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Review article

Pharmacovigilance in Dermatology

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ABSTRACT

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems. A huge quantity of adult people suffer from undesired side effects to pharmaceutical products at some stage in the way of their lives and can be classified as expected or A-type reactions and unexpected or B type reactions. The skin is a favoured target organ for B-type reactions and these skin reactions occur in 2–3% of hospitalized patients. Morbilliform drug rashes are the generally happening skin reactions to drugs, constituting up to 90% of all reactions, followed by drug induced urticaria, which constitutes about 6%. The Council for International Organization of Medical Sciences (CIOMS) considers as serious ADRs that are lethal or life-threatening, or need prolonged hospitalization or consequence in persistent or considerable disability or incapacity because hospitalization may depend on the socioeconomic status of the patient and on admittance to health care. The centre of attention of this summary is on pattern of cutaneous ADRs. Case evaluation must commence with a precise explanation of the skin lesions. The documentation of cases should be terminated by photographic pictures which can help for the retrospective evaluation of cases by experts. Concluded that, there is a need of active Pharmacovigilance centre with intensive monitoring for drug induced reactions in the dermatology department

Key words: Adverse drug reactions, Cutaneous drug reactions, Dermatology, Pattern, and Pharmacovigilance

INTRODUCTION

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems. [1] A huge quantity of adult people suffer from undesired side effects to pharmaceutical products at some stage in the way of their lives and can be classified as expected or A-type reactions and unexpected or B type reactions. The skin is a favoured target organ for B-type reactions and these skin reactions occur in 2–3% of hospitalized patients. Morbilliform drug rashes are the generally happening skin reactions to drugs, constituting up to 90% of all reactions, followed by drug induced urticaria, which constitutes about 6%. Severe cutaneous adverse reactions (SCAR) to drugs include:

- Anaphylaxis and angioedema
- Photosensitivity
- Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS)
- B ullous drug reactions, including toxic epidermal necrolysis (TEN)
- Most often involved drugs are
- Antibiotics – in particular b -lactam antibiotics, sulphonamids and fluoro quinolones
- Antiretroviral drugs, such as abacavir and nevirapin
- Allopurinol

- Anticonvulsants
- Contrast media
- NSAIDs
- Cytotoxic drugs such as platinum salt hypersensitivity

A-type reactions include drug toxicity, for illustration, over dosage or usual side effects at a dosage required to attain the desired effect as in the case of chemotherapeutic agents and drug interactions.

Examples of A-type reactions: Skin diseases comprise alopecia induced by chemotherapy, folliculitis induced by anti-EGF treatment, or severe dryness of the skin induced by retinoid treatment.

B-type reactions consequence from the particular properties of each active pharmaceutical ingredient and individual risk factors of the patient. These reaction include intolerance reactions (side effects that occur at low concentrations of a drug), idiosyncracy reactions (reactions depending upon patient-specific genetic or pharmocokinetic characteristics as well as allergic or pseudoallergic reactions.

Example: A pseudoallergic reaction to nonsteroidal anti-inflammatory drugs is implicit as an intolerance reaction, since the pathophysiological origin of this reaction is based upon the ordinary pharmacological effect of COX-inhibition. [2]

The Council for International Organization of Medical Sciences (CIOMS) considers as serious ADRs that are lethal or life-threatening, or need prolonged hospitalization or consequence in persistent or considerable disability or incapacity because hospitalization may depend on the socioeconomic status of the patient and on admittance to health care. The centre of attention of this summary is on pattern of cutaneous ADRs. [3]

Patterns of Cutaneous ADRs [4]

Exanthematous drug eruption

Exanthematous eruptions reported as 'drug rashes' or 'drug eruptions', are the majority common ADRs disturbing the skin. The key mechanism is possibly immunologic, and may match up to type IV delayed cell-mediated hypersensitivity reaction. The eruption typically occurs between 4 and 14 days subsequent to commencement a new therapy and yet a few days after it has ceased. The eruption consists of erythematous macules, papules, often symmetric and begins on the trunk, upper extremities, and increasingly become confluent.

