Hashemite University
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Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 1

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Drugs for dermatologic disorders

*First of all, we want to make a recap about the skin structure and function.

Skin is the Largest organ in the body. It's composed of 2 main layers, epidermis and dermis. Functions of the skin include: innate immunity, temperature regulation, vitamin D synthesis, sensory input.

• What are the advantages of the topical route?

Use of topical agents for treatment of dermatologic disorders is not only convenient but also minimizes systemic adverse effects. So it is additional route of administration.

- Topical agents may be formulated as:
  - **Sprays**: such as nasal sprays, they are of less effect than creams or lotions.
  - powders: powder is solid dosage form which contains mixture of finely divided drugs or chemicals in a dry form meant for internal or external use
  - **Lotions**: they are similar to creams, but lotions have higher water content, lotion is typically a mix of water and droplets of oil, is lighter weight than cream, and is non-greasy.
  - **Creams**: Creams are thicker in consistency than lotions and provide a barrier that keeps skin ultra-hydrated.
  - **Pastes**: they are semisolid dosage forms that contain one or more drug substances
  - **Packed dressings**: such as sterile gauze.
  - **Ointments**: It is a preparation of oil in water. An ointment is a preparation of a medication for topical use that contains an oil base, while ointments have a higher concentration of oil than creams.
  - **Aerated foams**: from their names, they are foams with creamy consistency that are aerated.

**The bioavailability of these agents and the ability to retain therapeutic effect on the skin involve factors such as the vehicle (whether the drug is lipophilic or lipophobic) and the physical methods used to localize them, such as the use of a patch formulation.

-Which agents are more readily absorbed topically?

Of-course lipophilic drugs, since they have the ability to cross the lipid layers present in cell membranes of keratinocytes.

-How do we determine the dosage of topical drugs?

The therapeutic efficacy of topical agents is dependent on the thickness of the stratum corneum, the drug concentration and permeability, frequency of dosing, and other factors such as age and health of the skin.

**Acne:

Acne vulgaris (common acne) is a common skin disorder that is characterized by pimples, comedones, pustules, and sometimes nodules and scarring.

*Note: Comedones are clogged hair follicles (pores) in the skin, which can be open (blackhead) they are black due to exposure to air, being oxidized. Or closed (whitehead) in which sebum is accumulated in occluded hair follicle.

- ✓ Acne occurs due to alterations in pilosebaceous units—skin structures that contain a hair follicle and a sebaceous (oil) gland. **Androgens stimulate sebaceous glands, thereby producing sebum that leads to follicular keratinization and obstruction**. Propionibacterium acnes, part of the normal skin flora, can enter the clogged pore and multiply, causing redness and inflammation and leading to papillary, pustulary, and cystic acne.

**Agents for Acne:

Treatments for acne help to reduce sebum production or control P. acnes. {Note: Use of oral contraceptives may help decrease circulating levels of free androgen and reduce symptoms of acne}.

1) Retinoids:

Retinoids are derivatives of vitamin A that are highly effective in the treatment of acne, as well as other skin conditions such as psoriasis and photoaging.

-Tretinoin and isotretinoin are **first-generation** retinoids that are used for the management of acne. **Third-generation** retinoids include includeadapalene and tazarotene.

Third generation agents are less irritating and more effective than first generation retinoids and are **considered first-line therapy for comedonal and inflammatory acne.

*All these agents are applied topically, with the exception of *isotretinoin*, which is an oral drug. Due to the adverse effect profile, use of *isotretinoin* should be reserved for severe cystic acne.

Mechanism of action: Retinoids influence a wide variety of biological activities, including cellular proliferation and differentiation, immune function, inflammation, and sebum production. The molecular actions of retinoids are mediated through nucleic retinoic acid receptors. Once bound to the receptors,. **Retinoic acid–receptor complex binds to chromatin (inside nucleus), activating the transcription of specific genes.** (retinoids function as transcription factors that enhance initiation of transcription)

**Alteration in transcription results in: significant reduction in sebum production, reduction of comedogenesis, reduction in the P. acnes population, anti-inflammatory properties, decreased hyperkeratinisation (most important effect) leading to open of the occluded ducts.

*Note: Unlike the first-generation agents, the third-generation agents do not influence sebum production. They are comedolytic and anti-inflammatory. Isotrentoin (3rd gen.) which is the only systemic retinoid, effectively reduces comedogenesis (mechanism is uncertain), and it has no antimicrobial activity. Isotretinoin alters the environment in the duct of sebaceous glands, making it unfavorable for bacteria to live in, leading to very effective change in the colony of bacteria. The anti-inflammatory effect is mainly due to modification of monocyte chemotaxis and other effects.

