

STUDIES OF FOOD DRUG INTERACTIONS

SYED FAISAL AMAN, FOUZIA HASSAN, BAQAR S NAQVI
AND SYED MUHAMMMAD FARID HASAN

Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Karachi-75270, Pakistan

ABSTRACT

Medicines can treat and alleviate many diseases provided that they must be taken properly to ensure that they are safe and useful. One issue related with the medicines is that whether to take on empty stomach or with food. The present work gives information regarding food-drug interactions that were studied by collecting seventy five prescriptions from various hospitals. In most of the collected prescriptions, food-drug interactions were detected using the literature available. It was also found that only few studies have been carried out so far on the effect of food on drug disposition in the Asian population. Thus more studies on food-drug interactions particularly in the local population is recommended in order to determine the effect of food and food components on drug disposition and to the kinetics of the drugs which has not yet well highlighted in this part of the world.

Keywords: Food-drug interactions, Asian population, prescriptions

INTRODUCTION

Once the drugs are prescribed by the doctor or in case of over the counter medications, herbal products, dietary supplements etc., usually the first question asked by the patient to the health care provider is whether to take the drug with food, fluid, juices or with milk. At times it was not easy to answer all these questions because of the non-availability of the data regarding food-drug interactions.

Food-drug interaction is a wide domain and the food that a patient takes can affect the rate and extent of drug bioavailability to the body. It is now being acknowledged by an increasing number of pharmacists, physicians and other research workers in medical sciences. The potential for food-drug interactions is sufficiently great that the US Food and Drug Administration now requires studies as to the effects of food on drug absorption as part of biopharmaceutic characterization of almost every new drug intended for oral administration and this requirement is also being applied for new dosage forms of established drugs (Gibaldi, 1991). Previously it was said that food intake generally impairs the absorption of drugs (Wagner, 1977, Melander, 1978) and drugs should be taken on an empty stomach whenever possible (Welling, 1977, Melander, 1978) and that the variations in bioavailability could be usefully decreased if drugs were administered with food only when their irritative effects on the gastric mucosa make this necessary (Koch-Weser, 1974, Melander, 1978). One reason for these assumptions seems to be that the rate and partly also the extent of drug absorption depends mainly on the rate of gastric emptying and that food intake affects drug absorption negatively because of its slowing of gastric emptying rate (Koch-Weser, 1974, Prescott, 1974, Heading *et al.*, 1973,

Melander, 1978). Many observations strongly challenge these generalizations (Melander, 1978).

Drug-food interactions may result in reduced, delayed, or increased systemic drug availability. The absorption of only a small number of drugs is unaffected by concomitant food intake (Welling, 1984). Food intake has been found to improve the bioavailability of several common drugs (Beermann and Groschinsky-Grind, 1978, Melander *et al.*, 1977a, Melander *et al.*, 1977b, Melander, 1978). Food may influence the rate of drug absorption without affecting the total amount absorbed, and both the rate and extent of absorption may be increased even though or rather because the rate of gastric emptying is reduced (Beermann and Groschinsky-Grind, 1978, Mattok and McGilveray 1973, Melander, 1978). Food may influence not only the absorption but also the first pass metabolism of drugs in the gut and in the liver (Kappas *et al.*, 1978, Melander, 1978). It should be worth mentioning that some medications are easier to tolerate when taken with food.

From the above description it is clear that food-drug interactions are very complex, of varying nature and our knowledge regarding food-drug interactions are not enough. Therefore, it seems necessary to investigate this type of interactions. The objective of the present work was to study, to update our information and to provide awareness regarding food-drug interactions.

MATERIAL AND METHODS

In the first phase of the study seventy five outpatient prescriptions from various hospitals located in Karachi were randomly collected, recorded and the patients or their guardians were also interviewed on the spot to get relevant information and to take them into confidence

Corresponding author: e-mail: faridsm2002@yahoo.com

about the purpose of the study and also to provide awareness regarding the food-drug interactions.

In the second phase of the study, prescriptions were checked and those prescriptions that containing same active prescribed for major infection but with different brand name were searched. One such prescription was selected for further evaluation while the remaining prescriptions were removed. This was done to avoid duplication of drugs.

In the third and final phase of the present study, a thorough literature survey was carried out using relevant search engines for any food-drug interaction of the selected drugs from the prescriptions orders and finally conclusions were drawn.

RESULTS AND DISCUSSION

As new drug approvals occur with increasing speed, there is less information available about their adverse effects and interactions when the drug reach the market (Bland, 1998). In the present work, we studied food-drug interactions by collecting seventy five outpatient prescriptions at a random from various local hospitals. Relevant literature was than searched in order to find any food-drug interaction as reported previously. Following Table present a summary of the information collected from the prescriptions orders with effect of food.

Various studies have been carried out in the past that evaluated the effect of food on several antibiotics. A similar work is presented by Staniforth *et al.* (1985). This work showed that aluminum hydroxide, milk and cimetidine do have some influence on the bioavailability of a single dose of oral Amoxicillin/clavulanate potassium, but the small differences observed are not likely to be of therapeutic importance and therefore Amoxicillin/clavulanate potassium may be administered in clinical practice with any of these substances (Staniforth *et al.*, 1985).

