

MSS



Sheet no. 1

Pharmacology



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Skin Pharmacology

Dermatologic pharmacology:

There are variables affect the pharmacologic response to a topically administered drug: (according to these variables, the proper formulation of the drug will be decided).

- 1) Regional variation in drug penetration:** The skin is a large organ that covers the whole body, and has different thicknesses and composition on different areas, for example palm of the hand is thicker than the dorsum, also underneath the eyes we have thin layer of skin which is more sensitive or prone to irritation.
- 2) Concentration gradient:** All chemicals or dugs cross membranes according to their concentration gradient (higher conc. → lower conc.), that's why if we want to increase the penetration of a drug through the skin, we apply more of it on that area. ****penetration not absorption** because scientifically absorption is the process of a drug moving from its site of delivery into the bloodstream, and here we're not talking about the drug reaching the blood but the affected area (here we're talking about the skin). Drugs that are applied through the skin will have some access to the circulation so they will eventually be absorbed into the circulation, but not as much as drugs that are given systematically, whether orally or by injection.
- 3) Dosing schedule:** Some drugs are given once a day, others are given twice, this depends on the drug and the condition that is being treated.
- 4) Vehicles and occlusion:** (**Occlusion:** إطباق, closing something) if a plaster was put on the top of the drug it's going to stay for longer period in that area, thus we maintain the drug to be released through a longer period. For example, using a cream to treat inflammation (cortisone, hydrocortisone)

without putting a gauze on it, it's going to be rubbed quickly and it's not going to give the effect or response for a long period of time, but when occlusion is applied it helps it to stay, so no need to give it twice or three times a day, maybe once a day will be sufficient.

Vehicle (it means carrier): an appropriate vehicle maximizes the ability of the drug to penetrate the outer layers of the skin. In addition, through their physical properties (moistening or drying effects), vehicles themselves have an important therapeutic effect.

Formulations of systemic drugs: tablet of pills, capsule, injection, or syrup (suspension).

Also, there are different **formulations of skin drugs** for example: iodide is watery (more aqueous), sun block is a cream.

Choosing the formulation depends on the condition of the patient.

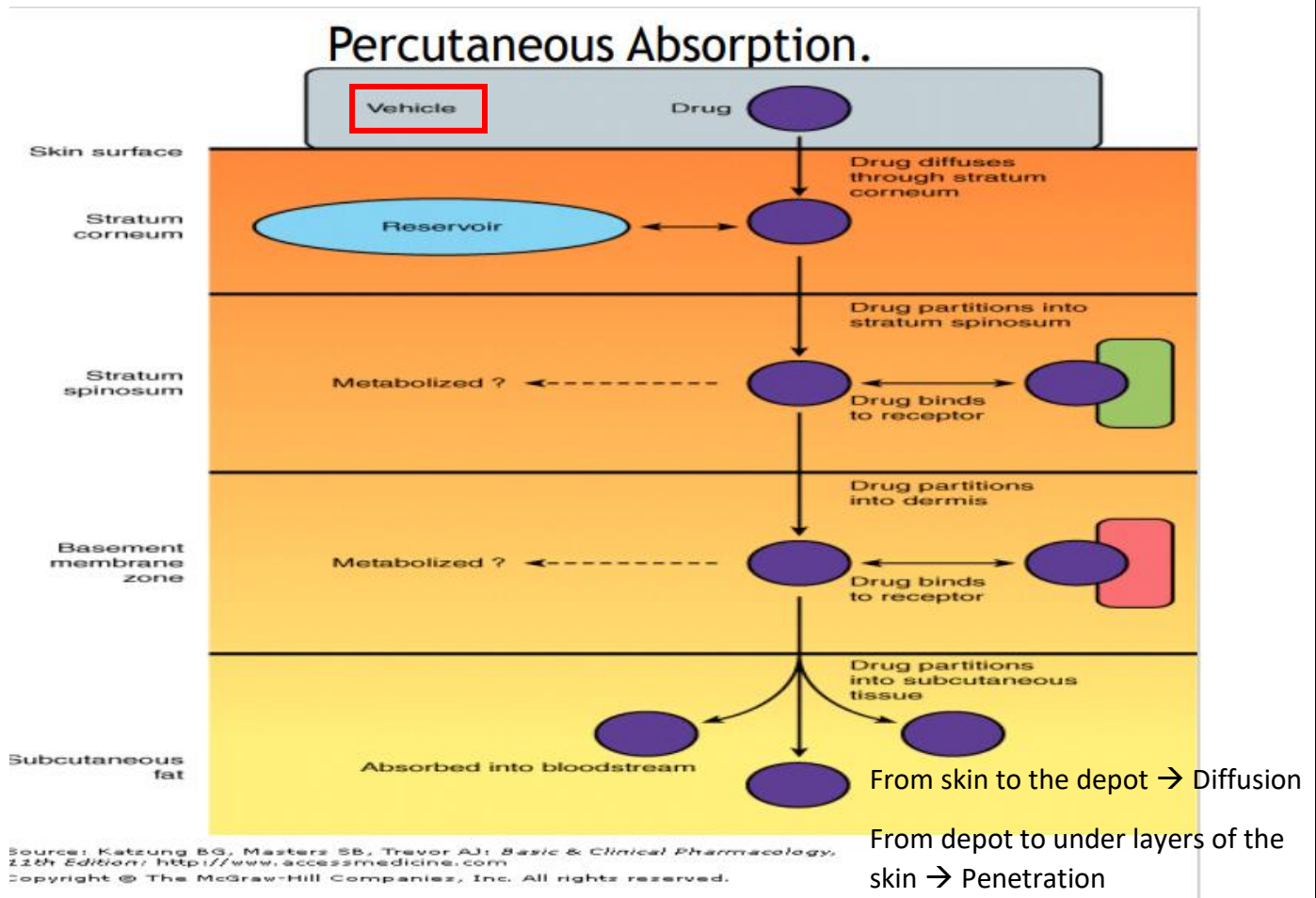
This is extra just to understand the idea of vehicles:

