MSS

Musculoskeletal System

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NO.

Pharmacology

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Skin Pharmacology 2

(00:00-08:18)

Topical antiviral agent

There are many types of antiviral agent that are used to treat many of the viral infection, many of these are available ether centrally, orally, and topically, which is:

1. Acyclovir
2. Valacyclovir
3. Penciclovir
4. Famciclovir

All the 4 previous topical antivirals are synthetic guanine analogs with inhibitory activity against members of the herpesvirus and varicella zoster virus.

-These are used in ointment and cream form, and are useful for treatment of recurrent orolabial herpes simplex infection as well as treatment of virus infection in immunocompetent adults

Let's remember the mechanism of Acyclovir -> it is acyclic guanosine derivative, it requires three phosphorylation steps for activation, so 1st is converted to monophosphate derivative, which is achieved by virus thymidine kinase, then converted to dientry phosphate compound by host cells enzyme. Since the drug requires activation by viral thymidine kinase, it has quiet selectivity, thus it reduces the toxicity of this agent.

Immunomodulators

Are drug that interfere with ImmunoSystems so they can either stimulate or inhibit the immune system.

These downs are drugs used to treat many kinds of pathologies:

1. **Imiquimod** -> it stimulates peripheral mononuclear cells to release interferon alpha and to stimulate macrophages to produce interleukins-1, -6, and -8, and tumor necrosis factor-α (TNF-α).

Uses:

- external genital and perianal warts in adults

- actinic keratoses on the face and scalp

- primary superficial basal cell carcinomas

2. **Tacrolimus**
3. **Pimecrolimus** -> with tacrolimus are important to treat immune disorders, benefit in the treatment of atopic dermatitis. Both agents inhibit T-lymphocyte activation and prevent the release of inflammatory cytokines and mediators from mast cells.

Remember that activation of T cell receptors increases the CO. Of calcium, which then interact with calmodulin to activate calcium urine. Calcium urine then dephosphorylates a transcription factor which is nuclear factor of activating T cells / also called n-fat, it is translocated to the nucleus and increase the activity of genes coding interliuken-2 and other cytokines, so **Tacrolimus** will prevent this dephosphorylation process of n-fat, thus inhibit the activity of T lymphocyte and the release of inflammatory mediators.

Uses (for tacrolimus)

- Systemically, in organ transplant patients, it is an immunosuppressant drug.
- Topically, to treat eczema, psoriasis and some form of refractory uveitis after bone marrow transplant.

Adverse effect

- Numerous if given systemically, this includes cardiac damage, hypertension, blurred vision, and kidney problems because its nephrotoxic.
- Hyperglycemia, hyperkalemia, hypomagnesemia, and diabetes.
- Topical application can cause itching, fluorites.

-Using of this agent in the skin is in form of ointment or cream, so we have tacrolimus ointment of CO. Of .03%, and pimecrolimus cream of .1% and this is approved for use of children older than 2years.

*this agent is used for treatment of atopic dermatitis, which is another name for eczema, it's an immune disorder that make your skin red and itchy, it is usually a chronic disorder that can fled up with retain allergens. It can happen for individuals with asthma or other allergens in the environment.

NOTE: drug administration has added black box warning regarded the long term used safety of topical use of these agents because of studies show that they cause animal tumorigenicity.

Black box warning: warning needs to be putted outside label box of certain drugs that cause serious adverse effect (ممكن يكتب بخط ابيض على خلفية سوداء, او يكون محاط بإطار اسود على العلبة).

(8:18-14:50)

Ectoparasiticides

Ectoparasites are microorganisms that infect humans and animals by living in or on the skin but not inside the body of the host e.g., fleas and lices. The drugs that are used to treat infection by these agents are:

1. Permethrin-> usually used to treat Pediculus humans, Pthirus pubis(القمل), and Sarcoptes scabiei, it's a cream that applied for 10 minutes rinsed of then rinsed off with hot water for pediculus, but for treatment of scabies a cream is applied to the body from the neck down, left on for 8–14 hours, and then washed off.

