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IDENTIFICATION OF ADVERSE DRUG REACTIONS (ADR) FOR MEDICATION CONCILIATION IN A TEACHING HOSPITAL

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ABSTRACT
Currently, Adverse Drug Rreactions (ADR/RAM) are a major problem in hospitals, causing serious health risks for patients and increasing costs of health care. In this context, this study aimed to analyze the main adverse drug reactions found in medical clinic sector a teaching hospital in Campos dos Goytacazes – RJ. We conducted a prospective study between the months from March to June 2015. A total of 194 patients were followed, adverse reactions were observed in 37 patients, involving 40 adverse reactions distributed in 27 active ingredients. The major drugs were involved in the ADR (12.5%) of losartan, 4 (10%) of dipyrone and 3 (7.5%) tramadol. The reactions of most patients were in males with 63%. As for the causality, 12 ADR (30%) were classified as definite, 19 (47.5%) probable and 9 (22.5%) possible, by the logotype of Naranjo. Thirty-five ADRs (87%) were defined as the type A (predictable) and only 5 (12.5%) type B reactions. The Pharmacovigilance Committee of the Hospital was reported to make notifications to ANVISA. The medication reconciliation process contributed to the identification of RAM, allowing the professional pharmacist for more effective action by the multidisciplinary health team in regard to undesirable reactions caused by drugs enabling the prevention of related harm to drug therapy and targeted actions to patient safety.

Keywords: Adverse reaction. Medication. Conciliation..

INTRODUCTION

According to the World Health Organization (WHO), the Adverse Drug Reactions (ADRs) are defined as "any harmful and unintended event that occurs in the presence of drug use at doses normally used in humans for therapeutic purposes, prophylactic or diagnostic " (1). So we do not include between the RAM overdoses (accidental or intentional) and the ineffectiveness of the drug for the proposed treatment[1].

Adverse drug reactions are a major problem in hospitals, causing serious health risks to patients and increasing costs of health care. These reactions vary from those considered mild, severe life-threatening and death[2:12]. Although they involve all age groups, the risk for the occurrence of ADR and hospitalizations resulting from them are higher in the elderly people than in younger ones, primarily through the use of various medications[3].

In the UK, it is estimated that seven to every 800 hospital beds are occupied by patients admitted with suspected ADR. There are reports of situations in which more than one ADR affected 15% of hospitalized patients by prolonging the stay in hospital environment (4).

In Brazil, the ADRs are of several cases of hospitalization, increase the time and costs of treating patients in all age groups[11].

Among the actions for the safety of medication use and patient, there is the process of Medication Reconciliation (MR/CM). The CM may possible that the treatment received by the patient go through a review process before and after transitions in care, from admission step to the hospital during the changes in inpatient units (wards) or prescription, or after

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discharge[5].

In this context, it is noteworthy that the CM also has a great potential for collaboration with the pharmacovigilance activities in the hospital environment, contributing to the identification, assessment, understanding and prevention of adverse drug events. In addition, the CM also allows greater integration of the pharmacist with a multidisciplinary team of physicians, nurses, nutritionists and other professionals, increasing actions for patient safety[5].

In Brazil, there is still a lack of studies involving both the CM as the identification of ADR, as well as the pharmaceutical professional interaction results in a multidisciplinary health team seeking the safety of pharmacotherapy. In this context, this paper analyzes the adverse drug reactions identified through drug reconciliation in a teaching hospital.

METHODOLOGY

This is a prospective longitudinal study involving patients treated in a nonprofit teaching hospital, located in the northern state of Rio de Janeiro. The survey was conducted in a clinical institution, the Medical Clinic sector, which has 10 wards and 32 beds.

Data collection occurred from March to June 2015, through interviews and hospital records by members of Hospital Pharmacists team, after prior training.

The inclusion criterion adopted was that the patient must be older than 18 years-old, and excluded those with any cognitive impairment.

