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Review

Mild cutaneous reactions to drugs

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Summary. Adverse reactions to drugs are not frequent in childhood. Cutaneous reactions are the most frequent in this age group. Mild cutaneous reactions are immediate or delayed adverse reactions that do not seriously compromise the clinical condition of children. The patients usually early improve and recover the state of health. Although it is difficult to define the prevalence accurately, we could affirm that the rate adverse reaction to drugs are often over estimated by both the families and the physicians. Therefore, children may be prone to loss of school days and inappropriate or sub-optimal treatments. However, the identification of a true adverse reaction to drugs allows adequate treatment and alert to further exposure to harmful drugs. (www.actabiomedica.it)

Key words: drug hypersensitivity reactions, children, skin test, specific IgE, drug provocation test, exanthema, urticaria

Introduction

An adverse drug reaction (ADR) is defined by the World Health Organization as "a response to a medicine which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" (1). Cutaneous adverse drug reaction (CADR) may be defined as an undesirable manifestation of the skin resulting from administration of a drug. CADRs are reported as type of ADRs (2) in either adult population and pediatric population (1). CADRs represent about 35% of all suspected ADRs in children (3). It could be estimated that 2.5% of children who are treated with a drug, and up to 12% of children treated with an antibiotic, will experience a CADR (4). Reactions are more frequently reported following intake of antimicrobials, neurology drugs, and dermatological agents (3). CADRs can be divided into different classes based on pathogenesis and clinical morphology. On the basis of pathogenesis, they are divided into 2 categories. Type A ("augmented") reactions are related to the pharmacologic effects of a drug and are dose dependant, predictable or expected, mild to moderate in severity. Type B ("bizarre") reactions are not related to the pharmacologic effects of a drug, are not dose dependent (occurring with low doses of medication too), unpredictable, idiosyncratic,

Table 1. Mild cutaneous adverse drug reaction

Exanthematous Drug Eruptions
- Maculopapular rash (morbilliform, scarlatiniform rubelliform eruptions)
- Eczematoid-like pattern
- Psoriasiform-like pattern
- Lichenoid-like pattern
Urticaria
Fixed Drug Eruptions
Photosensitivity Reactions
- Phototoxic reactions
- Photoallergic reactions
Other
- Serum Sickness–Like Reactions
- Acneiform eruptions

often severe (5, 6). Such reactions have been categorized as immunologic hypersensitivity (allergic) reactions, pseudo-allergic, and idiosyncratic (5,7). At variance from adults, type B reactions are more common in children. CADRs can also be identified on the basis of the clinical presentation. Distribution, morphology, configuration, and progression of the lesions should be adequately described. At least 29 mild to rarely severe clinical presentation of cutaneous drug reactions have been identified (8-12). We will discuss only mild cutaneous reactions in childhood (Table 1).

Exanthematous Drug Eruptions

Exanthematous drug eruptions (EDEs) include maculopapular rash (morbilliform, scarlatiniform rubelliform eruptions), eczematoid/psoriasiform/ lichenoid-like pattern (based on similarity with infectious or inflammatory diseases) (13). They are the most common CADR in children (8, 14) and occur in 1-5 % of cases at first drug exposure (15).

The most common type of EDEs is maculopapular rash (MPR) that is characterized by erythematous macules evolving in papules from 1 to 5 mm in diameter and may coalesce in plaques. MPR involves face, neck, or upper trunk and tipically spreads bilaterally and symmetrically toward the limbs. MPR could be accompanied by pruritus and mild fever (16). MPR is self-limiting and resolves within 7-14 days after stopping the drug. With resolution, lesions may become brownish and desquamation may occur. EDEs are usually considered delayed-type hypersensitivity reactions, although evidence of such a mechanism is rare. There is a distinguishing timing of occurrence of lesions (17). At the first drug exposure, lesions appear after a sensitization phase, 5-14 days after the start of therapy and sometimes after drug discontinuation (8). In previously sensitized patients, skin lesions develop following re-exposure to the same drug in 6 hours to 5-7 days. The most common implicated drugs include beta-lactams, sulfonamides, and antiepileptic medications (18). EDE develops in 5% to 10% of patients treated with ampicillin. This frequency increases substantially during a viral infection. Children who are infected with the Epstein-Barr virus are at increased risk of rash (19). In EDE, patch test and provocation test should be used to identify the culprit drug (20, 21). The management of EDE is supportive. Pruritus can be treated with topical steroids, emollients, oral antihistamines. Second generation H1 blockers are associated with fewer sedative effects when compared with first generation H1 blockers (22, 23). A post-inflammatory hypopigmentation or hyperpigmentation may follow which vanishes over months or years, and sun avoidance or protection should be advised (24). The choice of suspending the offending drug must be made on individual basis. It is unclear whether continuation of a drug can lead to Steven-Johnson Syndrome (25). Topical steroids and emollients are therapeutic options in children with eczematous reactions (26).