*There is some systemic absorption when these drugs are applied topically of about less than 2%.

- Scabies: caused my mites الجرب.
- Pediculus: caused by one of the pathogens depending on the area.

***Side effects**: transient burning, stinging, and pruritus (الحكة).

2. Lindane-> can be absorbed by CO. Of 10% and get concentrated in the fatty tissues, this is a serious amount because it can cause neurotoxicity and hematotoxicity, so be careful. It is available as shampoo or lotion for the treatment of pediculosis.

Recent concerns about the toxicity of lindane have altered treatment guidelines for its use in scabies, it was recommended to applied for longer time of treatment, now its recommended for single application to the entire body from the neck down, left on for 8–12 hours, and then washed off.

*side effects: it causes seizer in infants if used by pregnant woman/ irritation specially to the eyes and mucus membranes, so don't use near these areas.

3. Crotamiton-> called also N-ethyl-o-crotonotoluidide, treat scabicide with some antipruritic properties so it helps with itching. its mechanism of action is not known. Studies show that absorption have revealed small levels of crotamiton in the urine for those who used it topically. Available as a 10% cream or lotion. Usually, it is applied two times to the entire body from the chin down at 24-hour intervals, and it takes period of 48 to clean the drug and used as an alternative to lindane.

*side effects: when used topically there is contact dermatitis and irritation which might cause stop using the drug.

4. Sulfur-> it has a long history of being used for scabies, although it's not irritated it has unpleasant odor and cause staining, so that it isn't very widespread used.
5. Malathion-> organophosphate choline esterase inhibitor, it inhibits the enzyme choline esterase that breaks down acetylcholine. This drug can be hydrolyzed and inactivated by plasma carboxyl esterase, much faster in human than insects which provides therapeutic advantage of treating pediculosis. This drug is available as 1.5% lotion and can be applied to the hair when dry.

(14:50-21:12)

Agents affect pigmentation

There are two type of drugs that affect the skin pigmentation, one increases and restores skin pigmentation and other decreases it.

1. <u>hypopigmentation</u> of the skin->Hydroquinone, monobenzone and mequinol

Topical hydroquinone and mequinol usually result in temporary lightening, whereas monobenzone causes irreversible depigmentation.

* The mechanism of action of these compounds appears to involve inhibition of the enzyme tyrosinase, thus interfering with the biosynthesis of melanin.

* Monobenzone may be toxic to melanocytes, resulting in permanent loss of these cells. Mequinol reduces the hyperpigmentation of the skin.

2. Hyperpigmentation of skin-> trioxsalin and methoxsalin, both are psoralens(need certain light for their actions) used for the repigmentation of depigmented macules of vitiligo (البهاق where areas or patches of the skin that loss the melanin color, because the inability of melanocyte to produce melanin in these areas). These must be photoactivated by long-wavelength ultraviolet light in the range of 320–400 nm to produce a beneficial effect. After that, Psoralens intercalate with DNA, and cause adducts with pyrimidine bases intercalation, this will cause cross-linking with DNA.

*side effects: cataracts and skin cancer

Sunscreen and sunshades

Topical medications useful in protecting against sunlight contain either chemical compounds that absorb ultraviolet light, called sunscreens, or opaque materials such as titanium dioxide that reflect light, called sunshades. The three classes of chemical compounds most used in sunscreens are p-aminobenzoic acid (PABA) and its esters, the benzophenones, and the dibenzoylmethanes.

* Chronic exposure to light in this range induces aging of the skin and photocarcinogenesis.

* Para-aminobenzoic acid and its esters are the most effective available absorbers in the B region of ultraviolet light.

-on the other hand, benzophenones provide a broader spectrum of absorption (250-360) nm, but their effectiveness in the UVB erythema range is less than that of PABA. The dibenzoylmethanes include Parsol and Eusolex. These compounds absorb wavelengths throughout the longer UVA range, with maximum absorption at 360 nm. Patients particularly sensitive to UVA wavelengths include individuals with polymorphous light eruption, cutaneous lupus erythematosus, and drug-induced photosensitivity. In these patients, dibenzoylmethane-containing sunscreen may provide improved photoprotection.

