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Severe cutaneous adverse reactions to drugs: a case series study

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Abstract

Objective: to describe five cases of severe cutaneous adverse reactions to drugs (SCARD) that led to hospitalization and were investigated and diagnosed by the dermatology service of a university hospital. **Methods:** this is a descriptive observational study of the case series type in which were included patients aged 18 years old or older from both sexes, hospitalized between January 2015 and July 2019, in a university hospital in Rio de Janeiro, Brazil and whose reason for hospitalization was SCARD diagnosed by the dermatology service. For SCARD causality assessments, two internationally adopted criteria were used: the Naranjo algorithm and the WHO-UMC causality assessment system. **Results:** five cases of RCAG have been reported. Amongst these, three cases of erythroderma, one of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and one of drug reaction with eosinophilia and systemic symptoms (DRESS). The cases of erythroderma have presented as suspected drugs substances such as hydrochlorothiazide, furosemide, captopril and carbamazepine, which is consistent with the literature reports. In the reported case of SJS/TEN, both the suspected drug, allopurinol, and the presence of an anti-HIV positive laboratory test are also referred to in the literature. The case of DRESS has shown allopurinol as a suspected drug, which is already related to this well-described skin reaction. The causalities were assessed as possible for the first two cases and probable for the following three. The results of the study supported the proposal for a model of pharmacovigilance of SCARD in a hospital environment, consisting of spontaneous reporting, periodic checking of medical records and for requests of opinion from the dermatology service registered in the hospital's computerized system. **Conclusion:** this study contributes to add knowledge and better understanding about SCARD, in regards to the nature of the type of reaction, identification of patients at risk, early detection of these and the responsible drugs. Furthermore, it proposes a model for monitoring SCARD to be implemented in the hospital, which combines passive and active pharmacovigilance strategies and encourage notification by health professionals.

Keywords: drug-related side effects and adverse reactions, dermatology, pharmacovigilance.

Farmacodermias graves: um estudo de série de casos

Resumo

Objetivo: descrever cinco casos de farmacodermias graves/reações cutâneas adversas graves (RCAG) que motivaram internação e que foram investigados pelo serviço de dermatologia de um hospital universitário. **Métodos:** trata-se de um estudo observacional descritivo do tipo série de casos, no qual foram incluídos pacientes com 18 anos ou mais, de ambos os sexos, internados entre janeiro de 2015 e julho de 2019, em um hospital universitário no Rio de Janeiro, Brasil e cujo motivo de internação foram RCAG diagnosticadas pelo serviço de dermatologia. Para as avaliações de causalidade, utilizaram-se dois critérios adotados internacionalmente: o algoritmo de Naranjo e o sistema de avaliação de causalidade WHO-UMC. **Resultados:** Foram relatados cinco casos de RCAG, sendo três de eritrodermia, um de síndrome de Stevens Johnson (SSJ)/necrólise epidérmica tóxica (NET) e um de reação medicamentosa com eosinofilia e sintomas sistêmicos (DRESS). As eritrodermias tiveram como fármacos suspeitos, hidroclorotiazida, furosemida, captopril e carbamazepina, consistentes com os relatos da literatura. No caso de SSJ/NET, tanto o medicamento suspeito, alopurinol, quanto a presença de exame laboratorial anti-HIV positivo, estão referidos na literatura. O caso de DRESS teve como medicamento suspeito o alopurinol, o qual já tem relação com essa reação cutânea bem descrita. As causalidades das RCAG relatadas foram avaliadas em possível para os dois primeiros casos e provável para os três seguintes. Os resultados do estudo fundamentaram a proposição de um modelo de farmacovigilância de farmacodermias graves em ambiente hospitalar, composta por notificação espontânea e verificação periódica de prontuários e de pedidos de pareceres para o serviço de dermatologia registrados no sistema informatizado do hospital. **Conclusão:** Esse estudo contribui para agregar conhecimento e compreensão sobre as farmacodermias graves, quanto à natureza das reações, à identificação de pacientes em risco, à detecção precoce das mesmas e aos medicamentos responsáveis. Além disso, propõe um modelo de monitorização das reações cutâneas adversas graves a ser implantado no hospital, que conjuga estratégias passivas e ativas de farmacovigilância e estimula a notificação pelos profissionais de saúde.

Palavras-chave: efeitos colaterais e reações adversas relacionados a medicamento, dermatologia, farmacovigilância.

