International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 02 Issue 12 December 2022

Page No: 1447-1451

DOI: https://doi.org/10.47191/ijmscrs/v2-i12-15, Impact Factor: 5.365

Drug Eruptions: A Challenge for Dermatologists and First Contact Physicians

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ABSTRACT

Adverse drug reactions are quite frequent in current medical practice, being the skin manifestations the most commonly observed, and although they generally have a benign and self-limiting evolution, but in exceptional cases they can be serious and even fatal. The priority in the evaluation of toxicoderma is established in the identification and distinction of severe skin adverse reactions, the so-called SCAR, among which include Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome/drug reaction with the presence of eosinophilia and systemic symptoms (DISH-DRESS), to which should be added acute generalized exanthematous pustulosis (AGEP). Unfortunately, however, our current knowledge does not allow us to determine the true incidence of these reactions, to establish the diagnosis and its causal relationship with certainty, or even to be able to anticipate its appearance.

ARTICLE DETAILS

Published On:
08 December 2022

Available on:
https://ijmscr.org/

INTRODUCTION

Toxicoderma is defined as adverse drug reactions that occur on the skin. There are multiple types of skin drug reactions, with the most varied clinical aspects. On the other hand, toxicodermas can imitate an endless number of skin diseases, being considered for this reason, as in the case of syphilis, the great imitator. The severity of toxicodermas is highly variable. [1]

But in certain cases it can be important, with great risk to the lives of patients. This is especially serious in certain severe reactions, including drug hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms, Steven-Johnson syndrome/toxic epidermal necrolysis, and to a lesser extent in acute rash pustulosis. [2]

ETIOPATHOGENESIS

Virtually any drug can cause skin involvement. There are certain predisposing factors for skin reactions to medications. Drug reactions are more frequent in children due to the immaturity of their enzymes, and especially in the elderly because they receive drug treatments more frequently, many times polymedicated, with the consequent possibility of interactions between different drugs, they make dosage errors more frequently and they are more likely to have physiological or pathological alterations in the absorption, distribution and elimination of drugs.[3]

Patients with renal or hepatic disorders have a higher incidence of toxicoderma, since the degree of drug clearance is altered. Genetic polymorphisms of the different enzymatic systems mean that, for example, in patients with slow acetylators, adverse effects can occur with lower doses of the same drug. Reactions in women are slightly more frequent, since they tend to have a lower body mass and standard doses of drugs are used regardless of the gender and weight of each patient. [4]

Drug reactions are more frequent in patients who have had drug reactions before. Generally, the higher the dose, there is a greater risk of a drug reaction. [5]

Drug reactions are more frequent in the parenteral route than in the oral route. Sun exposure can trigger adverse drug reactions (photoinduced toxicoderma) or worsen them. There are certain viruses that increase the risk of drug reactions, such as the Epstein-Barr virus, which causes 90% of infected patients who take amoxicillin to have drug reactions. There

are two types of drug reactions, type A or dose-related, and type B or non-dose related. Type A constitutes approximately 80% of toxicodermas and are predictable based on the pharmacology of the medication; these include toxicity or overdose, secondary effects, side effects, the Jarisch-Herxheimer reaction, and drug interactions. Type B includes metabolic idiosyncrasies, nonimmunologic activation of effector pathways, and immunologic reactions. Within the immunological reactions, according to the Gell and Coombs classification. [6,7]

CLINICAL MANIFESTATIONS

Maculopapular rash

The most common clinical picture is maculopapular rash, which occurs in up to 3% of hospitalized patients. The most frequently implicated drugs are antibiotics (beta-lactams, sulfonamides, etc.), antiepileptics (carbamazepine, lamotrigine, valproate, etc.), allopurinol, etc. The characteristic lesions are erythematous macules or papules that sometimes coalesce to form plaques of different sizes. The most frequent location is the trunk and the roots of the extremities, and the lesions are not usually specific, so diagnosis is complex. [8]

There is usually no involvement of the mucosa. The main differential diagnosis is with viral exanthemas and thus, sometimes, the lesions resemble measles (morbilliform exanthemas) and other times scarlet fever with involvement of folds and desquamation (scarlatiniform exantemas. [9]

