Lecture 9
PK Considerations of the GIT

ORAL ABSORPTION:
- Consideration of the GIT absorption is primarily with respect to oral formulations/presentations
- To be absorbed, a drug given orally must be relatively impervious to low pH & GI secretions (incl. enzymes)
- Absorption of oral drugs involves transport across membranes of the epithelial cells in the GIT

ORAL ABSORPTION CAN BE AFFECTED BY:
- Differences in luminal pH along the GIT
- Surface area per luminal volume
- Blood perfusion
- Presence of bile and mucus
- The nature of epithelial membranes

PLACES ABSORPTION CAN OCCUR IN THE GIT:

ORAL MUCOSA:

<table>
<thead>
<tr>
<th>CHARACTERISTICS AFFECTING ABSORPTION</th>
<th>Favour</th>
<th>Prevent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin epithelium</td>
<td>Contact time is usually too brief for substantial absorption</td>
<td></td>
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<tr>
<td>Highly vascular</td>
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SYSTEMIC IMPLICATIONS: avoid first pass metabolism

EXCEPTIONS:
- Buccal administration (drug product absorbed across cheek)
- Sublingual administration (drug product under the tongue)

THE STOMACH:

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large epithelium surface area</td>
<td></td>
<td>Thick mucous layer</td>
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<tr>
<td></td>
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<td>Short transit time</td>
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ANATOMY AND PHYSIOLOGY OF THE STOMACH:
- Rugae increase surface area
- Thick muscular banding
- Fundus sheath, with moderate perfusion

STOMACH pH AS A FACTOR:
- Changes to the pH of the stomach can affect dissolution of drugs from their presentation/dosage forms (tablets, capsules, powders, suspensions, etc)
  - Increasing pH will decrease ionization of weak bases and promote absorption of the neutral species
  - Implications for bicarbonate (i.e. antacids)
  - Lowering pH and promote absorption of weak acids
  - Implications in disease states (i.e. ulcers)
- For example: increased gastric pH will delay tetracycline dissolution from its dosage form, causing much lower absorption

GASTRIC EMPTYING: critical parameter (most drugs absorbed in SI)
- Gastric emptying is usually function of volume of gastric contents
  - Lipids are emptied faster than solids
  - Volume of gastric contents is important regulating factor
  - Stretching of stomach tissue is the only physiological control that increases rate of gastric emptying
- Continuous electrical waves (“slow waves”) influence contractions at the antral sphincter to allow entry into the small intestine
  - These contractions are influenced by local and distant nervous reflexes, as well as hormones
- Usually the rate-limiting step for entry into the intestine is the gastric emptying rate
  - Changes to this rate can be caused by:
    - Food
    - Hormones
    - Severe pain
    - Gastric ulcer
    - Diabetes and other metabolic diseases
    - Drugs (alcohol, anticholinergics, narcotics, ganglion blocking drugs, antacids and metoclopramide)
- Usually, increasing the rate of gastric emptying and gastro-intestinal motility increases the rate of drug absorption
  - Delayed drug absorption usually causes therapeutic failure, especially if drug has short biological half-life (as stomach’s capacity for absorption is not high enough)

DRUG-DRUG INTERACTIONS (DDI):
Indirect DDI:
- Gastric emptying can be slowed by TCAs & opiates (co-administered drugs may not achieve therapeutic levels = lowers absorption)
- Drugs such as erythromycin that speed intestinal transit time, also potentially causing lack of absorption

Direct DDI:
- Can also occur where drug molecules interfere with each other
  - Excipients in the GIT altering another drug’s thermodynamic activity for absorption
  - Direct binding of tetracyclines with metal ions in the gut (don’t take them with milk because calcium ions will bind the tetracyclines and prevent absorption)

THE SMALL INTESTINE:
- The small intestine has the largest surface area for drug absorption in the GIT, and its membranes are more permeable than those in the stomach
  - For these reasons, most drugs are absorbed primarily in the small intestine, are absorbed faster in the intestine than in the stomach
- Movement down the small intestine is by peristalsis (rhythmic muscular contractions)
- The intraluminal pH is 4-5 in the duodenum but becomes progressively more alkaline, approaching 8 in the lower ileum
  - Similar to the pH effects observed for the stomach, weak acids are most successfully absorbed in the duodenum, whilst weak bases are better absorbed in the jejunum and ileum
**PLACES ABSORPTION CAN OCCUR IN THE GIT (CONTINUED):**