Introduction

The diversity of medications available contributed clear benefits to the treatment and prevention of many clinical conditions. However, they can increase the risk of health harms, such as adverse drug reactions (ADRs). An ADR is an "unwanted effect attributable to the administration of a medication, in doses commonly used in humans, to prevent, diagnose or treat a disease or to modify some physiological function".[1]

Among the most frequent and generally unpredictable ADRs are pharmacodermias or cutaneous adverse reactions to drugs (CARDs), which account for 10% to 30% of the reported ADRs, with an estimated incidence of 0.25% in the general population. It is estimated to affect 0.16% to 3.3% of hospitalized patients and 0.14% of non-hospitalized patients. The spectrum of the CARDs is broad and includes skin disorders mimicked, induced or aggravated by drugs.[2] They produce a wide spectrum of changes in the skin, appendages or mucous membranes, from mild and self-limited rashes to severe cutaneous adverse reactions (SCARs). These are less common and potentially fatal forms of late hypersensitivity, which account for 2% to 7% of the cases,[3-6] such as Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and ADRs with eosinophilia and systemic symptoms (DRESS).[7-8] The pathophysiology of the SCARs is not fully understood and, although rare, they can negatively impact quality of life and become chronic, as in the case of SJS/TEN.[6] Treatment often requires hospitalization, sometimes in an Intensive Care Unit or in Burns Units, to observe vital signs and internal organ functions.[8]

Thus, the monitoring of the SCARs, through activities in Pharmacovigilance, contributes to knowing the magnitude and nature of events, the identification of risk groups, and clinical management. In addition, it increases the notification of events identified to the regulatory body (National Health Surveillance Agency - *Agência Nacional de Vigilância Sanitária*, Anvisa), which is one of the axes of the National Patient Safety Policy.[9]

Pharmacovigilance (PV) is "the science and activities related to the detection, evaluation, understanding, and prevention of adverse effects or any other possible drug-related problems".[10] The most used method is spontaneous notification, which is essential for the identification of drug safety signs, which are hypotheses of risks associated with drugs.[11] However, the information obtained can be limited and insufficient for making clinical and regulatory decisions. Complementary active strategies, such as interviewing patients by health professionals and reviewing medical records using event tracking terms, expand the capacity for detecting and analyzing suspected ADRs.[10-14]

However, there are few Brazilian studies on adverse health events, including severe ADRs, such as SCARs.[15] Greater knowledge about the magnitude and characteristics of the SCARs can contribute to early identification, reduction of associated morbidity and mortality rates, as well as to identify opportunities for improving PV practices. In this context, the present study aimed to describe a series of five cases of SCARs, which led to hospitalization and which were investigated and diagnosed by the dermatology service in a Brazilian university hospital.

Methods

This is a descriptive and observational study of the case series type. The study population included patients aged 18 years or older, of both genders, admitted between January 2015 and July 2019, to a university hospital in Rio de Janeiro, Brazil, whose reason for admission was suspected of severe pharmacodermia or severe cutaneous adverse reaction (SCAR). The manifestations of the SCARs that could be included were the following: Acute Generalized Exanthematic Pustulosis (AGEP); Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or Drug-induced Hypersensitivity Syndrome (DiHS) or Hypersensitivity Syndrome (HSS); Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN); anaphylaxis; erythroderma; anticoagulant-induced skin necrosis; drug-induced vasculitis; and serum sickness-like reactions.[7-8]

Cases admitted to the dermatology ward or other wards were included, but with an opinion requested to Dermatology, and which were identified in the records of this service by the clinical team. Cases with unfinished diagnostic investigations were excluded. The cases were described based on demographic data (gender and age), clinical data (comorbidities, hospitalizations), laboratory data (skin biopsies), and treatment (medications in previous use and during hospitalization) of the participants, referring to the entire period of hospitalization. , including readmissions, and collected through review of electronic medical records. The drugs were expressed in the Brazilian Common Denomination (*Denominação Comum Brasileira*, DCB), as shown in the medical and dermatology records.

Causal assessment is the estimate of the probability that a drug is the cause of an adverse event.[1] Therefore, it is necessary to investigate the causal relationship between exposure (medication) and effect (ADR). The causality assessments between the events and the medications (causality) were carried out by the study team, using two internationally-adopted criteria, namely: the Naranjo[16] algorithm and the WHO-UMC[17] causality assessment system. The cases were evaluated by both criteria and, in the case of disagreement, the result obtained according to the WHO-UMC criteria prevailed.