Instead of applying active medicine directly onto the skin, "vehicles" are combined with the chosen medication to aid in its delivery. Vehicles are inactive creams, lotions, solutions and/or ointments that change the properties of the medicine mixed into them – assisting its application. The primary components of vehicles include powders, oils, and liquids. The inherent properties of these three ingredients are translated to the vehicle, and thus how the medicine is delivered on the skin. For example, a vehicle with a prominent liquid component can assist with the drying of wet skin lesions through evaporation, whereas oils can provide an occluding coating to the skin and enhance the penetration of the active medicine.

When vehicles are combined with active medicines, you get "formulations".

Percutaneous Absorption

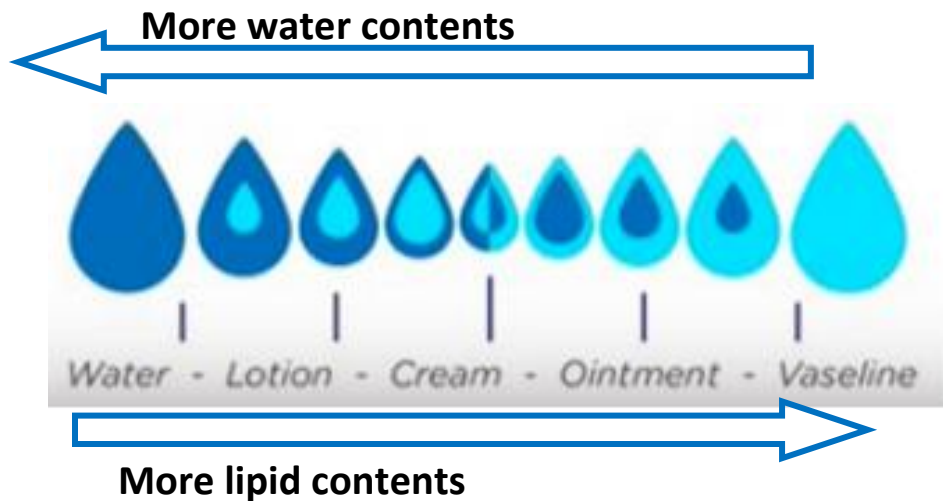
The subcutaneous layer of the skin can sometimes store the drug in it, (you learned about sustained release pills or deep injection (give the drug once a week or once a month) we call this depot (reservoir), the skin (stratum corneum) act as a depot for the drug so it continuously gets released to the surrounding area to keep giving the effect for a longer period (Increase the half-life).



Dermatologic formulations

Different formulations of drugs that can be used dermatologically according to their vehicles:

- Tinctures: (a medicine made by dissolving a drug in alcohol) iodine for example, and it evaporates right away because it has high alcohol content, so it dries very quickly.
- Wet dressings.
- Lotions.
- Gels.
- Powders.
- Pastes.
- Creams.
- Ointments.