### THE SMALL INTESTINE (CONTINUED):

#### PASSIVE DIFFUSION IN THE GUT:
- Drug characteristics favouring good paracellular absorption are:
  - Small molecules (molecular weight 500 Da)
  - Hydrophilic (ionized at intestinal pH of 5.5-7.0)
  - Positive charge (because cell junctions have negative charge)
- Caveat to the "positively charged" idea
  - Paracellular junctions are relatively rare in the gut (<0.1% of total surface area) and become less permeable as you travel along gut (from jejunum to colon)
    - Effectively, the junctions become "tighter"
  - Therefore, transcellular transport (i.e. lipid diffusion) is the most important
- The intestinal lumen also contains a 25 µm layer of water (= "unstirred water layer") – but doesn’t appear to affect PK
- Membranes on basolateral (blood) side of intestinal mucosal cells are thinner, and contain less cholesterol & glucolipids than on apical (GI lumen side)
  - This makes basolateral membranes more fluid and permeable than apical membranes = once apical membranes are crossed, permeability is higher
- GI microflora may also reduce absorption
  - Bacteria can break down drugs (ex// bacterial cleavage of abx in intestine) before they are systemically available
- Drug metabolizing enzymes in the intestines can cause low bioavailability (CYP3A4 and UGT 1A7/1A8/1A10)
- Decreased blood flow (ex// shock, ChF) may lower concentration gradient across intestinal mucosa and reduce absorption by passive diffusion
  - Dosage adjustment is almost always required in these pts

#### PARAMETER Pe:
- Pe = speed in cm s⁻¹ (usually 10⁻⁴ or 10⁻⁵ cm s⁻¹) at which a molecule is transported across a membrane, cell, endothelium or epithelium
- Determined by interplay between characteristics of membrane, cell, endothelium or epithelium & the molecules
- Molecular properties important for permeation include:
  - Molecular weight
  - Degree of ionization
  - Size and shape
  - Polar surface area / non-polar surface area
  - Lipophilicity
  - # of H-bonding acceptors & donors
- The MW and lipophilicity of new drug candidates have increased over time, leading to poorer intestinal Pe and/or solubility
  - Poor GI solubility is now the largest problem preventing good oral absorption and F from new drug candidates

#### TRANSPORTERS IN THE INTESTINE:
- Transporters differ in different parts of the intestine:
  - Expression of P-gp is 5 times higher in ileum than in duodenum and colon
  - OCT1, MRP3, OCTN2, and MCT1 highest expression in colon than in proximal intestine
- The drug transporter proteins also differ between apical and basolateral sides of the intestine:
  - P-gp, BCRP and MRP2 are efflux proteins on apical membrane
  - MP3 is an influx transporter on basolateral side
  - PEPT1 & ASBT are influx transporters on both sides

#### TRANSPORTERS AND LOWERING F:
- Been most studied with transporter P-gp
  - Digoxin, paclitaxel and HIV protease inhibitors (dinavir, nelfinavir and saquinavir) are known to have a major component of efflux back into intestine mediated by P-gp active transporters
  - In terms of dosing, this is built into the dosing profiles during development

#### TRANSPORTERS AND INCREASING F:
- Polymorphic variants of the transporter that are genetically inherited and may have low expression
  - Example: polymorphism in exon 26 (C3435T) → reduced intestinal expression level of P-gp = increased F of digoxin (potential to exceed therapeutic window)
  - ADR that has the potential for avoidance using precision medicine approaches

#### INTESTINAL TRANSIT TIME:
- Once into the intestine, transit time is about 4-10 h (on average) to get absorbed before entering colon
  - Colon is relatively impermeable because the solid contents are compacted for excretion
  - Fortunately, most drug absorption is rapid and a Tpeak is reached within 30 mins of administration
  - Arguments about diarrhea are technically correct but are physiologically difficult to support (except in severe cases such as dysentery for drugs with very narrow therapeutic indices)
  - Variations of intestinal transit time can alter drug absorption (and F)
    - For drugs absorbed by active transport (ex// B vitamins), even moderately decreased intestinal time can result in clinically sig lower drug levels entering portal circulation
    - When intestinal transit time is profoundly increased (ex// dysentery) almost all drugs suffer from a lack of absorption and therapeutic failures can occur