Nitrofurantoin is usually used in treating urinary tract infection and it has been stated that its bioavailability is enhanced by food or propantheline (D'Arcy, 1985).

A study was conducted by Fould *et al.* (1996) in which three new formulations of azithromycin that comprise of tablets, sachet and paediatric suspension were studied. The mean relative bioavailability of azithromycin following administration of a standard high-fat breakfast was 96% when administered as two 250 mg tablets, 113% when administered as 500 mg suspension and 112% when administered as 1000 mg sachet. It was concluded that azithromycin tablets, suspension and sachet may be given without regard to meals (Fould *et al.*, 1996). In another work by Alkhalidi *et al.* (2008) clarithromycin extended-

release tablets were assessed in fasting and fed conditions. In the fed study, the C_{max} and AUC of both formulations were significantly increased relative to the fasting study while the arithmetic mean T_{max} was 5.7 (2.8) and 6.7 (2.5) hours. The 90% CI for the ratio of log-transformed C_{max} and AUC values was within the acceptance range of 0.80 to 1.25 (Alkhalidi *et al.*, 2008). Thus administration with food significantly increased the rate and extent of absorption of both products in this study, with no significant effect on their bioequivalence.

The interaction between tetracyclines and milk and dairy products is well documented (Scheiner and Altemeir 1962; Rosenblatt *et al.*, 1966). In a study conducted by Kshirsagar and Ankalesaria (1987), significant differences were observed in AUC and C_{max} after administration of doxycycline with food in six healthy male volunteers (Kshirsagar and Ankalesaria, 1987). Therefore, patients should be advised to avoid dairy products when are on tetracycline therapy.

Pharmacokinetic parameters of cefroxadin and cephalexin were compared after simultaneous oral administration of the two cephalosporins to 21 subjects in a study conducted by Lecaillon *et al.* (1980). Both drugs were equally well absorbed from all of the tested formulations and the same percentages of the dose were recovered in the urine in all cases. Absorption was slowed after food intake, but the amounts absorbed were almost the same as those in fasted subjects (Lecaillon *et al.*, 1980). Fassbender *et al.* (1993) in a review evaluated the pharmacokinetics of new oral cephalosporins, including esters, non-esters and the carbacephem loracarbef in healthy volunteers, as described in the literature. Regarding the effect of food, it was stated that food increases the bioavailability of the ester cephalosporins but does not affect the absorption kinetics of the other new drugs (Fassbender *et al.*, 1993). In another study conducted by Vasu *et al.* (2000) and the purpose was to compare the effect of two types of Indian breakfast on the bioavailability of cefuroxime axetil in healthy volunteers. Diet-A included idly with chutney and Diet-B included poori and dal-fry. The AUC and C_{max} were significantly increased after oral administration of cefuroxime axetil with Diet-B as compared to Diet-A. It was concluded that the administration of cefuroxime axetil with poori and dal-fry may enhance the bioavailability when compared with idly and chutney (Vasu *et al.*, 2000). When the effect of different types of food that includes two vegetarian (high-fat and low-fat) and two non-vegetarian (high-fat and low-fat) diets were studied in healthy volunteers by Karim *et al.* (2003) after a single dose of 250 mg cefaclor capsule, the results showed that while the rate of absorption of cefaclor is significantly decreased after food, the extent of absorption and the rate of elimination are not significantly decreased in the presence of food (Karim *et al.*, 2003). From these results, it is clear that

food has a variable effect on the kinetics of cephalosporins.

Kawakami *et al.* (1994) studied the effect of food on the interaction of ofloxacin with sucralfate in healthy volunteers that took a single oral dose of ofloxacin (200 mg) on 4 occasions: alone after overnight fasting or after breakfast (non-fasting), and with sucralfate fasting or non-fasting. There were no significant differences in the plasma concentration-time profiles of ofloxacin after ofloxacin alone between fasting and non-fasting conditions (Kawakami *et al.*, 1994). In another study, Shah *et al.* (1999) studied the effect of food on the absorption of ciprofloxacin in healthy male subjects. The results showed that administration of ciprofloxacin suspension, in either a fasted or fed state, was not associated with significant changes in C_{max} or AUC_{0-inf} values (Shah *et al.*, 1999). The effects of food and sucralfate on the pharmacokinetics of levofloxacin was investigated by Lee *et al.* (1997) in healthy subjects. Levofloxacin was administered by oral route under three conditions: fasting, fed, and fasting with sucralfate given 2 h following the administration of levofloxacin. The only consistent outcome of the coadministration of levofloxacin with a high-fat meal for most subjects was that levofloxacin absorption was delayed and C_{max} was slightly reduced. It was concluded that the absorption of levofloxacin was slightly delayed by food, although the overall bioavailability of levofloxacin following a high-fat meal was not altered (Lee *et al.*, 1997). In another study, the pharmacokinetics of a single 200-mg dose of sparfloxacin were assessed in a 3-way crossover study that included 23 healthy male volunteers who had fasted, ingested 240 mL of skim milk, or had consumed a standard high-fat breakfast by Johnson *et al.* (1999). It was found that neither skim milk nor the high-fat breakfast had a statistically significant effect on sparfloxacin absorption and, therefore, sparfloxacin can be administered without regard to the ingestion of milk or meals (Johnson *et al.*, 1999). The effects of milk and a standard breakfast on the oral absorption of enoxacin were evaluated in eight healthy volunteers by Lehto and Kivistö (1995) in a randomized, balanced, four-way crossover design. In this study, 400 mg enoxacin was given with water, milk, a breakfast or with a breakfast and milk. The extent of enoxacin absorption was not affected by any of the three treatments. It was concluded that enoxacin can be taken together with food and dairy products (Lehto and Kivistö, 1995). From these findings, it seems that administration of levofloxacin after food may be avoided, while for the rest of the ofloxacin, this precaution seems unnecessary.

