INTRODUCTION:

The bioavailability of a drug is usually estimated in a fasting state to avoid the complicated interference with food. However, it is important to investigate the effects of food on the bioavailability, as drugs are often administered after food intake, and alteration of the bioavailability caused by food, if it occurs, may cause significant changes in clinical response. Solid food has been shown to decrease the stomach emptying rate, but gastrointestinal motility increases in the presence of food. Because most drugs are absorbed from the small intestine, delayed stomach emptying may delay the onset and reduce the rate of absorption. Food may reduce the extent of absorption of drugs that are unstable at low pH. On the other hand, prolonged retention in the stomach may increase the percentage of an administered drug that is in solution when it eventually passes into the small intestine and may thereby increase the extent of absorption. In a healthy digestive tract, the presence of food in the system triggers the release of stomach acid and contraction of the muscles of the stomach. Increasing the stomach’s sensitivity to the presence of food helps ensure that digestion progresses quickly. In a healthy digestive tract, the presence of food in the system triggers the release of stomach acid and contraction of the muscles of the stomach. Increasing the stomach’s sensitivity to the presence of food helps ensure that digestion progresses quickly. As a type of drug called a Prokinetic, Itopride treats non-ulcer dyspepsia and acid reflux by helping the contents of the stomach pass through the digestive tract more quickly. It makes the muscles of the stomach tighter and more sensitive to food. This study involves research to analyze the influence of food intake on the pharmacokinetics of Itopride, comparing AUC (area under the plasma concentration versus time profile), Cmax (peak plasma level), and Tmax (time to peak plasma level) at same dose of Itopride, after ingestion in both fasted and fed state.

EFFECT OF FOOD ON BIOAVAILABILITY OF DRUGS:

Absorption of an oral drug from the gastrointestinal tract is the first step in a series of pharmacokinetic processes before the drug can get into the systemic circulation. The absorption process can be affected by a number of factors including:

1) Physicochemical properties of the drug and the dosage form;
2) Gastric acidity;
3) Gastric and intestinal motility;
4) Gastro-intestinal (GI) related diseases; and
5) Concurrent food administration.

Amongst these, concurrent food administration is the most common and yet most easily controllable factor. The two pharmacokinetic parameters that may be affected are the extent of absorption i.e. oral bioavailability, and the rate of absorption (The pharmaceutical codex, 1994).

(A) Interaction mechanisms

Four main mechanisms involved in this type of interaction are:

- **Reducing gastric emptying rate:**
  Food, especially fatty food, slows the gastric emptying rate under normal physiological conditions. Consequently, the gastric residence time of the concurrently administered drug is prolonged. This may affect the pharmacokinetics of the drug in several ways. Firstly, rate of absorption of the concurrently administered drug is usually reduced. Most of the drug absorption occurs in the small intestine because of its large surface area in comparison with the stomach. Therefore, gastric emptying plays an important controlling role in the absorption rate of the drug. A decrease in gastric emptying rate leads to a corresponding decrease in the rate of delivery of the drug to the small intestine for absorption. This is of clinical concern when a rapid onset of action is required, as for analgesics, sedatives, and hypnotics. For this group of drugs, administration under fasting condition may be preferable. Secondly, oral bioavailability of the drug may also be affected. For those acid-labile drugs such as penicillin, erythromycin, and cephalosporin, the extent of absorption is reduced because drug lost by hydrolysis is increased as a result of increased gastric residence time. On the other hand, for those drugs that are poorly or slowly soluble, the extent of absorption may be increased. Since dissolution is usually the most important step in drug absorption, particularly for poorly aqueous soluble drugs, the prolonged gastric residence time and increased gastric secretion in response to food administration enhance dissolution of the drug. Consequently, oral bioavailability of the drug is increased. Furthermore, the fat components in diet also facilitate the absorption of fat-soluble drugs such as griseofulvin through the normal mechanisms for fat absorption (Berkow R, 1992).

