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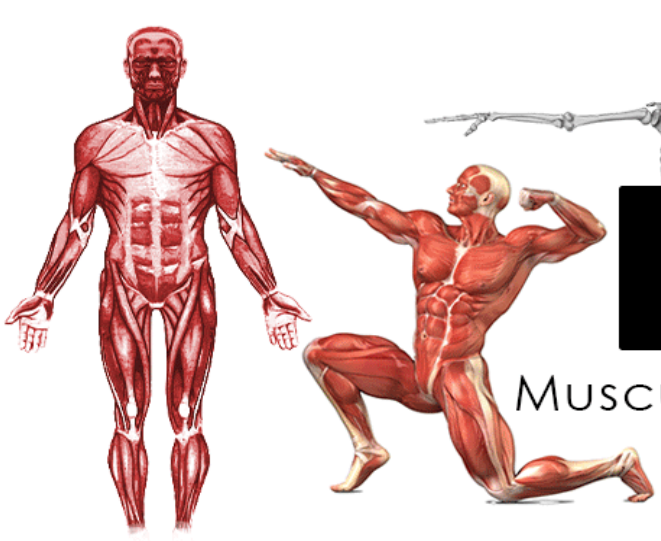

MSS

Musculoskeletal System

Pharmacology

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❖ Dermatologic Pharmacology … Continued:

❖ Acne Preparations:

- ✓ In the first lecture, we discussed some of the drugs used in the topical treatment of acne, such as: Clindamycin, erythromycin and benzoyl peroxide. However, acne is sometimes unresponsive to topical treatment, therefore, we resort to drugs administered systemically in such instances.
- ✓ One of the famous family of drugs used in acne treatment is: **Retinoic Acid Derivatives.**

Retinoic Acid Derivatives:

These drugs are structurally similar to vitamin A. Examples include:

- ✓ Retinoic acid
- ✓ Adapalene
- ✓ Tazarotene

- *Mechanism of action:*

- ✓ Generally, Vitamin A binds to an intracellular receptor and forms a complex that translocates to the nucleus, and then modulates the transcription of certain genes involved in proliferation.
- ✓ Retinoic acid (Tretinoin) is the acid form of Vitamin A. Some of its effects on the cellular level include:
  - ➢ *Stabilizing* lysosomes
  - ➢ *Increasing* RNA polymerase activity (increasing protein synthesis)
  - ➢ *Increasing* PGE2 (a prostaglandin), cAMP and cGMP levels (causing blood vessel dilation and increasing vascularization and nourishment of the skin, leading to healthier skin)
  - ➢ *Increasing* the incorporation of thymidine into DNA.
- ➢ It also *decreases* cohesion between epidermal cells and increases epidermal cell turnover. This will result in the expulsion of open comedones and the transformation of closed comedones into open ones.

- ✓ Clarification:

  Comedones are the clogged pores/bumps you see in acne. They may be closed (not exposed to the outer surface) or open (exposed and open to the outer surface). Retinoic acid and its derivatives increase epidermal cell turnover, increasing the shedding of cells from the upper layer of skin, while increasing proliferation from the basal layer. This assists in pushing the comedones upwards and exposing them to the outer surface, releasing their contents and this helps in getting rid of the comedones.

- ➢ Other effects include promotion of dermal collagen synthesis, new blood vessel formation, and thickening of the epidermis, which helps diminish fine lines and wrinkles.
  - ✓ Some patients even ask their doctors to prescribe isotretinoin for them because of the previously mentioned effect. But DO NOT immediately comply with their orders or requests! This drug is restricted for cases of severe cystic acne which did not respond to standard treatment.
  - ✓ Ask your patient to try topical treatment first. If unresponsive, try other antibiotics such as tetracyclines (e.g, Doxycycline) to treat Propionobacterium acnes infections, and it also happens to modulate metalloprotease activity, promoting healthier skin, and enhances fibroblast proliferation and collagen synthesis. Doxycycline has less severe side effects compared to isotretinoin. If the acne persists (resistant), we refer to retinoic acid derivatves.