Periodic visits were made to the bed of all patients in the internal medicine section during the study period. Data were recorded by an Evaluation Form and Form Monitoring during Hospitalization. These forms contained socio-demographic data, clinical report, pharmacotherapy in use before and during hospitalization, as well as those recommended in the hospital. On the first visit we presented the objectives and working methods, and asked to sign the Informed Consent and Informed.

After the first visit and accepted for participation, patients were followed every two days throughout the hospital stay. Additional data, such as test results, were obtained from medical records. When a ADR was identified, the multidisciplinary team was communicated to discuss the case.

The classification of drugs was carried out from the ATC (Anatomical Therapeutic Chemical), proposed by the WHO. The ATC is one of the classifications most used in the world for pharmaceuticals according to their therapeutic. In the case of ADR, the classification is made from different criteria. For classification as causation we used Naranjo algorithm, because it is a simple, practical, validated and high rate of reliability and reproducibility.

The algorithm consists of ten questions like "yes and no questions", and for each question are awarded partial points whose sum, at the end of the investigative process, allows the classification of adverse reactions as to its causality[1.6].

The ADRs were also classified as Type of reactions A (predictable) and Type of reactions B (unpredictable), as proposed by Rawlins and Thompson[7]. The type reactions include, for example, cytotoxicity, drug interactions and specific characteristics of the pharmaceutical form employed. They can be reversed by adjustment or replacement doses of the drug. The reactions of the type B correspond to hypersensitivity reactions, idiosyncrasy and intolerance reactions resulting from changes in the pharmaceutical formulation (decomposition excipients and active substance[7,8].

The data were tabulated and analyzed in Microsoft Excel software and the results presented in tables.

This study followed the ethical and legal aspects related to research involving human subjects, as recommended by Resolution no. 196/2012 and Resolution 466/2012 of the National Health Council. The project was approved by the Research Ethics Committee (CEP), with registration number 41627014.7.0000.5244.

RESULTS AND DISCUSSION

From March to June, 2015, 197 forms have been completed, but only 194 records were analyzed, whereas two patients were under 18 years-old and one refused to participate. From the analysis, we observed adverse reactions in 37 (19%), a total of 40 adverse drug reactions (Table 1). According to a study in a university hospital in Maringá - PR, between the years 1996 and 2000, the annual percentage of suspected adverse drug reactions ranged from

12% to 24.7%[6], which is in line with the profile observed in this study.

Table 1. Medications, medication classes, ADR observed, classification as causation and predictability, N=40, Campos dos Goytacazes, 2015

DCB Medication (ATC Code)	Class	ADR			
		Nº of occurrences (%)	Adverse Reacion (each case)	Casuality Analysis (each case)	Classification type A or B (each case)
Losartana (C09DB06)	Antagonist of Angiotensin II receptor	5 (12,5)	1) headache, dizziness and nauseas	1) possible	1) A
			2) dry cough	2) defined	2) A
			3) dry cough	3) defined	3) A
			4) dry cough	4) defined	4) A
			5) dry cough	5) defined	5) A
Dipirona (N02BB02)	Pirazolona	4 (10)	1) Bitter taste	1) probable	1) A
			2) hipotension	2) defined	2) A
			3) reaction of hipersensibility	3) defined	3) B
			4) reation of hipersensibility	4) defined	4) B
Tramadol (N02AX52)	Analgesic opioid	3 (7,5)	1) Constipation	1) probable	1) A
			2) dizziness	2) probable	2) A
			3) nauseas	3) probable	3) A
Alprazolan (N05BA12)	Benzodiazepínico	2 (5)	1) somnolence	1) probable	1) A
			2) cough and withdrawal abstinence	2) probable	2) A
Captopril (C09BA01)	Enzyme Inhibitor Angiotensin Converting	2 (5)	1) dificul-ty in swallowing and dry cough	1) probable	1) A
			2) dry cough and hawking	2) probable	2) A
Polimixina b (J01XB02)	Antimicrobial	2 (5)	1) breathlessness	1) possible	1) A
			2) numbness on face	2) defined	2) B
Glibenclamida (A10BB01)	Sulfoniluréia	2 (5)	1) diahrrea	1) possible	1) A
			2) dizziness and malaise	2) probable	2) A