For further understanding (not from the lecture) --->

1. polymorphous light eruption is rash caused by sun exposure in people who have developed sensitivity to sunlight. The rash usually appears as red, tiny bumps or slightly raised patches of skin.
2. cutaneous lupus erythematosus is autoimmune disease that affects a lot of systems in the body
3. drug-induced photosensitivity Is an abnormal skin reaction either to sunlight or to artificial light. **Drugs** may be a cause of photoallergic, phototoxic, and photo aggravated dermatitis.

(21:12-30:00)

Acne preparation

Acne is caused by microorganism called propionibacterium acne,

We have several agents that can be used topically or systematically for the treatment of acne, lets start:

1. RETINOIC ACID & DERIVATIVES, this includes:

- Retinoic acid: is the acid form of Vitamin A, it has different effects on treating acne, they

a. are Stabilizes lysosomes, increases RNA polymerase activity, increases PGE2, cAMP, and cGMP levels and increases the incorporation of thymidine into DNA.
b. Decreases cohesion between epidermal cells and increases epidermal cell turnover, This will result in expulsion of open comedones and the transformation of closed comedones into open ones.
c. Promotes dermal collagen synthesis, new blood vessel formation(by its effect on PGE, cAMP and cGMP), and thickening of the epidermis, which helps diminish fine lines and wrinkles.

*Side effect: erythema, dryness and Tumorigenic in animals. It can be used topically and systemically but it's associated with many toxicities, be careful.

• Isotretinoin (Accutane): a derivative that is restricted for severe cystic acne that is resistant to standard treatment, inhibits sebaceous gland size and function and usually given orally.

Toxicity --> dryness, itching, headache, corneal opacities, pseudotumor cerebri (which is elevation in the intracranial pressure, stimulate inflammatory bowel disease, anorexia ,فقدان الشهية alopecia فقدان الشعر,muscle and joint pains and lipid abnormalities which is Lipid abnormalities in triglycerides and high-density lipoproteins, thus it's important for patients who are prescribed this drug to have a baseline of lipid; because this drug can effect liver enzymes as well as increase in the lipid profile.

Another side effect is Teratogenicity ---> is a significant risk in patients taking isotretinoin; therefore, women of childbearing potential must use an effective form of contraception for at least 1 month before, throughout isotretinoin therapy, and for one or more menstrual cycles following discontinuance of treatment, because the drug will stay for some period after that.

On the other hand, any women who are planning to have a childe, must stop or avoid using these agents.

There are some side effects that's not reported but were noticed: depression, suicidal thoughts.

- Adapalene
- Tazarotene

2. Benzoyl Peroxide--> an effective topical agent in acne vulgaris treatment, penetrates the stratum corneum or follicular openings unchanged and is converted metabolically to benzoic acid within the epidermis and dermis.

The mechanism of action is because it has antimicrobial activity against P acnes and to its peeling and comedolytic effects.

We usually applied slow CO. of benzoyl peroxide of about 2% once daily (because we want to decrease the irritation) for the first week of therapy and increased in frequency when body gets tolerated to that dose.

A combination of :

benzoyl peroxide+ erythromycin base--> Benzamycin

benzoyl peroxide+ clindamycin--> BenzaClin

benzoyl peroxide+ adapalene-->

*remember: Adapalene is derivative from naphthalic acid that resembles retinoic acid in structure and effects, and usually applied as gel, cream or lotion. Unlike tretinoin, adapalene is photochemically and shows some decrease in efficacy when using in combination with benzoyl peroxide.

-side effects: bleaching of hair colored fabric, irritant for the eyes and mucus membranes, so must keep away.

3. Azelaic acid--> it has distinct and special mechanism of action; a drug is saturated dicarboxylic acid that is effective in the treatment of acne vulgaris and acne rosacea. The mechanism is not fully determined, but in addition to have antimicrobial activity against P acnes, it also has inhibitory effects on the conversion of testosterone to dihydrotestosterone. Usually used in form of 20% cream, 15% gel, and applied for affected area for 1 week twice daily.

