



MSS

Musculoskeletal System

Pharmacology

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Done by

Mohammad Aboshaban

Contributed In The Scientific Correction

Pikachu

Contributed In The Grammatical Correction

Pikachu

Doctor

Alia

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The skin covers our body from the outside; this puts at an increased risk to face external trauma and pathogens, and to ensure its function as an external barrier we need to make sure that our skin always remains intact and healthy.

As we mentioned in the last semester, when the drug enters the systemic circulation, the probability for side effects to develop increase; because the drug will be distributed to tissues other than the target tissue. The skin being an external organ helps us avoid, or at least reduce, the unwanted side effects by applying the drugs topically, you keep this in mind during this course.

The general pharmacokinetic principles governing the use of drugs applied to the skin are the same as those involved in other routes of administration that we learned in the last semester. Although the skin is a simple three-layered structure, yet it's a complex series of diffusion barriers.

-In order to treat a certain disease, we administer a drug to the target tissue (skin), so what are the variables that we should consider when choosing the drug?

1- Regional variation in drug penetration: as the name implies, the drug penetration of the skin varies according to what region of the skin we're applying it, which will help us decide on the formulation and dosage of the drug.

For example, the scrotum, face, axilla, and scalp are far more permeable than the forearm and may require less amount of drug for equivalent effect.

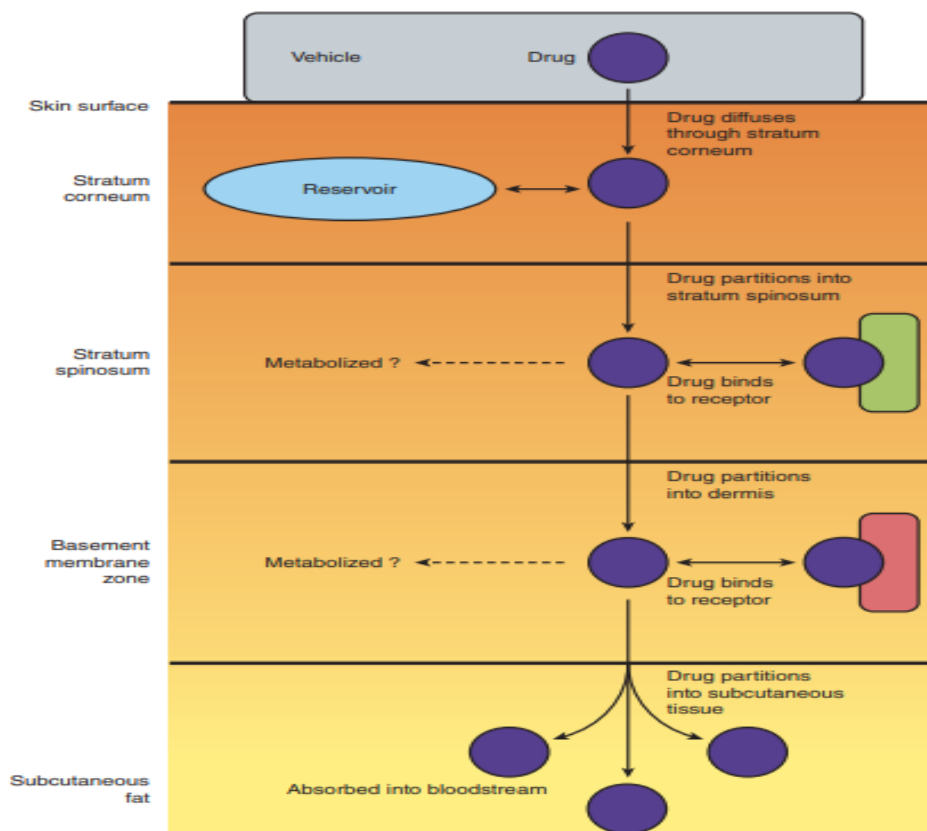
***Factors that affect the penetration:**

-  **Surface area:** the larger the surface area the higher the absorption.
-  **Vascularization:** Highly vascularized areas are more permeable, so we have to worry about the systemic absorption. KEEP IN MIND that my goal is to NOT absorb the drug to the systemic circulation.
-  **Thickness of the skin:** the amount of the drug that I apply to a highly keratinized area will be less absorbed than the thin area.
-  **Condition of the patients:** if the patient has burnt skin I have to take that into consideration.