Notice here, if we compare the lotion, cream, and ointment, as we move toward the water or lotion it has more water content, and as we move toward the ointment it has more lipid content or more Vaseline.

According to the affected area the proper formulation is decided, if it's a scalp inflammation or infection, eczema for example, it's not suitable to use ointment or cream to that area because of the hair, it's going to be interfering with the drug penetration, so in this case we will use watery or alcohol-based drug such as tincture, maybe lotion to some extent.

In a thick area (soles of the feet and palms of the hand), a cream can be applied because it will moisturize the area and it will penetrate at an easier rate when it's moisturized.

There are substances added on the dermatological formulation that will help increase its moisturization, such as:

- Urea: it's the same of this produced in the body and excreted with urine, it has a moisturization effect, a lot of creams contain urea to moisturize the area that is being treated.

Adverse effects of dermatological preparations:

In general, there are certain side effects that are associated with dermatological preparation, these are some of them, especially if they are alcohol based:

- Burning or stinging sensation
- Drying and irritation
- Pruritus (itching)
- Erythema (redness)
- Sensitization
- Staining
- Superficial erosion (for minimal superficial layers (تآكل لطبقات الجلد)).

TABLE 61-1
Local cutaneous reactions to topical medications.

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Reaction type	Mechanism	Comment
Irritation	Non-allergic	Most common local reaction
Photoirritation	Non-allergic	Phototoxicity; usually requires UVA exposure
Allergic contact dermatitis	Allergic	Type IV delayed hypersensitivity
Photoallergic contact dermatitis	Allergic	Type IV delayed hypersensitivity; usually requires UVA exposure
Immunologic contact urticaria	Allergic	IgE-mediated type I immediate hypersensitivity; may result in anaphylaxis
Non-immunologic contact urticaria	Non-allergic	Most common contact urticaria; occurs without prior sensitization

We will start talking about some of these medications:

Topical Antibacterial Agents

- **Gram-positive bacteria**
 - Bacitracin
 - Gramicidin

• Gram-negative bacteria

- Polymyxin B Sulfate
- Neomycin (very toxic)
- Gentamicin (toxic)

Known as Triple Antibiotic Ointment, it's composed of Neomycin + Bacitracin + Polymyxin B



Bacitracin:

- ✓ Active against streptococci, pneumococci, and Staphylococci. Also, most anaerobic cocci, neisseriae, tetanus bacilli, and diphtheria bacilli are sensitive.

*You are not required to memorize the bacteria names just know that it's against gram positive bacteria.

- ✓ Not given systematically because it's highly toxic, so it's used mainly by topical administration, when it's added topically not a lot of it will be absorbed to the circulation, so there are no worries about systemic toxicity.
- ✓ Bacitracin is poorly absorbed through the skin, so systemic toxicity is rare.
- ✓ Topical allergic reactions can occur such as **contact dermatitis** some form of skin inflammation or eczema.
- ✓ Allergic contact dermatitis occurs frequently, and immunologic allergic contact urticaria rarely.
- ✓ Mechanism of action (MOA): **inhibits bacterial cell wall synthesis** but doesn't belong to the family of Penicillin or Cephalosporin.
- ✓ Frequently used in combination with other agents (**polymyxin B and neomycin**), because it's used to treat skin infections and usually there are a lot of different pathogens that are affecting the skin.
- ✓ Forms: creams, ointments, and aerosol preparations.
- ✓ Usually, Anti-inflammatory agents are added (Hydrocortisone) * will talk about in the endocrine system, it belongs to steroids (glucocorticoids)



In Jordan we use **Fucidin more than Bacitracin and its **protein synthesis inhibitor**, both are used topically to inhibit the growth of bacteria, used with other drugs

(antibiotic or another anti-inflammatory agent) to treat bacterial skin infection. If the skin got injured (cut) and started to inflame we use these drugs to prevent infections.

Gramicidin

- ✓ Only for **topical use**, in **combination with other antibiotics** such as neomycin, polymyxin, bacitracin, and nystatin.
- ✓ Mechanism of action (MOA): NOT REQUIRED.
- ✓ Side effects (SE): Hemolysis

Polymyxin B Sulfate

- Mainly against gram-negative: Pseudomonas aeruginosa, Escherichia coli, Enterobacter, and klebsiella. ***Not required to memorize the bacteria.**
- Proteus and Serratia are **resistant**, as are all gram-positive organisms.
- Cortisone is added to decrease the inflammation.
- **Side effects:** severely **neurotoxic and nephrotoxic**, but it doesn't have high absorption (given by skin, not highly absorbed), but if there is a denuded area in the skin because of burns or open wound the absorption rate will be higher and we have to be careful about that, **total daily dose applied to denuded skin or open wounds should not exceed 200 mg to reduce the likelihood of toxicity "Neurotoxicity and nephrotoxicity"**.
- Allergic contact dermatitis **NOT common.**

Distinguish between the infection and the inflammation:

Infection: When there is a pathogen such as a bacterium or a virus.

