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Nucleic synthesis inhibitors

By: Yara Hani

Pharmacology 3

Dr. Heba Khader

Dr. Rawan Abudalo

Department of Clinical Pharmacy and Pharmacy Practice
Faculty of Pharmaceutical Sciences
Hashemite University

هذه اسماؤ المبيدات المضادة
لاد بغير الازدواج بالسلالات
مدواد / مضاد / مضاد
الازدواج بشكل واضح .

Inhibitors of NA synthesis

- Sulphonamides and trimethoprim

- Metronidazole

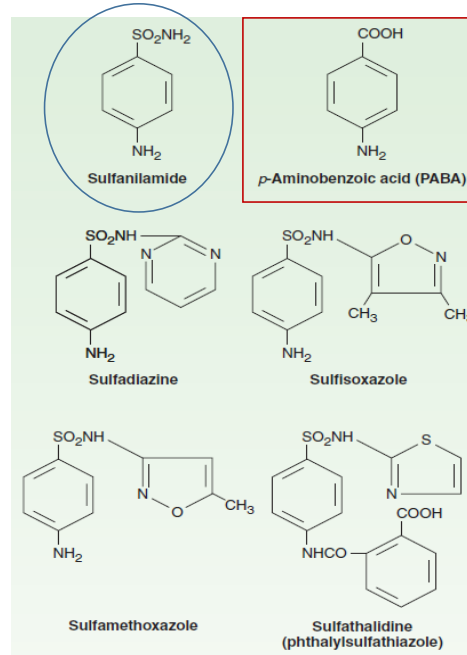
- Quinolones

- Rifampicin

← بالنسبة لـ (Sulfonamid) و
(Trimethoprim) مرة هكتوب لى لك انه
(Static) ومرة المتكبة مع بعض
الهم (Cidal)، عشان ما نخلط فيه هم هيك
هكتوبين . هل رج نسالنا عنهم بالامتحان وننتلخبط لا

Sulfonamides

- Bacteria can not utilize external folic acid (FA) for DNA synthesis (human cell can)
- Bacteria must synthesize FA from PABA.
- Sulfonamides are structurally similar to p-aminobenzoic acid (PABA)



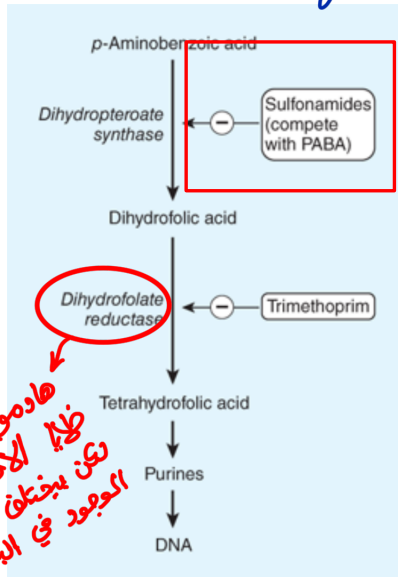
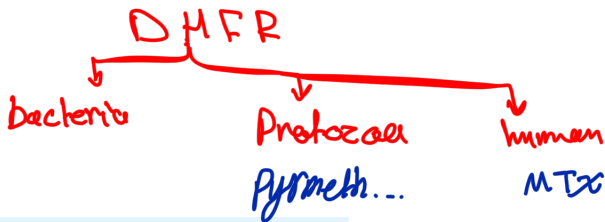
← قتل ما لدينا في الميسينال : البكتيريا ما بتقدر توفد FA الخارجي و تستخد في تصنيع DNA وتنمو وتتكاثر لكن خلايا الإنسان بتقدر لذلك بنعقد (dih) لنحصل على FA.

← هذا هادي البكتيريا نعمل على (PABA) حتى نحصل على FA.

← بعين العلماء وجعوا انه (sulbnamid) بيشه (PABA) ويمكن البكتيريا تلخبط بينه وبين (PABA) وتوقف عليه تصنيع (FA).

Sulfonamides Mechanism of Action

- Sulfonamide-susceptible organisms, unlike mammals, cannot use exogenous folate but must rely on their ability to synthesize folate from para-amino benzoic acid (PABA)
- This pathway is thus essential for production of purines and nucleic acid synthesis.
- As structural analogs of PABA, **sulfonamides inhibit dihydropteroate synthase** and folate production.
- The sulfa drugs, including cotrimoxazole, are **bacteriostatic**.



هنا هو موجود في
خلايا الإنسان
ولكن يختلف عن
الموجود في البكتيريا.

(Sulfonamide) يمتد تضييق (DMF)
وبالتالي يوقف تضييق (FA).