Food increases the bioavailability of various antihypertensives that includes propranolol, metoprolol and labetalol, this may be related to reduced presystemic clearance (Welling, 1984). But in case of atenolol, food

reduces the bioavailability of the drug about 20 percent (Melander *et al.*, 1979 and Stockley, 1991). In a review article written by Marino and Vachharajani (2001), it was stated that no significant interactions have been identified between irbesartan and hydrochlorothiazide, nifedipine, simvastatin, tolbutamide, warfarin, magnesium and aluminum hydroxides, digoxin or food. According to these workers, irbesartan has demonstrated minimal potential for drug or food interactions in trials conducted (Marino and Vachharajani, 2001). The pharmacokinetic properties of five newer ACE inhibitors (trandolapril, moexipril, spirapril, temocapril and imidapril) were reviewed by Song and White, (2002). Regarding food it was stated that moexipril should be taken 1 hour before meals, whereas other ACE inhibitors can be taken without regard to meal (Song and White, 2002). In another study conducted by Mäntylä *et al.* (1984) single oral doses of captopril were given to healthy volunteers at three different occasions; after fasting, after a standardized breakfast or with 50 ml of an antacid suspension. The peak captopril concentrations attained were 701 ± 81 ng/ml after fasting, 351 ± 56 ng/ml with an antacid and 140 ± 14 ng/ml after a meal. The peak concentrations were reached in 0.5, 0.9 and 1.5 h and the areas under the blood concentration-time curves were 782 ± 86 , 456 ± 60 and 344 ± 47 ng x h/ml respectively. From the results it is clear that food causes a decrease in the absorption of captopril and delay the hypotensive action of the drug (Mäntylä *et al.*, 1984).

Regarding antituberculosis drugs, various studies have been carried out in the past. In a study conducted by Peloquin *et al.* (1998), pharmacokinetics of pyrazinamide (PZA) were studied in healthy volunteers. Subjects ingested single doses of PZA 30 mg/kg under fasting conditions twice, without a high-fat meal and with an aluminum-magnesium antacid. They also received standard dosages of isoniazid, rifampin, and ethambutol. Both fasting conditions produced similar results. In the presence of the high-fat meal, mean C_{max} was 45.6 ± 9.44 µg/ml, T_{max} 3.09 ± 1.74 hours, and AUC_{0-inf} 687 ± 116 µg x hr/ml. It was concluded that small changes in C_{max} , T_{max} , and AUC_{0-inf} can be avoided by giving PZA on an empty stomach whenever possible (Peloquin *et al.*, 1998). Pharmacokinetics of isoniazid (INH) was also studied by Peloquin *et al.* (1999) under fasting conditions, with food, and with antacids in healthy volunteers. Subjects ingested single doses of INH 300 mg under fasting conditions twice, with a high-fat meal, and with aluminum-magnesium antacid. They also received standard doses of rifampin, pyrazinamide, and ethambutol. Both fasting conditions produced similar results. In contrast, the high-fat meal suggested by the FDA reduced INH C_{max} by 51%, nearly doubled T_{max} and reduced AUC_{0-inf} by 12%. It was concluded that these changes can be avoided by giving INH on an empty stomach whenever possible (Peloquin *et al.*, 1999a). Peloquin *et al.* (1999b) also

studied the pharmacokinetics of Ethambutol in healthy volunteers. Subjects ingested single doses of Ethambutol of 25 mg/kg of body weight under fasting conditions twice, with a high-fat meal, and with aluminum-magnesium antacid. Again reductions in C_{max} and AUC_{0-inf} and a delay in T_{max} were found in the presence of high-fat meal. It was concluded that these changes can be avoided by giving Ethambutol on an empty stomach whenever possible (Peloquin *et al.*, 1999b). Panchagnula *et al.* (2003) assessed the effect of hydrodynamic stress in presence of food and meal composition on two rifampicin containing fixed dose combination formulations by carrying out dissolution at different agitation rates as well as in the presence of different percentage of oil. Agitation intensity as well as presence of oil did not have any influence on rifampicin release from formulation A. But formulation B showed agitation rate dependent release and also release was affected in presence of oil. It was concluded that food may not have any effect on the release of rifampicin from the formulation and on its bioavailability if the formulation has excellent release profile (Panchagnula *et al.*, 2003). From these studies, it is clear that an interaction exists between food and these agents and therefore they should be taken in empty stomach whenever possible as recommended in these studies.