- Side effect: mild irritation with redness and dryness of the skin.

(30:00-37:43)

Drug of psoriasis (الصدفية)

Certain drugs in relation with tretinoin family are used for treatment of psoriasis:

1. Acitretin--> is related to isotretinoin, usually Given orally, it Is Hepatotoxic and teratogenic.

Patients should not become pregnant for 3 years after stopping treatment and should not donate blood.

- Ethanol must be strictly avoided during treatment with acitretin and for 2 months after discontinuing therapy because its effect on the liver.

-adverse effects: similar to that in isotretinoin, they resemble hypervitaminotic a level and toxicity, so watch the changes in the level of cholesterol /triglyceride and to monitor the level of enzymes because they could change with treatment of this drug.

2. Tazarotene--> is a topical acetylenic retinoid prodrug that is hydrolyzed to its active form by an esterase. The active metabolite, tazarotenic acid, binds to retinoic acid receptors, resulting in modified gene expression.

- The precise mechanism of action in psoriasis is unknown but may relate to both anti-inflammatory and antiproliferative actions. Its absorbed systemically, so be careful about systemic concentrations that may be achieved to more than 20% of the drug because it has teratogenic effect.

- Women of childbearing potential must therefore be advised of the risk prior to initiating therapy, and adequate birth control measures must be utilized while on therapy.

- Treatment of psoriasis should be limited to once-daily application of either 0.05% or 0.1% gel not to exceed 20% of total body surface area.

* Adverse local effects: include a burning or stinging sensation (sensory irritation), peeling, erythema, localized edema of the skin (irritant dermatitis) and Potentiation of photosensitizing medication, so patients should be cautioned to minimize sunlight exposure and to use sunscreens and protective clothing.

3. Calcipotiene--> Synthetic vitamin D3 derivative, (available as a 0.005% cream, scalp and lotion that is effective in the treatment of plaque-type psoriasis vulgaris of moderate severity.

Improvement of psoriasis is generally noted following 2 weeks of therapy, with continued improvement for up to 8 weeks of treatment. However, fewer than 10% of patients demonstrate total clearing while on calcipotriene as single agent therapy.

-side effects: burning, itching, and mild irritation, with dryness and erythema. Care should be taken to avoid facial contact, which may cause ocular irritation.

* two-compounds: calcipotriene +betamethasone (corticosteroid) is available. This combination is effective for patients because it suppresses the inflammation associated with psoriasis.

Calcitriol is another form of vitamin d3 which contain 1,25-dihydroxycholecalciferol, the hormonally active form of vitamin D. An ointment of 3 mcg/g Calcitriol is similar in efficacy to 0.005% calcipotriene.

Biological Effects

Used to treat psoriasis and most of them are immunomodulators.

1. Alefacept--> Immunosuppressive dimer fusion protein of CD2 linked to the Fc portion of human IgG1. It interferes with lymphocytic activation which play it all in the pathophysiology of psoriasis, thus it causes a reduction on the subset of CD-2 T lymphocyte and circulating CD-4 and CD-8 T lymphocytes count. Usually, the dose is 7.5 mg once a week as intra venous bolus or 15 mg once a week as intramuscular injection, and usually the duration of the treatment the 12 weeks.

-patients should have their own CD4 level monitors alefacept, and if the level goes down below 250 cells/micro liter the drug then needs to be stopped. Scince this drug is immunosuppressant agent; it should be immediately soft if patient has a significant infection.

-side effects: increased risk of malignancy, it shouldn't be administered to patient with systemic malignancy

2. Efalizumab--> Recombinant humanized IgG1 monoclonal antibody, progressive multifocal leukoencephalopathy (PML), and Can cause thrombocytopenia (is a condition characterized by abnormal low levels of platelets).
3. Etanercept--> Dimeric fusion protein of TNF receptor linked to the Fc portion of human IgG1.

