Antibiotic drug interaction

S. Elyasi
assistant professor of clinical pharmacy
MUMS
• In the early 1990s, patients experienced serious cardiac toxicity after taking antihistamine or prokinetic drugs in combination with macrolide antibiotics or azole antifungals.

• Caused by inhibition of cytochrome P450 (CYP450) 3A isoenzymes

• Subsequently, terfenadine, astemizole, and cisapride were withdrawn from the marketplace, in part because of safety concerns about drug interactions
• changes in the concentration of a medication in body fluids and tissues

• in the **absorption, distribution, metabolism, or elimination** of a medication

• **ABSORPTION:**
  - medications with **pH-dependent dissolution**: affected by antacids, proton pump inhibitors, and histamine H2-antagonist
    * some of the oral cephalosporins

  - tetracyclines or fluoroquinolones: **chelating** with antacids

  - antibiotics alter the normal GI flora and thus affect the metabolism and absorption of medications such as **warfarin and estrogens**.
• **distribution and protein binding**

- Rifampin is an inducer of PGP: decreased absorption of medications that are substrates for PGP

- Drug interactions involving protein binding and drug displacement have become less important clinically, because steady-state unbound drug concentrations often redistribute and remain unaltered

• **Metabolism (phase I & II)**

- inhibit, induce, substrate
- inhibition: competitively or non-competitively; **immediately**
- INH: both type
- induction: **gradually (as long as 2 weeks)** [rifampin]
<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Theophylline</td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Aminophylline</td>
</tr>
<tr>
<td></td>
<td>Dapsone</td>
<td>SMX/TMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isoniazid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metronidazole</td>
</tr>
<tr>
<td>CYP2C9</td>
<td></td>
<td>Rifampin</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Cyclosporine</td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td>...</td>
</tr>
<tr>
<td>OAT1</td>
<td>Cidofovir</td>
<td>Probencid</td>
</tr>
<tr>
<td></td>
<td>Oseltamivir</td>
<td>...</td>
</tr>
<tr>
<td>PGP</td>
<td>Quinolones</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Itraconazole</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Rifampin</td>
</tr>
</tbody>
</table>

*Abbreviations: OAT-1, organic anion transporter–1; SMX-TMP, trimethoprim-sulfamethoxazole.*
• renal excretion

- competitive interactions
- The organic anion transport proteins (OAT1 and 3): facilitate excretion of weakly acidic drugs, such as penicillins; Probenecid is an inhibitor of OAT1 and thus leads to decreased renal clearance of OAT1 substrates.

• Significant interindividual variability in the outcome of drug interactions
• patient-specific factors such as disease state, other concomitant medications, and genetics
• at least 10-fold interindividual variability in CYP450 content
• certain CYP450 enzymes (eg, CYP2D6, CYP2C9, CYP2C19) exhibit clinically important polymorphisms

Pharmacokinetic drug–drug interactions
Pharmacodynamic drug–drug interactions
b-lactams

- **Gastric acid suppression:**
  - cefuroxime axetil, cefaclor: 30-40% reduction in AUC with antiacid or H2B; separated by at least 2 hours

- **Inhibition of renal tubular secretion:**
  - The AUCs of amoxicillin, ampicillin, nafcillin, ceftizoxime, cefaclor and meropenem almost double when used with probenecid
  - minimal change with others
  - Benefical in meningitis or endocarditis: should be avoided in patients who are elderly, have renal dysfunction, or have a history of seizure disorder

- Interaction with methotrexate, aspirin, and indomethacin (?)
Pharmacodynamics interactions

- Other noteworthy interactions include an increased risk (threefold higher) for rash with the combined use of allopurinol and amoxicillin or ampicillin.
  - The mechanism of this interaction is not known.

- An increased risk for seizures is possible with the use of ganciclovir and imipenem/cilastatin, so concomitant use of these agents is not recommended.

- Use of imipenem/cilastatin in transplant recipients receiving cyclosporine has been associated with an increased risk for central nervous system toxicity.

- An increased risk for seizures has also been noted with use of valproic acid and carbapenems.
  - Associated with a rapid reduction in valproic acid concentrations: TDM of valproic acid/ dose increment.
• **OCPs & beta lactams**
  - breakthrough bleeding and pregnancies have been reported

  - likelihood of this interaction is rare (about 1%)

  - the recommendation to counsel patients about the potential for oral contraceptive failure **remains controversial**

• **Warfarin & beta lactams**
  - Alteration in gut flora that synthesize vitamin K

  - **augment the effect of warfarin**

  - semisynthetic cephalosporins such as **cefamandole**, **cefoperazone**, and **cefotetan** can prolong the prothrombin time: increase risk of bleeding
**macrolides (erythromycin and clarithromycin)**

- inhibition of the CYP450 system and PGP
  
  - Erythromycin: non-competitively; rapid
  - The interaction profile is greatest against orally administered **CYP3A substrates**
  
  - midazolam, cyclosporine, tacrolimus, lovastatin, simvastatin, and CCBs
    * 30% rise in atorvastatin AUC, rosuvastatin are not metabolized by CYP3A4