-Depending on the condition of the patient, the tissue I'm treating and the physical and the chemical properties of the drug, we choose the proper drug formulation.

2- Concentration gradient: Increasing the concentration gradient increases the mass of drug transferred per unit time, just as in the case of diffusion across other barrier. For example, we can decrease the resistance of topical corticosteroids by the use of higher concentration of drug.

3- Dosing schedule: Because of its physical properties, skin (specifically the first layer, **stratum corneum**) acts as a reservoir for many drugs. As a result, the “local half-life” of the drug will be extended, which may permit once-daily application of drugs with short systemic half-lives. For example, once-daily application of corticosteroids appears to be just as effective as multiple applications in many conditions. In this way we can limit the use of a drug to be once a day because the drug is reserved in the skin at that area and will be absorbed continuously even though the drug is not applied, as if you’re wearing a patch.



4- Vehicles and Occlusions:

-Vehicle: simply, it is a chemical substance that carries the drug and transports it from outside the body to the area where it will work (inner layers of skin in this case). Also, they determine the different formulation of the drug. For example, if the

vehicle is more water based, it appears as “Wet dressings” or “lotions”, but if it was oil based, it appears as “Ointments”. If half by half, it is a “Cream”.

-Occlusions: it's an application of a plastic wrap to hold the drug and its vehicle in close contact with the skin.

-As we said, depending upon the vehicle, dermatologic formulations may be classified as tinctures, wet dressings, lotions, gels, aerosols, powders, pastes, creams, foams, and ointments.

-Tinctures: it's a drug dissolved in Alcohol. This feature has certain value; it may have therapeutic benefit in the treatment. For example, we have acne which is pimples full of pus. So, when we treat it with Tinctures, we don't have to add Antiseptic drug due to the existence of Alcohol. Also, we must take into consideration having more side effects of irritation.



-Creams, on the other hand, are based more on water which can be valuable in certain conditions, for example, Actinic keratosis (pre-cancerous area of thick, scaly or crusty skin induced by UV light exposure). In order to treat this condition we have to “WET” this area, so we use water based formulation like Creams.

- Most of the dermatologic formulation have common side effects, e.g. if we use alcohol-based drugs it will cause **dryness, irritation** and some allergic reactions like contact dermatitis whether immunological or non-immunological which lead to **erythema, sensitization** or **pruritus**. Or it can cause **Burning and Stinging sensation**.
- Some drugs cause **staining**, due to either the drug itself is colored or it causes staining like hydrocortisone.
- Some drugs cause **superficial erosion**, for example after acne treatment. This may bother the patient but it may have therapeutic benefit, when we peel the layers of the skin we open up the infected papules in order to deliver more Antibiotic. Although, we have to be careful because the skin will be thinner so it will be easily exposed to UV Light. Sunblock may be used in this case.



TOPICAL ANTIMICROBIAL AGENTS: they may be useful in preventing infections in clean wounds “prophylactic use” or in the early treatment. Selection of a particular antibiotic depends upon the diagnosis or “in vitro” culture. The most common pathogens isolated from infected skin are group A β -hemolytic strep, staph aureus or both. The pathogens present in surgical wounds will be those residents in the environment. (makes sense)

1- BACITRACIN: it's a **cell wall synthesis inhibitor**, mainly used topically (NOT systemically due to its toxicity), Notice that it's not from Penicillin family “ β -lactams”, active against **Gram-positive organisms** such as streptococci, pneumococci, and staphylococci. We use Bacitracin for minor scratches or cuts “prophylactic use” or for treatment in infected



wounds with Gram-positive organisms. Bacitracin is compounded in an ointment base alone or in combination with neomycin or polymyxin B “which are Gram-negative active antibiotics” since the environment contains all spectrum of bacteria so we recover a broader spectrum of Bacteria to defeat.

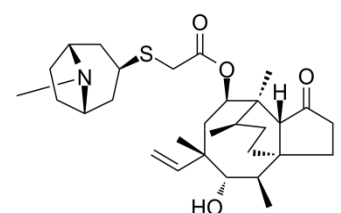
-usually an anti-inflammatory agent is added like Hydrocortisone to decrease the signs and symptoms of inflammation like swelling or itching.

-it may be found in several formulations like creams, ointments, and aerosol preparations.

