REVIEW

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Drug Eruptions

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ABSTRACT

Drug reaction are seen in the 8% of the general population; this number rises to 15% in the hospitalized patients. Drug eruptions can be classified according to the prognosis: benign reactions and malignant reactions. Second, they can be classified according to the clinical type as mild, moderate and severe reactions. This article dwells upon the clinical characteristics and treatment of drug eruptions.

Keywords: Drug, Moderate, Reaction, Severe

Introduction

Drug reactions are defined by the American Association of Dermatologists as any unwanted change in the skin, skin appendages or mucous membranes due to a drug; and as any unpredicted and harming reaction observed due to a drugs given at doses within the normal limits by the World Health Organisation. The prequistes for a reaction to be considered as a drug reaction are [1,2]:

- The dosage of the drug was within the normal limits,
- The reaction was unpredictable,
- The reaction was harmful for the patient.

Epidemiology

Drug reaction are seen in the 8% of the general population; this number rises to 15% in the hospitalized patients. The drugs that are known to cause unprectable reactions are penicillin, sulphonamides, non-steroidal anti-inflammatory drugs and anti-epileptic drugs. Symptoms are seen 8 to 21 days within the drug intake. The duration between the ingestion of the drugs and the initiation of the symptoms varies according to the disease presentation. The most commonly seen types of drug reactions are morbiliform drug reactions and urticaria; which are mild reactions that are not complicated [3,4,5].

Female patients are at increased risk for drug reactions compared to male patients. These reactions are seen more commonly in adults than in children. Patients of African American descent are at increased risk as well. Patients suffering of viral infections, eg. HIV, cytomegalovirus and Epstein-Barr virus, have a predilection for drug reactions. Comorbid diseases such as renal or hepatic insufficiencies increase the risk of drug reactions as well [6].

Classification

There are two different classification schemes of drug reactions. First, it can be classified according to the prognosis: benign reactions and malignant reactions. Malignant reactions have the potential of being fatal and are seen in 0.1% of the population. Second, it can be classified according to the clinical type as mild, moderate and severe reactions [7].

Severe Drug Reactions

Severe drug reactions require immediate diagnosis and treatment; and are as follows [3]:

- Anaphylaxis,
- Anticoagulant induced skin necrosis,
- Acute Generalised Exanthematous Pustulosis (AGEP),

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- Drug Induced Hypersensitivity syndrome [drug rash with eosinophilia and systemic symptoms (DRESS)],
- Generalised bullous fixed drug eruption,
- Steven-Johnson syndrome (SJS),
- Toxic epidermal necrolysis (TEN).

Symptoms suggestive of severe drug reactions are [3]:

- Fever,
- Facial edema,
- Lymphadenopathy,
- Bullous lesions,
- Pustuler lesions,
- Nikolsky positivity,
- Mucosal involvement,
- Systemic signs and symptoms,
- Peripheral eosinophilia, atypical lymphocytosis, increase in liver function test, increased creatinine in the laboratory work-out.

Duration

The time interval between the initiation of drug intake and the appearance of lesions differs according to the type of reaction. The earliest are urticaria or angioedema, which ocur within minutes to hours. AGEP occurs in less than four days. Exanthematous drug reactions ocur within 4 to 14 days. SJS or TEN ocur in 7 to 21 days. The latest reaction is DRESS, which ocurs in 15 to 40 days [5].

Mild (Non-complicated) Reactions

1. Urticaria and/or Angioedema

These reactions ocur within minutes to hours. The most common culprit drugs for urticaria are antibiotics such as penicilin, cephalosporins, sulphonamides and minocycline. Monoclonal antibodies, non-steroidal anitiinflammatory drugs and radiocontrast media may also cause urticaria or angioedema. Furthermore, aspirin or non-steroidal anti-inflamatory drugs may cause acute urticarial attacks in patients with chronic urticaria. Angioedema is frequently caused by penicilin, radiocontrast media, angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory drugs and monoclonal antibodies. H1 receptor antagonist antihistamines are used in the treatment of urticaria or angioedema along with the cessation of the culprit drugs [3].

2. Exanthematous Drug Eruption

Exanthematous drug reactions are also known as morbiliform drug reactions or maculopapuler drug reactions. This is the most frequently seen presentation of drug eruptions. It is seen within 7-14 days of the drug intake; this time interval decreases in the following exposures. The high risk drugs are aminopenicillin, cephalosporines, sulphonamides, allopurinol and aromatic anticonvulsants. The eruption starts at the trunks and upper extremities; is maculopapular and urticarial in character. It has symmetrical distribution. Mucosal involvement is not seen. Pruritus may be occasionaly seen. The differential diagnoses are viral exanthems in children. The symptoms cease without complication in a couple of weeks after the culprit drug is stopped. Supportive treatment is usually necessary: topical steroid formulations and oral antihistamines. Systemic streoid treatment may be necessary in recalcitrant cases [3].

