Evaluation of Medicinal Therapy of Patients with Primary Immuno Deficiencies

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Abstract

The study aimed to evaluate the drug therapy of patients with Primary Immunodeficiency (PID) in a pediatric hospital in the Northeast of Brazil. It is a descriptive, prospective and exploratory study, carried out in 3 stages, including: data collection through a questionnaire applied to the caregivers of patients, monitoring of nursing care in the preparation and administration of immunoglobulin and analysis of reports of suspicious reporting adverse reaction to the drug. The study included 16 patients, the majority being male, with a mean age of 11.06 years. It was found that among the types of PID diagnosed, the prevalence was of common variable immunodeficiency, and most reported other diseases, especially infections and diseases of the respiratory tract.

Regarding the use of domestic drugs, 87.5% (n = 14) cited 26 drugs, with an emphasis on antimicrobials and steroids. Analyzing the suspicions of adverse reaction, 43.75% (n = 7) presented 29 symptoms, with headache and chills being the most common. Based on these records, the possibility of failures in the preparation and administration of the drugs was investigated, with infusion rate and failure to reconstitute identified immunoglobulins. Pharmaceutical interventions were performed: increased infusion times, in-service training on the process of reconstituting drugs for the nursing team and requesting the change of the immunoglobulin brand. As a result, the symptoms related to its administration have ceased. Because they were unforeseen events that resulted in patient harm, the symptoms were classified as Sentinel Events.

Introduction

The integrity of the immune system is essential for the defense against infectious organisms and their toxic products. Serious disorders can be triggered from defects in one or more components of the immune system, thus characterizing immunodeficiency diseases [1]. Congenital or Primary Immuno Deficiencies (PID) is genetics that result in increased susceptibility to infections and manifest themselves frequently during childhood. Early diagnosis of immuno deficiencies allows for adequate treatment [1].

The treatment of PIDs involves drugs such as antimicrobials and stereo chemical anti-inflammatory, among others. However, since the last two decades, intravenous immunoglobulin infusion (IVIG) has become the most widely used therapy in the case of diseases of the primary immunodeficiency of the immune system [2]. IV Ig is a biological product derived from blood [3]. Its efficacy is well documented and these products contain almost all IgG class antibodies with preserved functions and traces of IgM and IgA [4] With IV Ig administration, there is a decrease in the incidence and severity of infections, resulting in a better quality of patient's health and significantly reducing morbidity and mortality in patients with Primary Immunodeficiency.

Human immunoglobulin is presented less than two pharmaceutical forms, solution and lyophilized powder for reconstitution. Instructions on the storage, dispensing and administration to the patient are presented by the manufacturers and in different sources of information to enable its beneficial effects, safe use and quality. With regard to the safety aspects of medicinal products, Pharmacovigilance, defined as science and practice relating to the detection, evaluation, understanding and prevention of adverse effects or any problems related to medicinal products, aims at educating health professionals to a balance between benefit and risk of drugs Commercialized [5]

It is important to mention that, in Brazil, the practice of Pharmacovigilance had great momentum in the 90's, with the creation of the Brazilian Society for Drug Surveillance (Sobravime), [6] which was extremely important for encouraging studies and scientific investigations on different aspects At the same time as Sobravime was created, there was also the Group for the Prevention of Drug Abuse (GPUIM), a center for teaching, research and extension linked to the Federal University of Ceará, aimed at activities related to rational use. Also, in the meantime, several centers for adverse drug reactions have been set up, such as the Ceará Pharmacovigilance Center (CEFACE), which since 1996 has been one of the centers that form the GPUIM [7].

In turn, the Adverse Drug Event (EAM) is defined by the World Health Organization (WHO) as "any unfavorable medical occurrence, which may occur during treatment with a medicinal product, but which does not necessarily have a causal relationship with that treatment" [8]. The AMI can result from the adequate, inadequate or even inadequate use of those clinically necessary drugs [8]. Among the most frequent adverse events Mails

Adverse Drug Reactions (ADRs), which are conceptually "any harmful or undesirable effect that occurs after the administration of doses of drugs normally used in humans for the prophylaxis, diagnosis or treatment of a disease [9]. "Due to the creation of the Sentinel Network, it has been used extensively to characterize drug incidents, the Sentinel Event concept. In its Glossary and Technical Terms of the Brazilian Manual of the National Accreditation Organization (NAO), ANVISA defines Sentinel Event as "any unforeseen event that may result in damage to the external and internal clients of the Health Service Organization" [10].

Immunoglobulin Adverse Events (IAE) are described in the literature and the majority seems to be related to infusion rate. Some adverse effects during infusion, such as tremors and fever, mimic infectious pictures. Among the most frequent symptoms are arthralgia, myalgia, abdominal pain, nausea and headache. Reactions such as chest tightness, dyspnoea, and tachycardia may also occur [4]. Serious adverse reactions include meningitis, aseptic, renal failure, thrombosis, hemolytic anemia, urticaria and anaphylaxis, but fortunately they are rare [11]. Headache usually has a

pattern similar to that of migraine, extending for 48 to 72 hours after infusion [12].

