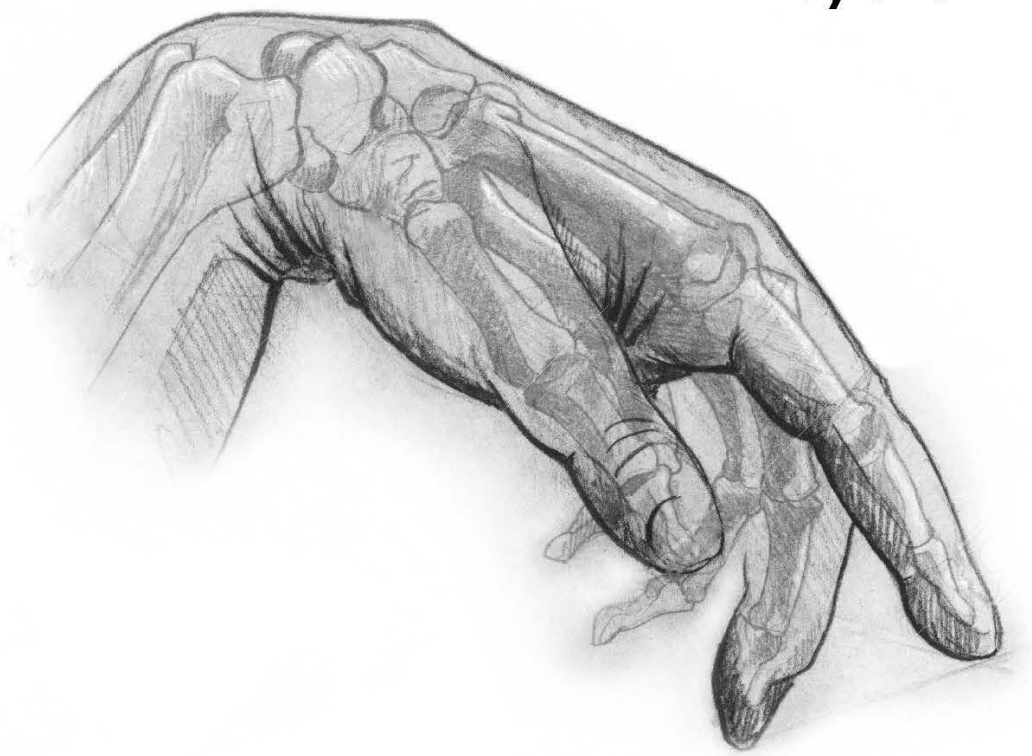
The

Musculoskeletal

System



Pharmacology

☑ Sheet ☐ Slide ☐ Handout

Number:	3
Subject:	Dermatologic Pharmacology
Done By:	Lina I. Mansour
Corrected By:	Russole emad
Doctor:	Alia shatanawi

Date: 0/00/0000

Price: .....

Dermatologic Pharmacology

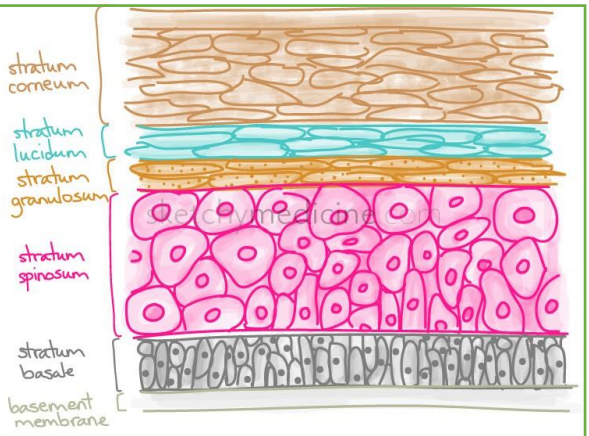
You can read this subject from the book , it's quite comprehensive.. however the doctor didn't mention a lot of details ..(Book ,Record)

the drugs that we are about to mention is not just used to treat skin alone , but also skin appendages like nails , the oral cavity mucosa..**....etc**

The pharmacologic response to drugs applied to the skin is determined by the following variables:

I. ***Regional variation*** **in drug penetration** :In some regions in the body ,the skin is thin. While , in other regions it is thicker, so a topical administered drug (like a cream) would have a higher penetration in a thin skin rather than a thick one. This variation would have a direct effect on the amount of drug used. For example : the amount of cream applied on the face is less than the amount applied on the palms.
<Thin Skin regions like: the face, the scalp ,the axilla ,the scrotum >
<Thick skin regions : the palms ,the back of the foot..>

It is a little bit important to revise Yourself with the skin layers (epidermis,dermis,hypodermis) epidermal layers:
(stratum corneum ,lucidum(?), granulosum,spinosum,basale then BM)



WiKi Box

*Thin skin *Vs* thick skin *it's a wiki box ,you can skip it

Thin Skin : There are only four layers in the epidermis of thin skin. The stratum lucidum layer is absent. **Dermis:** Thin skin actually has a thicker dermis than thick skin, which makes thin skin easier to suture, if it gets damaged. Thin skin also has fewer eccrine/merocrine sweat glands.