Many workers have reported the outcome of food on the bioavailability of nonsteroidal anti-inflammatory drugs. In a study, effect of food on aspirin absorption was evaluated by Wood (1967). In this study, 25 subjects were given 650mg aspirin in five different preparations. Food roughly halved their serum levels of the drug when measured later compared to that of fasting (Wood, 1967; Stockley, 1991). Another study also showed similar results (Spiers and Malone, 1967). Thus if rapid analgesia is required, aspirin should be given without food (Stockley, 1991). In another study conducted by Pargal *et al.* (1996) in Asian Indian volunteers, effect of food on the sustained release dosage forms of ibuprofen and flurbiprofen was examined. In study one a single 200 mg multiple-unit sustained release capsule of flurbiprofen were given while in study two, a single 800 mg erodible sustained release matrix tablet of ibuprofen were given after an overnight fast or a heavy vegetarian breakfast. Food produced a statistically significant increase in the mean maximal plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{0-48}) in study one while in study two although food did not affect the bioavailability of ibuprofen yet it significantly increase mean concentration of the first peak from $14.21 \pm 1.38 \text{ mg L}^{-1}$ in fasting to $20.14 \pm 1.38 \text{ mg L}^{-1}$ with food. Results indicate that changes in the plasma concentration versus time curves are primarily influenced by the nature of the formulation and the type of meal (Pargal *et al.*, 1996). Regarding Piroxicam, it has been stated in the literature that food and antacids do not

interfere with its bioavailability (Verbeeck *et al.*, 1986). Zmeili *et al.* (1996) studied *in vitro* characterization, bioavailability, pharmacokinetics and effect of food by using two different sustained-release formulations of diclofenac sodium. When the effect of food on the bioavailability of diclofenac sodium was evaluated in randomly selected 6 male volunteers, results showed that following light and heavy meals, the AUC_{0-30} and C_{max} were minimally affected by food whereas a significant increase in T_{max} and T_{lag} as compared to fasting conditions was observed (Zmeili *et al.*, 1996). In another study conducted by Hasan *et al.* (2005) in healthy volunteers, diclofenac sodium enteric coated tablets was given to the volunteers in a randomized cross over design, results revealed slightly increase in T_{max} and a decrease in absorption half life (Hasan *et al.*, 2005). Influence of food on the bioavailability of 250 mg mefenamic acid from two commercial capsules in healthy volunteers were studied by Hamaguchi *et al.* (1987). This study revealed a significant difference in bioavailability between the two products in the fasting condition but in nonfasting condition, the difference was not significant (Hamaguchi *et al.*, 1987). Marzo *et al.* (1998) studied bioavailability and effect of food on naproxen using 550 mg S-Naproxen betainate sodium salt monohydrate in capsule dosage form that corresponds to 327 mg of naproxen in healthy volunteers and plasma concentrations of the drug were measured on days 1 to 6 in three different situations; i) after the morning dose on day 7 in a fasting state, ii) after the evening dose and dinner on day 7 and iii) after the morning dose of day 8, taken after a high-fat content breakfast. The extent of absorption of the drug did not differ in the situations tested and the rate of absorption was fastest in fasting, lowest with the evening dose and intermediate after the high-fat content breakfast (Marzo *et al.*, 1998). From the above studies, it is evident that presence of food influences the bioavailability and pharmacokinetics of NSAIDs, however in some cases it appears to be minimum.

Nomeir *et al.* (1996) studied the effect of a high-fat breakfast on the bioavailability of the components of an extended-release tablet containing 10 mg loratadine in the immediate-release coating and 240 mg pseudoephedrine sulfate in the extended-release core in healthy male volunteers. The drug was administered after overnight fast or within 5 minutes after consuming a standardized high-fat breakfast. The plasma was analyzed for loratadine and its active metabolite descarboethoxyloratadine (DCL). For pseudoephedrine, C_{max} and AUC_{0-inf} were similar after both treatments. Plasma concentration-time profiles and values for C_{max} and AUC_{0-inf} of DCL were similar for the two treatments. In contrast, for loratadine, administration with food resulted in a significantly increased mean C_{max} (53%) and AUC_{0-inf} (76%). It was concluded that the effect of food on the bioavailability and pharmacokinetic profiles of the components of a combination loratadine/

pseudoephedrine extended-release tablet is not likely to be clinically significant (Nomeir *et al.*, 1996).

The ingestion of food with glimepiride can lower the overall blood levels of the drug by nearly 10%. Though this is a minor reduction, maximum effectiveness would be achieved if glimepiride were taken on an empty stomach (Sifton, 2000). Marathe *et al.* (2000) studied pharmacokinetics and bioavailability of a metformin/glyburide tablet administered alone and with food. The results showed that food do not affect the bioavailability of either component to an appreciable extent (Marathe *et al.*, 2000).