On occasions, the lesions may coalesce to form erythroderma (involvement of practically the entire skin surface), which is a serious condition that can cause thermoregulation abnormalities and increased cardiac output. The lesions resolve without leaving pigmentation a few days after discontinuing the offending drug. Treatment is suppression of the drug involved, oral antihistamines, topical corticosteroids and, in extensive cases, oral corticosteroids. In cases that present with erythroderma, medical admission with hydroelectrolytic support treatment is necessary. [9]

Erythroderma

The term erythroderma defines erythema and scaling of more than 90% of the body surface. The causes of erythroderma are medications, but also primary dermatological conditions such as atopic dermatitis and psoriasis, as well as cutaneous lymphoma (Sezary syndrome). 20% of erythroderma is caused by drugs, the most frequent being allopurinol, penicillin, barbiturates and gold salts. [10]

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DISH-DRESS)

It is characterized by the appearance of a severe maculopapular drug rash accompanied by eosinophilia in the blood count and systemic symptoms. The rash is usually more intense than in mild toxicodermas with facial involvement, more edematous and infiltrated lesions with their confluence and with a more violaceous coloration of the lesions; sometimes manifests as erythroderma. Fever is the most common symptom, being present in more than 90%, and is usually accompanied by general malaise, lymphadenopathy, and multiorgan manifestations. [11]

The picture presents a mortality of 10% that is usually caused by fulminant hepatitis with hepatic necrosis. Multiorgan involvement includes a wide variety of organs such as myocarditis, pericarditis, interstitial nephritis, encephalitis, meningitis, colitis, and thyroiditis. Liver involvement is the most frequent, occurring in 50-60% of patients. Historically it was related to phenytoin, even being called phenytoin hypersensitivity syndrome, changing the name when many other drugs were involved. The most frequently implicated drugs are anticonvulsants and sulfonamides. The latency period between the administration of the drug and the onset of symptoms ranges from two to six weeks. The clinical diagnosis must include an examination of the lymph nodes and be completed with laboratory tests and imaging tests to assess internal organ involvement and eosinophilia in the complete blood count. Topical corticosteroids can be used as treatment, but the use of systemic corticosteroids is generally necessary. Admission to an Intensive Care Unit is required, consulting the different specialists depending on the affected organs. [11]

Urticaria/angioedema

They are indistinguishable from urticaria produced by other mechanisms. They are produced by a type I immune mechanism. The drugs that most commonly produce them are non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. The characteristic lesions are wheals or wheals, which are erythematous, edematous plaques without desquamation, intensely pruritic and evanescent, with individual lesions disappearing in less than 24 hours. The picture appears a few hours or days after taking the medication. In angioedema, the inflammation is deeper and the patients present pain, this condition being much less frequent. [12]

Anaphylaxis is the most severe form of type 1 hypersensitivity reaction and is characterized by multi-organ symptoms with pruritus, urticaria, angioedema, laryngeal edema, nausea, vomiting, tachycardia, and occasionally shock. Medications are the second or third cause of anaphylaxis. Lichenoid eruptions These are similar to lichen planus with itchy violaceous papules and plaques. The lesions usually leave a transient postinflammatory pigmentation after their resolution. Unlike idiopathic lichen planus, mucosal involvement is rare and Wickham's striae are not usually seen. The most common drugs that cause it are angiotensin-converting enzyme (ACE) inhibitors, diuretics, antimalarials, and gold salts. [13]

Drug introduction can precede toxicoderma by months or even years, making diagnosis often difficult. The treatment is the interruption of the administration of the causative drug and the prescription of topical formulations of corticosteroids and antihistamines. Very purging and extensive cases may

benefit from short courses of oral corticosteroids. Phototoxic and photoallergic reactions Require topical or systemic administration of a drug and solar radiation. They can be produced by two different mechanisms, toxic and allergic. [13] Phototoxic reactions can occur in any individual from the first administration, while photoallergic reactions only occur in previously sensitized patients. The lesions are identical to those of eczema, being edematous and vesicular at times and later scaly. They are usually located in sun-exposed areas such as the face, neckline, arms and legs. There are many medications that cause photoinduced reactions including NSAIDs, ACE inhibitors, tetracyclines, and diuretics. Epicutaneous tests (photopatch) are used to establish the diagnosis. Treatment includes stopping the medication involved, avoiding sun exposure, and topical antihistamines and corticosteroids. [13]