The average age of patients affected by ADR was 62 years-old. This aspect is relevant, since the elderly people are more susceptible to adverse drug effects. This feature can be explained due to physiological changes inherent to the aging process, which promote pharmacokinetic and pharmacodynamic changes in the body of the elderly people. These changes make them more susceptible to the effects of drugs and therefore, the ADR appearance. These data are consistent with American and Brazilian studies[9,17].

Reactions attacked 23 (62.2%) males and 14 (37.8%) female. Although some authors have reported higher incidence of adverse reactions in women[8,10,17], due to factors such as differences in body weight, hormone levels or consumption of drugs, most often to medical appointments and greater compliance/adherence to prescriptions[8]. There are also other studies that show that men are more likely to be hospitalized for possible ADR[2, 11, 18]. A survey conducted in Hospital School in India reported ADRs were slightly more frequent in males (53%)[2] and notifications on a Sentinel Hospital in Fortaleza showed that the ADR occurred mostly in men (81.9%)[11].

The main drugs involved in ADR are represented in Table 1: losartan [5 (12.5%)], dipyrone [4 (10%)] Tramadol [3 (7.5%)]), alprazolam [2 (5%)]), polymyxin b [2 (5%)], captopril [2 (5%)] and glyburide [2 (5%)], a total of 20 (50%) adverse reactions. This profile differs from that observed in other Brazilian cohort study, conducted over nine months in the medical clinic of a teaching hospital Porto Alegre (RS), which pointed out the drugs for the metabolism (18.9%), anti-infective (18.1%), nervous system (14.4%) and gastrointestinal (13.9%) as more often associated with the onset of adverse effects on admission[6].

The classes of medications most commonly used have been anti-hypertensives [12 (30%)], analgesics [7 (17.5%)] and antibiotics [5 (12.5%)] respectively with 5, 2 and 4 active principles. Other authors found that drugs for the cardiovascular system were the most were involved in the ADR (26.8%), followed by antimicrobials (13.1%) and analgesics (8.9%)[6].

Prospective observational study of two English hospitals for eight months showed that among the 25 therapeutic classes found, the most commonly involved in adverse events were: non-steroidal anti-inflammatory drugs (29.6%), diuretics (27.3%), oral anticoagulants (10.5%), converting enzyme inhibitors Angiotensin (7.7%), antidepressants (7.1%), β-blockers (6.8%), opioids (6.0%) and digitalis (2.9%)[12].

Study in a Pharmacovigilance Center in Ceará showed that certain classes of drugs are more likely to cause adverse reactions than others. Antibiotics, anticoagulants, hypoglycemic, anti-cancer, non-steroidal anti-inflammatory drugs and action on the cardiovascular system are responsible for 60% of ADR that lead to hospitalization and 70% of them have occurred in hospital[11].

Among the most frequent symptoms are dry cough [6 (15%)], nausea [4 (10%)], dry mouth [3 (7.5%)], dizziness [3 (7.5%)] sleepiness [3 (7.5%)], diarrhea [3 (7.5%)], constipation [2 (5%)], retching [2 (5%)] and headache [2 (5%)]. Studies show that the systems more affected by ADR are: gastrointestinal, cardiovascular and respiratory; and even more susceptible to elderly people[6.19].

The analysis of causality according to Naranjo algorithm (13) showed that 12 (30%) ADRs were considered defined, 19 (47.5%) probable and 9 (22.5%) possible. This profile differs from that observed in other Brazilian studies[6], wherein the defined reactions represented 2.2% of the total, while 33.9% were probable and possible, appeared as the most frequent with 62.5%[6].

