

MSS



Sheet no.2

Pharmacology



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SKIN PHARMACOLOGY 2

this sheet discusses a variety of drugs that treat different skin conditions, each headline represents different drug class. GOOD LUCK 🏆

Immunomodulators

1) Imiquimod:

- **MAO:** (mechanism of action)

Stimulates peripheral mononuclear cells to release interferon- α and to stimulate macrophages to produce interleukins-1,-6, and -8 and tumor necrosis factor- α .

- **Uses:**

- For external genital and perianal [warts](#).
- [Actinic keratosis](#) on the face and scalp.
- Primary basal cell [carcinoma](#).

Basal cell carcinoma is a malignancy with a good prognosis

its not very dangerous although it's a malignant tumor because:

- its localized
- doesn't have high recurrence rate
- doesn't metastasize in a high rate

2) Tacrolimus & Pimecrolimus

- **MAO:**

calcineurin inhibitors

→ Inhibit immune response by inhibiting T-lymphocyte activation and prevent release of inflammatory cytokines and mast cell mediators.

- **Uses:**

inflammatory conditions, e.g. atopic dermatitis (a form of eczema)

- **Side effects:**

-since these drugs are immunosuppressive, superimposed infections can occur

-highly nephrotoxic, liver-toxicity and drug interactions

patient will be under observation for kidney function during drug administration in the hospital.

it has **Black box warning** which is a warning written on the outside box of drugs that have serious side effects

Ectoparasiticides Anti-parasitic drugs

1) Permethrin

- **Uses:**

used to treat lice, has two formulations (shampoo or lotion) depending on the infected site.

Toxic to different types of parasites

1) *Pediculus humanus* (skin lice)

2) *Pthirus pubis* (pubic area)

3) *Sarcoptes scabiei* (causes scabies الجرب)

– Examples:

Pediculosis: cream applied for 10 minutes and then rinsed off with warm water.

Scabies: cream applied for the whole body for 8-14 hours.

2) Lindane (Hexachlorocyclohexane)

10% absorbed to the systemic circulation and concentrated in fatty tissues because it can be stored there.

- **Side effects** (systemic toxicity)

can cause **neurotoxicity** and **hematotoxicity** (blood dyscrasia)

– it's preferred to use an alternative for lindane especially when it needs to be used on a large surface area of the skin

(i.e., large surface area → huge amount of the drug will penetrate the skin and make its way to the systemic circulation → systemic toxicity & serious side effects)

other options: Crotamiton, Sulfur, Malathion.

Agents affecting skin Pigmentation

→ either increasing or decreasing pigmentation depending on the case

1) Drugs for hyperpigmentation

hyperpigmentation can be caused by high exposure to sunlight, aging, pregnancy due to hormonal changes.

- **Hydroquinone & Monobenzone.**

Toxic to melanocytes (cells that produce the melanin) as a result their effect is irreversible leading to permanent depigmentation

- **Mequinol**

Reduce hyperpigmentation of skin by inhibiting the enzyme tyrosinase which will interfere with biosynthesis of melanin.

2) Drugs for hypopigmentation used for re-pigmentation

- **Trioxsalen & Methoxsalen**

Are **Psoralens** meaning drugs that need to be activated by light to perform their action.

they're photoactivated by long-wave-length ultraviolet light (320-400nm) to produce a beneficial effect.

*Numbers aren't required

- **Uses:**

for the re-pigmentation of depigmented areas on their skin like macules of vitiligo (البهاق) where patients have white patches on their skin

- **MAO:**

They intercalate with DNA (i.e. insert molecules between DNA base pairs)

- **Side effects:** can cause cataract (eye-lens cloudiness)

skin cancer or the patient becomes more prone to developing skin cancer

Sunscreens and Sunshades

protect us all from the harmful effects of UV radiation from the sun light.

- Considered drugs when a subpopulation of people needs to use them for medical purposes as they are more prone to be affected by the serious side effects of sunlight exposure.

such as:

- 1) **polymorphous light eruption:** skin vesicle formation caused by sun exposure for long periods of time

- 2) **lupus erythematosus:** these people have highly sensitive skin so their skin would get burned by the sun

3) **drug-induced photosensitivity**: acne treatments like isotretinoin (Roaccutane) causes desquamation of skin layers making the skin more light and sun-sensitive, so in this case sunscreens are used as drugs to protect against skin damage or sunburns.

• Difference between sunscreens and sunshades:

Sunscreens absorb UV light, examples are para-amino benzoic acid (**PABA**) and its esters.

Sunshades are opaque materials that contain minerals that act as a physical barrier reflecting sunlight and preventing it to reach the skin, like **titanium dioxide**.