Multiform exudative erythema

It is a picture generally produced by the herpes virus or Mycoplasma, but sometimes it can be caused by medications. It is characterized by papular lesions or erythematous, intensely edematous plaques in the shape of a cockade or target, located symmetrically in acral areas, especially hands and elbows. In drug cases, treatment is suspension of the drug involved, in addition to topical or systemic corticosteroids depending on the severity of the symptoms. Steven Johnson syndrome/toxic epidermal necrosis Currently, both entities are considered to be the two extremes of the same disease. [14]

They are the most serious pictures of toxicoderma that exist. They are generally produced by medications, although there are some cases related to infections. The list of drugs involved is very long, the most common being sulfonamides, anticonvulsants, NSAIDs, allopurinol, and some antibiotics. The clinical picture is characterized by erythematous or erythematous-violaceous plaques, some of which may be in the shape of a target that evolves into large blisters that, when broken, leave large areas of erosions and, on occasions, ulcers. Nikolsky's sign is typical, consisting of detachment of the epidermis with superficial friction of the skin. [15]

There is involvement of the oral mucosa in 80% of cases in the form of vesicles and blisters that usually heal with the formation of scabs that are usually observed on the lips. It is common to observe systemic symptoms such as pain in the skin, eyes and mucous membranes, headache, rhinitis, malaise and myalgia. Based on the affected body surface, a classification has been made, calling Stevens Johnson syndrome in cases with an extension of less than 10%, overlapping syndrome in cases with a surface area of 10-30%, and toxic epidermal necrolysis in cases in which there is more than 30% affection. The severity of the condition and its prognosis can be established using the SCORTEN scale, which takes into account factors such as age, malignant diseases, affected surface, heart rate, BUN, glycemia, and serum bicarbonate. In cases with more than 5 negative factors, mortality is 90%.[16]

Diagnosis is clinical and can be complemented by performing a skin biopsy that will show intense keratinocyte necrosis affecting all epidermal layers, accompanied by dermoepidermal detachment with a variable degree of superficial perivascular inflammatory infiltrate. The most important treatment, apart from the identification and suspension of the drug involved, is supportive, including local cures and an adequate intake of calories, fluids, and electrolytes. The use of systemic corticosteroids has not been shown to be useful. There is also no consensus regarding the use of intravenous immunoglobulin. The most recent trend to use tumor necrosis factor inhibitors or cyclosporine also lacks definitive clinical data. [17]

Permanent drug erythema

It is a condition characterized by the appearance, a few hours after taking a drug, of one or several lesions in the form of an erythematous and intensely edematous plaque that can present vesicles and even bullae, and that always affects the same zone or zones. The appearance in the genital area is quite frequent. The lesions usually leave behind an area of residual hyperpigmentation. After successive administrations of the medication, the onset time decreases. The most involved agents are NSAIDs and antibiotics (sulfonamides and tetracyclines). The diagnosis is usually reached by such characteristic symptoms, and epicutaneous tests can be performed that consist of placing a patch impregnated with the suspected drug in the area where the lesions appear. These tests are useful in the case of anti-inflammatory reactions, but are not very reactive in the case of antibiotics and allopurinol. Treatment consists of discontinuing the drug and topical application of corticosteroids. [18,19]

Acral erythema

Acral erythema, also known as manopie syndrome or palmoplantar erythrodysesthesia, is characterized by paresthesias and a sensation of local pain, followed by symmetrical erythema and edema on the palms and soles that, on some occasions, may progress to blistering and necrotic lesions. It usually appears in cancer patients undergoing treatments with doxorubicin, docetaxel and capecitabine. [20]

Contact dermatitis due to topical medications

They occur after the topical administration of medications on the skin. The lesions produced are eczematous and can be acute, subacute or chronic with erythema, vesiculation and desquamation. Initially they are located in the drug administration area, although they can later spread. The drugs most frequently implicated are NSAIDs and antibiotics, and there may be cases of contact dermatitis even from topical corticosteroids. In this type of reaction, the diagnosis is made by epicutaneous tests. The treatment is the suspension of the offending drug and the application of topical corticosteroids and antihistamines. [21]

Pemphigus and medicamentous pemphigoid

These are autoimmune diseases mediated by antibodies against certain antigens of the epidermis or the dermal-epidermal junction that lead to detachment of part or all of the epidermis with the formation of blisters and erosions. Medications can induce the disease or trigger it in predisposed individuals. The drug most implicated in the case of medicamentous pemphigus is d-penicillamine, followed by ACE inhibitors and antibiotics. The picture is similar to that of idiopathic pemphigus foliaceus, beginning with an urticarial or morbilliform picture followed by pemphigus lesions. Regarding medicated pemphigoids, the patients involved are usually younger than those with the idiopathic variant. The most frequently associated drug is usually furosemide. In both cases, treatment is suppression of the drug involved, local cures for blisters and erosions, and topical and/or systemic corticosteroids depending on the severity of the condition. [22]