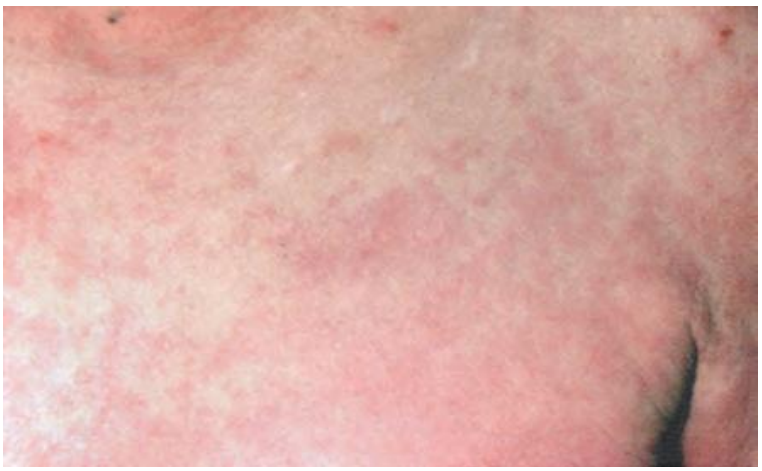

Figure 1- Exanthematous morbilliform eruption

Cutaneous pathological slides display an extremely gentle lymphocytic infiltrate in the region of vessels of the dermis, and a little necrotic keratinocytes within the epidermis. Treatment is mainly supportive, typically after the exclusion of the felonious agent, associated with topical corticosteroid and systemic antipruritic agents. Most drugs can induce an erythematous eruption in about 1% of users. The following drugs had privileged risks are allopurinol, aminopenicillins, cephalosporins, antibacterial sulphonamides and most antiepileptic agents.

Urticaria and Angioedema [5]

Urticaria is a transitory eruption of erythematous and oedematous papules and plaques, habitually coupled with pruritus. When dermal and subcutaneous tissues are concerned, this reaction is known as Angioedema. Urticaria, Angioedema and anaphylaxis might be a type I hypersensitivity

reaction mediated by IgE antibodies. They are localized anywhere on the body, including the palm, soles and scalp. They normally last a few hours and wane within 24 hours. Angioedema is related with urticaria, consisting of pale or pink swellings which affect the face but also buccal mucosa, the tongue, larynx, pharynx, and so on. Urticaria is histologically non-specific with a surface and deep limited infiltrate of mononuclear cells accompanied by eosinophils, neutrophils, oedematous reticular dermis, vascular and lymphatic dilatation.

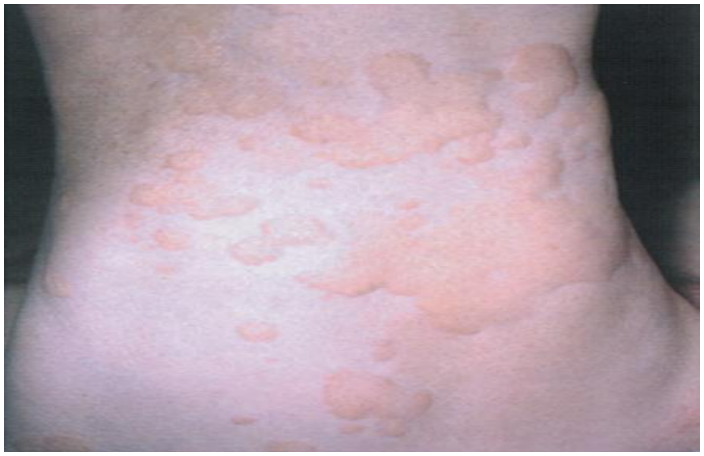

Figure 2-Urticaria with oedematous papules and plaques

The two most frequent causes of drug-induced non-IgE-mediated urticaria and Angioedema are NSAIDs and angiotensin-converting enzyme (ACE) inhibitors. Angioedema occurs in 2 to 10 per 10 000 new users of ACE inhibitors, a rate that is almost certainly higher than the risk allied with penicillins (about 1 per 10 000 courses). Withdrawal of the causative agent is the main treatment.