Some studies on the effect of food on Proton pump inhibitors are also available in the literature. In one such study, carried out by Sostek *et al.* (2007), pharmacokinetics of esomeprazole before a high-fat meal vs. fasting was investigated. On days 1 and 5, subjects received esomeprazole 15 min before a high-fat meal (fed) or 4 h before a non-high-fat meal (fasting). On days 1 and 5, ratio of fed to fasting area under the plasma

concentration-time curve [0.56, 90% confidence interval (CI) 0.50, 0.64, and 0.78, 90% CI 0.74, 0.82, respectively] and peak plasma concentration (0.34, 90% CI 0.28, 0.41, and 0.47, 90% CI 0.41, 0.52, respectively) were outside of the limits of bioequivalence. It was concluded that esomeprazole bioavailability was reduced when taken within 15 min before eating a high-fat meal vs. that while fasting (Sostek *et al.*, 2007). Similarly in another study, conducted by Thomson *et al.* (1997), the influence of food on the bioavailability of omeprazole (20 mg) enteric-coated tablet under repeated dose conditions was taken into evaluation. During each treatment period, an enteric-coated tablet of omeprazole was taken once daily either under fasting conditions, or immediately before or after a standardized breakfast. The maximum plasma concentration was not found to differ significantly among any of the treatment regimens but the time to reach maximum plasma concentration was significantly different when fasting and after breakfast regimens were compared. It was concluded that under repeated dose conditions, food has no influence on the bioavailability of omeprazole given as the enteric-coated tablet formulation

Table: Summary of the information collected from the prescription orders with effect of food

S. No.	Age (years)	Sex	Major Infection	Drug Prescribed for major infection	Effect of food	References
01.	04	F	Wound infection	Cephalexin	Absorption slowed	Lecaillon <i>et al.</i> ,1980
02.	55	M	Fever, sore throat	Amoxicillin/ clavulanate potassium	Small differences in bioavailability	Staniforth <i>et al.</i> ,1985
03.	14	F	Pain in kidney and in urinary tract	Enoxacin	No effect	Lehto and Kivistö 1995
04.	52	M	Eye infection	Ciprofloxacin	No effect	Shah <i>et al.</i> ,1999
05.	35	F	Diabetic retinopathy	Captopril	Decrease in bioavailability	Mäntylä <i>et al.</i> ,1984
06.	25	M	Hypertension	Atenolol	Bioavailability reduced	Melander <i>et al.</i> ,1979, Stockley 1991
07.	32	F	Tuberculosis	Rifampicin	No effect	Panchagnula <i>et al.</i> ,2003
				Isoniazid	Decrease C_{max} Increase T_{max} , Decrease AUC_{0-t}	Peloquin <i>et al.</i> ,1999a
				Pyrazinamide	Small changes in C_{max} , T_{max} , AUC_{0-inf}	Peloquin <i>et al.</i> ,1998
				Ethambutol	Decrease bioavailability	Peloquin <i>et al.</i> ,1999b
08.	35	F	Gastric ulcer	Ranitidine	Decrease bioavailability	Juárez-Olguin <i>et al.</i> ,2002
09.	28	F	Pain	Diclofenac sodium	Increase T_{max} , T_{lag} Increase T_{max} and decrease absorption half life	Zmeili <i>et al.</i> ,1996 Hasan <i>et al.</i> , 2005
10.	19	F	Chronic bronchitis	Levofloxacin	Absorption delayed	Lee <i>et al.</i> ,1997
11.	25	F	Pelvic inflammatory disease	Doxycycline	Decrease AUC and C_{max}	Kshirsagar and Ankalesaria, 1987
12.	40	F	Peptic ulcer	Omeprazole	T_{max} affected	Thomson <i>et al.</i> ,1997
13.	30	M	Pyrexia	Aspirin	Decrease bioavailability	Wood 1967, Spiers and Malone 1967
14.	42	F	Epilepsy	Phenytoin	Increase bioavailability	Sindhu <i>et al.</i> ,2004
15.	40	F	RTI	Azithromycin	No effect	Fould <i>et al.</i> ,1996

Continued...

Continued...

S. No.	Age (years)	Sex	Major Infection	Drug Prescribed for major infection	Effect of food	References
16.	08	F	Fever	Ibuprofen	No effect	Pargel <i>et al.</i> ,1996
17.	05	M	Pharyngitis	Clarithromycin	Increase rate and extent of absorption	Alkhalidi <i>et al.</i> ,2008
18.	20	M	Bronchitis	Cefeclor	Decrease rate of absorption	Karim <i>et al.</i> ,2003
19.	51	M	Conjunctivitis	Sparfloxacin	No effect	Johnson <i>et al.</i> ,1999
20.	45	M	Gout	Flurbiprofen	Increase C_{max} & AUC_{0-t}	Pargel <i>et al.</i> ,1996
21.	32	F	Inflammation	Mefenamic acid	No effect	Hamaguchi <i>et al.</i> ,1987
22.	40	M	Chronic prostatitis	Ofloxacin	No effect	Kawakami <i>et al.</i> ,1994
23.	55	M	Gastro-esophageal reflux	Esomeprazole	Decrease bioavailability	Sostek <i>et al.</i> ,2007
24.	49	M	Angina	Propranolol	Increase bioavailability	Welling 1984
25.	55	F	Glaucoma	Naproxen	Extent of absorption not effected	Marzo <i>et al.</i> ,1998
26.	20	F	Anemia	Folic acid	Decrease bioavailability	Alemdaroglu <i>et al.</i> ,2008
27.	32	F	UTI	Nitrofurantoin	Increase bioavailability	D'Arcy 1985
28.	35	M	Ankylosing spondylitis	Piroxicam	No effect	Verbeeck <i>et al.</i> ,1986
29.	40	M	Duodenal ulcer	Trandolapril	No effect	Song and white, 2002
30.	28	F	Cardiac arrhythmia	Metoprolol	Increase bioavailability	Welling 1984
31.	30	M	Hypertension	Irbesartan	Minimal effect with food	Marino & Vacharajani 2001
32.	51	F	Diabetes	Glimepiride	Lower blood levels	Sifton 2000
33.	22	M	Epilepsy	Carbamazepine	Increase bioavailability	Sindhu <i>et al.</i> ,2004
34.	20	M	Allergy	Loratadine	Increase C_{max} and AUC_{inf}	Nomeir <i>et al.</i> ,1996