Panniculitis

Panniculitis is inflammation of the fatty panniculus or subcutaneous cellular tissue that generally affects the distal areas of the lower extremities. Drug panniculitis is usually of the erythema nodosum type, and the lesions are hot erythematous nodules on the legs that may be accompanied by fever and systemic symptoms. The most common causative drugs are oral contraceptives, sulfonamides, and vemurafenib has recently been implicated. Diagnosis is based on clinical examination and skin biopsy. Treatment consists of rest with the legs elevated, application of local cold and, if the lesions are very painful, oral NSAIDs, potassium iodide, colchicine or oral corticosteroids may be prescribed. [23]

DIAGNOSIS OF TOXICODERMAS

Clinical history

The diagnosis of toxicodermas is based on the clinical history and physical examination. It must be taken into account that the same medication can cause a multitude of different skin conditions, and that the same clinical condition can be caused by many different medications. This means that reaching an exact diagnosis is, on many occasions, very complicated or even impossible, especially when the patient often receives multiple drugs. Thus, in most cases, the diagnosis is based on the probabilities of each drug having caused the reaction in question, based on existing publications and pharmacovigilance databases. [24]

There are publications of databases of drug reactions and even mobile applications that can facilitate the task. It is possible to use different algorithms that establish probability scales, taking into account factors such as the temporal sequence (time between drug administration and the appearance of toxicity), prior knowledge of this type of reaction (based on scientific literature), the effect of the withdrawal, the effect of a new administration and the existence of an alternative cause to the medication. Among the best known algorithms are those of Karch-Lasagna, Naranjo and the one proposed by the World Health Organization. [25]

Skin tests These tests are not useful at the time of onset of toxicoderma, since they are performed when the condition has already resolved. Depending on the type of suspected reaction, they are of different types. For IgE-mediated toxicoderma, prick tests can be performed, administering the drug using a lancet to the very superficial dermis and intradermal reaction with different dilutions of a drug (the latter can also be useful in non-IgE-mediated reactions). In reactions produced by cellular immunity, epicutaneous or contact tests are used, in which a dilution of the suspected drug is administered in a patch that is left on the surface of the skin for 48 hours, taking a reading of the results at the time after removing the patch and 96 hours later, it being possible to perform a third reading a week if the previous two have been negative. [26]

Challenge tests These consist of re-administering the suspected drug in a hospital setting. With these tests a certain diagnosis can be reached but, since the reaction that can be triggered can be serious, they are reserved for selected cases and must be carried out under medical supervision and prior informed consent. Skin biopsy Sometimes, especially when the differential diagnosis with other primary skin diseases is not clear, a skin biopsy can be performed and its subsequent histological study. [27]

The histopathological findings, like the clinical findings, can be highly varied and, on many occasions, nonspecific. The most common findings in histological samples are apoptosis and eosinophilia, in addition to other specific findings for each type of toxicoderma. In vitro tests They can be performed if the antigenic component is known, as occurs with beta-lactams. There are more complex techniques that are mainly used in research studies, such as lymphocyte blast transformation tests and histamine release and basophil degranulation tests. [28]

CONCLUSIONS

By simulating drug eruptions many times to a multitude of idiopathic dermatological clinical pictures, diagnostic tests for these skin diseases can be useful, such as serologies for different types of microorganisms (Epstein-Barr virus, cytomegalovirus, herpes simplex virus, parvovirus B19, etc.), as well as the histological findings of the biopsies in the cases in which these have been performed

In the description of the different types of Drug eruptions, the different treatments have been briefly described, being the basis in all cases the identification and suspension of the drug involved. In addition, symptomatic treatment with topical corticosteroids and antihistamines can be added and, in extensive or highly symptomatic cases, oral corticosteroids can be used. In severe drug reactions, hospital admission under close medical supervision is necessary, as well as the necessary support measures to guarantee the hydroelectrolytic balance, local care for erosions and blisters,

and the use of antibacterial medications if there is superinfection of the lesions.

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