Photosensitivity [6]

Cutaneous photosensitivity diseases may be idiopathic, produced by endogenous photosensitizers or associated with exogenous photosensitizers like drugs. The relationship of light and a drug can be accountable for acute inflammation of the skin. The photosensitivity reactions are divided into two types like phototoxicity and photoallergy was displayed in table 1.

Table-1- Differences between phototoxicity and photoallergy

Phototoxicity	Photoallergy
Results directly from photochemistry involving the skin	Result of cell-mediated hypersensitivity
Exaggerated sunburn occurring in sun-exposed areas only, hyperpigmentation	Mainly eczematous, pruritic, erythematous, scaling and lichenification dominate
Histologically characterized by epidermal cell degeneration with necrotic keratinocytes, oedema, sparse dermal lymphocytic infiltrate and vasodilatation	------
Minimal dose of UV (UVA more often than UVB) inducing an erythema will be decreased in all subjects during treatment	Removal of the offending agent and/or avoidance of sun exposure. Topical corticosteroid, systemic antipruritic agents may be useful
	Antibiotics (sulphonamides, pyrimethamine, fluoroquinolones), fragrances, NSAIDs, phenothiazine, thiazide diuretics

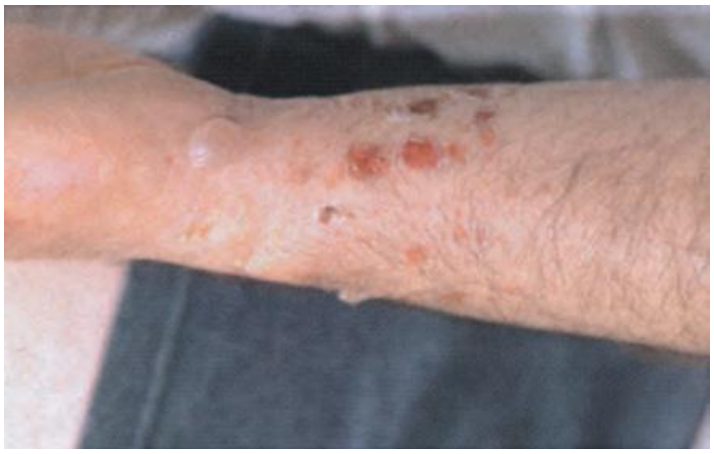

Figure 3- Bullous eruption of the arm (phototoxic eruption on a sun-exposed area)

Vasculitis

Vasculitis corresponds to immune-mediated inflammation and injure to a blood vessel's wall. Direct drug toxicity aligned with a vessel's wall, auto-antibodies reacting with endothelial cells and cell-mediated cytotoxic reactions aligned with vessels were projected as explanations. The specific mechanism is still unknown. It consists of palpable purpuric papules which preponderate on the lower extremities.