Children and neonates are particularly susceptible to the onset of ADR. The use of drugs by individuals belonging to these groups requires careful clinical monitoring and a rigorous assessment of the benefit / risk ratio according to the severity of the condition, the possible adverse drug reactions, and the degree of patient impairment [13].

Children may experience pharmacokinetic and / or Pharmacodynamic variations, as well as other changes that are peculiar to this age group, altering patterns of growth and differentiation that reflect development. Pharmacodynamic changes may lead to an increase or decrease in sensitivity to some drugs, the causes of which are not always and may be due to changes in the number of receptors or their affinity for the receptor [14].

In view of this scenario, the present study aimed to perform the analysis of the drug therapy of patients with Primary Immuno deficiencies, assisted at the outpatient level, in a pediatric hospital. This evaluation involved the knowledge of the socio-demographic profile, the associated risk factors, the analysis of suspected adverse drug reactions, and their associated factors, as well as the clinical outcome after performing pharmaceutical interventions.

Methods

Study design

This is a descriptive, prospective and exploratory study, carried out at the Allergology / Immunology outpatient clinic of Albert Sabin Children's Hospital (HIAS), Fortaleza, Ceará. The sample consisted of all the patients who presented primary immuno deficiencies, attended at the Ambulatory Pharmacy of the hospital, and who received a medical prescription consisting of human immunoglobulin, using the drug during the study period.

Data collect

Data collection consisted of three main steps, namely:

Step 1

Patients were treated at the outpatient clinic and submitted to human immunoglobulin infusion once a month. The consultation dates of all patients were previously defined by the medical team. Thus, at the time of drug dispensation, interviews were conducted with those responsible for the patients using a semi-structured questionnaire after signing the informed consent form. The questionnaire contains a block referring to the socio-demographic profile, including name, sex, provenance and age, and another one related to general information about the patient's health, including prescription drugs, medicines used at home, and occurrence of adverse reactions and presence of Comorbidities.

Step 2

The work of the nursing team was monitored by observing and recording nonconformities, if it occurred, in the context of medication administration. Techniques used for reconstitution and administration of immunoglobulin were considered, considering hygiene and manipulation, as well as the ambient temperature. The techniques were compared to the guidelines provided by the manufacturer's package insert which served as standard guidelines in the evaluation process.

Step 3

Finally, in order to collect patient data and suspected ADRs, in addition to the questionnaires, all suspected ADRs were inserted into the adverse drug reaction reporting form through voluntary reports from health professionals. In addition, the medical records physicians by means of the following indicators: a) Registry of the health professional about the suspected ADR; b) Abrupt interruption of treatment; C) Use of antidotes (antihistamines and / or corticosteroids) and, d) Drug change, mainly immunoglobulin. Suspicions of ADR were inserted into the HIAS standard Pharmacovigilance record. The analysis and classification of the suspected ADRs were made at weekly technical meetings held by the team of the Ceará Pharmacovigilance Center (CEFACE), linked to the UFC GPUIM. After confirmation of suspected ADR, a procedure was performed to identify possible sentinel events, such as problems related to the reconstitution or infusion of the product. The feedback of the conclusion of the case was made by means of letter of reply sent to the professional notified. The suspected reactions were coded using the WHO-ART (World Health Organization - Adverse Drug Reaction Terminology; WHO-ART 2005) and the drugs were coded according to the first level of the WHO-ATC (World Health Organization - Anatomical Therapeutically Chemistry) Standardization of nomenclature and standardization of language in scientific circles.

Data analysis and ethical aspects

The information obtained in the questionnaires was inserted into the Epic Info program database version 3.5.1. Data were analyzed and presented in frequency and percentage form. The study was started with the approval of the Ethics and Research Committee of Albert Sabin Children's Hospital under registration number 087/09. It is worth noting that for the accomplishment of Step 2, the nursing team was previously informed about the accomplishment of the research.

Results and Discussion

The socio-demographic and clinical profile of the patients (n = 16) was delineated, with 56.25% (n = 9) of the patients being male and the mean age found was 11.06 years. Analyzing the clinical conditions of the patients, it was verified that among the types of PID diagnosed, the prevalence was IDCV, corresponding to 62.5% (n = 10), followed by Hyper IgM Syndrome (18.75%, n = 3), Hyper IgE Syndrome (6.25%, n = 1), IDCG (6.25%, n = 1) and Agammaglobulinemia (6.25%, n = 1).