The drugs involved in the reactions correspond to 27 different active ingredients. These ones, according to the classification of the ATC code (Table 2), belong mainly: 15 (37.5%) of the nervous system class, 10 (25%) of the cardiovascular system, 6 (15%) for anti-infective for systemic use and 5 (12.5%) of the gastrointestinal tract and metabolism, which corresponded to 87.5% of the medicines used responsible for ADR. In a study that depicts the contribution of Latin America to Pharmacovigilance, drugs that act on the central nervous system are the second in the ranking of drugs involved in adverse reactions[8].

The majority of adverse reactions (35; 87.5%) was classified as predictable reactions (type A) and 5 (12.5%) unpredictable (type B of reactions), this result is consistent with other studies[14]. It is noteworthy that the Type A of reactions are related to the pharmacological properties of drugs, so they are considered predictable.

Only two reactions were considered serious by the team involved during the case discussion. The first case involved a 49 year-old patient who presented hypersensitivity reaction to carbamazepine, with scaly lesions throughout the body and clinical and laboratory

diagnosis (biopsy) of pharmacodermia. Immediately after the withdrawal of the drug, the patient had improved clinically in a few days and total regression of symptoms.

Table 2. Classification ATC (Code), Nº and ADR reported

Classification ATC (Code)	Nº (%)	ADR reported
Nervous System (N)	1 (37,5)	Drowsiness, cough, withdrawal symptoms, constipation, hypersensitivity, bitter taste, hypotension, withdrawal syndrome, dizziness, nausea, drug-induced hepatitis.
Cardiovascular system (C)	10 (25)	Dry cough, hoarseness, difficulty swallowing, dry mouth, anorexia, nausea, vomiting, dizziness, headache.
Anti-infective of systemic use (J)	6 (15)	Shortness of breath, dry mouth, altered taste, nausea, numbness in the face.
Tralimentary tract and metabolism (A)	5 (12,5)	Nausea, dry mouth, diarrhea, dizziness, malaise, hypoglycemia.
Antineoplastic and immunomodulating agents (L)	1 (2,5)	Diarrhea.
Sensory organ (S)	1 (2,5)	Itching.
Blood and blood forming organs (B)	1 (2,5)	Vasculitis in the abdominal area.
Respiratory system (R)	1 (2,5)	Difficulty in breathing.

In the second case (27 years-old), there was serious drug-induced hepatitis by the use of sodium valproate, hepatomegaly, and jaundice. The results of serological tests for viral hepatitis were negative and test for HIV 1 and 2 was nonreactive. The patient had clinical improvement in a few days after the replacement of the drug.

Adverse reactions represent a serious problem in public health, so their record is very important for patient safety and the prevention of complications involving the use of drugs. Their monitoring has the potential to prevent hospital admissions as well as improving patient safety in both outpatient and hospital context. In addition to being involved with hospital admissions, the ADRs prolong the length of stay, reflecting directly on the increase in costs and morbidity[2,3].

The ADR provides the development of effective routines and record, and the ADR monitoring seems desirable and indispensable. For this, the participation of a multidisciplinary team of pharmacists, doctors, nursing staff and other health professionals, aims to promote better patient care, ensuring patient safety and satisfactory clinical results[15,20].

FINAL CONSIDERATIONS

This study analyzed 194 forms of patients and identified 40 Adverse Drug Reactions in 37 (19%) patients. The medication of the classes of nervous and cardiovascular system totaled 24, representing 60% of the drugs involved in the adverse reactions observed.

The methodology allowed the achievement of objectives and contributed to a better understanding in the health unit on the problems of ADRs. The main limitations of this study relate to the fact that only one hospital and a clinic were analyzed, which requires caution in generalizing the results obtained. However, it is clear the importance of incorporating this practice in promoting humanized care and security.

The process of Medication Conciliation contributes significantly to the pharmacist to remain informed and vigilant about the undesirable reactions caused by medications enabling the prevention of diseases related to drug

therapy. It also allows greater integration of this professional with the multidisciplinary team of physicians, nurses, nutritionists and among others, increasing the actions for patient safety.