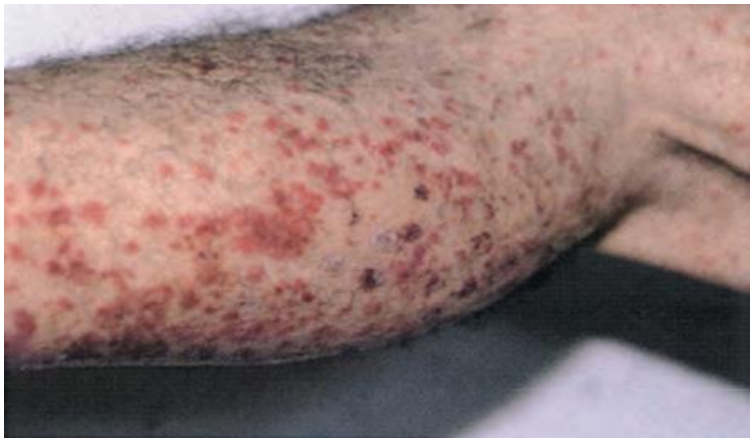

Figure 4- Cutaneous necrotizing vasculitis consisting of purpuric papules

The histology of small blood vessels exhibits necrotizing and/or leukocytoclasic vasculitis. Vasculitis occurs 7 to 21 days subsequent to drug administration and less than 3 days after rechallenge. Withdrawing the drug generally leads to a quick decree. A systemic corticosteroid may benefit some patients. The main drugs concerned are allopurinol, NSAIDs, cimetidine, penicillin, hydantoin, sulphonamides and propylthiouracil.

Acute generalized Exanthematous pustulosis [7]

AGEP is considered by fever, which usually begins the same day as the pustular rash. Abundant, tiny, chiefly non-follicular pustules happen on a extensive oedematous erythema, burning pruritic or both. Oedema of the face and the hands, purpura, vesicles, blisters, erythema multiforme-like lesions and mild involvement of mucous membrane also allied. Pustules are primarily restricted on the main folds, trunk and upper extremities. The histopathology shows spongiform pustules positioned beneath the stratum corneum, the mainly superficial layer of the epidermis. Papillary dermal oedema and perivascular polymorphous infiltrate are generally present. The eruption lasts 1 to 2 weeks, and is followed by a superficial desquamation. The removal of the liable drug is the foremost treatment, allied with a topical corticosteroid and occasionally a systemic antipruritic agent. Antibiotics (béta-lactam, some macrolides and quinolones) are the major drugs concerned in AGEP.

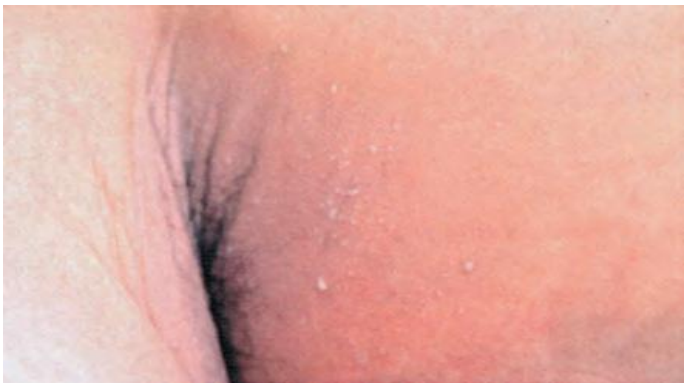

Figure 5- Acute generalized Exanthematous pustulosis

DRESS/Hypersensitivity

The short form of DRESS for Drug Reaction with Eosinophilia and Systemic Symptoms had projected as more precise than hypersensitivity, which would be suitable for generally types of drug reaction. It was approximate to happen in between one in 1000 and one in 10 000 exposures with drugs such as antiepileptics and sulphonamides. This syndrome is normally considered by a severe eruption, lymphadenopathy, fever, hepatitis, interstitial nephritis, pulmonary infiltrates and occasionally arthralgias. They commence 2 to 6 weeks after the first drug use. Fever and skin rash are the mainly general symptoms. Liver abnormalities with elevated aminotransferase, alkaline phosphatase, bilirubin levels and irregular prothrombin time are present in about 50% of patients. Histopathology exhibits a quite thick lymphocytic infiltrate in the superficial dermis and/or perivascular, coupled with dermal oedema. Topical high-potency corticosteroids could supportive in skin manifestations. Systemic corticosteroids are frequently planned when internal organ contribution exists. The aromatic antiepileptic agents (phenobarbital, carbamazepine, phenytoin), minocycline and sulphonamides are the common causes of hypersensitivity syndrome.