The project was approved by the Research Ethics Committee (REC) of the Clementino Fraga Filho University Hospital, under CAAE No. 20046719.6.0000.5257.

Results

Five cases were included in the study, three in women and two in men, with four cases in individuals aged 60 years old or more. The SCAR in three cases was erythroderma, followed by 1 case of SJS/TEN and 1 case of DRESS (Table 1).

CASE 1

Male patient, 66 years old, hospitalized in the Dermatology sector in January 2015. Previous comorbidities: hypertension, type 2 diabetes and benign prostatic hyperplasia, with no information on the time of diagnosis. He had diffuse erythematous-desquamative lesions for eight months, especially in photoexposed areas; erythematous-vesic-exudative and crusted lesions on the lower limbs, with signs of lipodermatosclerosis; and intertrigo in fold areas, notably infra-abdominal and inguinal region. Previous

histopathological examination (skin biopsy), performed four months before admission, indicated suspicion of erythroderma due to pharmacodermia or psoriasis and acute stasis eczema. Previous reported medications: hydrochlorothiazide and furosemide (no dosage information), both suspended before hospitalization, due to suspected pharmacodermia; promethazine (25 mg 3x/day); hydroxyzine (25 mg 3x/day); loratadine (10 mg 1x/day); nifedipine retard (20 mg 2x/day); atenolol (25 mg 1x/day), dutasteride + tamsulosin (0.5 + 0.4 mg, often unreported); metformin (850 mg 3x/day); NPH insulin (40 IU in the morning, 6 IU in the afternoon, 20 IU in the evening), and ranitidine (150 mg 2x/day). There was no information on the time using any of the medications. At hospital admission, promethazine was suspended and, during hospitalization, hydroxyzine. Histopathological exams of the skin of the right and upper limbs indicated a clinical hypothesis of pharmacodermia. Treatment included rest, elevation, and application of 0.1% dexamethasone 2x/day to the lower limbs, prednisone 30 mg/day, nystatin ointment with zinc oxide in the fold areas 2x/day and mineral oil 2x/day throughout the integument. There was an evolutionary improvement in erythroderma seven days after admission; and hospital discharge occurred after 25 days, with improvement of erythematous-scaly and crusted lesions in the lower limbs, presenting only mild erythema and desquamation mainly in photoexposed areas, as well as intertrigo resolution in fold areas.

In June 2015, four months after hospital discharge, the patient was readmitted for worsening of generalized skin lesions on the face and upper and lower limbs, mainly in photoexposed areas, nearly a month ago, with intense itching and local skin sensitivity. Reported medications in use, without information on time of use: promethazine for pruritus, prescribed in a basic health unit, prednisone 20 mg/day (reduced), potassium chloride 10% 20 ml/day, calcium carbonate 1 g/day, vitamin D3 10 drops/day, ranitidine 300 mg/day, hydroxyzine 75 mg/day, losartan 50 mg/day, atenolol 50 mg/day, dutasteride + tamsulosin 0.5 + 0.4 mg/day, NPH insulin 44 UI before breakfast, 5 IU before lunch, 20 IU before dinner, and application of anionic cream (Lanette) 2x/day throughout the body. He received treatment with prednisone 40 mg/day, dexamethasone 1% cream, and Lanette cream for 5 days, with improvement of the clinical condition, being discharged from hospital.

One month later (July 2015), the patient was readmitted with a condition similar to his previous hospitalization. Losartan was suspended due to possible photosensitization, which can worsen the condition, and the use of clonidine was started. Treatment was carried out with prednisone 20 mg/day, dexamethasone 1% cream, and lanette cream, with discharge from the hospital 19 days later, with clinical improvement and outpatient return scheduled.

The causal relationship between pharmacodermia (erythroderma) and hydrochlorothiazide, the main suspected drug, was assessed as "possible" by both adopted criteria, because the alternative explanations for erythroderma induced by furosemide or psoriasis could not be ruled out.

Table 1. Clinical and pharmacological aspects of the severe pharmacodermia case series. Rio de Janeiro, HUCFF/UFRJ, January 2015 to July 2019.