3. Fixed Drug Eruption

Fixed drug eruption is seen a couple of days after the intake of the culprit drug. The recurrent attacks ocur within 24 hours. Clinically, one or more oval/circular erythematous and edematous macule with distinct borders are seen. Vesicles, bullae or erosions may be present as well. Lips, face, hands, feet and the genital region are the most frequent locations. The lesions ocur at the same locations in each attack; new locations may be added in recurrent attacks. The lesions fade away within several days, leaving post-inflammatory hyperpigmentation. The most frequent culprits are antibiotics (sulphonamides, tetracyclins, betalactams, flouroquinolones, macrolides), non-steroidal anti-inflammatory drugs, asetaminophen, aspirin, barbiturates, dapsone, proton-pump inhibitors and azole antifungals. Generalised bullous fixed drug eruption should be considered in patients with multiple lesions; and the prognosis is determined according to the extent of epidermal detachment. The treatment is composed of the cessation of the culprit drugs and topical steroid preperations [3].

Potentially Fatal (Complicated) Reactions

1. AGEP

AGEP is also known as pustular drug reaction or toxic pustuloderma. It occurs within four days after the ingestion of the culprit drug. It is important to note that, AGEP presents earlier than exanthematous drug eruption. Multiple edematous small (<5 mm) non-follicular sterile pustules are observed on an erythematous base. Burning and pruritus are common; fever frequently accompanies the eruption. The lesions begin at the face and intertriginous areas; and distrubute witihin hours. Facial and acral edema may also be observed. Neutrophilic leukocytosis, mild eosinophilia, increased liver and renal function test and hypocalcemia are observed on the lab work-out. Subcorneal spongioform pustules are seen in the histopathology. The most frequent causes are antibiotics (aminopenicillins, sephalosporins, clindamycin, sulphonamides, metranidazole), calcium canal blockers (especially diltiazem), hydroxychloroquine, non-steroidal anti-inflammatory drugs,

acetaminophene, terbinafin and proton pump inhibitors. Pustuler psoriasis and TEN may be considered in the differential diagnoses according to the clinical presentation. Treatment includes the cessation of the culprit drugs, oral antipyretics, topical steroids and systemic cyclosporine or corticosteroids if necessary [3].

2. DRESS

DRESS occurs 2 to 6 weeks after the ingestion of the culprit drug, later compared to other drug reactions. Fever accompanies the typical rash that starts morbilifom and then becomes edematous that is showing follicular accentuation. The rash starts at the face, abdomen and upper extremities. Mucosal involvement is not frequent, and is mild if it is present. Liver and renal functions are affected. Lymphadenopaties are seen Facial edema and eosinophilia are characteristic. The most frequent culprit drugs are aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital) and sulphonamides. Less frequently minocycline, allopurinol, dapsone and abacavir may cause DRESS. Maculopapuler drug eruption can be considered in the differential diagnosis due to the cutaneous lesions; however, organ involvement differentiates these two diseases. The culprit drug should be stopped and topical steroids are added in mild cases. Systemic steroids can be added in severe cases [3].

3. SJS and TEN

Both SJS and TEN have high mortality and morbidity. The risk is especially increased in the elderly and HIV positive patients. The symptoms suggestive of SJS and TEN are mucosal involvement, flaccid vesicles and bullae, nikolsky positivity, fever and pain. Symptoms ocur 7-21 days after the ingestion of the drug. Erythematous, dusky macules and patches appear at first, flaccid bullae ocur within hours to days. The disease spectrum is determined according to the body surface area that shows epidermal detachment. If less than 10% is detached SJS is considered. If greater than 30% is detached TEN is considered. Oral mucosa is affected in 70% of the patients, ocular symptoms are seen in 75% of the patients. Gastrointestinal, genitourinary or pulmonary symptoms may be seen as well. The differential diagnoses include erythema multiforme major, generlized fixed drug eruption, staphylococcic scalded skin syndrome, autoimmune bullous diseases and exfoliative erythroderma. Biopsy can be used to differentiate [5].

Mortality is up to 30% in TEN. On the contrary, SJS has a 5% mortality rate. The treatment includes the cessation of the culprit drug and hospitalisation at the intensive care unit. Supportive treatments such as antibiotics and hydration are often necessary. Topical treatment with antibiotics, wet dressings and epitelizing agents are beneficial. Systemic steroids, intravenous immunoglobulins and cyclosporine are contraversial therapies [5].

Ethics

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Authorship Contributions

Concept: D.Ö., T.K.Ü.U., Ö.A., S.S., Design: D.Ö., T.K.Ü.U., Ö.A., S.S., Literature Search: D.Ö., T.K.Ü.U., Ö.A., S.S., Writing: D.Ö., T.K.Ü.U.

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References

1. Warnock JK, Morris DW. Adverse cutaneous reactions to antidepressants. Am J Clin Dermatol 2002;3:329-339.
2. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. Am J Clin Dermatol 2003;4:561-572.
3. Bolognia JL, Schaffer JV, Cerroni L. Drug Reactions. In Dermatology. Philadelphia: Elsevier; 2018.
4. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA 1986;256:3358-3363.
5. Swanson L, Colven RM. Approach to the Patient with a Suspected Cutaneous Adverse Drug Reaction. Med Clin North Am 2015;99:1337-1348.
6. Tüzün Y. İlaç Erüpsiyonları. In Dermatoloji. İstanbul: Nobel Tıp Kitabevleri; 2008. p. 270.
7. Revuz J. When drugs make patients worse. Acta Derm Venereol 2003;83:161.