(Thomson *et al.*, 1997).

The effect of food over the bioavailability of ranitidine was studied by Juárez-Olguín *et al.* (2002) in healthy Mexican volunteers. In the first phase, the volunteers took a 300 mg of oral dose of ranitidine after fasting and blood samples were drawn. After two weeks, the volunteers took a normal diet just before ranitidine intake. The AUC, C_{max} and $t_{1/2}$ were found statistically different after these treatments (Juárez-Olguín *et al.*, 2002).

Effect of food (butter) on antiepileptic drugs was studied by Sindhu *et al.* (2004) in white rabbits. The studied drugs were phenytoin and carbamazepine. Butter increased the absorption of both phenytoin and carbamazepine, but no significant difference in T_{max} was observed (Sindhu *et al.*, 2004).

Pharmacokinetic interaction between tea and folic acid (0.4 mg and 5 mg) was studied by Alemdaroglu *et al.* (2008) in healthy volunteers. Water was used as the reference drink in this study. Subjects ingested 0.4 mg folic acid tablets with water, green or black tea (0.3 g extract/250 ml) or 5 mg folic acid tablets with water or green tea (0.3 g extract/250 ml). The results indicated an *in vivo* interaction between tea and folic acid thus yielding a decrease in the bioavailabilities of folic acid tablets (Alemdaroglu *et al.*, 2008).

In the present work, out of thirty four drugs, food drug interactions were found in twenty seven cases. It means that absorption of approximately 80% of the drugs studied in the present work found to be affected by food. This corroborate with Welling who had already stated that absorption of only a small number of drugs is unaffected by concomitant food intake (Welling, 1984). Although our data is small, yet sufficient to highlight the gravity of food-drug interactions.

CONCLUSIONS

It is clear that food drug interactions are very complex and investigations in this field of study should be expanded, documented and all such information must be gathered concerning effects of food, different kinds of food and food components on all aspects of drug kinetics that is on bioavailability, on systemic distribution and elimination of drugs. We also found lack of such studies in Asian population. Therefore, we recommend such type of studies to be carried out in Asian population in the future. In order to avoid food drug interactions, the patient should be advised to carefully read container label, leaflet as well as any ancillary labels and anything not clear should be asked by the physician or the pharmacist before starting drug therapy. The patients must also be advise not to mix their medication with tea, coffee or any other drink unless advised by their doctor nor take vitamins, minerals, antacids, iron preparations etc. at the same time with the drug because the chances of interactions always exists in

these conditions. Further they should be warned that during the treatment period, they should consult their physician or the pharmacist immediately, if they experience any untoward affect after taking the drug immediately with food. These are some of the ways to get rid off such type of interactions that in some case have been found to be fatal also.