N'	Age (years old) and Gender[a]	Suspected SCAR[b]	Symptoms	Suspected medication	Plausible temporal sequence	Alternative explanation removed	Positive response to withdrawal	Re-exposure to the medication	Biopsy confirmation	Causality
1	66 M	Erythroderma	Diffuse erythematous-scaling lesions; erythematous-vesico-exudative and crusted lesions; intertrigo in fold areas	Hydrochlorothiazide	Yes	No (furosemide and psoriasis)	No	No	Yes	Possible
2	70 F	Erythroderma	Erythematous-desquamative, spreading pruritic lesions	Captopril	Yes	No (psoriasis)	Yes	No	Yes	Possible
3	60 F	Erythroderma	Disseminated pruritic erythematous maculopapules with desquamation and hyperlinearity	Carbamazepine	Yes	Yes	Yes	No	Yes	Probable
4	26 F	SJS/TEN[c]	Residual hyperchromic macular lesions; exulcerated lesions; erythematous-scaling lesion; and fissures in the labial mucosa	Allopurinol	Yes	Yes	Yes	No	Yes	Probable
5	72 M	DRESS[d]	Scaly maculopapular rash, pruritic, with some crusty lesions and worsening renal function.	Allopurinol	Yes	Yes	Yes	No	Yes	Probable

[a] F: Female; M: Male; [b]Severe Cutaneous Adverse Reaction; [c]Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis; [d]Drug Reaction with Eosinophilia and Systemic Symptoms

CASE 2

Female patient, 70 years old, hospitalized in the Dermatology sector in November 2015, by referral from another hospital, where she underwent irregular follow-up. Previous comorbidities: hypertension and chronic obstructive pulmonary disease (COPD), with no information on the time of diagnosis. She had erythematous-desquamative, widespread pruritic lesions associated with joint pain in the hands, knees, and feet. She had erythematous-scaling plaques on the scalp a year and three months ago, which progressed to the entire integument, associated with severe itching and joint pain. At the time of admission, she was in regular general condition, in poor hygiene, dehydrated, afebrile, tachycardic, eupneic, erythrodermic with intense desquamation, and with an ulcerated lesion with purple edges in the digital pulp of the first right finger. Previous medications reported: prednisone 30 mg/day for seven days, mometasone and hydroxyzine cream and continuous use of captopril. There was only information on dosage and duration of use of predsnisone. The hypothesis of erythroderma by pharmacodermia by captopril or psoriasis was raised. Captopril was suspended and the use of losartan and amlodipine was started. Three histopathological exams (skin biopsy) were performed at different sites (upper right dorsum, right upper limb, and right lower limb) that indicated a hypothesis of pharmacodermia. During the course of hospitalization, the patient presented disorientation, agitation, tachycardia, and fever, setting up a condition of sepsis, and antibiotic administration was started. The treatment of the dermatological condition was carried out with the application of mineral oil 3x/day throughout the body, hydroxyzine 75 mg/day, and prednisone 40 mg/day. The patient showed an evolutionary improvement in erythroderma and pruritus after corticosteroid therapy. She was discharged 32 days later, with outpatient return scheduled and improvement of the cutaneous lesions, but still with fine flaking throughout the integument and itching.

The patient was readmitted 17 days after discharge (January 2016) for incorrect use of prednisone at home and return of erythematous-scaling, itchy, disseminated lesions. Amlodipine and losartan were maintained, and it was decided to resume prednisone 40 mg/day and to administer hydroxyzine and emollients for regular use during hospitalization. The patient evolved with a significant improvement in the erythrodermic condition, and was discharged 16 days later.

The causal relationship between pharmacodermia (erythroderma) and captopril was assessed as “possible” by both adopted criteria, and the alternative explanation of psoriasis-induced erythroderma cannot be ruled out.