2- MUPIROCIN: (pseudomonic acid A) it's a **protein synthesis inhibitor** “its target is tRNA” and it is structurally unrelated to other currently available topical antibacterial agents. It's active against **most gram-positive aerobic bacteria**, including *methicillin-resistant Staph aureus* (MRSA). It is effective in the treatment of impetigo caused by Staph aureus and group A β -hemolytic streptococci. it may be in two forms either as ointment or used intranasally for eliminating nasal carriage of Staph aureus, but sadly it may be associated with irritation of mucous membranes caused by the polyethylene glycol vehicle.

- Mupirocin is not appreciably absorbed systemically after topical application to intact skin so it's kinda safe.

3- RETAPAMULIN: it is a semisynthetic pleromutilin derivative and **protein synthesis inhibitor** effective in the treatment of uncomplicated superficial skin infection caused by group A β -hemolytic streptococci and Staph aureus , **excluding MRSA**.



- Topical RETAPAMULIN 1% ointment is indicated for use in adult and pediatric patients, 9 months or older, for the treatment of impetigo.
- Recommended treatment regimen (prescription) is twice-daily application for 5 days. Retapamulin is well tolerated with only occasional local irritation of the treatment site.

4- POLYMYXIN B SULFATE: is a peptide antibiotic works by **affecting the cell membrane**, it is effective against **gram-negative** organisms, including *Pseudomonas aeruginosa*, *Escherichia coli*, *enterobacter*, and *klebsiella*. Most strains of *proteus* and *serratia* are resistant, as are all gram-positive organisms.

5- NEOMYCIN and GENTAMYCIN:

Neomycin and gentamicin are aminoglycoside antibiotics that **affects protein synthesis**, they're active against gram-negative organisms, including *E. coli*, *proteus*, *klebsiella*, and *enterobacter*. Gentamicin generally shows greater activity against *P. aeruginosa* than neomycin. Gentamicin is also more active against staphylococci and group A β -hemolytic streptococci. Widespread topical use of gentamicin, especially in a hospital environment, should be avoided to slow the appearance of gentamicin resistant organisms.

VERY IMPORTANT: we don't use GENTAMYCIN and NEOMYCIN systemically because of their nephrotoxicity and neurotoxicity. Although, GENTAMYCIN may be used systemically in rare cases but we have to measure kidneys' function.

/Side note/: we don't use VANCOMYCIN topically because of many side effects such as RED MAN syndrome.

TOPICAL ANTIBACTERIALS IN ACNE: Acne may be treated either systemically or topically. Systemic antibiotics traditionally used in the treatment of acne vulgaris have been shown effective when applied topically. Effectiveness of topical therapy is less than that achieved by its oral administration. Therefore, topical therapy is generally suitable only in **mild to moderate** cases of inflammatory acne.

1-CLINDAMYCIN: it's a **protein synthesis inhibitor** that has in vitro activity against *Propionibacterium acnes* "the major cause of acne". Approximately 10% of an applied dose is absorbed to the systemic circulation following topical application. Although, there is still a chance of developing *Pseudomembranous colitis* and bloody diarrhea.

-Recap: Pseudomembranous colitis is swelling or inflammation of the colon due to an overgrowth of *C. difficile*, one of the causes of this condition is using Antibiotics such as Clindamycin. It may be treated with Vancomycin and Metronidazole.

-So as we said, Acne Vulgaris may be treated systemically or topically. Clindamycin is a topical Antibiotic, it may be used in several formulations. The hydroalcoholic vehicle and foam formulation (Evoclin) may cause drying and irritation of the skin, with complaints of burning and stinging. The water-based gel and lotion formulations are 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, Onexton) and with tretinoin (Velitin, Ziana).

*side note: Benzoyl peroxide is like bleach so we advise people who use Clindamycin combination with benzoyl peroxide to wear white clothes.

2- METRONIDAZOLE: it is an antibiotic that is used to treat a wide variety of infections. It works by stopping the growth of certain bacteria like anaerobic micro-organisms and parasites “protozoa” like Amoeba.

***Mechanism of action:** it has a nitro group (-azole), which serves as an electron acceptor, forming reduced cytotoxic compounds that bind to proteins and DNA to result in cell death. Also, some anaerobic protozoan parasites (including amoebae) possess ferredoxin-like electron transport proteins that participate in metabolic electron removal reactions, so the interaction of this reduced form of METRONIDAZOLE with the ETC of the protozoa leads to decrease the metabolic processes of the protozoa.