Inflammation: The body response to that pathogen.

* Sometimes we may have an inflammation without an infection, like in eczema and autoimmune diseases. Also, sometimes after the infection we may still have inflammation without the pathogen.

When we use a drug, we try to use it for all aspects, treat the infection and reduce the inflammation.

Neomycin & Gentamicin

Neomycin

- ❖ **Aminoglycoside antibiotics**, ribosomes inhibitors so they are protein synthesis inhibitors.
- ❖ Target gram-negative: E coli, proteus, klebsiella, and Enterobacter.
- ❖ SE (Side Effect): **Allergic contact dermatitis**.
- ❖ Gentamicin generally shows greater activity against P aeruginosa than Neomycin.
- ❖ Gentamicin more active against staphylococci and group A β -hemolytic streptococci (streptococcus pyogens).
- ❖ Be careful with **systemic toxicity**: especially in renal failure, as we said if we use the drug in an open wound, denuded area of the skin, or in a thin, large surface area we worry about absorption to the systemic circulation and about the side effects, which is **neurotoxicity or nephrotoxicity**.
- ❖ Hospital acquired resistant.

Topical Antibacterial in Acne

- **Roaccutane** (commercial name), the scientific name is **Isotretinoin**, a drug that is given systematically as pills that will enter the GI system and get absorbed to treat acne. **we don't need to revert to this drug because it has some serious side effects, so we only use it in the case of severe acne and cystic acne, for mild cases we use topical preparation such as:
- **Clindamycin**: Protein synthesis inhibitor.
- **Erythromycin**: Protein synthesis inhibitor.
- **Metronidazole**: (Flagyl), used to:
 1. Treat **rosacea** (skin condition where there is a reddening of the face or an area of the skin, blushing or flushing and visible blood vessels in the face, caused by Demodex brevis parasite can be associated with this disease, it's not a severe infection but it can bother some patients).
 2. Antibiotic for parasite.
 3. Treat Amebiasis.
 4. Treat anaerobic bacteria, and GI infections.

- **Sodium sulfacetamide.**
- **Dapsone:** belongs to the family of Isotretinoin, used to prevent the infection of the bacteria that causes acne.

Clindamycin

- 10% absorbed, so, possibility of Pseudomembranous colitis (its side effect).
- Regards to the **topical administration** we have **different formulations**:
 - 1- The hydroalcoholic vehicle and foam formulation (Evoclin) → may **cause drying and irritation of the skin**, with complaints of burning and stinging.
 - 2- The water-based gel and lotion formulations → **well tolerated** and less likely to cause irritation. (Allergic contact dermatitis **is uncommon**).
- Clindamycin is also available in fixed-combination topical gels with benzoyl peroxide (Acanya, BenzaClin, Duac), and with tretinoin (Ziana), to **treat acne infection**.

Metronidazole

- ✓ Effective in the **treatment of rosacea**.
- ✓ The mechanism of action is unknown for this particular use, but it may relate to the inhibitory effects of metronidazole on Demodex brevis; this drug may act as an **anti-inflammatory agent** by direct effect on neutrophil cellular function.
- ✓ Adverse local effects associated with topical administration include **dryness, burning, and stinging**.
- ✓ Less drying formulations may be better tolerated (MetroCream, MetroLotion, and Noritate cream). If we use cream of it, we will have less irritation problem.
- ✓ Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing (because of irritation).

Erythromycin

- In topical preparations, erythromycin base rather than a salt is used to facilitate penetration.
- One of the possible complications of topical therapy is the development of antibiotic-resistant strains of organisms, including staphylococci.
- Adverse local reactions to erythromycin solution may include a burning sensation at the time of application and drying and irritation of the skin.
- Erythromycin is also available in a fixed combination preparation with benzoyl peroxide (Benzamycin) for topical treatment of acne vulgaris.