REFERENCES

- Alcmdaroglu NC, Dietz U, Wolfram S, Spahn-Langguth H and Langguth P (2008). Influence of green and black tea on folic acid pharmacokinetics in healthy volunteers: potential risk of diminished folic acid bioavailability. *Biopharm. Drug Dispos.*, **29**(6): 335-348.
- Alkhalidi BA, Tamimi JJ, Salem II, Ibrahim H and Sallam AA (2008). Assessment of the bioequivalence of two formulations of clarithromycin extended-release 500-mg tablets under fasting and fed conditions: a single-dose, randomized, open-label, two-period, two-way crossover study in healthy Jordanian male volunteers. *Clin. Ther.*, **30**(10): 1831-1843.
- Beermann B and Groschinsky-Grind M (1978). Gastrointestinal absorption of hydrochlorothiazide enhanced by concomitant intake of food. *Eur. J. Clin. Pharmacol.*, **13**: 125.
- Bland SE (1998). Drug-food interactions. *J. Pharm. Soc. Wis.*, Nov/Dec., 28-35.
- D' Arcy PF (1985). Nitrofurantoin. *Drug Intell. Clin. Pharm.*, **19**(7-8): 540-547.
- Fassbender M, Lode H, Schaberg T, Borner K and Koepe P (1993). Pharmacokinetics of new oral cephalosporins, including a new carbacephem. *Clin. Infect. Dis.*, **16**(5): 646-653.
- Foulds G, Luke DR, Teng R, Willavize SA, Friedman H and Curatolo WJ (1996). The absence of an effect of food on the bioavailability of azithromycin administered as tablets, sachet or suspension. *J. Antimicrob. Chemother.*, **37**(Suppl. C): 37-44.
- Gibaldi M (1991). Biopharmaceutics and Clinical Pharmacokinetics, 4th Edn., Lea and Febiger, Philadelphia, p.33.
- Hamaguchi T, Shinkuma D, Yamanaka Y and Mizuno N (1987). Effects of food on absorption of mefenamic acid from two commercial capsules differing in bioavailability under the fasting state. *J. Pharmacobiodyn.*, **10**(1): 21-25.
- Hasan SMF, Ahmed T, Talib N and Hasan F (2005). Pharmacokinetics of diclofenac sodium in normal man. *Pak. J. Pharm. Sci.*, **18**(1):18-24.
- Heading RC, Nimo J, Prescott LF and Tothill P (1973). The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmacol.*, **47**: 415-421.
- Johnson RD, Dorr MB, Hunt TL, Jensen BK and Talbot GH (1999). Effects of food on the pharmacokinetics of sparfloxacin. *Clin. Ther.*, **21**(6): 982-991.
- Juárez-Olguín H, Flores J, Pérez G, Hernández G, Flores C, Guillé A, Camacho A, Toledo A, Carrasco M and Lares I (2002). Bioavailability of ranitidine in healthy Mexican volunteers: Effect of food. *Proc. West Pharmacol. Soc.*, **45**: 156-158.
- Kappas A, Alvares AP, Anderson KE, Pantuck EJ, Pantuck CB, Chang R and Conney AH (1978). Effect of charcoal – broiled beef on antipyrine and theophylline metabolism. *Clin. Pharmacol. Ther.*, **23**: 445-450.
- Karim S, Ahmed T, Monif T, Saha N and Sharma PL (2003). The effect of four different types of food on the bioavailability of cefaclor. *Eur. J. Drug Metab. Pharmacokinet.*, **28**(3): 185-190.
- Kawakami J, Matsuse T, Kotaki H, Seino T, Fukuchi Y, Orimo H, Sawada Y and Iga T (1994). The effect of food on the interaction of ofloxacin with sucralfate in healthy volunteers. *Eur. J. Clin. Pharmacol.*, **47**(1): 67-69.
- Koch-Weser J (1974). Bioavailability of drugs. *N. Engl. J. Med.*, **291**: 233-237, 503-506.
- Kshirsagar NA and Ankalesaria PS (1987). Effect of food on doxycycline absorption. *J. Postgrad. Med.*, **33**:117-119.
- Lecaillon JB, Hirtz JL, Schoeller JP, Humbert G and Vischer W (1980). Pharmacokinetic comparison of cefroxadin (CGP 9000) and cephalexin by simultaneous administration to humans. *Antimicrob. Agents Chemother.*, **18**(5): 656-660.
- Lee LJ, Hafkin B, Lee ID, Hoh J and Dix R (1997). Effects of food and sucralfate on a single oral dose of 500 milligrams of levofloxacin in healthy subjects. *Antimicrob. Agents Chemother.*, **41**(10): 2196-2200.
- Lehto P and Kivistö KT (1995). Effects of milk and food on the absorption of enoxacin. *Br. J. Clin. Pharmacol.*, **39**(2): 194-196.
- Mäntylä R, Männistö PT, Vuorela A, Sundberg S and Ottoila P (1984). Impairment of captopril bioavailability by concomitant food and antacid intake. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **22**(11): 626-629.
- Marathe PH, Arnold ME, Meeker J, Greene DS and Barbhaya RH (2000). Pharmacokinetics and bioavailability of a metformin/glyburide tablet administered alone and with food. *J. Clin. Pharmacol.*, **40**(12 Pt 2): 1494-1502.
- Marino MR and Vachharajani NN (2001). Drug interactions with irbesartan. *Clin. Pharmacokinet.*, **40**(8): 605-614.
- Marzo A, Dal Bo L, Wool C and Cerutti R (1998). Bioavailability, food effect and tolerability of S-naproxen betainate sodium salt monohydrate in steady state. *Arzneimittelforschung.*, **48**(9): 935-940.
- Mattok GL and McGilveray IJ (1973). The effect of food intake and sleep on the absorption of acetaminophen. *Revue Canadienne de Biologie*, **32**: 77-84.
- Melander A, Stenberg P, Liedolm H, Schersten B and Wahlin-Boll E (1979). Food induced reduction in