***Adverse effects:** Irritation, dryness, and skin peeling are all complications with the use of retinoids. Photosensitivity, patients should be cautioned to wear sunscreen. Dry mucous membranes and dry eyes in 40% of patients. Abnormal lipid metabolism, leading to Hypertriglyceridemia, low HDL-C (25%). It also alters the liver function leading to increase in liver enzymes (Elevated liver function test). Suicide or suicide attempts have been associated with the use of oral *isotretinoin.* There is a very high risk of birth defects if pregnancy occurs while taking *isotretinoin*, and this drug as well as other retinoids are contraindicated in pregnancy. (Teratogenicity)

Black Box Warning of Isotretinoin:

- Do not use in female patients who are or may become pregnant, because of high risk of teratogenicity (Documented embryofetal effects include internal and external abnormalities, IQ scores of <85, spontaneous abortion, premature birth, and fetal death).
- Discontinue immediately if pregnancy occurs and refer patient to an obstetrician-gynecologist experienced in reproductive toxicity for evaluation. That's why female patients on isotretinoin treatment MUST take contraceptives to prevent pregnancy.
- Patients of childbearing potential must not be pregnant or breastfeeding, must be capable of complying with approved contraceptive methods (progestogen-only pills are ineffective).
- Depression and psychosis reported; rare reports of suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors.

*Necessary Laboratory Testing

- Pretreatment monitoring: LFTs (1 day before starting initiating therapy), 2 pregnancy tests (negative result 2 weeks before using the drug), and fasting lipid profile (including triglycerides).
- During treatment: Monitor LFTs and lipids at weekly or biweekly intervals until response to isotretinoin established.
- Blood glucose, CPK (particularly in those undergoing vigorous physical activity).
- Ongoing negative pregnancy tests required according to iPLEDGE rules.

2) Benzoyl Peroxide:

Benzoyl peroxide is considered the first-line agent for mild to moderate acne with no inflammation.

❖ Mechanism of action: The mechanism of action includes antiseptic effects against P. acnes as well as opening of the pores.

- *Benzoyl peroxide* is a topical agent that is available in many over-the-counter acne treatment products, as well as some prescription products.

-Local adverse effects include: Dry skin, peeling, and irritation are local adverse effects.

3) Azelaic Acid:

-Azelaic acid is a dicarboxylic acid.

❖ Mechanism of action: has antibacterial activity against P. acnes as well as anti-inflammatory actions. *Azelaic acid* normalizes keratinization and is anticomedogenic.

* It is available as a topical preparation for the treatment of mild to moderate inflammatory acne.
*It is generally well tolerated, with mild skin irritation as the most common adverse effect.
*Benefits of azelaic acid for tt of acne: gently encouraging cell turnover so your skin heals more quickly and scarring is minimized as well as clearing your pores of bacteria that may be causing irritation or breakouts.

4) Salicylic Acid:

Topical salicylic acid.

❖ Mechanism of action: penetrates the pilosebaceous unit and works as an exfoliant to clear comedones.

* *Salicylic acid* is used as a treatment for mild acne and is available in many over-the-counter facial washes and medicated treatment pads. Adverse effects are similar to Azelaic acid.

5) Antibiotics:

*As noted above, P. acnes is a gram-positive rod that is associated with inflammatory lesions in acne.

* Topical formulations of *erythromycin* and *clindamycin* (preferred) are used. These agents may be combined *benzoyl peroxide* or the retinoids for better effectiveness.

*Oral antibiotics commonly used for the management of **moderate to severe acne** include *minocycline*, *doxycycline*, and *erythromycin*.

*Best approach to give oral antibiotics is: administration of oral antibiotics until the patient's condition is improved, then we switch to topical antibiotics to continue with.

Topical Antibacterial Agents:

Common skin infections: Folliculitis, Skin abscesses, Fasciitis, Cellulitis, Impetigo and others.
*Impetigo is an infection of the epidermis caused by staph. Aureus or strep. Pyogens. Giving a honey-colored crusts on the face (characteristic).

Gram-positive infections:

• Bacitracin: is a peptide antibiotic active against many gram-positive organisms. It is used mainly in topical formulations; if used systemically, it is toxic. *Bacitracin* is mostly used for the prevention of skin infections after burns or minor scrapes, it is frequently found in combination products with neomycin (which covers gram (-)).

• Mupirocin: is a protein synthesis inhibitor that is useful in treating impetigo (a contagious skin infection caused by streptococci or staphylococci) and other serious gram positive skin infections, including infections caused by *methicillin* resistant Staphylococcus aureus (MRSA). As a cream or ointment or intranasal spray for MRSA carriers or people at high risk.

• Retapamulin: is a newer protein synthesis inhibitor that treats impetigo. Available as ointment.

Gram-negative infections:

• Polymyxin: *Polymyxin B* is a cyclic hydrophobic peptide that disrupts the bacterial cell membrane of gram-negative organisms (cell wall synthesis inhibitor). As noted above, it is commonly combined with neomycin and bacitracin ("triple antibiotic") in topical products used for the prevention of skin infections after minor skin trauma.