Pharmacokinetics of Sulfonamides

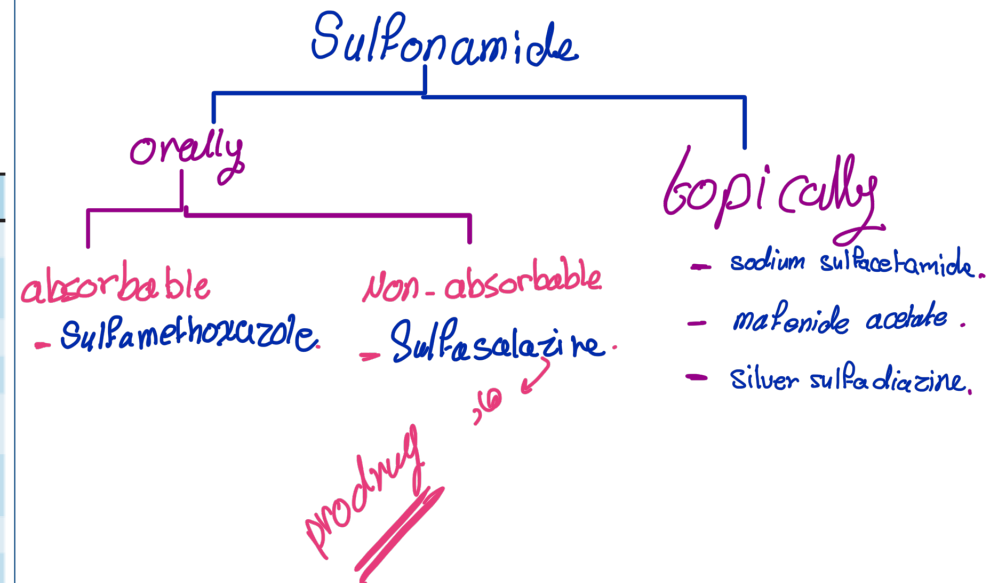
- Sulfonamides can be divided into three major groups:

- oral, absorbable (sulfamethoxazole)
- oral, nonabsorbable (Sulfasalazine)
- topical (Sodium sulfacetamide, mafenide acetate, silver sulfadiazine)

- The oral, absorbable sulfonamides can be classified as short-, intermediate-, or long-acting on the basis of their half-lives

من حفظ

Drug	Half-life	Oral Absorption
Sulfonamides		
Sulfacytine	Short	Prompt (peak levels in 1-4 hours)
Sulfisoxazole	Short (6 hours)	Prompt
Sulfamethizole	Short (9 hours)	Prompt
Sulfadiazine	Intermediate (10-17 hours)	Slow (peak levels in 4-8 hours)
Sulfamethoxazole	Intermediate (10-12 hours)	Slow
Sulfapyridine	Intermediate (17 hours)	Slow
Sulfadoxine	Long (7-9 days)	Intermediate
Pyrimidines		
Trimethoprim	Intermediate (11 hours)	Prompt
Pyrimethamine	Long (4-6 days)	Prompt



Sulfonamides (أي يتأخذون) وجرعاتها قصيرة
 Short
 Intermediate ← (half-life)
 Long acting ←

Clinical Uses

• A. ORAL ABSORBABLE AGENTS

- Sulfisoxazole and sulfamethoxazole are short- to medium-acting agents used almost exclusively to treat **urinary tract infections**.
- Sulfadiazine in combination with pyrimethamine is first-line therapy for treatment of acute **toxoplasmosis**.
- Sulfadoxine in combination with pyrimethamine is used as an **antimalarial** drug.

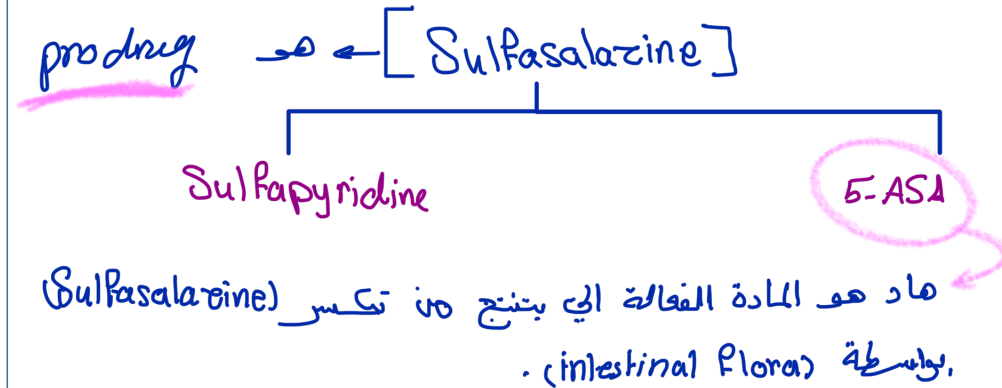
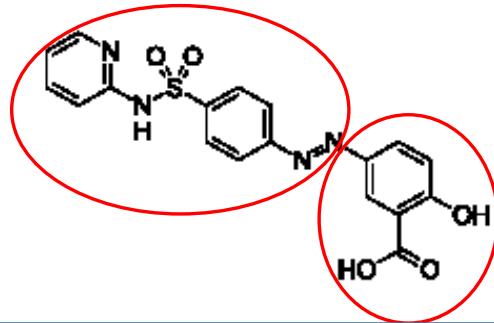
(short - intermediate) ← (Sulfisoxazole + Sulfamethoxazole) ←
يستخدموا بشكل أساسي لعلاج (UTI).