Urticaria

Drug-induced urticaria is one of the most common drug eruption along with EDEs and represents approximately 5% of all cutaneous drug eruptions (27, 28, 29).

Urticaria is characterized by wheals due to swelling of the dermis and/or angioedema due swelling of lower dermis and subcutis or mucous membranes (30). Wheal are characterized by central swelling surrounded by an erythematous area and pruritus (rarely burning) (30). Each wheal resolves in 24 hours but new

lesions may appear. Urticaria caused by drugs is usually acute, and rarely chronic (>6 weeks) (31). Acute urticaria is triggered by drugs in about 7% of children and beta-lactams followed by non-steroidal anti-inflammatory drugs (NSAIDs) are the most common causative drugs (32). Drug-induced urticaria is due to mediators, including histamine, and citokines released by activated mast-cells (31). Mast-cells can be degranulated by an IgE-mediated mechanism or directly by the drug (33). NSAIDs usually elicit a nonimmune mediated urticaria and should be cautiously administered in children with chronic urticaria since it may aggravate symptoms (34).

In acute urticaria, skin prick test should be used to identify the offending drug. Drug provocation test should be performed when it is appropriate (21, 30) in a setting where personnel and emergency treatment is available (35). Treatment includes discontinuation of the causative drug and administration of 2nd generation H1-antihistamines (32). If there are sleeping problems caused by pruritus, sedative antihistamines could be used at night, but do not improve control of symptoms (36). Oral corticosteroids in addition to antihistamines may be beneficial (37). The problem arises when the causative drug cannot be halted and urticaria is not controlled by reliever medications. In these cases, probiotics that are mainly used in the prevention of infectious diseases (38, 39), seem to be promising in reducing symptoms (40).

Fixed Drug Eruptions

Fixed drug eruptions (FDEs) are common in children, accounting for approximately 10-14% of cases of drug eruptions (41, 42). FDEs begin as soon as 30 minutes-8 hours after drug intake and as long as 2 months after drug exposure (8, 13). Lesions are characterized by well-demarcated, solitary or multiple papules or plaques. Their colour varies from dusky red to violet. They can be intensely pruritic (8). Lesions resolve in 7-10 days but hyperpigmentation can persist for years (24). The sites of lesions include lips, trunk, legs, arms, and genitals. Genitals are affected particularly in adolescents. Most reactions occur in multiple sites (43-48). Multiple lesions are rarely associated with systemic symptoms including malaise, high fever, nausea, and arthralgia (49-52). In previously sensitized patients, a flare develops at the same site following re-exposure (8, 53) to the offending drug within 1-8 hours (54). In the pediatric population, the most common drugs that cause FDEs are: antimicrobials (amoxicillin, teicoplanin, vancomycin, co-trimoxazole), NSAIDs (paracetamol, ibuprofen, nimesulide, naproxen, metamizol), barbiturates, sulphonamides (55).

The exact pathogenic mechanisms remain unknown. However, there is evidence that it is a CD8+ T-cell mediated reaction. The offending drug may induce local reactivation of memory CD8+T-cell lymphocytes localized in epidermal and dermal tissues and targeted initially by the viral infection and protect against the virus (53, 56). FDEs are probably underdiagnosed in primary care (57). The gold standard for diagnosis of FDEs is re-challenge, depending on the severity of the initial reaction (13). The cornerstone of the treatment is discontinuation of the causal drug that can worse the lesions (8). Management of FDE is supportive and is based on topical steroids.

Photosensitivity Reactions

Drug-induced photosensitivity refers to the development of cutaneous disease due to the interaction between a given chemical agent and sunlight (58). Exposure to either the chemical or the light alone is not enough to induce the disease. When photoactivation of the chemical occurs, one or more cutaneous manifestations may arise. In general population up to 8% of cutaneous drug eruptions are photosensitivity reactions (59), in infants and children the prevalence is quite low because of the restricted use of causal drugs. such as: hydrochlorothiazide and doxycycline. Based on their pathogenesis, they can be classified as phototoxic or photoallergic drug eruptions, although in many cases it is not possible to determine whether a particular eruption is due to a phototoxic or photoallergic mechanism (60).