- **Drug binding and/or complexing with food, and decreasing drug's access to the absorption sites**
  Some dietary components may bind or complex with some drugs to form products of decreased
aqueous solubility in comparison with the parent drugs. The consequence of this effect is reduced drug absorption. Tetracycline is a typical example of a drug that undergoes this type of interaction. Tetracycline will form poorly soluble complexes with metal ions such as Ca++, Mg++, Fe++, and Al++. Therefore, concurrent administration of tetracycline and foods or drugs that contain these metal ions should be avoided, as reduced oral bioavailability may lead to subtherapeutic drug level and treatment failure. For absorption to take place, the drug molecules must reach their absorption sites in the GI tract and be in an absorbable form. For drugs that do not disintegrate or dissolve readily, the drug aggregates or particles may be mixed with the food thus preventing the drugs from reaching the sites of absorption. As such, the bioavailability is decreased and may become highly variable (Micromedex Inc., 1974-1997).

- Altering dissolution rate and pH of the GI contents: especially for enteric-coated preparations

Enteric-coated preparations are designed for drugs that are likely to cause nausea or irritation to the gastric mucosa. The dissolution of enteric coating in acidic medium is slow, but proceeds rapidly in alkaline medium such as that in the small intestine. Since absorption of the enteric-coated drugs occurs only in the small intestine, the time of onset of absorption is highly dependent on the rate of gastric emptying and thus, concurrent food administration. The enteric-coated formulation is also used for acid labile drugs which are susceptible to degradation in an acidic environment. Therefore, if these formulated preparations are taken with alkaline food such as tea, milk, and coffee, the enteric coating will dissolve in the stomach prematurely. This may lead to increased degradation of the drug because of premature exposure of the contents to the acidic environment, resulting in a decreased amount of drug absorption. Moreover, if the drug is irritating to the gastric mucosa, premature release of the drug in the stomach may also lead to an increase in the incidence of drug-induced gastric adverse effects.

- Increasing splanchnic blood flow

Blood flow to the splanchnic area is increased in response to food intake. This physiological response, together with changes in absorption rates, plasma protein binding, and the activity of drug-metabolizing enzymes, may reduce the extent of first-pass metabolic loss of certain drugs. The net result and significance depends on the overall contribution of the involved factors on the first pass metabolism of the drug. An increase in oral bioavailability has been observed for several drugs including hydralazine and some beta adrenergic blocking agents such as labetalol,
metoprolol and propranolol (Knoben JE, 1993).

(B) A potential therapeutic strategy
Administration of oral medication at fixed time in relation to meals is expected to improve patient's compliance by acting as a reminder to the patients. In fact, this has been used as a strategy by some to guide the patients when to take their medication. Concurrent administration of a drug with food may also be used therapeutically to reduce the adverse effect of some drug on GI tract. Examples are NSAIDs and some antibiotics. Use of NSAIDs is associated with a high incidence rate of GI upset. Consequently, concurrent administration of NSAIDs with food (or antacid) is usually recommended in order to reduce drug-induced GI discomfort. In this case, although the rate of absorption of NSAIDs is reduced, this is of minor clinical significance in comparison with the potential drug-induced adverse effects (Stocklcy IH, 1996).

ITOPRIDE:
Non-ulcer dyspepsia (NUD), gastro-esophageal reflux disease (GERD), gastritis, diabetic gastroparesis and functional dyspepsia are commonly encountered disorders of gastric motility in clinical practice. Prokinetic drugs such as metoclopramide, domperidone, cisapride, mosapride etc. are the mainstay of therapy in these disorders. These drugs are used to relieve symptoms such as nausea, vomiting, bloating, belching, heartburn, epigastric discomfort etc. Prokinetic drugs act by promoting gastric motility, increase gastric emptying, prevent the retention and reflux of gastric contents and thus provide symptomatic relief (Mcquaid KR, 2002). All the drugs in this group are efficacious with modest Prokinetic activity but the matter of major concern is their side effect profile. Itopride hydrochloride, a novel Prokinetic agent has been introduced in the Indian market (Banka NH, 2003). This drug was first developed by Hokuriku Seiyaker Co. Ltd. and has been marketed in Japan since Sept. 1995 (Hokuriko Seiyaku, 2001).