(T. gondii) is ←
toxoplasmosis = (Sulfadiazine + pyrimethamine) ←

antimalarial drug = (Sulfadoxine + pyrimethamine) ←

Clinical Uses

- **B. ORAL NONABSORBABLE AGENTS**
- Sulfasalazine is an integrated sulfapyridine and 5-amino salicylic acid (5-ASA)
- It is widely used in ulcerative colitis, enteritis and other inflammatory bowel disease (Local intestinal flora split sulfasalazine into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect).



الـ تأثير (anti-inflammatory) يستخدم في علاج:

- Ulcerative Colitis.
- Enteritis. or Crohn's disease.
- Other inflammatory bowel diseases.

Clinical Uses

- **C. TOPICAL AGENTS**
- **Sodium sulfacetamide** ophthalmic solution or ointment is effective in the treatment of **bacterial conjunctivitis** and as adjunctive therapy for trachoma (eye infection caused by bacterium *Chlamydia trachomatis*).
- Another sulfonamide, **mafenide acetate**, is used topically but can be absorbed from **burn** sites. The drug and its primary metabolite inhibit carbonic anhydrase and can cause metabolic acidosis, a side effect that limits its usefulness.
أقل سمية
- **Silver sulfadiazine** is a less toxic topical sulfonamide and is preferred to mafenide for prevention of infection of **burn wounds**.
بأقل سمية من (mafenide)

← (Sodium Sulfacetamide) يستخدم لعلاج (bacterial)

(Conjunctivitis) ، وهو التهاب بسبب
بكتيريا (*Chlamydia trachomatis*).

← (Mafenide acetate) يستخدم بشكل موضعي في حالات
الحروق .

يكن لها بديل (metabolite) ينتج مادة بشط (Carbonic)
← (anhydrase) ويحل (metabolic acidosis) لذلك ما يستخدم كثير.

← (Silver sulfadiazine) هاد يوضع يستخدم لمنع (infection) في
حالات الحروق ، وهو أقل سمية من (mafenide).

Side effects of sulfonamides

- **Crystalurea** due to precipitation (reversed by adequate hydration & alkalization of the urine)
- **Hypersensitivity:**
 - rash
 - Angioderma
 - Steven-Johnson syndrome (SJS) which is caused by separation of the epidermis from the dermis



Steven-Johnson syndrome



Angioderma

Side Effects

- Crystalluria.
- Hypersensitivity.
- Hematopoietic Disturbances.
- Kernicterus.

Side effects of sulfonamides

نقص في الصفائح الدموية

• HEMATOPOIETIC DISTURBANCES

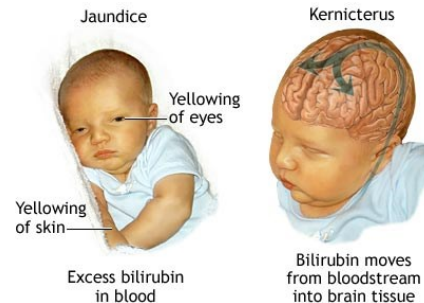
- Sulfonamides can cause granulocytopenia or thrombocytopenia.
- Sulfonamides may provoke hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency.



• Kernicterus

فقر الدم الانحلالي أو ما يسمى بفقر الدم

- Occurs in newborns
- Sulfa drugs displaces bilirubin from serum albumin
- Free bilirubin go to CNS and cause injury to brain
- **Shouldn't be given to newborns & infants (< 2 months) , pregnant at term**