CASE 3

Female patient, 60 years old, hospitalized in the Dermatology sector in June 2016. Previous comorbidities: hypothyroidism, depression, anxiety, memory disorder, and psychotic episode), without information on the time of diagnosis. She reported pruritic erythematous maculopapules that started in the antecubital fossae, with subsequent craniocaudal dissemination nearly 45 days ago. On admission, she presented erythroderma with involvement of the face, scalp, and retroauricular region, throat, neck, chest, upper limbs, abdomen, thighs and knees, sparing part of the back, legs and feet, with flaking and hyperlinearity. Previous use medications reported: levothyroxine, escitalopram 10 mg/day, flurazepam 15 mg/day, and carbamazepine 200 mg/day in subdose as a mood stabilizer, in addition to having been treated with prednisone and oral antihistamine in the emergency room (ER). There was no information on the time using the medications. The patient reported a cutaneous condition to the beginning of treatment with carbamazepine and her son reported a resurgence of the condition after the suspension of prednisone. The hypothesis of erythroderma by carbamazepine was raised, drug which was suspended after hospitalization. Three histopathological exams (skin biopsy) were performed at different sites (abdomen, anterior aspect of the right thigh, and internal aspect of the left forearm) that indicated a clinical hypothesis of pharmacodermia. To treat the dermatological condition, hydroxyzine 100 mg/day was administered initially for three days, prednisone 20 mg/day, and application of anionic cream (lanette) 4x/day, both throughout the hospitalization. The patient evolved with improvement of the cutaneous condition, with disappearance of erythema and progressive improvement of desquamation, being discharged after 9 days of hospitalization.

The causal relationship between pharmacodermia (erythroderma) and carbamazepine was assessed as “probable” by both adopted criteria.

CASE 4

Female patient, 26 years old, hospitalized in the Dermatology sector in January 2017, no previous comorbidities. She had residual macular hyperchromic lesions in the lower limbs, upper limbs, and back; exulcerated lesions in limbs with the appearance of ruptured vesicles; erythematous-scaling lesion on the back of the neck; and fissures in the labial mucosa without ulcerated intraoral lesions. The patient reported the appearance of lesions 48 to 72 hours after using allopurinol without a prescription, as indicated by a pharmacist. According to the report, there was a bullous lesion with citrus content in the left plantar region, and the patient suspected a uricemic crisis. She sought several clinical emergency services, and allopurinol pharmacodermia was suspected, drug which was suspended, but with no established therapeutic conduct. She did not report the use of other previous medications. The lesions were compatible with pharmacodermia (SJS/TEN). A histopathological examination (skin biopsy) was performed, with a result compatible with drug eruption. In the course of hospitalization, an HIV positive laboratory test was found. The dermatological treatment was carried out with the application of mineral oil to lesions on the back, upper and lower limbs, sunflower oil in palm regions, oral hydration, and replacement of potassium, magnesium, iron, and vitamin B12. The patient evolved with significant improvement of the lesions, being discharged after 9 days of hospitalization with a scheduled return to the dermatology clinic.

The causal relationship between pharmacodermia (SJS/TEN) and allopurinol was assessed as “probable” by both adopted criteria.

CASE 5

Male patient, 72 years old, hospitalized in the Medical clinic sector in June 2019. Comorbidities: systemic arterial hypertension, kidney disease II, hypothyroidism, gold 2 chronic obstructive pulmonary disease, cirrhosis by virus and alcohol, with no information on diagnosis times and hepatocellular carcinoma, diagnosed in 2018, ex-alcoholic and ex-smoker. He had a maculopapular rash in the abdomen, limbs and face, scaly, pruritic, with some crusty lesions

and worsening of the renal function. The blood count showed thrombocytopenia and eosinophilia. There were no reports of febrile episodes or presence of lymph node enlargement. Previous use medications reported: lactulose 10 mL/day, levothyroxine 100 mcg/day, simvastatin 20 mg/day, furosemide 40 mg/day, doxazosin 2 mg/day, and allopurinol 300 mg/day. The patient reported using allopurinol nearly eight weeks ago, but there was no information on the duration of use of the other medications. Allopurinol pharmacodermia was suspected as the cause of cutaneous and renal symptoms, more specifically, DRESS. Dermatology was requested to investigate the condition, and performed a histopathological examination (skin biopsies) of two different sites, left thigh and abdomen, the result of which was, for both samples, "subtle, perivascular and interstitial vacuolar interface dermatitis with tissue eosinophilia and extravasation of red blood cells, compatible with drug eruption". Allopurinol was suspended and, initially, prednisone 40 mg/day, promethazine 25 mg/day, anionic cream (lanette) with application to body injuries after bathing and moisturizing facial cream for dry and sensitized skin on facial lesions twice a day were prescribed. In the course of hospitalization, there was an increase in the dose of prednisone to 60 mg/day and of promethazine to 50 mg/day, with a subsequent reduction in the dose of prednisone to 40 mg/day again and an increase in the dose of promethazine to 75 mg/day. The patient evolved with a significant improvement in the skin condition, with no pruritus and maculopapular lesions, in addition to improved renal function, being discharged after 29 days of hospitalization, with outpatient return scheduled for prednisone weaning.

