Commentary

Food & drug bioavailability

The bioavailability of drugs is determined by gastrointestinal physiological factors and the physicochemical property of drugs. The presence of food changes the physiological functions of gastrointestinal mucosa (e.g., gastric pH, gastric emptying, hepatic blood flow) which may lead to increase or decrease in the bioavailability of drugs. Intestinal absorption of penicillin, captopril, ciprofloxacin, quinidine and zidovudine was reported to be reduced when given with food. On the other hand, bioavailability of clarithromycin, griseofulvin and leukotriene antagonists was increased by the presence of food. It is difficult to predict the interaction of drug with food based on its chemical structure.

The food habits of different populations vary and the dietary composition was shown to alter the bioavailability of drugs. The dietary intake of carbohydrate, protein, lipids, micronutrients and phytochemicals will change based on the dietetic habits of the population.

Excessive intake of carbohydrate was reported to delay the gastric emptying, raise gastric pH and increase luminal fluid volume which may alter the bioavailability of drugs (e.g., indinavir, phenytoin). Oral glucose treatment decreased the AUC of propranolol. The activities of hepatic CYP1A2, 2C6, 2C11 and 3A2 enzymes were shown to be significantly decreased in glucose treated rats compared to controls.

Dietary proteins affect the function of mixed function oxidase system and conjugating enzymes. Intake of high protein diets was shown to enhance the metabolism of numerous drugs such as cholestyramine, tetracycline. Low intake of protein was reported to cause 20-40 per cent decrease in phenazone and theophylline clearance. The conjugation of acetaminophen and oxazepam was decreased on changing from high protein to low protein diet. It was reported that feeding a charcoal broiled beef diet markedly lowered the plasma concentration of phenacetin without altering the plasma half life suggesting that first-pass phenacetin metabolism is enhanced. Low protein diet decreased the renal clearance of allopurinol and oxyurinol.

The ingestion of lipids stimulates the secretion of bile and pancreatic juice. The presence of bile facilitates the dissolution and solubility of low lipid soluble drugs in the intestine. It has been reported that bile increases the dissolution rate of griseofulvin, danazol, etc., that may affect the entry of drugs in the intestine. Studies have shown that microsomal oxidation is impaired by total parenteral nutrition. This effect may be altered when the caloric source changes from carbohydrate to lipid, especially when administered as medium-chain/long chain triglyceride mixtures.

In our country, a few studies have been done on diet-drug interaction. Multiple dose administration of Coca cola has been shown to increase the bioavailability of phenytoin and ibuprofen in rabbits. They also reported that high fat diet (butter) increased the bioavailability of phenytoin and carbamazepine in rabbits. But these data need to be confirmed by human studies. The same group showed that single dose administration of grape fruit juice did not alter the phenytoin bioavailability in epileptic patients and healthy volunteers. Studies done elsewhere showed that piperine increases the bioavailability of phenytoin, theophylline, propranolol and curcumin in healthy volunteers. The clinical benefits of these findings need to be established.
The effect of honey on drug kinetics has been studied. Multiple doses of honey significantly decreased the plasma levels of diltiazem and carbamazepine (substrates of CYP3A4) in rabbits\textsuperscript{18,19}. In a human study, single dose administration of honey did not alter the carbamazepine kinetics\textsuperscript{20}. In contrast to above, multiple doses of honey significantly increased the rate and extent of absorption of phenytoin (substrate of CYP2C9) in rabbits\textsuperscript{21}. Since, honey is ingested commonly for various purposes by all age groups, a detailed study on its interactions with drugs is warranted.

Recent studies show that CYP3A4 and P-glycoproteins (P-gp) have important role in limiting the bioavailability of drugs\textsuperscript{22}. CYP3A4, one of the important cytochrome P450 enzymes, is found in the columnar epithelial cells lining the intestinal lumen, besides liver and other organs. It metabolises about 50 per cent of the currently available drugs. The activities of CYP3A4 are known to be induced (rifampicin) or inhibited (ketoconazole) by many drugs. It is also sensitive to dietary effects. Grapefruit juice, red wine, green tea and ginseng were reported to inhibit the CYP3A4 activity. Herbal drugs like St.John’s wort and Echinacea induced this enzyme\textsuperscript{23-24}. These effects may profoundly affect the oral bioavailability of drugs.

P-glycoprotein is an efflux transporter localized in the apical membrane of the intestinal cells, besides other drug eliminating organs. It actively extrudes drugs from the cell back into the intestinal lumen. CYP3A4 and P-gp, work together to co-ordinate an absorption barrier against xenobiotics. Similar to CYP3A4, P-gp activity can be induced (clotrimazole, erythromycin, phenobarbital, rifampicin) or inhibited (quinidine, verapamil) by drugs\textsuperscript{25,26}. The influence of diet on the P-gp activity is poorly studied. Flavanoids, particularly flavanols and coumarins were found to modulate P-gp function. In a human study\textsuperscript{27}, administration of grapefruit juice was shown to inhibit P-gp activity leading to increased bio-availability of talinolol. In an in vitro study, methoxyflavones (a component of orange juice) specifically inhibited P-gp without altering the CYP3A4 activity\textsuperscript{28}. This may have potential clinical application for reversing the multi-drug resistance of anti-cancer drugs. Other studies have shown that CYP3A4 and P-gp are co-regulated through the nuclear receptor like SXR/PXR (steroid and xenobiotic receptor/pregnenolone X receptor)\textsuperscript{29}. The effects of dietary component on this receptor need to be investigated.

In this issue, Sharma et al\textsuperscript{30} describes the effects of north Indian and south Indian breakfasts on the bioavailability of lamotrigine. The north Indian diet has high calorie and high fat compared to the south Indian diet. Both types of diets significantly decreased the bioavailability of lamotrigine when compared with the fasting group. Since lamotrigine is having a narrow therapeutic index, this finding may be clinically important. The two types of breakfasts did not produce differential effects on lamotrigine absorption. In contrast, in an earlier study\textsuperscript{31} the north Indian diet (poori with dal fry) was found to significantly increase the bioavailability of cefuroxime axetil when compared to south Indian diet (idly with chutney). This difference may be due to the difference in physico-chemical property and/or pharmacokinetic profile of lamotrigine and cefuroxime axetil.

India is a vast country with populations having different dietary habits. The dietary composition of Indian diet is different from that of the western diet. Indian diet has more phytochemicals, besides having other differences in the macro-and micronutrients composition. Therefore, more research is needed to investigate the diet-drug interaction in our population. Since several phytochemicals were shown to modulate the CYP3A4 and P-gp activities, future research should have more focus on this.

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References