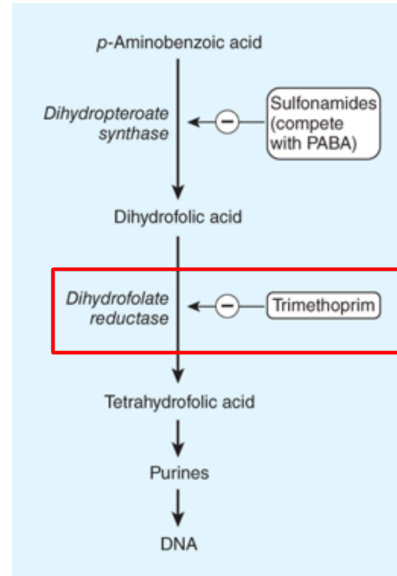


Trimethoprim & trimethoprim-sulfamethoxazole mixtures

Mechanism of Action

- **Trimethoprim**, selectively **inhibits bacterial dihydrofolic acid reductase**, which converts dihydrofolic acid to tetrahydrofolic acid, a step leading to the synthesis of purines and ultimately to DNA (much less efficient inhibitor of mammalian dihydrofolic acid reductase).
- **Pyrimethamine**, selectively **inhibits dihydrofolic acid reductase of protozoa** compared with that of mammalian cells.

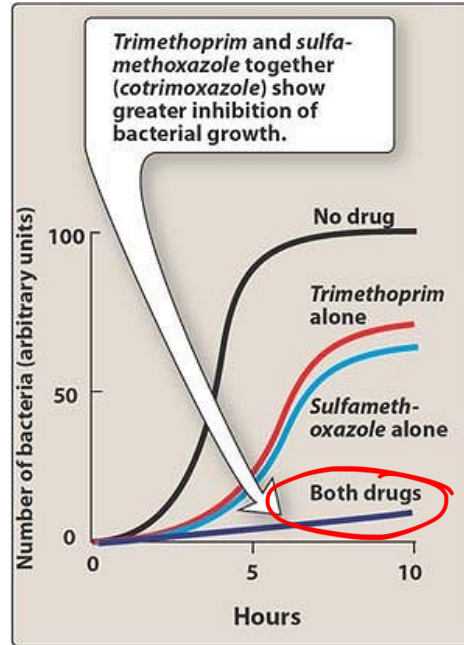
← هاد يستخدم بشكل رئيسي لعلاج (protozoal)
infection (عدوى):
- malaria .
- toxoplasmosis .



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology
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Cotrimoxazole

- Trimethoprim & trimethoprim-sulfamethoxazole mixtures
- Trimethoprim and sulfamethoxazole are **rarely used alone today**.
- Individually, these drugs (alone) are **bacteriostatic**....
- This combination in **co-trimoxazole** provides a synergistic combination and **bactericidal** effect



- **Pharmacokinetics**

- Trimethoprim is usually given orally, alone or in combination with sulfamethoxazole, which has a similar half-life. Trimethoprim-sulfamethoxazole can also be given intravenously.
- Trimethoprim (a weak base) concentrates in prostatic fluid and in vaginal fluid, which are more acidic than plasma. Therefore, it has more antibacterial activity in prostatic and vaginal fluids than many other antimicrobial drugs.



- Clinical Uses

ORAL TRIMETHOPRIM

- Trimethoprim can be given alone in acute urinary tract infections and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred).

ORAL TRIMETHOPRIM-SULFAMETHOXAZOLE (Cotrimoxazole)

A combination of trimethoprim-sulfamethoxazole is effective treatment for a wide variety of infections including *P jiroveci pneumonia* (This is a common opportunistic infection complicating AIDS. Cotrimoxazole is the most effective therapy), shigellosis, salmonella infections, urinary tract infections, prostatitis.

ORAL PYRIMETHAMINE WITH SULFONAMIDE

- Pyrimethamine and sulfadiazine are used in the treatment of toxoplasmosis and falciparum malaria.



1 Oral Trimethoprim: حالة يستخدمه لعلاج UTI و (Prostatitis) لكن Fluoroquinolones الأفضل تستخدمهم.

2 Cotrimoxazole: يستخدم في علاج infections, من بكتيريا (*P. jirovecii* Pneumonia) وهي بكتيريا انتهازية تصيب مرض AIDS, ومرض في (*Salmonella*) و (*Shigellosis*) و (UTI) ومرض في (Prostatitis).

3 Pyrimethamin + Sulfadiazine: يستخدم في علاج (Toxoplasmosis) و (*Falciparum malaria*).

- **Side effects**

- Similar to the effects of **folic acid deficiency**
- Anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those having very poor diets
- Can be reversed by the simultaneous administration of folinic acid, which does not enter bacteria.

Drug Interactions

- On the basis of protien binding displacement → Potention of effect of (?) warfarin , phenytoin
- And on the basis of Inhibition of metabolism → Potentiation of effect of (?)

برصو نفس التي الادوية
التي يصير لها (metabolism)
عن طريق الإنزيم .

يقي الادوية الى يرتبط
بقوة بروتينات البلازما