  - **Erythromycin** can directly increase the QTc interval and also increase concentrations of antiarrhythmics such as quinidine, sotalol, dofetilide, amiodarone, and bretylium

  - Serum concentration of **TCAs** such as amitryptilline and antipsychotic agents such as haloperidol, respiridone, and quetapine can all become elevated
    * cause QTc prolongation, leading to **torsades de pointes** and death

- **priapism (sildenafil)**, disorientation (clozapine), neutropenia (vinblastine), delirium (fluoxetine)
- **Inhibition of CYP2C9, CYP2C19**
  - Key substrates of these isoenzyme: warfarin, phenytoin & sulfonylureas
  - much less possible with clarithromycin

- **Inhibition of CYP1A2**
  - **Theophylline & erythromycin**: The reported consequences have ranged from GI adverse events to more serious effects such as VF
  - just 20% rise with clarithromycin

- **Inhibition of P-glycoprotein**
  - Erythromycin and clarithromycin are also PGP inhibitors
  - **Digoxin toxicity**: even with azithromycin
    “hospital admissions due to digoxin toxicity were 13 times more likely to occur in elderly patients who had received clarithromycin therapy within the past week”
  - **colchicine**: inh. CYP3A4 and PGP

- The potential drug interaction of OCPs with macrolides is **minimal**
• The oral bioavailability of FQs can be significantly reduced by cations: clinically relevant

• In general, multivalent cations, such as aluminum, magnesium, iron, and zinc, have been noted to have more serious interactions than does calcium

• The recommended administration schemes have been based on the manufacturer-dependent study designs.

• FQs have also been associated with fatalities secondary to hypoglycemia in patients receiving medications to manage diabetes

• drug- and dose-dependent prolongation of the QTc interval
  * levofloxacin=gemifloxacin=ciprofloxacin>ofloxacin
  * higher risk of torsade de pointes in pts with a history, uncorrected electrolyte abnormalities or those receiving antiarrhythmic agents
ciprofloxacin

- Simultaneous administration of iron, magnesium, aluminum, and zinc can result in 50% to 90% reduction in both the Cmax and AUC of oral ciprofloxacin

- calcium or sevelamer: 30-40% reduction

- Bismuth: 10% reduction

- 2 hours prior to or 6 hours after the administration of ciprofloxacin

- Hypoglycemia requiring urgent management with use of ciprofloxacin in a previously stable patient receiving glyburide has been reported

- About 30% increase in theophylline concentrations has been reported with use of concomitant ciprofloxacin, leading to symptoms of theophylline toxicity: TDM, dose reduction

- A 10-fold increase in AUC of tizanidine and resultant hypotensive effects in healthy volunteers receiving concomitant ciprofloxacin
Levofloxacin/ofloxacin

• Less interaction with cations

• Administration of levofloxacin 2 hours before or 2 hours after these multivalent cation-containing products is recommended to limit this interaction

• Lower risk of hypoglycemia

• Ofloxacin does not significantly alter the clearance of theophylline
Gemifloxacin

- Cations should not be taken within a period 3 hours before or 2 hours after the dose of gemifloxacin, with the exception of sucralfate, which should be administered 2 hours after gemifloxacin.

- The specific risk for gemifloxacin alteration of glucose homeostasis is not known, but no specific cases have been reported in the literature to date.

- Gemifloxacin is not known to alter the clearance of other concomitantly used medications.
Increased risk for developing nephrotoxicity with amphotericin B, cisplatin, cyclosporine, vancomycin: should be avoided or used with caution

An increased risk for ototoxicity with loop diuretics: used cautiously at the lowest possible doses

Aminoglycosides may potentiate the effects of neuromuscular blocking agents

** Patients should be monitored for prolonged signs of respiratory depression and paralysis during the perioperative and postoperative periods.
Vancomycin

• The most notable drug–drug interaction of vancomycin is the potentially increased incidence of nephrotoxicity with the concurrent administration of aminoglycosides (5-7% alone, up to 35% concurrent)

• Other drug interactions have included case reports of the possible inactivation of vancomycin by heparin when administered through the same IV line, decreased clearance of high-dose methotrexate following recent vancomycin administration, and depression of neuromuscular function after concurrent vecuronium therapy

• Vancomycin may bind to anion-exchange resins such as colestyramine
Linezolid

- The drug interaction profile of this antibiotic class is typically associated with **MAO inhibition**, which results in an increase in serotonin concentrations and the development of the serotonin syndrome: *caution in administration with SSRIs or SNRIs*
  **Cyproheptadine** to relieve symptoms

- Potential for drug interactions involving **OTC cough and cold preparations** that contain adrenergic agents such as pseudoephedrine (HTN)

- **No symptoms** of serotonin syndrome or changes in blood pressure, heart rate, or temperature were observed when dextromethorphan (a known serotonin reuptake inhibitor) was coadministered with linezolid.
The plasma concentrations of tetracyclines are markedly reduced (30% to 90%) with the concurrent administration of products containing divalent and trivalent cations. The administration of each agent should be staggered by at least 2 hours.