- *Recommendations and Other Notes:*

- ✓ Sunscreen: Patients using retinoic acid derivatives are advised to apply sunscreen (as these drugs have side effects associated with the increased desquamation and erythema, consequently increasing the sensitivity of the skin)
- ✓ Hydration: Patients are advised to drink sufficient water to avoid dehydration of the skin and mucous membranes caused by such drugs. Doctors will usually prescribe moisturizers/sunscreens/eye drops alongside these drugs.
- ✓ Liver function must be monitored (these drugs are hepatotoxic and may increase the level of liver enzymes in the blood). If tests reveal high enzyme levels, treatment is stopped or doses are adjusted.
- ✓ Depression: One of the most important yet neglected side effects of isotretinoin is **depression**, and it also increases the incidence of suicidal thoughts. It is important

to consider this especially since the majority of acne patients are adolescents and teenagers who are going through a critical and stressful stage of life. Such drugs may further compound their stress and depression. Thus, patients who experience mood swings/suicidal thoughts after the use of these drugs must consult a doctor.

- ✓ These drugs are contraindicated in pregnant women (teratogenic). Even after stopping treatment, they must avoid becoming pregnant within the following 6 months or more due to the drug's long half-life, causing the drug to persist in the body even after stopping treatment. The longer the period during which the patient was taking the drugs, the longer she should avoid getting pregnant after cutting the treatment.
- ✓ Cholesterol and triglyceride levels should be monitored.
- ✓ Due to the structural similarity between these drugs and vitamin A, any patient being treated with such drugs should avoid taking any supplements/vitamin complexes containing vitamin A to avoid toxicity.
- ✓ Can cause erythema and dryness
- ✓ Tumorigenic in animals

- *Isotretinoin (Accutane):*

- ✓ Restricted for severe cystic acne resistant to standard treatment.
- ✓ Inhibits sebaceous gland size and function.
- ✓ Toxicity: dryness, itching, headache, corneal opacities, pseudotumor cerebri (increase in intracranial pressure), inflammatory bowel disease, anorexia, alopecia, muscle and joint pain, and lipid abnormalities.
- ✓ Teratogenic.

Benzoyl Peroxide

- ✓ Benzoyl peroxide is another drug used in acne treatment. It is used topically, and has activity against anaerobic bacteria.

- *Mechanism of action:*

- ✓ It penetrates the stratum corneum or follicular openings and is converted to benzoic acid within the epidermis and dermis.
- ✓ It generates free radicals, which causes it to be effective against anaerobic bacteria.

- *Notes:*

✓ It has antimicrobial activity against P. acnes, as well as peeling and comedolytic effects (inhibits formation of comedones).
✓ It can be combined with erythromycin or clindamycin.
✓ It can cause bleaching of hair or colored fabrics.

Azelaic Acid

✓ This drug has antimicrobial activity.

Extra Note: The retinoic acid derivatives we discussed earlier are given orally, but some of them, like Adapaline, can be present in the form of topical creams. The side effects we discussed above, however, apply to the oral forms of the retinoic acid derivatives.

❖ Drugs for Psoriasis

- Psoriasis is an autoimmune skin disorder

Acitretin

✓ This drug is related to isotretinoin.
✓ Given orally

- *Side effects:*
  - ✓ It is hepatotoxic and teratogenic.
  - ✓ Most of the side effects associated with isotretinoin also apply to acitretin.
  - ✓ Patients should not become pregnant for 3 years after stopping treatment (has an even longer half-life than that of isotretinoin), and should not donate blood (especially to other pregnant woman) during this period.

- Acitretin is not our first drug of choice in treating psoriasis. Patients usually start with glucocorticoids (steroids). Some respond while others do not, and some may be bothered by the side effects. In this case, we resort to other drugs (which we will discuss later). If all the previous drugs fail, we resort to acitretin.