Thick Skin : the epidermis is "complete"

Dermis: Thick skin has a thinner dermis than thin skin, and does not contain hairs, sebaceous glands, or apocrine sweat glands.

Thick skin is only found in areas where there is a lot of abrasion - fingertips, palms and the soles of your feet.

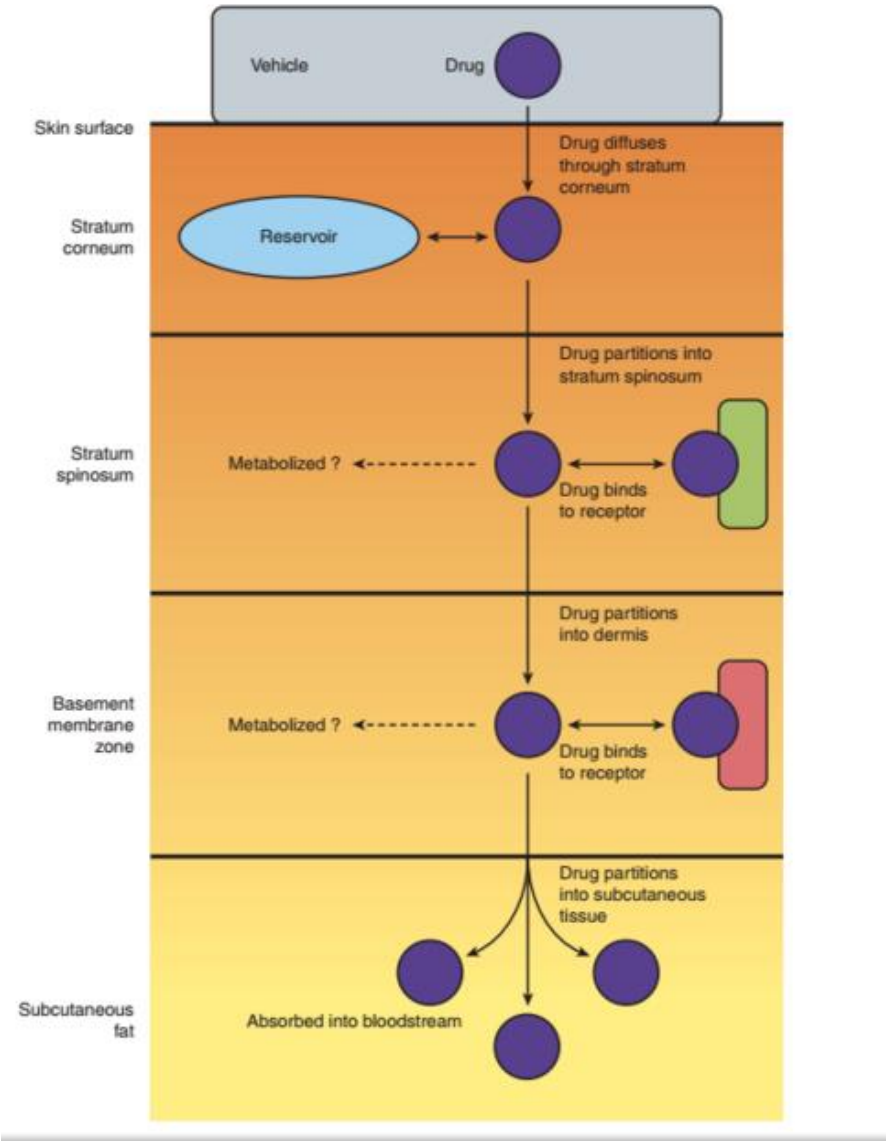
II. ***Concentration* gradient :** increasing the concentration gradient increases the mass of drug transferred per unit time (diffusion rate). Thus resistance to topical ***corticosteroid*** **can sometimes be overcome by use of higher concentration of drug.**

So if you want to increase the amount absorbed, you increase the amount of drug applied, this may induce some side effect since these drugs are mostly toxic and are used topically to limit their entry to the systemic circulation, so it's a matter of balance between therapeutic effect and side effects.