Like beta lactams, drug–drug interactions have been reported between tetracyclines and warfarin, digoxin, and oral contraceptives.

May increase plasma concentrations of theophylline.

May potentiate the toxicities of lithium and methotrexate.

The combination therapy with retinoids (eg, acitretin, isotretinoin) is not recommended because of the additive effects of pseudotumor cerebri.

Barbiturates, phenytoin, carbamazepine, rifampin, and chronic ingestion of ethanol can decrease the elimination half-life and plasma concentrations of doxycycline but do not appear to affect the pharmacokinetics of other tetracycline products.
<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effects</th>
<th>Management recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>Decreased tetracycline concentration</td>
<td>Space administration by at least 2 hours.</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Decreased (40%) atovaquone concentration</td>
<td>Use alternative therapy when possible.</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Decreased doxycycline concentration</td>
<td>Use other tetracycline products.</td>
</tr>
<tr>
<td>Bismuth</td>
<td>Decreased tetracycline concentration</td>
<td>Space administration by at least 2 hours.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Decreased doxycycline concentration</td>
<td>Use other tetracycline products.</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Decreased tetracycline concentration</td>
<td>Space administration by at least 2 hours.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Increased digoxin concentration and toxicity</td>
<td>Monitor digoxin concentration and adjust dose appropriately.</td>
</tr>
<tr>
<td>Ergotamine tartrate</td>
<td>Increased ergotism</td>
<td>Monitor for ergotism; use alternative therapy when possible.</td>
</tr>
<tr>
<td>Ethanol, chronic ingestion</td>
<td>Decreased doxycycline concentration</td>
<td>Use other tetracycline products.</td>
</tr>
<tr>
<td>Iron</td>
<td>Decreased tetracycline concentration</td>
<td>Space administration by at least 2 hours.</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Pseudotumor cerebi</td>
<td>Avoid concurrent use.</td>
</tr>
<tr>
<td>Kaolin-pectin</td>
<td>Decreased tetracycline concentration</td>
<td>Space administration by at least 2 hours.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Increased lithium concentration and toxicity</td>
<td>Monitor lithium concentration and adjust dose appropriately.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Increased methotrexate concentration and toxicity</td>
<td>Monitor methotrexate concentration and maintain leucovorin rescue as needed.</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>Risk of nephrotoxicity</td>
<td>Avoid concurrent use.</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Reduced contraceptive effectiveness</td>
<td>Counsel patient to use additional forms of contraception.</td>
</tr>
<tr>
<td>Phenyltoin/ Fosphenytoin</td>
<td>Decreased doxycycline concentration</td>
<td>Use other tetracycline products.</td>
</tr>
<tr>
<td>Quinine</td>
<td>Increased quinine concentration</td>
<td>Monitor for quinine toxicity.</td>
</tr>
<tr>
<td>Rifampin/ Rifabutin</td>
<td>Decreased doxycycline concentration</td>
<td>Use other tetracycline products.</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Decreased tetracycline concentration</td>
<td>Space administration by at least 2 hours.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Increased theophylline concentration</td>
<td>Monitor theophylline concentration and adjust dose appropriately.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Enhanced anticoagulation</td>
<td>Monitor prothrombin time/ international normalized ratio and adjust warfarin dose appropriately.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Decreased tetracycline concentration</td>
<td>Space administration by at least 2 hours.</td>
</tr>
</tbody>
</table>
Clindamycin

- Clindamycin may **enhance the effects of neuromuscular blocking agents** (e.g., d-tubocurarine, pancuronium, vecuronium) and result in a prolonged duration of neuromuscular blockade.

- reversal agents (e.g., calcium, neostigmine) are not always effective.

- several studies have suggested that clindamycin is a potential risk factor for the **development of nephrotoxicity** when administered concurrently with aminoglycosides.
Metronidazole

- Metronidazole produces a disulfiram-like reaction (eg, flushing, palpitation, tachycardia, nausea, vomiting) in some patients who drink ethanol while taking the drug.

- should not drink ethanol within 2 to 3 days of taking metronidazole.

- several oral products (eg, cough and cold preparations) and intravenous products (eg, diazepam, nitroglycerin, phenytoin, trimethoprim-sulfamethoxazole) contain ethanol.

- Metronidazole increases the hypoprothrombinemic effect of warfarin by increasing the plasma half-life and plasma concentrations of the S-isomer of warfarin.
Metronidazole has also been reported to decrease total body clearance and increase plasma drug concentrations of lithium, busulfan, cyclosporine, tacrolimus, carbamazepine, and phenytoin.

Toxicities associated with 5-fluorouracil are enhanced by metronidazole, and coadministration of these two agents should be avoided.

Phenobarbital, phenytoin, rifampin, and prednisone have been reported to increase total body clearance and lower plasma concentrations of metronidazole.

Doses of metronidazole may need to be increased in selected patients, especially those who are not responding to therapy.
Thanks for your Attention