➢ As mentioned before, some retinoic acid derivatives are available in topical forms and can be used to treat psoriasis, such as Tazarotene.

Tazarotene

- A topical retinoid.
- It has anti-inflammatory and antiproliferative actions
- *Side Effects:*

✓ Teratogenic (Despite being topically administered, systemic absorption can occur)
✓ Side effects related to topical administration: Burning, stinging, peeling, erythema, and localized edema of skin.

- Note: Most drugs used for skin conditions share many side effects, and this is related to the topical way of administration of these drugs. It is advisable to pay more attention to the special/unique side effects of each drug.

Calcipotriene

- This drug works in a different way in comparison to previous drugs.
- It is a synthetic vitamin D3 derivative.
- It has been shown to help in the treatment of psoriasis, however, the exact mechanism of action is not well-recognized.

➢ ***Biologic agents used to treat psoriasis:*** These include humanized antibodies that can target certain receptors or markers on the surface of immune cells. Examples include:

Alefacept

- It is an immunosuppressive dimer fusion protein of CD2 linked to the Fc portion of human IgG1.

Efalizumab

- It is a recombinant humanized (recall: -zumab=humanized) IgG1 monoclonal antibody.
- It was withdrawn, as it was associated with progressive multifocal leukoencephalopathy (PML).
- It can cause thrombocytopenia.

Etanercept

- It is a dimeric fusion protein of TNF receptor linked to the Fc portion of human IgG1. (A monoclonal antibody)

❖ Anti-inflammatory Agents

- Some of these agents (e.g. glucocorticoids) can be used in the treatment of psoriasis.
- Glucocorticoids have various effects on different organs (especially when used systematically). But we will focus more on the topical use of these drugs.

Topical Corticosteroids

- ✓ Hydrocortisone
- ✓ Prednisolone and Methylprednisolone
- ✓ Dexamethasone and Betamethasone
- ✓ Triamcinolone
- ✓ Fluocinonide

- *Uses of Topical Corticosteroids:*

✓ Dermatologic disorders very responsive to steroids:

  - Atopic dermatitis, seborrheic dermatitis, allergic contact dermatitis, eczematous dermatitis
  - Lichen simplex chronicus (an immunological disorder involving white plaques on the skin)
  - Pruritis ani
  - Psoriasis

✓ These drugs are often used in allergic conditions of the skin. They are also used alongside chemotherapeutic agents. For instance, some of the preparations of antifungal agents for tinea infections include: Miconazole with hydrocortisone, and this helps in reducing the signs and symptoms of inflammation (itching, erythema, swelling). Bacitracin is also sometimes combined with hydrocortisone.

✓ Recall: Keloid scars (where excessive scar tissue is deposited following exaggerated repair/abnormal healing of a wound (e.g. a surgical wound). Mostly associated with dark-skinned individuals). This keloid scar may be bothersome to the patient (cosmetically). One of the drugs used for this is Triamcinilone (injected into the scar tissue).

✓ Some inhalers include corticosteroids such as prednisolone and dexamethasone.

- *Adverse Effects:*

✓ Suppression of hypothalamous-pituitary-adrenal axis (HPA):
Glucocorticoids are synthesized endogenously by the adrenal gland. If an exogenous source of glucocorticoids is used (e.g. corticosteroid drugs), this will activate negative feedback mechanisms that will shut down the production of glucocorticoids from the adrenal gland (because there are sufficient circulating levels of glucocorticoids). A problem arises if the patient abruptly stops the treatment, leading to adrenal crisis, where the adrenal gland does not produce adequate glucocorticoids (which are necessary for normal function of the body) due to its long-term shut-down from previous use of drugs. This is why patients are recommended to gradually reduce (taper) the dose (e.g. Cut the dose down from 80 to 40 (then remain so for 3-5 days), cut it down again to 20 (wait again)

and so on until they can completely abandon the drug). This gives time for the adrenal gland to adapt and restart glucocorticoid production.