Considered to be rare, PIDs are estimated to occur in more than 1 each 2,000 births [15-16] and seem to prevail in males (5:1), since some PIDs are linked to the X chromosome. Data from the literature report that in the pediatric age group, approximately 50% of patients with recurrent respiratory infections are healthy, 30% 10% have chronic diseases, and 10% may have immunodeficiency [17]. Such information corroborates Characteristics of our population and support the number, relatively of the sample studied.

Regarding the clinical conditions, similar results were found by several authors [18-19]. IDCV is a disease that affects a heterogeneous group of patients at any stage of life, although it is more common in young adults [20]. When questioned about the occurrence of Comorbidities, in addition to the PIDs, 87.5% (n = 14) responded affirmatively, of which 100% (n = 14) had infections and diseases of the respiratory tract, Including asthma and allergies.

In our study, patients who reported having had other diseases (28.57%, n = 4) reported having diseases not related to the respiratory tract, such as reflux, seizures, depression and Down's syndrome. When questioned about the use of home medications, 87.5% (n = 14) of the interviewees reported using several drugs, each patient using more than one drug, which were grouped by the pharmacological class and categorized by the international ATC code (Table 1). Antimicrobials and corticosteroids preponderated and this is consistent with the profile of diseases and clinical conditions presented in our population.

Class	Number of Medicines frequency (N)	%	WHO - ATC[c]
Antimicrobial	10	38,46	J01
Corticoid	5	19,23	D07
Beta 2 agonist	2	7,7	R03
Proton Pump Inhibitor	2	7,7	A02
Vitamin	2	7,7	A11
Antihistamine	1	3,84	R06
Antidepressant	1	3,84	N06
anticonvulsants	1	3,84	N03
	1	3,84	N05
Neuroléptico			
Hormone	1	3,84	H
Total	26	100	

Source: direct search, AIDP: primary immuno deficiencies, BHIAS: Albert Sabin Children's Hospital, c WHO - ATC: World Health Organization - Anatomical Therapeutically Chemistry.

Table 1: Classes of drugs used at home by patients with PIDa HIASb outpatient pharmacy, Fortaleza-CE.

It is important to highlight that the expectation and quality of life of patients with some PIDs have increased significantly due to better clinical management of infections and other Comorbidities, as well as Development of potent antimicrobials, as well as specific therapeutic alternatives, such as the use of immunoglobulins [21].

The administration of medicines at home was, for the most part, done by caregivers; In fact, directly responsible, since the population involved pediatric patients. The only patient who indicated the "Self-Care" option was 19 years old. It is worth noting that HIAS treats patients up to seventeen and a half years, however when the patient cannot be relocated to another location, the care continues so that the patient is not left without the treatment. Of the 16 patients evaluated, 43.75% (n = 7) had suspected ADR, and 29 signs and symptoms were identified during the study period (Table 2).

Signals And Symptoms	Frequency (N)	%	code ARTc
Headache	6	20	109001
Chills	5	16,67	731005
Tremor	4	13,34	154001
Fever	4	13,34	725001
Nausea	2	6,68	308001
Vomiting	1	3,33	228001
Dizziness	1	3,33	101001
Cough	1	3,33	513001
Tachycardia	1	3,33	224001
Hypertension	1	3,33	210001
Erythema	1	3,33	28003
Itching	1	3,33	24001
Pallor	1	3,33	220001
TOTAL	29	100	

Source: spontaneous notifications by the nursing team; AIDP: primary immunodeficiencies; BHIAS: Albert Sabin Children's Hospital;c WHO - ART: World Health Organization - Adverse Drug Reaction Terminology

Table 2: Frequency of signs and symptoms detected as suspected ADR in patients with IDPa. HIASb outpatient pharmacy, Fortaleza-CE.

During the occurrence of suspected adverse reaction, the nursing team reported the fact to the medical team, the infusion

of the drug was suspended and the patient received hydration and administration of specific drugs according to the clinical picture. After a time, the drug was slowly reinfused, with an increase in infusion rate, obeying the tolerance of the patient. Then, the infusion rates of the immunoglobulin were calculated based on the values suggested in the literature. For the pharmaceutical form of human immunoglobulin dispensed in the hospital, the infusion should not exceed 1mL / kg / h for the first half hour and may only be gradually increased to a maximum of 4mL / kg / hr. In addition, since sucrose is the excipient, maximum infusion rate of 3mg / kg / min is recommended. In 93.75% (n = 15) of the patients, the values found were below the recommendation, ie, there were practically no errors in the calculation of the infusion rate. However, it should be considered that this value is standard, not taking into account the other factors inherent to the patient.

