Factors Affecting Bioavailability

(08/08/2018)
Objectives:

– Bioavailability
– Bioequivalence
– Chemical Equivalence
– Pharmaceutical Equivalence
– Therapeutic Equivalence
– Clinical Equivalence
– Factors Affecting Bioavailability
  • Pharmaceutical factors
  • Pharmacological factors
What is BIOAVAILABILITY?

- The *rate* and *extend* to which the *active concentration* of a drug is available at the desired site of action (or bloodstream).
How does it differs from BIOEQUIVALENCE?

• If two or more, similar dosage forms of the same drug reach the blood circulation at the *same relative rate* and *extend*, those are BIOEQUIVALENT preparations of that generic drug.

• Difference in bioavailability is usually seen with *ORAL* dosage forms, bioavailability of *I.V* is 100%, *I.M* and *S.C* are assumed to be close to 100%.

• Differences of *less than 25%* in bioavailability among several formulations of one drug will usually have no significant effect on clinical outcome, hence such formulations can be called BIOEQUIVALENT.
• **Chemical Equivalence**
  - If two or more dosage forms of the same drug contains the *same labeled quantities* of the drug as specified in Pharmacopoeia, these are Chemical Equivalent drugs.

• **Pharmaceutical Equivalence**
  - If the two or more Chemical Equivalent drug’s dosage forms also contains *other similar ingredients*, e.g. excipients (binders), those dosage forms are considered to be Pharmaceutical Equivalent.
• **Therapeutic Equivalence**
  – If they provide an *identical in vivo pharmacological response*, as measured by control of symptoms or disease and safety profile.

• **Clinical Equivalence**
  – If one structurally different drug can provide the *same clinical response* as another mechanically related drug, they are considered to exhibit clinical equivalence.
What are the factors influencing BIOAVAILABILITY?

- Pharmaceutical factors
- Pharmacological factors
• Pharmaceutical Factors:

   - It is expected that, bioavailability of drugs to be in this *decreasing* order-
     - Solutions > Suspension > Capsule > Tablet > Coated Tablet
The Pharmaceutical factors include:

– **Particle Size**
  
  • The rate at which a drug is dissolved can be *increased* by increasing its surface area by decreasing its *PARTICLE SIZE*.

– **Salt Form**
  
  • The rate at which a particular salt dissolves differs from its parent compound.
  
  • Salts of weakly acidic drugs are highly water soluble, free acidic drugs is precipitated from these salts is *micro crystalline form*, which has a faster dissolution rate and *increases* bioavailability.

– **Crystal Forms**
  
  • The rate of absorption and bioavailability of a drug also depends on its crystalline form.
  
  • This is because *amorphous* forms dissolve faster compared to *crystalline* forms, because no energy is needed to break up the crystalline lattice, thus *increasing* their bioavailability.
– **Water of Hydration**
  - Many drugs incorporate water to produce a crystalline form called *hydrates*.
  - If water molecules are already present in a crystal structure, the tendency of the crystal to attract additional water to initiate dissolution process is *reduced*, compared to anhydrous forms.

– **Nature of Excipients and Adjuvants**
  - These pharmacologically inert substances, (e.g. starch, lactose, calcium sulfate, gum) which are added as filling material or as binding agents or to obtain proper granular size, have tremendous effects on bioavailability of drugs.
  - Some of these excipients are wetting agents, which enhance solvent penetration and ensures *faster* dissolution and in turn absorption.
  - We should be particularly careful in drugs which follows *zero order* or *mixed order kinetics* or have a *low margin of safety*.

– **Degree of Ionisation**
  - *Non-ionised, lipid soluble* drugs are better absorbed, *increasing* their bioavailability, compared to strongly acidic or strongly basic drugs or highly ionised drugs.
• Pharmacological Factors:
The Pharmacological factors include:

– **Gastric Emptying and Gastrointestinal Motility**
  • Factors that accelerate gastric emptying *increases* the bioavailability.
  • This is because the drug is exposed to the larger surface area of the small intestine.

– **Gastrointestinal Diseases**
  • There are many gastrointestinal diseases which have an effect on drug absorption, the outcome of *Coeliac disease* is complex, it *increases* the absorption of cephalaxin, whereas *reduces* of amoxycillin.
  • In case of *Crohn’s disease*, there is disproportionate absorption of individual components of cotrimoxazole, *increases* absorption of sulfamethoxazole, *decreases* of trimethoprim

– **Food and Other Substances**
  • In general, GI absorption rate is *reduced* after ingestion of food, although *it has no effect on extend of absorption.*
  • Both *rate* and *extend* of absorption of certain antibiotics like *rifampicin* is *reduced* after meals.
• Absorption of *tetracyclines* is *reduced* if taken with milk because it forms poorly absorbed complexes with calcium.
• Vit. C *increases* absorption of iron because it keeps it in its ferrous form.

– **First Pass Metabolism**
  • It means that drug degradation occurs, *reducing* its bioavailability, when it passed through GIT wall and then through portal system, before it reaches systemic circulation.

– **Drug-Drug Interactions**
  • Drug-drug interactions can also cause difference in bioavailability.
  • Liquid paraffin *decreases* the bioavailability of fat soluble vitamins as it emulsifies fat.
  • Antacids *reduces* bioavailability of tetracyclines because it forms chelated complex.

– **Pharmacogenetic Factors**
  • Large difference in bioavailability often occurs among humans due to pharmacogenetic reasons.
  • Slow and fast acetylators show *increased* and *decreased* bioavailability of isoniazid respectively.
- **Miscellaneous Factors**
  - Area of Absorptive Surface
  - State of Circulation at the Site of Absorption (shock, where tissue perfusion decreases)
  - Route of Administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous (IV)</td>
<td>100 (by definition)</td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>75 to ≤100</td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td>75 to ≤100</td>
</tr>
<tr>
<td>Oral (PO)</td>
<td>5 to &lt;100</td>
</tr>
<tr>
<td>Rectal (PR)</td>
<td>30 to &lt;100</td>
</tr>
<tr>
<td>Inhalation</td>
<td>5 to &lt;100</td>
</tr>
<tr>
<td>Transdermal</td>
<td>80 to ≤100</td>
</tr>
</tbody>
</table>
References:


– Sharma H. L, Principles of Pharmacology, 3\textsuperscript{rd} Edition, New Delhi, Paras Medical Publisher, 2018
Thank You!