Chemistry

Mechanism of action
Itopride has anticholinesterase (AchE) activity as well as dopamine D2 receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders (Iwanga Y, 1994; Iwanga Y, 1990) It is well established that M3 receptors exist on the smooth muscle layer throughout the gut and acetylcholine (ACh) released from enteric nerve
endings stimulates the contraction of smooth muscle through M3 receptors (Tadashi Tsubouchi, 2003). The enzyme AChE hydrolyses the released ACh, inactivates it and thus inhibits the gastric motility leading to various digestive disorders. Besides ACh, dopamine is present in significant amounts in the gastrointestinal tract and has several inhibitory effects on gastrointestinal motility, including reduction of lower esophageal sphincter and intragastric pressure. These effects appear to result from suppression of ACh release from the myenteric motor neurons and are mediated by the D2 subtype of dopamine receptors (Pasricha PJ, 2001). Itopride, by virtue of its dopamine D2 receptor antagonism, removes the inhibitory effects on ACh release. It also inhibits the enzyme AChE which prevents the degradation of ACh (Iwanga Y, 1990; Iwanga Y, 1993). The net effect is an increase in ACh concentration, which in turn, promotes gastric motility, increases the lower esophageal sphincter pressure, accelerates gastric emptying and improves gastro-duodenal coordination.

Pharmacokinetics

On oral administration, Itopride is rapidly and extensively absorbed and peak serum concentrations are achieved within 35 minutes after oral dosing (Nakajima M, 1993). Thus it has a rapid onset of action, unlike cisapride and mosapride, which take around 60 minutes to reach peak plasma concentrations (Banka NH, 2003; Noda T, 2001). Itopride is metabolized in the liver by N-oxidation to inactive metabolites by the enzyme flavin-containing monooxygenase (Mushiroda T, 2000). The half life of Itopride is about 6 hours (Banka NH, 2003). It is excreted mainly by the kidneys as metabolites and unchanged drug (Mushiroda T, 2000; Banka NH, 2003).

Therapeutic Indications

Various prokinetic studies were conducted in patients of NUD, reflux esophagitis and chronic gastritis, diabetic gastro paresis and functional dyspepsia. The results of these studies indicated that Itopride is an effective prokinetic agent for the treatment of symptoms caused by altered gastrointestinal motility in all the above mentioned conditions (Tadashi Tsubouchi, 2003; Otsuba T, 1998; Inoue K, 1999; Noritake M, 1997). Few studies have shown that Itopride is superior in efficacy to metoclopramide (Kamath, 2003) and cisapride (Miyoshi A, 1994) in patients of NUD. Sawant et al in a comparative trial found Itopride to be comparable in efficacy to Domperidone in the symptomatic management of NUD (Sawant P, 2002).

Dosage and Administration
The usual daily dosage for adults is 50mg of Itopride hydrochloride orally in 3 divided doses (Banka NH, 2003).

**Drug Interactions**

Unlike cisapride and mosapride citrate, Itopride is metabolized by the enzyme mono oxygenase and not by the cytochrome P450 enzyme system. It is thus devoid of the risk of significant pharmacokinetic drug interaction with cytochrome P450 enzyme inhibitors such as macrolides andazole antifungal agents (Mushiroda T, 2000).

**Tolerability**

Following the restriction imposed on cisapride usage and the subsequent report of the arrhythmic potential of mosapride, safety of a prokinetic drug has been a cause of concern. Itopride is well tolerated with few minor adverse drug reactions in the form of diarrhea, headache, abdominal pain etc. It has no significant effects on central nervous system and thus is devoid of extra pyramidal side effects and hyper prolactinaemia as is seen with other prokinetic drugs such as metoclopramide and domperidone. It also has no effect on the cardiovascular system. Preclinical and clinical studies till date indicate that this drug is not having the potential to cause prolongation of QT intervals unlike cisapride and mosapride (Kakuichi M, 1997; Takuma K, 1997; Ohki R, 2001). The affinity of cisapride for 5HT4 receptors in the heart has been implicated in the undesirable cardiac effects of the drug but Itopride has no affinity for 5HT4 receptor which makes this drug a better and safer Prokinetic agent. Safety of this drug has not been established in the pregnant females although no abnormalities in the organogenesis and foetal developments were observed in animal studies (Kawakami Y, 1992; Shimomura K, 1992).