The causal relationship between pharmacodermia (DRESS) and allopurinol was assessed as "probable" by both adopted criteria. Only this case had the causality assessment validated by the Anvisa, because the others were not informed to the hospital's pharmacovigilance service.

Discussion

Five cases of severe pharmacodermias investigated by the Dermatology service during the study period have been reported: erythroderma, Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). In all the cases, the resolution was hospital discharge.

Erythroderma is characterized by erythema and desquamation of more than 90% of the skin surface.[18] It is a rare condition, with an incidence in adults estimated at 1 case/100,000 individuals-year.[19] Nearly 20% of erythroderma are hypersensitivity reactions to medications, including penicillins, sulfonamides, carbamazepine, phenytoin and allopurinol.[20] The drugs suspected in the cases reported in this study were hydrochlorothiazide, furosemide, captopril, and carbamazepine, consistent with the literature. Hydrochlorothiazide and furosemide have the chemical structure of s sulfonamide, carbamazepine is among the drugs most associated with erythroderma, and there are reports of the occurrence of these reactions by captopril.[21]

The incidence of SJS/TEN is 2 to 7 cases/1 million individuals-year,[22] being higher (0.95 to 1 case/1,000 individuals-year) among those infected with the human immunodeficiency virus (HIV).[23] A German study with national registry data estimated an incidence of 1 to 2 cases/1 million individuals-year.[24] The differentiation between SJS and TEN considers the percentage of detachment from the body surface area (SJS < 10% and TEN > 30%). There is an overlap of SJS/TEN when 10% to 30% of the body surface area is affected. Mortality rates vary between 1% and 5% for SJS and between 25% and 35% for TEN.[25] The most commonly implicated drugs are allopurinol, aromatic antiepileptic drugs and lamotrigine, antibacterial sulfonamides (including sulfasalazine), nevirapine, and non-steroidal anti-inflammatory drugs of the oxicam class.[26] The reported case of SJS/TEN had allopurinol as a suspected drug and a positive test for HIV, according to the literature.

As for DRESS, the incidence is 1.2 to 6 cases/1 million individuals-year and, among those exposed to drugs, it varies from 1:1,000 to 1:10,000, leading to death in nearly 10% of the cases. The manifestations of DRESS include extensive mucocutaneous eruption, fever, lymphadenopathy, hepatitis, hematological abnormalities with eosinophilia, thrombocytopenia, and atypical lymphocytes, and can compromise other organs, such as the kidneys. The most frequently associated drugs are anticonvulsants, allopurinol, minocycline, sulfasalazine, and abacavir.[27-28] In the case reported in this study, there was renal impairment, thrombocytopenia, and eosinophilia, and the suspect drug was allopurinol, whose causal relationship with DRESS is well described.

There is no gold standard method for assessing ADRs, including the SCARs. However, obtaining complete information regarding the start and duration of use of the medication, start of the reaction, history of similar reactions, responses to the withdrawal of the suspected medication and re-exposure, can help in the early diagnosis and reduce morbidity and mortality.[6] Pharmacodermias have great clinical and prognostic variability and there may be difficulties in differential diagnosis in relation to other skin diseases. Although histological characteristics are often insufficient to confirm the diagnosis, immunohistochemical exams, based on skin biopsy, allow for the identification of cellular actors with precision and of molecules present in situ, effectors and skin targets.[29]

In the five reported cases, skin biopsies were performed, which allowed for a better application of the causality assessment criteria, as both the Naranjo algorithm and the WHO-UMC system include questions about objective evidence and abnormalities in laboratory tests.[16-17]

For the analysis of the cases, it was important to obtain information about the response to the withdrawal of the suspected drug and about the use of other possible aggravating drugs, such as photosensitizers (promethazine and losartan) in case 1. In addition, it is essential to follow the therapeutic protocol after hospital discharge and pay attention to the gradual reduction of the dose of some drugs, such as glucocorticoids, to avoid the exacerbation of underlying diseases, after abrupt withdrawal of the drug, due to the deficiency of cortisol resulting from suppression the Hypothalamic-Pituitary-Adrenal (HPA) axis during the therapy period.[30]