• Neomycin: *Neomycin* in combination with other agents can be used to treat skin infections caused by gram-negative organisms such as Pseudomonas, E. coli, and Klebsiella sp. (in severe cases)

Agents Used In Ectoparasitic Infections

-Ectoparasites are parasites that live on the skin of animals from which they derive nutrition. Pediculosis and scabies are caused by these parasites.

-Pediculosis (infestation with lice) are caused by Pediculus capitis (head louse), Pediculus corporis (body louse), or Pthirus pubis (pubic or crab louse).

-Scabies (caused by Sarcoptes scabiei, human mite)

Agents Used In Ectoparasitic Infections:

- Lindane: is a cyclohexane derivative that is available as a cream or shampoo. *Lindane* is toxic when absorbed by the parasite and is an effective pediculicide (kills lice) and scabicide.
- Permethrin: is a synthetic pyrethroid that is neurotoxic to lice, and is effective in 5% concentration by prescription to treat scabies. *Permethrin* is preferred over *lindane* for the treatment of lice and scabies, since *lindane* can cause

neurotoxicity. [Note: Oral *ivermectin* is an alternative treatment for lice and scabies].

- Pyrethrins + piperonyl butoxide: approved to treat head and pubic lice. Pyrethrins are pesticides and piperonyl butoxide prevents the lice from metabolizing the pyrethrins, thereby enhancing their effect. Due to a low risk of toxicity, this agent is considered a first-line treatment for pediculosis.
- Crotamiton: *Crotamiton* is a scabicide and has antipruritic functions, its mechanism of action is unknown.

**Note: pyrthroids and DDTs block the Vg-Na+ channels in the brain of parasite, blocking impulses transmission. Whereas organophosphates and carbamates block the Acetyl choline esterase enzyme, inhibiting the destruction of Ach, leading to paralysis of parasite.

Agents For Pigmentation Disorders

1) **Hydroquinone:** *Hydroquinone* is a topical skin whitening agent that reduces hyperpigmentation associated with freckles and melasma. It is often **used in combination with topical retinoids to treat the signs of photoaging**.

*Melasma is a brown to black coloring of skin, due to aging.
*Photoaging is skin hyperpigmentation due to aging.

- Mechanism of action: the mechanism of action of *hydroquinone* is inhibition of the tyrosinase enzyme required for melanin synthesis.

***Hydroquinone* lightens the skin temporarily and **is commonly used as a 4% preparation**. It should not be used in higher concentrations, or in excessive quantities for an extended duration, as it is associated with possible carcinogenicity. Local skin irritation is the most common adverse effect.

2) **Methoxsalen:** *Methoxsalen* is a photoactive substance (psoralen) that stimulates melanocytes and is used as a repigmentation agent for patients with vitiligo. It must be photoactivated by UV radiation **to form a DNA adduct inhibiting DNA replication by a method called PUVA (psoralen plus UVA radiation).**

-*Methoxsalen* inhibits cell proliferation and promotes cell differentiation of epithelial cells. Topical *methoxsalen* may be used for small patches of vitiligo and psoriasis, and oral therapy is used for more widespread disease.
*Must be used in caution since it may be carcinogenic.

Drugs for Psoriasis

-Psoriasis is a skin disease that presents with erythematous scaling plaques. It manifests with increased epidermal cell proliferation and epidermal hyperproliferation. Psoriasis appears to have both genetic factors and T-cell–mediated immune components. The majority of patients have mild to moderate psoriasis. Severe cases require systemic treatment.

-**Drugs for Psoriasis**: 1)Retinoids:

1) **Tazarotene:** *Tazarotene* is a topical retinoid used for the treatment of plaque psoriasis. Adverse effects are similar to other retinoids.

2)**Acitretin**: is a second-generation retinoid used orally in the treatment of pustular forms of psoriasis, since ingestion of ethanol can increase transesterification of *acitretin* to *etretinate*, ethanol is contraindicated with this agent (alcohol is contraindicated with this drug).

* Like other retinoids, *acitretin* is teratogenic and women must avoid pregnancy for at least 3 years after the use of this drug (due to the long duration of teratogenic potential).
Cheilitis, pruritus, peeling skin, and hyperlipidemia are common adverse effects.

-**Drugs for Psoriasis**: 2) Vitamin D analogues:

- ✓ **Calcipotriene and Calcitriol**: *Calcipotriene* and *calcitriol* are synthetic vitamin D3 derivatives used topically to treat plaque psoriasis.
  - ❖ Mechanism of action: They inhibit keratinocyte proliferation and increase keratinocyte differentiation.