Acne Preparations

• Retinoic Acid and Derivatives (administered orally or topically)

1) Retinoic Acid

2) Adapalene

3) Tazarotene

1) Retinoic Acid (Tretinoin): is the acid form of Vitamin A

• **MAO**: The retinoic acid receptor is a nuclear receptor that binds to DNA altering the expression pattern of a certain gene causing cell proliferation as acne treatment

Retinoic acid has multiple **effects** summarized as following: (A+B+C)

A) inducing cell proliferation by:

stabilizing lysosomes, increases RNA polymerase activity to increase protein synthesis, increases PGE₂, cAMP, and cGMP levels causing vasodilation, more blood will reach the area helping in proliferation and tissue regeneration, it also increases the incorporation of thymidine into DNA which helps in cell replication.

B) Decreases cohesion between epidermal cells and increases epidermal cell turnover and desquamation, this will result in expulsion of open comedones and the transformation of closed comedones into open ones.

→ Comedones: are clogged pores with accumulated dirt, dead skin cells, bacteria composing a puss that will result in the formation of a pimple, cell turnover opens these closed pores and clear their content.

This explains why **when using this drug initially** acne & pimples formation increase

C) Skin tightening by promoting dermal collagen synthesis, new blood vessel formation, and thickening of the epidermis, which helps diminish fine lines and wrinkles.

- **Side effects:**

- Can cause erythema and dryness → physicians usually prescribe face & body moisturizers, eye drops and recommend drinking water to prevent severe dryness
In addition, sunscreens and sunshades are a must because the skin is exfoliated by the drug and is more sensitive.

- Tumorogenic in animals

- **Isotretinoin (Accutane):**

- isotretinoin is NOT the first line treatment for acne

it is **Restricted** for severe cystic acne resistant to standard treatment

Standard treatment → topical antibiotic like clindamycin and erythromycin combined with benzoyl peroxide, tetracycline and its derivatives doxycycline and minocycline that are protein synthesis inhibitors in microorganisms with an added effect of releasing metalloproteases that help in fibrous tissue regeneration in the skin.

- **MAO:** inhibits sebaceous gland size and function.

- **Administration:** Given orally.

- **Side effects:** dryness, itching, headache, corneal opacities, muscle, and joint pains. Also, lipid abnormalities, and causes elevation of liver enzymes (must be periodically checked) along with lipid profile and LDL levels as well.

- Depression: acne causes self-image issues and induces stress especially in youngsters so mental health should be taken in account.

- Rare side effects:

pseudotumor cerebri (increase in intracranial pressure), inflammatory bowel disease, anorexia, alopecia.

– Teratogenicity (MOST ALARMING SIDE EFFECT)

meaning it causes fetus malformations if administered during pregnancy

females shouldn't get pregnant while using this drug and are recommended to not to get pregnant after one month of stopping this treatment, in order to give the body the time to clear the drug and its residual traces out of our system

Topically administered drugs used in acne treatment:

Benzoyl Peroxide:

– Penetrates the stratum corneum or follicular openings and converted to benzoic acid within the epidermis and dermis.

- **MAO:** has antimicrobial activity against P. acnes by producing ROS plus, peeling and comedolytic effects; opens clogged comedones and lyse its contents
- Can be combined with erythromycin or clindamycin.
- Potent contact sensitizer.
- Can cause bleaching of hair or colored fabrics.

Azelaic Acid:

– Has antimicrobial activity and inhibits conversion of testosterone to dihydrotestosterone.

→ dihydrotestosterone is the hormone responsible for the secondary sex characteristics and is responsible for the hormonal changes in puberty or adolescence inhibiting this hormone will prevent its hormonal effect on acne formation.

Drugs for Psoriasis

Psoriasis: is an auto-immune disease where inflammation and hyper-keratinization of the tissue take place

1) Acitretin:

- Related to isotretinoin (retinoic acid derivative)
- Given orally.
- Side effects: Hepatotoxic and teratogenic, very similar to isotretinoin

– Patients should not become pregnant for 3 years after stopping treatment, and should not donate blood, due to prolonged administration and half-life of this drug, drug residue will take time to be cleared out of the body.

2) **Tazarotene:**

– Topical, also a retinoic acid derivative.
– Anti-inflammatory and antiproliferative actions.

–Side effects:

Teratogenic → although it is applied topically, it can get absorbed and make its way to the systemic circulation and cause serious side effects

Also, can cause burning, stinging, peeling, erythema, and localized edema of skin.

3) **Calcipotriene:** Synthetic vitamin D3 derivative

exact MOA in treating psoriasis isn't well known yet, but has shown effectiveness in reducing symptoms of this condition

4) **Biologic Agents:** (monoclonal antibodies that inhibit the immune system)

a) **Alefacept:**

Immunosuppressive dimer fusion protein of CD2 linked to the Fc portion of human IgG1, it prevents the activation of immune cells.

b) **Efalizumab:**

- Recombinant humanized IgG1 monoclonal antibody.
- Withdrawn from the market: because it caused progressive multifocal leukoencephalopathy (PML)
- Can cause thrombocytopenia.

c) **Etanercept:**

- Dimeric fusion protein TNF receptor linked to the Fc portion of human IgG1.