Recall: Benefits to risk ratio.

Note: corticosteroids are a group of drugs used in skin infection a lot , like cortisol but actually cortisol is not used topically and other members of this family are used like betamethasone. This family of drugs can be used systematically but they would exert a lot of side effects.

III. ***Dosing Schedule,*** *think of the skin as a multi-level structure that has a reservoir in its first level .. this reservoir stores the topical applied drug and release it (throughout the day)to other skin layers beneath it ..*



level 1 stratum corneum (the reservoir)
level 2 stratum spinosum
level 3 basement membrane..

because of the physical properties of the skin ,it acts as a reservoir mainly in it's stratum corneum for some drugs like corticosteroids. As a result the local half life may be long enough to permit once – daily application of drugs with short systemic half life because the drug is accumulated in the stratum corneum and released slowly to the surrounding areas.

So in case of topical ***Corticosteroid*** -because it is kept in the corneum reservoir - we apply it just once a day, in contrast oral corticosteroid are given 2-3 times a day .

Note : local half life is not synonymous to the half life of a drug because the first is concerned with the half life in a specific area of the body that would affect it's absorption and thus it's half life.

IV. ***Vehicles and occlusion ,*** any vehicle is a carrier . in terms of pharmacology the vehicles is a chemical substance that holds the drug and transfer it . a lot of drugs(creams , ointments ..) can not be easily dissolved in certain preparation .. what a vehicle does , that it ease the entry of the drug to the skin .

<there are different kinds of vehicles <<thus different formulation of drugs>

Depending upon the vehicle drugs formulations for muco-cutaneous system are classified to:

-Cream ex. Acyclovir for herpes labialis

-ointment

- powder

- Gel(for mucous membrane like eye)

-Lotion

-tinctures(they are actually dyes like iodine)

when to apply a tincture?

when there's a wound and it is exposed and oozing (تنز)and it is WET. I apply my drug through a tincture(rem. it is the vehicle) , some components of the tincture will evaporate and all of the sudden everything dry out.. and the wound is not wet anymore..

<moisture is not recommended in wounds as it helps the pathogens to gain entry to >

wet dressing
lotions
gels
powders
pastes
creams
ointment

from bottom to the tip of the arrow
the evaporation decreases
the viscosity of the formulation increases..
for a dry and thickened skin conditions (like scaling) use the more viscous formulation as it can penetrate well..

Now Occlusion , a substance that helps in keeping the drug in its place for a longer period of time (it's like potentiation recall :pharma introduction . it's different but similar in the main purpose) it's actually away of increasing the concentration gradient..
so instead of increasing the amount of drug applied , we put the same amount but with occlusion increasing the time of exposure>> thus increasing the concentration gradient and accordingly diffusion rate.
make sense .as:
<diffusion rate is the mass transferred through a barriers per unit of time>

O O O O O O O O O

Adverse Effects of upcoming drugs

Oral drugs cause adverse effects like :itching , rash ..
like oral drugs ,topical drugs do have have adverse effect ,why?
they are applied on the skin ,and because it's in a direct communication with the environment it can induce flight or flight response or immune response..
certain signs may appear :
-**dryness**
-burning sensation
-**itching**
-redness
-staining of the skin:like yellow stains that go away soon after stopping the

administration of the drug. But this is not always the case as some drugs like tetracycline will exert stains that won't degenerate after stopping the administration of the drug.
note: tetracycline causes permanent staining of the bone and teeth, that's why it is contraindicate to give them to children as they have GROWING bones and teeth.

Contact Dermatitis :inflammation of the skin when it comes in a direct contact with a particular substance.

There are 3 types of contact dermatitis :

- ✓ Allergic contact dermatitis :when the skin develops an allergic reaction after being exposed to foreign substance. This can causes the body to release inflammatory chemicals that may cause itchiness and irritation. It's usually associated with type 4 delayed hypersensitivity.
- ✓ Irritant contact dermatitis :when the skin comes in contact with a toxic material. It's usually associated with common local reactions in the skin. So it's caused by the drug itself.
- ✓ Photo contact dermatitis : is very uncommon, occurs when the active ingredient of a drug is activated by exposure to sun light especially UV light. It is usually associated with type 4 delayed hypersensitivity.