(34:43-54:28)

Anti-inflammatory Agents

A)Corticosteroids are used to treat many pathologies in skin, they are considering as anti-inflammatory agents, so e.g.:

1–Hydrocortisone.

2– Prednisolone and Methylprednisolone.

3–Dexamethasone and Betamethasone.

4–Triamcinolone.

5– Fluocinonide.

The original topical glucocorticoid was hydrocortisone, its natural of the adrenal cortex. These drugs are only minimally absorbed following application to normal

skin; for example, approximately 1% of a dose of hydrocortisone solution applied to the ventral forearm is absorbed. Long-term occlusion with an impermeable film such as plastic wrap is an effective method of enhancing penetration, yielding a tenfold increase in absorption .

- There is a marked regional anatomic variation in the anatomy of different part of the body which lead to variation in corticosteroid penetration.

Compared with the absorption from the forearm, hydrocortisone is absorbed 0.14 times as well through the plantar foot arch, 0.83 times as well through the palm, 3.5 times as well through the scalp, 6 times as well through the forehead, 9 times as well through vulvar skin, and 42 times as well through scrotal skin.

* Penetration is increased severalfold in the inflamed skin of atopic dermatitis is application of occlusion, also in severe exfoliative diseases, such as erythrodermic psoriasis, there appears to be little barrier to penetration.

These drugs also can be given as intralesional injection, this is one way to overcome the limited penetration of topical corticosteroid e.g. triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, and betamethasone acetate-phosphate. When these agents are injected into the lesion, measurable amounts remain in place and are gradually released for 3–4 weeks. This form of therapy is often effective for the lesions that are unresponsive to topical corticosteroid therapy.

….so, what kind of lesions are very response to topical corticosteroids therapy?

• Atopic dermatitis.

• Seborrheic dermatitis.

• Lichen simplex chronicus.

• Pruritus ani.

• Allergic contact dermatitis.

• Eczematous dermatitis.

• Psoriasis

Now there are some conditions that seem less response to this treatment

- Discoid lupus arithmetosis
- Psoriasis of the palms and the souls
- Sarcoidosis like in strayatas
- Pemphigoid Velgaras

The least response

- Keloids
- Hypertrophic scars
- Hypertrophic lichen planus
- Alopecia areata
- Acne cysts

*adverse effects of corticosteroids:

1. Suppression of pituitary-adrenal axis; since there is some systemic absorption of these compound into the body, we would have the risk of suppression of pituitary-adrenal axis, even though, this suppression had been only noted in laboratory testing, some patients show cases of sever impaired stress response that might occurs
2. Cushing's syndrome may occur as a result of protracted use of topical corticosteroids in large quantities. For example, applying potent corticosteroids to extensive areas of the body for prolonged periods, with or without occlusion, increases the likelihood of systemic effects.
3. Atrophy
4. skin erythema
5. pustules
6. Acne
7. cutaneous infections
8. Hypopigmentation
9. allergic contact dermatitis
10. Hypertrichosis
11. increased intraocular pressure.

B) Tar compounds

Used Mainly for treatment of psoriasis, dermatitis, and lichen simplex chronicus. These compounds have antipruritic properties, making them particularly valuable in the treatment of chronic lichenified dermatitis.

-side effect s:

- Irritant folliculitis
- Photoirritation /phototoxicity
- Allergic contact dermatitis

Keratolytic and Destructive Agents

1. Salicylic acid: it solubilizes cell surface proteins resulting in desquamation of keratotic debris, it's a keratolytic in 3-6% concentration, but destructive of the outer layer in higher concentrations. Can result in salicylism due to systemic absorption.

- Adverse effects:
- Urticaria
- anaphylactic and
- erythema multiforme reactions
- Irritation
- Inflammation
- ulceration
- The mechanism of this drug is poorly understood, but it seems to cause solubilization of surface protein that keep stratum cornea intact, which will result in discrimination the keratin layer.