Anti-inflammatory Agents

Topical Corticosteroids:

completely block the inflammatory response by inhibiting the release of arachidonic acid from cellular membranes by inhibiting the synthesis of phospholipase A2.

• Examples include:

- **Hydrocortisone.**
- **Prednisolone and Methylprednisolone.** (available as creams, suspension, or serums)
- **Dexamethasone and Betamethasone.**
- **Triamcinolone.** (IV administration)
- **Fluocinonide.** (IV administration)

Anti-inflammatory Agents

Topical Corticosteroids:

– Absorption:

- **1% of hydrocortisone applied to the ventral forearm.**
- **0.14 times of hydrocortisone applied to the plantar foot.**
- **0.83 times of hydrocortisone applied to the palm.**
- **3.5 times of hydrocortisone applied to the scalp.**
- **6 times of hydrocortisone applied to the forehead.**
- **9 times of hydrocortisone applied to the vulvar skin.**

• Absorption of topical Corticosteroids

- Absorption increased with inflammation, because the inflamed tissue is highly vascularized
- increasing the concentration does not proportionally increase the absorption to the systemic circulation
- Can be applied topically as cream or given by intralesional injection, meaning treating the skin by directly injecting the drug into the lesion
Example: **keloids scars** are treated by injecting triamcinolone in the lesion

Slide 37

The doctor said to skip this slide it basically emphasizes the percentage of absorption of hydrocortisone applied to different regions of the skin of different thicknesses.

Remember that we take into consideration regional variation of drug penetration in the skin, in which the amount of the drug that is absorbed and get in the systemic circulation causing systemic side effects and toxicity is determined by these percentages.



keloids scars

– **Dermatologic disorders very responsive to steroids:**

Atopic dermatitis, Seborrheic dermatitis, Lichen simplex chronicus (autoimmune problem where white, flaky, keratinized tissue formation on the skin occurs), Pruritus ani (itching in the anal region), Allergic contact dermatitis, Eczematous dermatitis, Psoriasis.

– **Adverse Effects:** (mainly related to systemic use not topical administration)

- Suppression of pituitary-adrenal axis (**serious**)

→ prolonged administration of these drugs will suppress the function of the adrenal gland and inhibit the natural synthesis of cortisol in the body.

→ Systemic administration of these drugs isn't stopped abruptly but rather drug dose is tapered down gradually, in order to give the body the chance to go back again and produce the normal levels of cortisol

→ we don't worry about this problem if the patient has taken the drug for 2 weeks or less

- Infections. (bacterial & fungal caused by immunosuppression)

- buffalo hump due to abnormal fat distribution

• oral thrush in asthma patients; fungal infection of the oral cavity caused by immune suppression & imbalance in the normal flora, in which candida albicans accumulate on the lining of the mouth

- Skin atrophy. (Thinning of the skin)

- Erythema.

- Pustules. (because of bacterial growth)

- Acne.

- Hypopigmentation.

- Moon face

- Allergic contact dermatitis.

- Systemic effects.

- **Tar compounds:**

– Mainly for psoriasis, dermatitis, and lichen simplex chronicus

– Can cause irritant folliculitis, phototoxicity, and allergic contact dermatitis.

–not used nowadays

Keratolytic and Destructive Agents

- **Salicylic acid:**

- Solubilizes cell surface proteins resulting in desquamation of keratotic debris, used for acne and blackheads.
- causes killing of the microorganism and inhibition of the inflammation
- Keratolytic in 3-6% concentration, but destructive in higher concentrations.
- Can result in salicylism due to systemic absorption in salicylic acid sensitive patients.
- Locally, can cause urticaria (احمرار في الجلد مع حكة), anaphylactic and erythema multiforme reactions, irritation, inflammation, and ulceration.

erythema multiforme reactions: an auto immune disease with characteristic called target lesion (red circle surround a white area), usually associated with Stevens Johnson syndrome, its mucocutaneous meaning it affects the skin and mucus membranes.

- **Propylene Glycole:**

- Usually used as a vehicle for organic compounds.
- Used alone as a keratolytic agent in concentrations of 40%-70%, with plastic occlusion, or in gel with 6% salicylic acid.
- Minimally absorbed, oxidized in liver to lactic acid and pyruvic acid.
- Develops an osmotic gradient through the stratum corneum, thereby increasing hydration of the outer layers of skin.

- **Urea:**

- Has a humectant activity, i.e. softening and moisturizing effect on the stratum corneum.
- Increases water content as a result of its hygroscopic characteristics that's why its added to a lot of creams and moisturizing formulation to increase the water content and penetration
- Decreases the unpleasant oily feel of dermatologic preparations.
- When absorbed, it is excreted in urine.

- **Podophyllum Resin and Podofilox: (The doctor said know the name only)**

- An alcoholic extract of Podophyllum peltatum(Mandrake root or May apple).
- Used in the treatment of condyloma acuminatum and other verrucae.
- Cytotoxic activity with specific affinity for the microtubule protein of the mitotic spindle.
- Can cause N, V, muscle weakness, neuropathy, coma, and even death.