The SCARs tend to increase globally due to the speed of introduction of new drugs, with changes in the patterns of reactions and uncertainties regarding the safety profile.[2] Atopy, genetic variation in drug metabolism, variation of genes in the HLA (Human Leukocyte Antigens) system, comorbidities, underlying disease, active viral infection, the patient's immune status, and concomitant intake of other drugs can alter the rate, presentation, course, and outcome of the SCARs.[6]

Only nearly 50% of the ADRs are detected in pre-marketing tests.[6] In this context, a good pharmacovigilance (PV) service is essential to detect ADRs early and improve knowledge about the benefit/risk ratio of drugs. PV plays an important role in decision-making in pharmacotherapy, both individually and collectively[1].

Clinical observation and spontaneous notification of suspected ADRs are the fastest and most effective methods for generating safety signals, as well as for designing active pharmacovigilance strategies[1].

The probabilistic approach to the causal relationship between medication and event will always leave some uncertainty as to possible alternative causes. Even in epidemiological studies, a statistically significant result will provide an estimate of the probability of an event being caused by a medication, but it does not rule out other causal relationships with other determinants.[30]

Despite the various methods available, there is no causality assessment tool considered to be the gold standard. The Naranjo algorithm and the WHO-UMC scale are, however, more commonly used.[2] In this study, the evaluation was carried out by two methods adopted by the national pharmacovigilance program, the Naranjo algorithm and the WHO-UMC system, as a strategy to reduce the effects of low reliability between methods identified in the literature.[31]

The study hospital has an electronic medical record system (Pront HU), through which it is possible to report suspected ADRs to the PV service. However, it is a tool little known by the health professionals. During the study, a suspected SCAR (case 5) was identified by the lead author, during her clinical activities, having asked the physician to make the notification to the PV service. Therefore, it was the only case notified to the Anvisa. Such situations can be recurrent in hospitals, even in those with PV services. Therefore, it is important to expand the dissemination of the tool available in the hospital's system, as well as the role of hospital PV.

The results obtained supported the proposal for a model of active pharmacovigilance of severe pharmacodermia, which includes the encouragement of notification directly in Pront HU and the active search for suspected pharmacodermia, through systematic consultation of the opinions requested from the Dermatology service and from the electronic medical records. For any of the forms of monitoring, PV must carry out an investigation of the cases with the clinic, in order to obtain more detailed information. In this context, the clinical pharmacists, in the exercise of their practices and in direct contact with hospitalized patients and the multidisciplinary team, can contribute to the detection and investigation of SCARs, as in case 5 of this study.

To improve patient safety, it is essential to develop a culture of investigation and communication, which includes the ability to gather more complete information about adverse reactions and medication errors.[32] In this sense, active PV methods are important to complement information from spontaneous notifications. The results of this study and the suggested proposals can contribute to the effectiveness of national post-marketing surveillance and patient safety programs.

Conclusion

The study reported five cases of severe pharmacodermia diagnosed by the Dermatology service in a university hospital. The causality of the SCARs was assessed by the two methods most commonly accepted and recommended globally. As it deals with rare, serious, unpredictable, and life-threatening adverse reactions, this study contributes to add knowledge and understanding about severe pharmacodermia, in terms of the nature of the reactions, identification of patients at risk, their early detection, and the medications responsible. The limitations of the study are inherent to the case series, which are retrospective without a comparison group, whose sources are clinical records, which are not always complete, and which do not allow for generalizations. As a contribution, the study proposed a model for monitoring serious adverse skin reactions to be implemented in the hospital, which combines passive and active pharmacovigilance strategies. The model, applicable to other hospitals, involves the multidisciplinary health team, with strategic participation by the pharmacist. It was intended to contribute to increase the detection of severe pharmacodermia and encourage notification, which are fundamental aspects for the effectiveness of post-marketing surveillance and patient safety policies.

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Collaborators

CFGRC and GCM participated in the conception, design, and planning of the study. CFGRC participated in data collection and interpretation, and also wrote the article. NCF participated in data collection, discussion of the results, and critical review of the article. GCM and CAAT coordinated the project, participated in data analysis and discussion, and critically reviewed the article. All the authors are responsible for the information presented in the paper and approved the final version of the manuscript.

Conflict of interests statement

The authors declare that there are no conflicts of interest regarding this article.

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