IDENTIFICAÇÃO DE REAÇÕES ADVERSAS A MEDICAMENTOS (RAM) DURANTE CONCILIAÇÃO MEDICAMENTOSA EM HOSPITAL ESCOLA

RESUMO

As Reações Adversas a Medicamentos (RAM) representam um grande problema nos hospitais, acarretando sérios riscos à saúde dos pacientes e aumentando os custos da atenção à saúde. O presente estudo teve o objetivo de analisar as principais Reações Adversas a Medicamentos encontradas no setor de Clínica Médica de um hospital escola em Campos dos Goytacazes – RJ. Realizou-se um estudo longitudinal prospectivo entre os meses de março a junho de 2015. Um total de 194 pacientes foram acompanhados, sendo observado reações adversas em 37 deles, totalizando 40 reações adversas que envolveram 27 princípios ativos. Os principais medicamentos envolvidos nas RAM foram losartana (12,5%), dipirona (10%) e tramadol (7,5%). As reações acometeram principalmente pacientes do sexo masculino (60%). Quanto à causalidade, 12 (30%) RAM foram classificadas como definidas, 19 (47,5%) prováveis e 9 (22,5%) possíveis, pelo algoritmo de Naranjo. Trinta e cinco RAM (87,5%) foram classificadas como reações do tipo A (previsíveis) e apenas 5 (12,5%) reações do tipo B (imprevisíveis). A Comissão de Farmacovigilância do Hospital foi comunicada para proceder as notificações à ANVISA. O processo de conciliação de medicamentos contribuiu para a identificação de RAM, permitindo ao profissional farmacêutico atuação mais efetiva junto à equipe multiprofissional de saúde no que se refere às reações indesejáveis causadas pelos medicamentos possibilitando a prevenção de agravos relacionados à terapia medicamentosa e ações voltadas para a segurança dos pacientes.

Palavras-chaves: Reação Adversa. Medicamentos. Conciliação

IDENTIFICACIÓN DE REACCIONES ADVERSAS A MEDICAMENTOS (RAM) DURANTE CONCILIACIÓN MEDICACIÓN EN UN HOSPITAL UNIVERSITARIO

RESUMEN

Las Reacciones Adversas a Medicamentos (RAM) representan un gran problema en los hospitales, causando serios riesgos a la salud de los pacientes y aumentando los costos de atención a la salud. En este contexto, este estudio tuvo como objetivo analizar las principales Reacciones Adversas a Medicamentos encontradas en el sector de Clínica Médica de un hospital universitario en Campos dos Goytacazes-Rio de Janeiro-Brasil. Se realizó un estudio longitudinal prospectivo entre los meses de marzo a junio de 2015. Un total de 194 pacientes fueron acompañados y fueron observadas reacciones adversas en 37 pacientes, totalizando 40 reacciones adversas que involucraron 27 principios activos. Los principales medicamentos involucrados en las RAM fueron losartán (12,5%), dipirona (10%) y tramadol (7,5%). Las reacciones acometieron principalmente pacientes del sexo masculino (60%). En cuanto a la causalidad, 12 (30%) RAM fueron clasificadas como definidas, 19 (47,5%) probables y 9 (22,5%) posibles, por el algoritmo de Naranjo. Treinta y cinco RAM (87,5%) fueron clasificadas como reacciones del tipo A (previsibles) y solo 5 (12,5%) reacciones del tipo B (imprevisibles). El Comité de Farmacovigilancia Hospitalaria fue comunicado para emprender las notificaciones a la ANVISA. El proceso de conciliación de medicamentos contribuyó a la identificación de RAM, permitiendo al profesional farmacéutico una actuación más eficaz junto al equipo multidisciplinario de salud en lo que se refiere a las reacciones indeseables causadas por los medicamentos, posibilitando la prevención de agravios relacionados a la terapia medicamentosa y acciones dirigidas a la seguridad del paciente.

Palabras clave: Reacción Adversa. Medicamentos. Conciliación..

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