequency of adverse reactions in the female population is known and has been described in various works[2,3,17]. Wiffen and collaborators [8], in a systematic review, stated that the female gender was a risk factor for development of ADR. In accordance with Edwards, 1997, cited by Magalhães and Carvalho [18], women are more susceptible to the adverse reactions possibly by an association of factors such as obstetric complications, episodes of dysmenorrhea that require the use of drugs, of contraceptives and a greater concentration of adiposic tissue. It is also possible to have a hormonal determinant that can affect the metabolism, predisposing to the appearance of ADR.

The races more frequently involved were mulatto and black, explained by the predominance of these races in the composition of the Bahian population, according to IBGE, 2004.

With regard to the organs and systems more frequently involved, our results are consistent with those already described by other authors [6,7,8,17] .The reactions that affected the skin, the nervous system, the liver and gallbladder, the general state, the respiratory system and the gastrointestinal tract were the most observed events. This is also true for the medicamental classes more commonly involved in the reactions, the antiretrovirals and antibiotics being the principal triggering agents of ADR, as reported in the literature. [15,17]

Previous studies have estimated that 60 to 80% of reactions can be avoided[1,2,3,6,8,17]. These data are similar to the ones found in the present study, since type A reactions arrived at 66.4% and could have been avoided. This should generate an alert and a promotion of the rational use of drugs, early detection and prevention of ADRs.

The moderate ADRs were the most frequent, as already described in other studies [15]. The severe reactions had a noticeable expression, in which the great majority of these (83%) could have been avoided.

With regard to life risk, 82.8% of the cases did not have a life-threatening reaction for the patient, in which this information was based on the evaluation of the reporting professional. This frequency was proven by the analysis of the severity of reactions, since the vast majority was of a moderate nature.

The mortality rate was 3.3% (4/122) and the rate for patients who had adjusted risk of life was 19% (4/21), were 2 cases were due to complications of the base disease and two had an adverse reaction as cause of death that could have been avoided since it was preventable.

The reaction suspicions were stratified according to the origin of the notification in the ambulatory center and hospital. In the hospital, the notifications of the medical clinic infirmaries had a greater representation due to their care of many acute and chronic cases that require a greater use of drugs, predisposing the appearance of ADR.

With regard to the large number of prescribed drugs (maximum of 13), it is worth emphasizing that these drugs are not always administered, due to the practice of medical prescription practice known as "if necessary" where drugs are only administered when the patients show the symptoms, mainly in the cases of pain, fever, nausea and vomiting. As already addressed in other studies [1,8], the greater number of drugs in use increases the probability of appearance of ADR. In this study, patients using 3 drugs or more had a greater number of notified reactions.

The frequency of certain and probable ADRs, around 55%, surpassed those described in the metanalysis of Lazarou, Pomeranz and Corey [5] of 15.1%. This can be possibly explained by the use of different methodologies in the detection of adverse reactions, as well as various methods used for the evaluation of the causality relation in the studies selected for the metanalysis. Lower frequencies of 6.7% were also described by Wiffen and collaborators[8], and this finding can be explained by the inclusion of only severe reactions in the data analysis of this systematic review, whereas in our study all the severities were included in the analysis.

In accordance with Table 4, WHO and European Union's algorithms followed a line of results that can be confronted, however, a divergence is noted when both are compared to Naranjo's algorithm. The vast majority of the same reactions classified as certain by WHO or the European Union were classified as probable when evaluated with Naranjo's algorithm.

A possible explanation for the divergence in the results of the algorithms can be the fact that Naranjo's algorithm is objective, consisting of questions and answers that generate a final score. Probably due to a local limitation, its ten questions cannot be answered to confirm a reaction that is classified as certain. Macedo and collaborators[19] evaluated the agreement between algorithms and a panel of specialists using WHO's algorithm for the evaluation of causality of the same cases of ADR. The authors concluded that in all the evaluation levels there was no agreement among the algorithms and WHO's method. The confounding variables had a positive association with the low levels of agreement among the algorithms and WHO's method, which compromised the sensitivity and specificity of the algorithms.

As for the reporting professionals, physicians were the most frequent, followed by pharmacists and nurses. Conversely, in the study of Bordet and collaborators [7], the nursing professionals and the physicians were the only notifying professionals. The high frequency of physicians can be explained by the incentive they received to report the suspicion of ADR. In the cases of ambulatory origin, where drug dispensing in healthcare programs occurs, pharmacists were the main notifying agents.

In conclusion, ADRs are a public health problem. Data of this study reinforce the importance of Pharmacovigilance programs in the early detection and monitoring of risk factors for the reduction of the number, severity and costs of adverse reactions to drugs. The establishment of a profile for both patients and drugs more frequently involved in the reactions will give a greater consistency in the preventive measures that are so necessary and targeted by the pharmacovigilance programs.

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