The brand used in the study period was in the form of lyophilized powder accompanied by a diluents bottle and transfer system. Storage and maintenance should be done at a temperature below 25ºC, away from light and cannot be frozen. Its reconstitution should be performed at room temperature, according to the guidelines described in the manufacturer's package leaflet. The first vial of the drug should be infused in approximately one hour and the others with a gradual increase in speed, which should not exceed 1mL / kg / h during the first half hour. It can then be increased gradually to a maximum of 4 ml / kg / hr. The occurrence of a sentinel event is interpreted as a sign that the quality of services may be in need of improvement and, as a result, welfare structures and processes are causing or increasing the risk of harm to customers and should be improved. It is understood, therefore, that whenever this occurs, the surveillance system should be triggered for the event to be investigated and the prevention measures adopted [22]. The processes of reconstitution of drugs performed by the nursing team were monitored by the researcher. Among these, in some situations, process failures were identified, including: hygiene failure, bottle insertion in a position divergent from that in the package insert, sudden rotation movements between the hands and temperature below that recommended for infusion. It is important to note that reconstitution requires certain precautions, such as room temperature and careful observation of the product before starting the infusion [4,11-12].

In order to minimize the occurrence of such events, the outpatient pharmacy staff performed some pharmaceutical interventions. Pharmaceutical intervention occurs when the professional performs Pharmacotherapeutics monitoring, which is a continuous process that identifies and solves problems related to medications. In view of this, the pharmacist can carry out interventions aimed at increasing effectiveness and reducing the risks of pharmacotherapy [23].

In partnership with the medical team, the infusion times of

all patients who had suspected ADRs, although they were already calculated within the standards, were increased by one hour, providing a more gradual increase in infusion rate. In addition, the pharmacy team provided in-service training on the drug reconstitution process for the nursing staff. To help with the training, a Pharmaceutical Report was prepared with some basic guidelines needed.

Finally, the pharmacy team, in partnership with the medical experts, requested the change of the brand of immunoglobulin to another in a liquid pharmaceutical form, in order to minimize the symptoms by the pharmaceutical form and by failures in reconstitution. It was observed that after the pharmaceutical interventions carried out, the symptoms ceased. Because they were unforeseen events that resulted in harm to the patients, and these were avoidable, the symptoms were classified by the CEFACE team in a meeting as Sentinel Events, where the damages caused were the signs and symptoms described in table 2 and the speed factors of infusion and reconstitution of drugs increased the risk of such harm to patients. Some studies cited in the literature in the investigation of adverse events using the same immunoglobulin brand of the present study found similar signs and symptoms; however, the most frequent were laryngeal edema, tachycardia, cough and tremor [22]. They also associated suspicions of reactions to same factors of the present study. Other studies did not find between the symptoms and the pharmaceutical form of the drug, but considered the rate of infusion [18].

There are (IAC) described in the literature, most of them related to infusion rate, which varies according to the product. Patients who have never received IVIg or those who are infected have an increased risk of adverse events. These are, in part, related to the formation of complexes antigen-antibody and can be reduced if the patient is not suffering from fever or receiving anti-infective treatment [4]. Another related factor is the presence of immunoglobulin aggregates in lyophilized products diluted prior to use. It is important to note that reconstitution requires certain care, such as temperature and careful observation of the product before and during the infusion. In addition, consideration should be given to the exchange of the commercial product [4,12]. Some adverse effects during infusion, such as tremors and fever, mimic infectious pictures. Among the most frequent symptoms, arthralgia, myalgia, abdominal pain, nausea and headache are also observed. If any symptoms are observed, the infusion should be interrupted, the patient should be hydrated and analgesic / antipyretic, antihistaminic and / or antiemetic administered according to the clinical picture. After the symptoms improve, the patient should receive the medication at the initial rate, increasing to the speed that is tolerated. In some situations, one can use pre-medication as antipyretics, analgesics, antihistamines or corticosteroids at usual doses. Reactions such as chest tightness, dyspnea, and tachycardia may also occur [4]. It is very important to remember that the success of this work is mainly due to the involvement of the entire multiprofessional team. Teamwork is a strategy that promotes quality of service, favoring planning, prioritization, reduction of duplication of services, generation of more creative interventions, reduction of unnecessary interventions due to lack of communication between professionals and cost reduction [22].

Conclusion

The research made possible the characterization of the drug therapy of the pediatric patients with PID, as well as an analysis of the profile of patients, being observed predominance of males and average age of approximately 11 years. It has been observed that, in general, patients with PID tend to have Comorbidities, such as respiratory tract diseases and recurrent infections, with a strong tendency to use antimicrobials and corticosteroids.

Due to the frequency of adverse events associated with the use of human immunoglobulin, it was extremely relevant to identify the causes involved in which interventions could be performed. It was observed that, after the pharmaceutical interventions, all adverse symptoms ceased. Thus, it can be concluded that the findings may contribute to the improvement of care for PID patients in the Brazilian public health context, as it points to the need for vigilance regarding the use of this medication. The importance of Pharmacovigilance centers, since they can support the recording and documentation of information, make it possible to carry out interventions.

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