- bioavailability of atenolol. *Eur. J. Clin. Pharmacol.*, **16**: 327-330.
- Melander A (1978). Influence of food on the bioavailability of drugs. *Clin. Pharmacokinet.*, **3**(5): 337-351.
- Melander A, Danielson K, Hanson A, Rudell B, Schersien B, Thulin T and Wahlin E (1977a). Enhancement of hydralazine bioavailability by food. *Clin. Pharmacol. Ther.*, **22**: 104-107.
- Melander A, Danielson K, Schersten B, Thulin T and Wahlin E (1977b). Enhancement by food of canrenone bioavailability from spironolactone. *Clin. Pharmacol. Ther.*, **22**: 100-103.
- Nomeir AA, Mojaverian P, Kosoglou T, Affrime MB, Nezamis J, Rodwanski E, Lin CC and Cayen MN (1996). Influence of food on the oral bioavailability of loratadine and pseudoephedrine from extended-release tablets in healthy volunteers. *J. Clin. Pharmacol.*, **36**(10): 923-930.
- Panchagnula R, Rungta S, Sancheti P, Agrawal S and Kaul CL (2003). *In vitro* evaluation of food effect on the bioavailability of rifampicin from antituberculosis fixed dose combination formulations. *Farmaco*, **58**(11): 1099-1103.
- Pargal A, Kelkar MG and Nayak PJ (1996). The effect of food on the bioavailability of ibuprofen and flurbiprofen from sustained release formulations. *Biopharm. Drug Dispos.*, **17**(6): 511-519.
- Peloquin CA, Namdar R, Dodge AA and Nix DE (1999a). Pharmacokinetics of isoniazid under fasting conditions with food, and with antacids. *Int. J. Tuberc. Lung Dis.*, **3**(8): 703-710.
- Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, Childs JM and Nix DE (1999b). Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. *Antimicrob. Agents Chemother.*, **43**(3): 568-572.
- Peloquin CA, Bulpitt AE, Jaresko GS, Jelliffe RW, James GT and Nix DE (1998). Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. *Pharmacotherapy*, **18**(6): 1205-1211.
- Prescott LF (1974). Gastrointestinal absorption of drugs. *Med. Clin. North Am.*, **58**: 907-916.
- Rosenblatt JE, Barrett JE, Brodie JL and Kirby WMM (1966). Comparison of *in vitro* activity and clinical pharmacology of doxycycline with other tetracyclines. *Antimicrob. Ag. Chemother.*, **6**: 134-141.
- Scheiner J and Altemeier WA (1962). Experimental study of factors inhibiting absorption and effective therapeutic levels of declomycin. *Surg. Gynec. Obstet.*, **114**: 9.
- Shah A, Liu MC, Vaughan D and Heller AH (1999). Oral bioequivalence of three ciprofloxacin formulations following single-dose administration: 500 mg tablet compared with 500 mg/10 mL or 500 mg/5 mL suspension and the effect of food on the absorption of ciprofloxacin oral suspension. *J. Antimicrob. Chemother.*, **43**(Suppl A): 49-54.
- Sifton DW (2000) (ed.). Physicians Desk Reference. Medical Economics Company, Inc., Montvale, N.J., pp.1346-1349.
- Sindhu S, Malhotra S and Garg SK (2004). Influence of high fat diet (butter) on pharmacokinetics of phenytoin and carbamazepine. *Methods Find Exp. Clin. Pharmacol.*, **26**(8): 634-638.
- Song JC and White CM (2002). Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: An update. *Clin. Pharmacokinet.*, **41**(3): 207-224.
- Sostek MB, Chen Y and Andersson T (2007). Effect of timing of dosing in relation to food intake on the pharmacokinetics of esomeprazole. *Br. J. Clin. Pharmacol.*, **64**(3): 386-390.
- Spiers ASD and Malone HF (1967). Effect of food on aspirin absorption. *Lancet*, **i**: 440.
- Staniforth DH, Clarke HL, Horton R, Jackson D and Lau D (1985). Augmentin bioavailability following cimetidine, aluminum hydroxide and milk. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **23**(3): 154-157.
- Stockley IH (1991). Drug interactions, 2nd Edn., Blackwell Scientific Publications, Oxford, pp.43, 150-151, 313.
- Thomson AB, Sinclair P, Matisko A, Rosen E, Andersson T and Olofsson B (1997). Influence of food on the bioavailability of an enteric-coated tablet formulation of omeprazole 20 mg under repeated dose conditions. *Can. J. Gastroenterol.*, **11**(8):663-667. Comment in: *Can. J. Gastroenterol.*, **11**(8): 655-656.
- Vasu S, Adithan C, Shashindran CH, Asad M, Koumaravelou K and Topno I (2000). Effect of two types of Indian breakfast on bioavailability of cefuroxime axetil. *Indian J. Med. Res.*, **112**: 104-108.
- Verbeeck RK, Richardson CJ and Blocka KL (1986). Clinical pharmacokinetics of piroxicam. *J. Rheumatol.*, **13**(4): 789-796.
- Wagner JG (1977). Drug bioavailability studies. *Hosp. Pract.*, **12**: 119-127.
- Welling PG (1984). Interactions affecting drug absorption. *Clin. Pharmacokinet.*, **9**(5): 404-434.
- Welling PG (1977). How food and fluid affect drug absorption. *Postgrad. Med.*, **62**: 73-82.
- Wood JH (1967). Effect of food on aspirin absorption. *Lancet*, **ii**: 212.
- Zmeili S, Hasan M, Najib N, Sallam E, Deleq S and Shubair M (1996). Bioavailability and pharmacokinetic properties of 2 sustained-release formulations of diclofenac sodium, Voltaren vs inflaban: Effect of food on inflaban bioavailability. *Int. J. Clin. Pharmacol. Ther.*, **34**(12): 564-570.