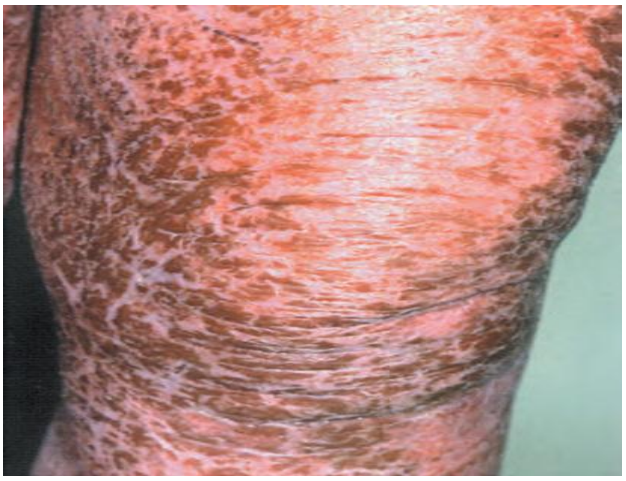

Figure 6- DRESS syndrome presenting as exfoliative dermatitis

Fixed drug eruption [8]

Clinically, considered by an introverted or few, round, sharply demarcated erythematous and oedematous plaques, occasionally with a central blister. The lesions extend usually less than 2 days after the drug intake. Histopathology reveals a superficial and deep dermal and perivascular infiltrate (composed of lymphocytes, eosinophils, and sometimes neutrophils) linked with necrotic keratinocytes. The drugs linked with fixed drug eruption are phenazone derivates, barbiturates, tetracycline, sulphonamides and carbamazepine

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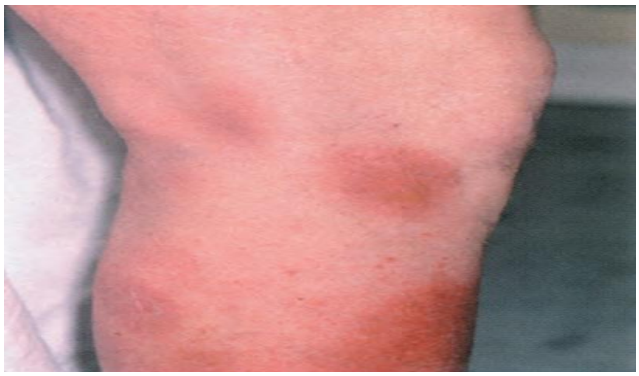

Figure 7- Fixed drug eruption (round, sharply demarcated erythematous plaques)

Drug-induced Pemphigus [9, 10]

Pemphigus is a continual autoimmune blistering disease aggravated by autoantibodies reacting with ordinary constituents of desmosomes, the structures that afford addition between epidermal cells. Clinically, flaccid intra-epidermal blisters and erosions of the skin and mucous membranes. The histology exhibits impassiveness of epidermal cells, accountable for intra-epidermal blisters positioned sub-corneally or in the lower epidermis. It begins several weeks or months after drug therapy are started. The main drugs accountable are d-penicillamine, captopril and piroxicam.

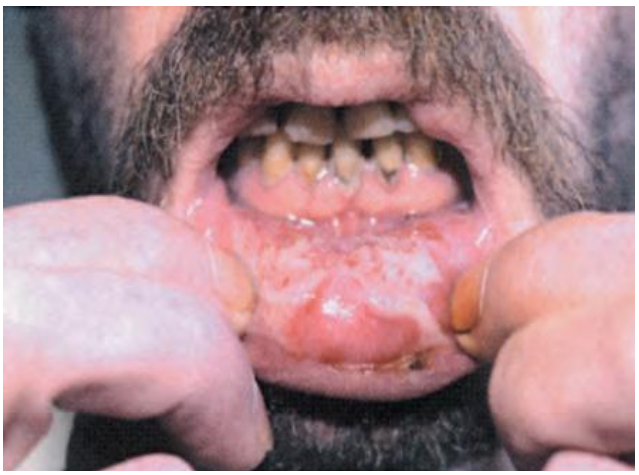

Figure 8- Drug-induced Pemphigus with erosion of mucous membrane

Steven Johnson syndrome and Toxic epidermal necrolysis [12, 13]

