Q17 With regard to ORAL drug dosing, describe the factors that affect the fraction of drug reaching the systemic circulation (80% marks). How may these factors be altered in a patient with shock (20% marks)? (March 2010)

Bioavailability →

- The fraction of a drug dose reaching the systemic circulation compared with the same dose given IV
- In general, the oral route has the lowest bioavailability of any route of administration
- Bioavailability can be found form the ratio of the areas under the concentration-time curves for an identical bolus both orally and IV

FACTORS INFLUENCING ORAL BIOAVAILABILITY

- Factors affecting absorption
    - Drug factors
        - Pharmaceutical aspects – large, enteric coated drugs will have delayed absorption
        - Interactions with coadministered drugs (eg, the absorption of tetracyclines is reduced by coadministration with calcium, such as in milk)
        - Lipophilicity / hydrophilicity – drugs that are highly hydrophilic are poorly absorbed as they cannot easily cross the lipid membrane; drugs that are highly lipophilic ay be unable to cross the water layer near the cell membrane

    - Patient factors
        - Metabolism by gut flora (eg, digoxin)
        - Malabsorption syndromes
        - Gastric stasis

- First pass metabolism
    - Drugs absorbed from the gut may undergo metabolism in the gut wall (eg, GTN), or pass into the portal vein and be subject to first pass metabolism in the liver
    - For PO administration, the bioavailable fraction (FB) is given by: $F_B = F_A \times F_G \times F_H$, where F_A is the fraction absorbed, F_G is the fraction remaining after metabolism in the gut mucosa, and F_H is the fraction remaining after hepatic metabolism

- Extraction ratio
    - ER is the fraction of drug removed from blood by the liver
    - It depends on hepatic blood flow, uptake into the hepatocyte, and enzyme metabolic capacity within the hepatocyte
    - ER = CL liver / Q, where Q is hepatic blood flow
    - Hence any alteration to liver blood flow (low cardiac output state, shock, portal vein thrombosis), hepatocyte uptake or enzyme function (hepatocyte dysfunction, cirrhosis, hepatitis)

In a patient with shock, oral bioavailability is uncertain due to:

- Absorption may be reduced due to poor GI motility or reduction in GIT blood supply due to poor cardiac output state
- First pass metabolism may be impaired due to reduction in hepatic blood flow
- Enzyme function may be altered due to drug interactions with other medications (induction of or competition for enzymes)