- ✓ Systemic effects: e.g. fat redistribution (buffalo hump, moon face). These effects are associated with the systemic use of these drugs. However, continuous topical use may lead to significant systemic absorption and such side effects may occur.
- ✓ Skin atrophy, erythema, pustules, acne
- ✓ Infection (because these drugs cause immunosuppression, increasing susceptibility to infection)
- ✓ Hypo-/Hyperpigmentation and allergic contact dermatitis

- *Mechanism of Action of glucocorticoids:*

  - ✓ Inhibition of phospholipase A2 (preventing arachidonic acid production, and subsequently reducing prostaglandin and leukotriene synthesis. This affects recruitment of inflammatory cells)
  - ✓ Binding to intracellular receptors (it modulates transcription of certain genes, reducing proliferation of immune cells)
  - ✓ The exact mechanism of action is not well-understood yet.

Tar compounds

- ✓ These drugs are mainly used for the treatment of psoriasis (and other skin conditions such as: dermatitis and lichen simplex chronicus).
- ✓ They are irritant. They can cause irritant folliculitis, phototoxicity, and allergic contact dermatitis.

- ➢ **Note:** There are other types of drugs that can also be used for the treatment of psoriasis. For instance, cyclosporine can be used to treat psoriasis that is unresponsive to other treatment. But we often avoid cyclosporine as an early choice due to its toxicity (used systemically). Also, topical forms of tacrolimus and its derivatives have been developed and can be used for psoriasis.

❖ Keratolytic and destructive agents

- Keratolytic agents are compounds that break down the keratin layers in the skin for clearing, cleaning and getting rid of acne and black heads.

Salicylic Acid

- Salicylic acid is present in many of the face washes used to prevent the development of acne or to clear the skin from black heads.
- It solubilizes cell surface proteins resulting in desquamation of keratotic debris.
- It is keratolytic in 3-6% concentration, but destructive in higher concentrations.
- Locally, it can cause urticaria, anaphylactic reactions, erythema multiforme, irritation, inflammation and ulceration.

Propylene Glycole

- *Uses:*

1. It is usually used as a vehicle for organic compounds (present in many cream combinations and ointments used to treat skin conditions).
2. It can be used alone as a keratolytic agent in concentrations of 40%-70%, with plastic occlusion, or in gel with 6% salicyclic acid.

- *Notes:*
  - ✓ It is minimally absorbed, oxidized in the liver to lactic acid and pyruvic acid.
  - ✓ As mentioned above, it is used in combination with other drugs. Why? It works by "wetting" the skin, because propylene glycol develops an osmotic gradient through the stratum corneum, thereby increasing hydration of the outer layers of the skin, and facilitating penetration of other drugs.

Urea

Naturally, toxic compounds (such as ammonia) are converted into urea by the liver to be eventually discharged by the kidney (in urine). One of the enzymes involved in this conversion is (Arginase).

- Urea has humectant activity (i.e. softening and moisturizing effect on the stratum corneum). This is due to its hygroscopic characteristics (it attracts water), and increases water content as a result. So, urea attracts water causing wetting and hydration of the skin.
- It is also used to decrease the unpleasant oily feel of dermatologic preparations.
- When absorbed, it is excreted in urine (so absorption is not much of a problem).

Fluorouracil

- The doctor skipped this drug. Read it just in case
- An antimetabolite that resembles uracil and inhibits thymidylate synthetase, thus it interferes with DNA and maybe RNA.
- Used in multiple actinic keratosis

Nonsteroidal anti-inflammatory drugs

- Examples: diclofenac sodium and diclofenac potassium.
- When used as a gel (3% get formulation diclofenac), they have the ability to act as keratolytic agents. We will talk more about diclofenac preparations and their anti-inflammatory, antipyretic and analgesic properties in the upcoming lectures.

Aminolevulinic Acid

- It is used in actinic keratosis.
- After topical application (20%) and exposure to light, it produces a cytotoxic superoxide and hydroxyl radicals which can harm the skin.