The incidence of TEN is evaluated to 0.4 to 1.2 cases per million person-years and of SJS from 1 to 6 cases per million person-years. The immune-pathologic outline of early lesions suggests a cell-mediated cytotoxic reaction aligned with epidermal cells. SJS is considered by small blisters arising on purple macules. Toxic epidermal necrolysis is considered by the same lesions as SJS but with a convergence of blisters important to a positive Nikolski sign and to the objectivity of huge epidermal sheets on more than 30% of the body surface area. Skin pathology displays necrosis of full-thickness epidermis and negative immunofluorescence. Death occurs in 10% of patients with SJS and more than 30% of patients with TEN, primarily from sepsis or pulmonary participation. SJS and TEN characteristically begin within 4 weeks of starting therapy, generally 7 to 21 days after the first drug exposure and occasionally a few days after the drug has been withdrawn. It happens more rapidly with rechallenge. The treatment is mostly symptomatic, consisting of nursing care, safeguarding of fluid and electrolyte balance and nutritional support. Untimely withdrawal of all potentially accountable drugs is necessary. Antibacterial sulphonamides, anticonvulsants, oxicam and pyrazolone NSAIDs, allopurinol and chlormezanone are the drugs allied with the privileged risks.

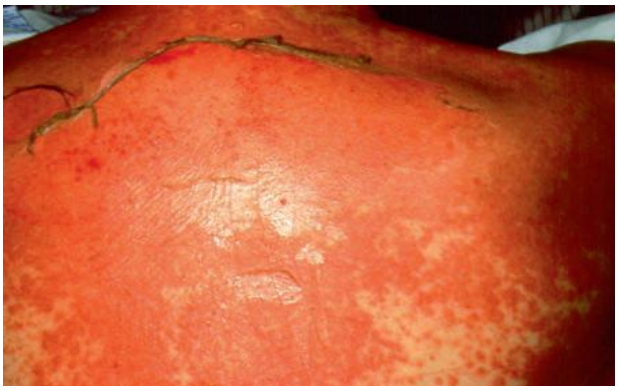

Figure 9- Toxic epidermal necrolysis

Serum sickness-like eruption

This condition is mainly reported in children and characteristically includes fever, arthralgias and rash and lymphadenopathy. It occurs 1 to 3 weeks subsequent to drug coverage and occurs as regards 1 in 2000 children given cefaclor, which along with minocycline, penicillins and propranolol are the chief drugs accountable for eruption.

Anticoagulant-induced skin necrosis

Usually begins 3 to 5 days after therapy is started. Red, painful plaques develop to necrosis, hemorrhagic blisters, ulcers, and as a result of occlusive thrombi in vessels of the skin and subcutaneous tissue. Of the persons who take warfarin, 1 in 10 000 will build up skin necrosis. People with a hereditary lack of protein C are at the utmost risk. Therapy includes discontinuing warfarin, administering vitamin K, giving heparin as an anti-coagulant, and purified protein C concentrate. [19-22]

Case evaluation must commence with a precise explanation of the skin lesions. Appropriate clinical information includes:

1. Distribution of lesions
    - Face, hands, feet vs. thorax and abdomen
    - Photo-exposed vs. covered areas
2. Number of lesions
3. Outline of individual lesions (macules, purpura, blisters, pustules, etc.)
4. Mucous membrane contribution.
5. Period of the eruption
6. Allied symptoms/signs
    - Fever
    - Pruritis
    - Lymph node swelling.

CONCLUSION

Case evaluation must commence with a precise explanation of the skin lesions. The documentation of cases should be terminated by photographic pictures which can help for the retrospective evaluation of cases by experts. Concluded that there is a need of active Pharmacovigilance centre with intensive monitoring for drug induced reactions in the dermatology department.

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