there are some facts about the immune system , that we must know :
there are type one immune rxn and type four.
Type 4: is when the allergic rxn is Delayed , what does this mean ?
say there is a foreign antigen that u encounter for the first time in your life, certain antibodies are formed against it.
once u get subjected to this material again , the antibodies that were made earlier are used now -see it's delayed- (not directly , but through the memory cells as the this response is actually mediated by T-cells not immunoglobulins ,so this is type IV allergic non-immunoglobulin rxn (delayed)
type one (also known as acute immunological rxn/immediate):caused when the person has *Anaphylaxis shock*, means that he/she has an allergy toward a

Chemical/ drug/food/anything. usually an allergy is igE mediated (igE is an immunoglobulin , so it's immunoglobulin rxn) and allergy signs in response to exposure will appear : swollen throat , breathing difficulties .

so , **Contact Dermatitis**

can be immunologic (by immunity)or allergic(by the drug itself)

Wiki box

Type	Alternative names	Often mentioned disorders	Mediators
One	Allergy (immediate)	Anaphylaxis	IgE
Four	Delayed-type hypersensitivity, cell-mediated immune memory response, antibody-independent	Contact dermatitis	T cells

Were not (directly) mention , but skipping these information is not recommended ..to understand (type I & IV)

<irritation is not always immunological it might be caused by a chemical or something alike.>

-**Photo-irritation or photo toxicity :**when exposed to UV light ,certain drugs are activated in a harmful way that may cause sensitization.

O O O O O O O O O

Topical Antibacterial Agents

Some of them cover G+ve, some G-ve , but there is really some cross activity between them .

I. ***Bacitracin & Gramicidin:***covers
   a) G+ve (streptococci ,staphylococci ,pneumococci)
   b) Anaerobic cocci
   c) Neisseria
   d) bacilli (tetanus bacilli and diphtheria bacilli)

Mechanism of action (MOA) ***:***

The same as penicillin ,it is a cell wall inhibitor although they don't belong to the same family.

usually Gramicidine is used in combination with Bacitracin, polymixin and neomycin and this combination is sold under the trade name Neosporin.

Note: polymixin and neomycin are G- drugs so using them with Gramicidin and Bacitracin which are mainly G+ will be sufficient for topical empirical treatment.

Neosporin (bacitracin / neomycin / polymyxin b topical)
it's available Over the counter .
used topically on a cut wound that is infected or would be infected.

We don't use Bacitracin systematically as it cause nephrotoxicity (kidney failure) , that's why when IM injection of Bacitracin are given to infants who have pneumonia, kidney function must be monitored.

Adverse Effect (topically):

a) mainly *Allergic* Contact dermatitis (CD) (I made up this abbreviation ,sorry :P),immunologic CD is less common ..
b)serious Toxification is Related to systematic

administration..(nephrotoxic)
fortunately , a very small amount of this drug reach the blood when applied topically .
< after wearing a lap gloves if you had red rash between ur pharynx then you have CD from it >

II. **Mupirocin:** same spectrum as the previous drugs (Gramicidin and Bacitracin)
used topically & never systematically.

Mechanism of action : work on the plasma membrane by increasing the membrane premability >>the cell rapture >>the bacteria die .
Adverse Effect : Hemolysis (break down of RBCs) if the concentration that reach the blood through the skin is high which not usually ,but if we're treating a burned patient (the skin is exteamly thin) this side effect is usally present and monitoring is required.

we finsh G+ve antibiotics
now , moving on to G-ve

III. ***Polymixin b sulfate:*** covers:
G- Pseudomonas , E.coli, Enterobacter , Klebsiella
Certain G-ve strains are resistant to it (proteus and serratia) as well as G+ve organisms .
side effects:

a) this drug is VERY toxic , so if it was given to burned patient who has diluted peeling skin , we should monitor the amount of drug that reach the systematic circulation (making sure it does not exceed 200 mg) ,to avoid the toxicity of this drug (nephrotoxicity , neurotoxicity)

b) Allergic contact dermatites to topically applied polymixin b sulfate is uncommon.

IV. *Neomycin* & Gentamicin: covers :

G-ve (E. coli , proteus, klebsiella , enterobacter)

Mechanism of action: Protein synthesis inhibitor ,so it is bacteriostatic

Side effects:

allergic contact Dermatitis and the others main side effects mentioned earlier.

Note:

- ✓ when used systematically,Gentamicin causes Kidney failure so it is contraindicate to give it to kidney patient . also the doses for Geriatrics differ from Young adults . as their kidney function is reduced.
- ✓ these drugs have been used A LOT in hospitals so Bacteria gained resistance to it.

Topical treatment of ACNE

***later on we are going to discus the oral acne drugs but for now* , Topicals**

Acne is a skin infection caused by Propionibacterium acnes . the first option to heal the acne is Topical drugs ,if it did not work we use oral /systematic drugs.