### DISEASE STATES:

#### ULCER:
- In addition to pH changes, treatment with sucralfate can be problematic if other drugs will be co-administered
  - Sucrelafate is a viscous drug that coats the ulcer allowing for healing from underneath which can decrease absorption of several drugs (theophylline, digoxin, fluoroquinolones)

#### MALABSORPTION SYNDROMES:
- Malabsorption syndromes occur when bowel is prevented from absorbing critical food constituents
  - They also affect drug absorption
  - Malabsorption can be caused by conditions such as celiac disease, Crohn’s disease, IBD, lactose intolerance and intestinal damage

#### INFLAMMATORY BOWEL DISEASES:
- Most drugs have reduced absorption in IBD, esp. abx and analgesics
  - In contrast, propranolol has increased absorption in Crohn’s (due to inflammation causing leaky inter-cellular junctions in intestine)
  - Celiac is similar – generally drugs are absorbed further down GIT (absorptive characteristics not favourable = lower F)

#### BLOOD FLOW:
- Any disease affecting blood flow can affect absorption from GIT
  - For rapidly absorbed lipophilic drugs, intestinal blood flow may be rate limiting step (ex// ethanol, newer lipid formulations)
  - In critical illnesses (HF, Hypovolemia, shock) intestinal blood flow can be so low that it will be the rate-limiting step for many or all drugs = alternative route of administration required

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*Collier*
SLOW RELEASE/CONTROLLED RELEASE FORMULATIONS:

• Controlled-release forms are designed to reduce dosing frequency for drugs with a short elimination half-life and duration of effect
  o These also limit fluctuation in plasma drug concentration, providing a more uniform therapeutic effect while minimizing adverse effects
  o SR formulations have also been developed to slow absorption of drugs with high abuse potential
    ▪ Oxydodone original formulation could be crushed and when taken orally had a Ka closer to IV than oral → Purdue Pharma re-formulated the drug after the opioid epidemic into a gel matrix that is resistant to crushing effects and will not release powdered drug
• Absorption rate is slowed by:
  o Coating drug particles with wax or other water-insoluble material
  o Embedding the drug in a matrix that releases it slowly during transit through the GIT
  o Complexing the drug with ion-exchange resins
• Most of the absorption of SR formulations is in the large intestine – which is empirically sensible, as the drug is absorbed slowly over the transit time and spends longer in the larger intestine than the small
  o Crushing or otherwise distributing a CR tablet or capsule can often be dangerous due to large-scale release of drug (overdose)
• SR formulations must balance GI transit time with slowed Ka very well so that absorption & therapeutic efficacy are reached before the dosage form is expelled

SUPPOSITORIES:

• Generally, oral administration is the route of choice for ease of administration; however in some circumstances it is impractical or impossible (ex// N&V, convulsions or recurrent fitting)
  o In these cases, rectal administration may be a practical alternative
  o Rectal administration is now well accepted for delivering anticonvulsants, analgesics, and for inducing anesthesia in children
• The rate and extent of rectal drug absorption is usually lower than with oral administration, because:
  o Relatively small surface area available for drug uptake
  o Compaction in colon with other material
  o Lack of paracellular pathway
• Composition of the rectal formulation is an important factor in the absorption process by determining the pattern of drug release
  o Adjuvants used are primarily glyceride mixtures (acts as carrier) and/or non-ionic surfactants (disrupts cellular membrane slightly to promote absorption)
• For a small subset of drugs, the extent of bioavailability from the rectal route exceeds oral values
  o This is NOT an absorptive characteristic, but reflects avoidance of first-pass metabolism in the liver, producing higher systemic values
  o Drugs for which this is clinically relevant include: morphone, metoclopramide, lidocaine and propranolol
• Local irritation is an acknowledged problem with some formulations
  o Ex// in the past, long-term medication with rectal ASA caused ulceration = no longer recommended
  o Localized irritation has been described for several drugs and their formulations even after a single administration
  o The very action of some of the excipients and adjuvants used to increase absorption (i.e. disruption of membrane properties) are the cause of this SE