03 - Oral administration

Oral administration

1. Principles of pharmacokinetics Pharmacokinetics refers to the time course and disposition of drugs in the body (what the body does to the drug). The pharmacokinetics for the same drug will differ to some extent on the basis of the route of administration of the drug. Commonly utilized routes of administration of psychotropic drugs include oral, intramuscular, intravenous and rectal routes. Other possible routes include inhalation, topical, subcutaneous, sublingual and intra-arterial but are not generally used in psychiatric practice Pharmacokinetics involves the processes of (ADME); Absorption, Distribution, Metabolism, and Elimination. We will consider each of the above processes in further detail below. A. Absorption The route of administration and chemical properties of a drug influences its absorption. The various factors that affect rate of absorption include The form of the drug (e.g. enteric coating of a tablet slows down its disintegration in the stomach) The rate of blood flow at the site of administration (higher the blood flow, greater will be the rate of absorption) Solubility of the drug which depends on the pH of the drug, size of particles in the formulation and the pKa of the drug (pKa is the pH at which precisely half of the drug is in its ionized form) Oral administration This is one of the most common routes of drug administration. It leads to a variable plasma concentration, as the absorption may be erratic and subject to metabolism by liver and gut mucosa (first-pass effect). Drugs absorbed from the gut undergo extensive metabolism before entering the systemic circulation. The main mechanisms of absorption of drugs from the GI tract are 1. Active transport 2. Passive diffusion (most common mechanism) 3. Pore filtration Factors influencing absorption of drugs from GI tract include Intestinal motility Gastric emptying Gastric and intestinal pH Intestinal microflora Area available for absorption

  Integrity of blood flow Presence or absence of food Poor oral absorption leads to lower bioavailability of the drug in plasma compared to intravenous administrations. This is mainly due to lack of absorption from the intestine related to the presence of inhibitory factors like food or gastric acid or due to changes in intestinal motility e.g. having diarrhea or vomiting can affect drug absorption. The presence of food delays gastric emptying. The anticholinergic activity of some psychotropic drugs like tricyclic antidepressants, opiates, etc. can lead to delayed gastric emptying. The intestinal flora or intestinal wall enzymes can have drug-metabolizing activity, which could affect the rate of absorption. For e.g. Chlorpromazine is sulfated in the gut; this reduces its absorption. Site of absorption: The small intestine is less acidic than the stomach and most

absorption takes place here. This is aided by a large surface area and long transit time via the small intestine. Although oral administration occurs primarily in the small intestine, the absorption of many ‘slow or sustained release’ drugs occurs in the large bowel. Special preparations: With oral administration, the rate and sometimes the extent, of absorption are largely determined by disintegration and dissolution of the dosage form, both being important for absorption. Tablets and capsules must disintegrate into smaller pieces to expose a greater surface area for absorption. Enteric coating slows down the rate of disintegration. Disintegration is often prolonged by hard compaction or by incorporating wax in a drug matrix. As a result of this, such modified release preparations can prolong the effects of the drugs and reduce peak plasma concentrations and therefore may reduce side effects (E.g. lithium, carbamazepine, sodium valproate, quetiapine XL) Liquids or syrups are more quickly absorbed than tablets because disintegration and dissolution are not required. Dissolution rate is dependent on P-GLYCOPROTEIN

Presence of reverse transporters such as Pglycoprotein can affect drug absorption. P glycoprotein pumps certain drug molecules actively out into gut lumen from the gut cells.

Inhibition of P-glycoprotein (e.g. by grapefruit juice) can increase absorption of certain medications. The “grapefruit juice effect” is due to components of grapefruit juice - bergamottin, 6,7-dihydroxybergamottin, and naringenin – that significantly increase drug oral bioavailability by selectively and rapidly downregulating intestinal (but not liver) CYP3A4 and to a lesser extent, CYP1A2.

This effect is greatest for drugs with high first pass metabolism such as calcium antagonists felodipine and nimodipine, terfenadine, carbamazepine, triazolam and midazolam (to some extent diazepam), simvastatin and methylprednisone. Grapefruit also significantly affects buspirone and pimozide.

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