Topical Antifungal Agents

● Azole Derivatives:

- Clotrimazole
- Econazole.
- Ketoconazole.
- Miconazole.
- Oxiconazole.
- Sulconazole.
- Activity against dermatophytes that causes Tinea disease (Epidermophyton, Microsporum, and Trichophyton) and yeasts, including Candida albicans and Pityrosporum orbiculare.

- Ciclopirox Olamine.
- Naftifine and Terbinafine.
- Tolnaftate.
- Nystatin and Amphotericin B.

- Only for Candida albicans.
- Available as topical preparations, oral suspension, or vaginal tablets.

(Oral suspension: to treat the fungal infections in the GI tract, Nystatin doesn't get absorbed through membranes so we can use it as a mouth wash or treat

infection of the GI tract and not going to worry about absorption systematically and side effects).

- These drugs are highly toxic, they **cause nephrotoxicity** and shouldn't be used systematically, it's given by IV injection in the case of treating a systemic infection, but because it's highly toxic it's only used for certain cases.

Tinea Versicolor: A fungal infection, the color of the skin changes in certain areas, we can use any of previously drugs for it. (Ciclopirox olamine is the best drug to use in this case).



Oral Antifungal Agents

*Sometimes we can use them orally (systematically) to treat fungal skin infection

- **Azole Derivatives:**

- Fluconazole.
- Itraconazole.
- Ketoconazole.
- ✓ Affect the permeability of fungal cell membrane through alteration (inhibition) of sterol synthesis.
- ✓ Effective in systemic mycosis, mucocutaneous candidiasis, and other cutaneous infections.
- ✓ Might have **systemic side effects: hepatitis and liver enzyme elevations** and interactions. (Dysfunction in liver enzymes).

- ✓ We must watch for the liver function because they can cause liver toxicity, liver enzymes must be monitored when these drugs are used for a long period of time, and interactions.

- **Griseofulvin:**

- ✓ Effective against Epidermophyton, Microsporum, and Trichophyton.
- ✓ Usually, it's used to treat the different fungal infections, and **depending on the organ the period is decided** (Requires prolonged treatment):
 - 4-6 weeks for the scalp. (In Tinea capitis)
 - 6 months for fingernails.
 - 8-18 months for toenails.
- ✓ Has many side effects, but if the topical treatment didn't work out, we must revert to systematic treatment.

- **Terbinafine:**

- ✓ Recommended for Onychomycosis.
- ✓ 6 weeks for fingernails.
- ✓ 12 weeks for toenails.

Onychomycosis



Nystatin & Amphotericin b

- Topical therapy of C albicans infections but ineffective against dermatophytes.
- Cutaneous and mucosal candida infections, infections of oral cavity as well.
- Amphotericin B: broader antifungal.
- Because it doesn't get absorbed to the systemic circulation, it's given intravenously in the treatment of many systemic mycoses and to a lesser extent in the treatment of cutaneous candida infections. (Usually for hospitalized patients (severely ill) where we keep monitoring the kidney function, so we don't go into toxicity, but we must be very careful about the side effects).
- Toxicity with systemic administration.

Topical Antiviral Agents

- Acyclovir.
 - Valacyclovir.
 - Penciclovir.
 - Famciclovir.
- ✓ They all belong to the same family; they are **inhibitors of viral replication**.
 - ✓ Synthetic Guanine analogs (their structures look alike) with **inhibitory activity against herpes viruses**, they get incorporated into the DNA of the virus and stop its replication because they have different structure.
 - ✓ Ointments and creams are useful for **recurrent orolabial herpes simplex infection**. Herpes labialis, it will stop the propagation of that condition.
 - ✓ We may have other skin infections like the **herpes zoster infection** (dormant pathogen, it gets stored in the dorsal root ganglia and it gets reactivated when our immunity gets low) a severe condition of it we will use systematic antiviral agents, but usually we use them as a cream to treat skin or mucous membrane, lips, or the face.
 - ✓ **These drugs should be given early on**, once the patient felt the symptoms, if you give it after 2 or 3 days, the virus has already affected the cell so the drug will not be beneficial. Same as in corona cases. If you want to get the benefit of antiviral medications it must be given early on.

Multiple Choice Questions

- 1) All is true about bacitracin; EXCEPT:
- a. Can cause allergic contact.
 - b. Systemic use can cause nephrotoxicity.
 - c. It is highly absorbed through the skin, so systemic toxicity quite frequent.
 - d. It interferes with cell wall and peptidoglycan synthesis.
 - e. Usually administered in combination neomycin, polymyxin B, or both.

Answer: C

Best of Luck