➡ Would it affect the Host? “the doctor said she will look for the answer but maybe it won’t affect the host probably related to the dose, so the dose that is needed to disrupt the host is much more than the dose that is needed to disrupt the protozoa”

-In the previous paragraph we discussed the mechanism of action for METRONIDAZOLE in common with its anti-parasitic action, but when we use it topically, it appears that it’s effective in the treatment of rosacea الوردية

*The mechanism of action for treating rosacea is unknown, but they noticed that this poor woman in the picture who has rosacea also has infection with a parasite or a “mite” called demodex brevis that affects the skin and hair follicle, so maybe the mechanism of action is related to the inhibitory effect of METRONIDAZOLE on this mite leading to this facial effect of rosacea. Although, not



all rosacea cases should have this mite infection, maybe 10 or 20 percent. Also this drug may act as an anti-inflammatory agent by direct effect on neutrophil cellular function.

Adverse local effects of the WATER-BASED GEL FORMULATION (MetroGel) include dryness burning and stinging. Less drying formulations may be better tolerated (MetroCream, MetroLotion, and Noritate cream). Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing.

3-ERYTHROMYCIN: it's a macrolides that **inhibits protein synthesis**, for a patient who is allergic to penicillin we use erythromycin.

/side note/: we don't use Cephalosporins to treat patients with penicillin allergy because 20% of these people are also allergic to Cephalosporins.

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.

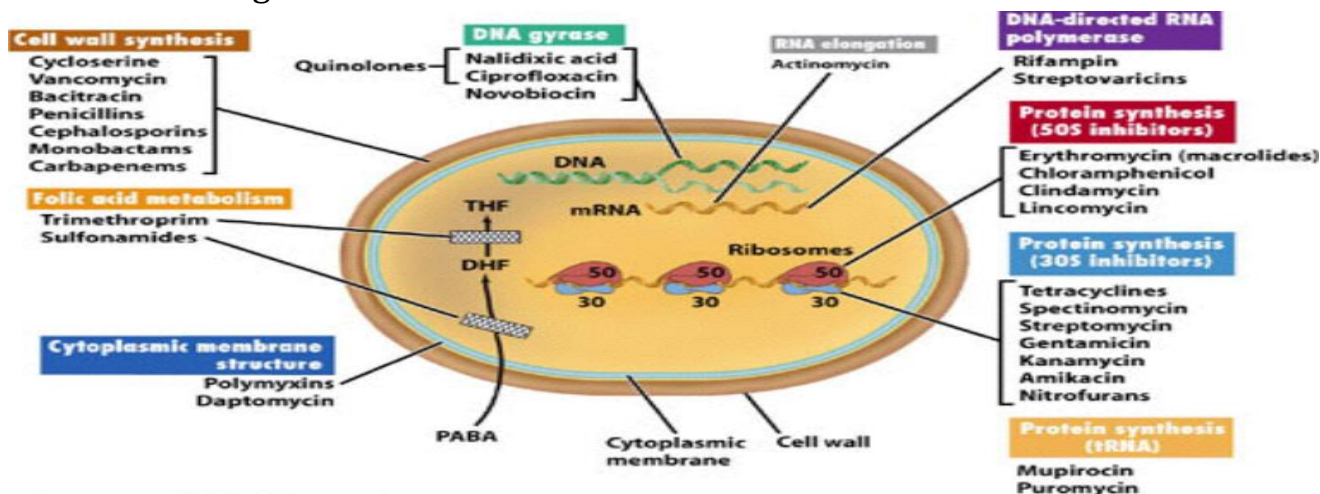
In the topical use: Erythromycin is also available in a fixed combination preparation with benzoyl peroxide (Benzamycin) for topical treatment of acne vulgaris. Also adverse local reactions to erythromycin solution may include a burning sensation at the time of application and drying and irritation of the skin

In the systemic use:

*It causes GI irritation.

*Also, it is an inhibitor for Cytochrome p450, so for example a patient came to the clinic with pharyngitis and he's penicillin allergic, so I gave him Erythromycin without asking him if he takes Warfarin or not. If you're unlucky and the patient was taking warfarin, he would start bleeding ... why?

Warfarin is an anti-coagulant that is metabolized by Cytochrome p450, so if I give the patient Erythromycin it will inhibit Cytochrome p450 which decreases the metabolism of Warfarin and its concentration increases in the blood which leads to severe bleeding.



لما تخلص دراسة
الشيت وتكون فاهم