I. ***Clindamycin*** ,

Mechanism of action :protein synthesis inhibitor

Side effect:

The major side effect is pseudomembranous colitis (associated with C. difficile),

because clindamycin is used a lot in acne with every topically applied dose, 10% of it reaches the systematic circulation , so it causes this pseudomembranous colitis .

< pseudomembranous colitis is treated by Vancomycin or metronidazole (Flagyl) >

II. ***Erythromycin,***

Mechanism of action (MOA) : it belongs to the macrolide family, a protein synthesis inhibitor.

III. ***Metronidazole,*** covers :anaerobic bacteria and a Protozoa ((the Ameba))
Mechanism of action : inhibits DNA polymerase .It is a bactericidal (cytocidal)
This drug is mainly used to treat a skin infection caused by microorganism called Mites العُثّ ,this condition is Known as *Rosacea* which is characterized by Redness , dilation of the skin blood vessels and consequently the formation of vesicles over the skin.
Metronidazole Kills these Mites .

IV. ***Sodium Sulfacetamide,*** contains sulfur (which is bacteriotoxic)
side effects:

a) causes yellow pigmentation of skin .
b) It has a high absorbance to the systemic circulation, and it's use is contraindicated in patients having a known hypersensitivity to sulfur.

V. **Dapsone** , it can treat acne , also it is known to treat Leprosy .
Mechanism of action (MOA): not Known .

*a Student asked about actinide / isotre**tino**in (Known as cure acne) a Re**tino**ic acid deratavative is supposed to be discussed in the next lecture (at Acne Preparation section) but here we are ☺
it can be given topically (but mainly orally) .
These drugs kill the micro-organisms associated with acne. But , the General MOA of them is desquamation of skin (peeling it over

and over until reaching the hair follicle that usually acne is associated with) and this is time consuming , that's why all of acne drugs are given together in combinations for long periods of time.(6-7 months).

o o o o o o o o o

Topical Antifungal Agents

I. **the AZOLES** (drug family) like (coltrimazole , econazole, ketoconazole,oxiconazole,strataconazole..)

- ✓ all the azoles work in the same way , they inhibit the ergosterol production
  (ergosterol is a steroid present in the fungi plasma membrane like cholesterol in the plasma membrane of human)
  this give these drugs a high selectivity toward Fungi , so they do not affect our plasma membrane thus they are usually not associated with side effects.
- ✓ some of these Antifungi are oral , but mainly they are topical..
- ✓ used to treat:
  - dermatophytes(Epidermophyton, Microsporum *and* Trichophyton *genera*)
  - candida / yeast .

now concerning **candida** ,
it's associated with a condition know as **throat Thrush. (in babies)**
how does it happen ?
the candida is part of our flora so when taking excessive antibiotics or in certain conditions like stress the equilibrium of all flora is affected .
and somehow the candida increase in number and cause candidatis .
now we are going to talk about anti fungal drugs other than azoles family

*the doctor mentioned them without details except Nystatin & amphotericin B.

II. **Ciclopirox olamine**
III. **Naftifine & Terbinafine**
IV. **Butenafine**
V. **Tolnaftate**
VI. **Nystatin & amphotericin B,** are given mainly for candida infection .
so they are given for the babies to treat their thrush , or for the ladies to treat vaginal candidatis .
administration: topically..
in immune compromised patients (aids , cancer…) candidiatis cause a mucocutanous infection , here we use **amphotericin B** systematically.

Oral Antifungal drugs

1-Azole family: when the infection is not on the skin itself by in it's appendages such as nail beds. Here topical coltrim**azole** won't make the required pharmacological response, as it's applied on a roughened area ..the drug cannot penetrate it.. so we give a patient with such condition these Oral Azole derivatives:
-fluconazole –ketoconazole –itraconazole
sometimes they treat the vaginal candidatis with a one pill of fluconazole because it has a long half life.
same MOA of topical azoles.
Systematic Side effects :
liver enzymes are affected (elevated)
Drug-Drug Interactions :
remember the cytochrome P450 (some drugs are inducers of it others are inhibitors)
azole derivatives are inhibitors of p450..

imagine that a patient who has myocardial infraction .. and he's on Warfarin (anticoagulant drug) knowing that warfarin is metabolized by one isoform of P450 .. azole derivatives (ketoconazole) can inhibit this particular isoform …then ,what?
Warfarin is not metabolized which leads to have a high concentration of it and subsequently having the risk of bleeding.

2-Griseofulvin

3-Terbinafin