Drug-induced phototoxicity occurs when photoradiation interacts with a chemical within the skin to generate free radicals, which induces host cytotoxic effects. The site of the eruption coincides with sun-

exposed areas of the skin. Phototoxic reactions are non-immunologic and dose dependant and often occur soon after initial ingestion of the drug. There are 3 general variations of phototoxic reactions (61). The first is an intense and delayed erythema and edema that occurs 8 to 24 hours after exposure to sunlight. This reaction can involve hyperpigmentation and be a darker red than sunburn. Hydrochlorothiazide is an example of a trigger for this first type of phototoxic reaction. A second, more-immediate variation can occur within 30 minutes after light exposure and can last for a day or two. In this variant, erythema occurs without edema and is accompanied by local burning and pruritis. This more-immediate variation is often associated with doxycycline and the coal-tar derivatives such as anthracene and acridine. The third variant is associated with porphyrins and manifests as a rapid, transient, urticarial-like eruption that can be activated by room lighting.

In contrast, photoallergic reactions occur after a period of sensitization and can reoccur with small doses of the offending drugs. The reactions may appear with papulovesicular eruption, pruritis, and eczematous dermatitis 1 to 14 days after exposure to sunlight. Photoallergic reactions should be differentiated from lupus, solar urticaria (61-65).

Phototesting and photopatch testing can be useful for achieving the diagnosis. The mainstay of management is prevention, including informing patients of the possibility of increased sun sensitivity and the use of sun protective measures. Moisturizes and emollients can be useful to treat the burning. In severe cases, topical antibiotic can be considered for vesicles and blisters. Oral antihistamines and topical corticosteroids can provide symptomatic relief of skin lesions due to photoallergic reactions (13, 61).

Other forms

Serum Sickness-Like Reactions (SSLRs) are characterized by fever, pruritis, urticaria, and arthralgias (13). Lymphadenopathy and eosinophilia may be present. Unlike the "true serum sickness reaction", SSLRs do not exhibit immune complexes, hypocomplementemia, vasculitis, or renal lesions (25). They have claimed mostly associated with cefaclor therapy. The development of bacterial resistance to cefaclor has limited its utility in the treatment of pediatric infections (66). For this reason, SSLRs might be less common now than in the past. Cross-reaction of cefaclor with other beta-lactam antibiotics is rare and, in general, other cephalosporins are well tolerated (67). However, some physicians recommend that all beta-lactam antibiotics should be avoided in patients who have experienced cefaclor induced SSLR (68).

Other drugs that have been implicated include biological agents (efalizumab, omalizumab, rituximab, infliximab) (69-73), antibiotics (meropenem, minocycline, ciprofloxacin, rifampicin) (73-79), antimycotics (griseofulvin, itraconazole) (80, 81) and other agents such as bupropion (82), clopidogrel (83), fluoxetine (84), insulin detemir (85), immunoglobulin (86), mesalamine (87), or streptokinase (88).

SSLRs usually occur 1-3 weeks after drug exposure and resolve soon after drug discontinuation (25). The suspected drugs should be avoided by patients who had SSLRs. The underlying cause of SSLRs remains unknown. Therefore, treatment is symptomatic, consisting in identification and discontinuation of the offending drug. Antihistamines are prescribed in case of urticaria and NSAIDs in case of persistent arthralgia and/or arthritis. It is unclear whether a short course of systemic glucocorticoids improves SSLRs (89).

Acneiform eruptions are pustular induced eruptions by drugs that often affects the arms and legs at variance from acne vulgaris. The lesions are usually monomorphous and heal without scarring. They occur with iodides, bromides, adrenocorticotropic hormone, corticosteroids, isoniazid, androgens, lithium, actinomycin D, and phenytoin. Topical medications that are oil-based could be the cause of a type of acne known as pomade acne. Sometimes corticosteroids worsening testosterone-induced acne within 2 weeks by the beginning of treatment. The risk appears to be directly proportional to the dose and duration of the therapy and severity of pre-existent acne (90). Treatments is the same as acne vulgaris and include topical benzoyl peroxide, topical antibiotics, and topical tretinoin (25).

Conclusions

CADRs are a frequent reason of primary care visit (91). In childhood there is a misattribution of cutaneous drug reactions. Diagnosis could be difficult because CADRs can closely mimic other diseases (e.g., viral infections); the identification of the causative drug can become complex especially in the patient on treatment with more than one drug.

CADRs are confirmed with a drug challenge in a very low number of cases (92, 93). Furthermore, the anxiety of parents could mislead the clinician to consider the child "allergic" to a drug (7). In the case of a true allergy the drug involved should be avoided. On the other hand, an incorrect diagnosis can limit therapeutic options and increase the risk of using more toxic, less effective and more expensive drugs (94). A detailed history is necessary in order to evaluate the real occurrence of the adverse reaction. Therefore, good management of suspected CADRs requires an efficient method of estimating the probability of the drug reaction. Causality assessments based on clinical history, such as the Naranjo assessment (94), have proven to be a valid method of estimating the probability of ADR (18, 95-100) but provocation test is the gold standard in the diagnosis of ADR (21).

Conflict of interest: None to declare

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