**Adverse effects include itching, dryness, burning irritation, and erythema.

-**Drugs for Psoriasis**: 3) Keratolytic agents

- ✓ **Coal tar, salicylic acid:** are effective in localized psoriasis, especially on the scalp. They improve corticosteroid penetration.
  - ❖ Mechanism of action**:** *Coal tar* inhibits excessive skin cell proliferation and may also have anti-inflammatory effects.

**Note: Because it is cosmetically unappealing, *coal tar* may have a low acceptance rate among patients and, consequently, its use has been largely supplanted by the newer topical agents.

-**Drugs for Psoriasis:** 4) Apremilast

-It is administered orally, usually used in Moderate-severe plaque psoriasis.
Mechanism of action: It inhibits phosphodiesterase-4 enzyme which is very important for cAMP synthesis, **inhibiting** signalling processes for inflammation, **decreasing** transcription of many cytokine genes and **increasing** anti-inflammatory cytokines.

Adverse effects include: N/V/D, headache and depression.
*Note: Apremilast is an CYP450 inducer, thus involved in many drug/drug interactions.

-Drugs for Psoriasis: 5) Biologic Agents

Remember that psoriasis is an autoimmune disease
-Biologic agents are antibodies (produced by DNA recombination), these drugs are injectable, and used for moderate to severe psoriasis.

- **Drugs and targets:**

1. Etanercept, infliximab, adalimumab, certolizumab, golimumab (TNF-α blockers)
2. Ustekinumab (anti-IL-12 and IL-23)
3. Guselkumab (anti-IL-23)
4. Secukinumab, ixekizumab, brodalumab (anti-IL-17A)

**All these cytokines are involved in pathogenesis of psoriasis, and induction of inflammation, so we tend to inhibit them.

Topical Corticosteroids:

Corticosteroids (glucocorticoids) have immunosuppressive and anti-inflammatory properties. Topical corticosteroids are used for the treatment of psoriasis, eczema, contact dermatitis, and other skin conditions manifested by itching and inflammation.

- Mechanism of action: Corticosteroids work via intracellular receptors and initiate several transcriptions and translations leading to their multiple effects. The actions include inhibitory effects on the arachidonic acid cascade, depression of production of many cytokines, and effects on inflammatory cells. In psoriasis, they inhibit epidermal cell mitosis.

Trichogenic Agents

- **Minoxidil:** are trichogenic agents that are indicated for the treatment of androgenic alopecia (“male pattern baldness”).

***Minoxidil*, originally used as a systemic antihypertensive, was noted to have the adverse effect of increased hair growth. This adverse effect was turned into a therapeutic application in the treatment of alopecia.

As a topical therapy, it does not cause systemic hypotension. *Minoxidil* is effective at halting hair loss in both men and women.
Note: Although the mechanism of action is not fully known**, it is believed to act, at least in part, by shortening the rest phase of the hair cycle. The drug must be used continuously to maintain effects on hair growth.**

- **Finasteride:** *Finasteride* is an oral 5-α reductase inhibitor that blocks conversion of testosterone to the potent androgen 5-α dihydrotestosterone (DHT). This is mechanism of action.

**High levels of DHT can cause the hair follicle to miniaturize and atrophy. *Finasteride* decreases scalp and serum DHT concentrations, thus inhibiting a key factor in the etiology of androgenic alopecia.

-Adverse effects include decreased libido, decreased ejaculation, and erectile dysfunction. The drug should not be used or handled in pregnancy (contraindicated), as it can cause hypospadias in a male fetus.

Study questions

Which of the following drugs is taken orally before using UVA radiation in the treatment of severe cases of psoriasis?
A. Methoxsalen.
B. Hydroquinone.
C. Finasteride.
D. Minoxidil.
E. Tazarotene.

Correct answer = A. In severe cases of psoriasis, methoxsalen is taken orally followed by UVA phototherapy. Other drugs are not options for treating severe cases of psoriasis. Hydroquinone is a topical depigmenting agent used for the treatment of photoaging. Finasteride is an oral drug for the treatment of alopecia, and minoxidil is a topical drug for alopecia. Tazarotene is a topical agent indicated for the treatment of acne or psoriasis.

Which of the following is correct regarding trichogenic agents?
A. Minoxidil is known to decrease the microcirculation surrounding the follicle, thus decreasing cutaneous blood flow.
B. A frequent adverse effect of topical minoxidil is orthostatic hypotension.
C. Finasteride inhibits the 5-α reductase enzyme that controls the production of DHT from testosterone.
D. An adverse effect associated with finasteride is increased libido.
E. Only 6 months of finasteride is necessary for a lifelong benefit.

Correct answer = C. Androgenic alopecia is associated with DHT concentrations, and finasteride is known to inhibit the 5-α reductase enzyme required for the formation of DHT from testosterone. Continuous use of finasteride is needed to maintain therapeutic benefit for alopecia. Finasteride can decrease libido.