❖ Antipruritic Agents:

- These drugs are used to relieve the itching sensation (pruritis) that accompanies different conditions. Their mechanism of action usually involves modulating histamine release.

- During hypersensitivity reactions, one of the events that occur is histamine release from mast cells (degranulation). Histamine is associated with many of changes we see during allergic reactions:
    - ✓ It Increases the permeability of the endothelial cell layer (edema), increases blood flow and vascularization (erythema), causes itching (by stimulating certain receptors), increases the secretion of mucus. Therefore, antihistamines are used to treat allergies and certain respiratory conditions.
- Since histamine causes itching, many antipruritic drugs are simply antihistamines such as: Doxepin.

Doxepin — A potent H1 and H2 receptor antagonist. It can cause drowsiness and anticholinergic effects.

- *Why does it cause drowsiness/sedation?* Because it can cross the blood brain barrier (enters CNS) where it acts on certain receptors producing drowsiness.
- *Note:* There are 1st generation and 2nd generation antihistamines. 2nd generation antihistamines do not cause drowsiness, *NOT* because of a difference in selectivity, but instead because of their inability to enter the CNS, and are thus unable to act on receptors there, so no drowsiness occurs.
- Some people use antihistamines because of their sedative effects (for instance: during long plane flights). Sometimes, these drugs can produce the opposite effect in children, as they become hyperactive instead of drowsy.

Pramoxine — It is a topical anesthetic agent. It causes anesthesia in the applied area, causing loss of itching sensations.

❖ Trichogenic and Antitrichogenic Agents

- Trichogenic agents are drugs that help in hair growth and production. They are used in conditions in which there is absence or lack of hair growth (such as male pattern baldness). On the other hand, antitrichogenic agents minimize hair growth and are used in conditions where hair is growing at a faster rate in unwanted regions of the body.

Minoxidil (Rogaine)

This drug was first developed as an antihypertensive agent. (*Mechanism of action for this effect:* It opens K+ channels, leading to efflux of K+ from the cell which causes hyperpolarization of the vascular smooth muscle cells which will ultimately inhibit calcium channels (no Ca+2 entry), thus no contraction occurs (the muscles relax and blood vessels dilate). This causes blood pressure to decrease).

- It was also found that this drug has trichogenic properties. So they began using it as a spray or cream to treat male pattern baldness.
- It is effective in reversing the progressive miniaturization of terminal scalp hairs associated with androgenic alopecia (male pattern baldness). Vertex balding is more responsive than frontal balding.
- The mechanism behind the trichogenic effects of this drug is not well-understood.

Finasteride (Propecia)

This drug serves as both a trichogenic and antitrichogenic agent.

- It is a 5α-reductase inhibitor which blocks the conversion of testosterone to dihydrotestosterne. So it decreases the concentration of dihydrotestosterone in the hair follicles, scalp and the different tissues of the body. In men, it was found to play a role in treating androgenic alopecia (trichogenic). However, in women, it was found to decrease hair growth (antitrichogenic) and was thus used to stop excessive and unwanted hair growth in women.
- It is present in the form of oral tablets.
- Another indication for the use of finasteride is prostate hyperplasia (because it decreases dihydrotestosterone levels that rise in benign prostate hyperplasia).
- *Side effects:* Since it decreases the concentration of dihydrotestosterone in different organs, including the testicles, it will affect and reduce sexual function in men. It causes decreased libido, ejaculation disorders, and erectile dysfunction.

Eflornithine

It is an antitrichogenic agent. It is an irreversible inhibitor of ornithine decarboxylase - an enzyme that converts the amino acid ornithine into polyamines (which are important molecules associated with proliferation and division of cells, particularly hair follicle cells). So, this drug blocks polyamine synthesis, and thus reduces hair growth. It is effective in reducing facial hair growth in 30% of women when used for 6 months.

Good luck