2.Propylene Glycole: –Usually used in topical preparation because its excellent vehicle for organic compounds, but used alone as a keratolytic agent in concentrations of 40%- 70%, with plastic occlusion, or in gel with 6% salicylic acid. Minimally absorbed when applied topically, oxidized in liver to lactic acid and pyruvic acid for the body metabolism.

Approximately 45% of the absorbed agent is excreted unchanged in the urine. It's used for removal of hyperkeratotic debris. It is also an effective humectant and increases the water content of the stratum corneum(moisturization) .

- hygroscopic characteristics may help it to develop an osmotic gradient through the stratum corneum, thereby increasing hydration of the outermost layers by drawing water out from the inner layers of the skin.

3. Urea: Has a humectant activity, so it softening and moisturizing effect on the stratum corneum, it decreases the unpleasant oily feel of dermatologic preparations and if absorbed throw the skin or the amount absorbed is minimal, it is excreted in urine.

- Urea is a natural product of metabolism, and systemic toxicities with topical application do not occur

- urea is used in concentrations of 2–20% in creams and lotions. And as a keratolytic agent, it is used in 20% concentration.

الجزئية الجاية ما حكت عنها شي الدكتورة لهيك كتبتها مثل ما هي

4. Podophyllum Resin and Podofilox.
5. Flurouracil: – Antimetabolite that resembles uracil and inhibits thymidylate synthetase, thus interferes with DNA and may be RNA synthesis. – Used in multiple actinic keratosis.
6. Nonsteroidal Anti-inflammatory Drugs: – 3% gel formulation diclofenac.
7. Aminolaevulinic Acid: – Used in actinic keratosis. – After topical application (20%) and exposure to light, produces a cytotoxic superoxide and hydroxyl radicals.

انتهت الجزئية

Antipruritic Agents

There are drugs used to decrease the itching sensation which is stimulated by the release of histamine

1. Doxepine: – Potent H1 and H2 – receptor antagonist (histamine).

5% cream may provide significant antipruritic (antiitching) activity when utilized in the treatment of pruritus associated with atopic dermatitis or lichen simplex chronicus.

- Side effects: drowsiness and anticholinergic effect
2. Pramoxine: a topical anesthetic that can provide temporary relief from pruritus associated with mild eczematous dermatoses. It is available as a 1% cream, lotion, or gel and in combination with hydrocortisone acetate. It's applied to the affected area two to four times daily may provide short-term relief of pruritus

- Local adverse effects : transient burning and stinging, care should be exercised to avoid contact with the eyes.

Trichogenic and Antitrichogenic Agents

1. Minoxidil (Rogaine): its originally designed as an antihypertensive agent, its hyperpolarizing agent that causes hyperpolarization of vascular smooth muscle cells leading to open K channels, this will cause blockage of calcium channels so the intracellular Ca CO. Will decrease and then lowering the BP.
- It can increase the growth rate of hair, so they had utelize this effect by modulating it use in reversing the progressive miniaturization of terminal scalp hairs associated with androgenic alopecia.
2. Finasteride (Propecia): is a 5ά-reductase inhibitor which blocks the conversion of testosterone to dihydrotestosterne which is the androgen responsible for androgenic alopecia.
- Oral administration and dose of 1 mg/d, promotes hair growth and prevents further hair loss in a significant proportion of men with androgenic alopecia. Treatment for at least 3–6 months is necessary to see increased hair growth or prevent further hair loss.
- Adverse effects: include decreased libido, ejaculation disorders, and erectile dysfunction.
3. Eflornithine: is an irreversible inhibitor of ornithine decarboxylase, this enzyme converts ornithine to Polyamines, therefore, inhibits polyamine

synthesis. Polyamines are important in cell division and hair growth. – Effective in reducing facial hair growth in 30% of women when used for 6 months.

To simplify the previous:

- Ornithine+ ornithine decarboxylase--> +Polyamines --> + hair growth
- Eflornithine--> -ornithine decarboxylase->- Polyamines --> - hair growth

- Sides effects: stinging, burning, and folliculitis

ظَهْري لِغَيرِكَ لَسْتُ أسنُدُه

يا رَبّ أنتَ العونُ و السَّنَد