Research Article

Are all types of food safe with prescribed medicines? A study of potential food-drug interactions in patients attending Medicine OPD

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Abstract

Background: In this era of polypharmacy in chronic disease such as hypertension and diabetes, there are more chances of food-drug interactions. Significant food-drug interaction can cause failure of drug therapy or serious adverse effect to patient.

Objective: To assess the potential food-drug interaction (pFDI) patients attending Medicine outpatient department (OPD) at a tertiary-care teaching hospital in Valsad, Gujarat, India.

Materials and Methods: The prescriptions of patients attending Medicine OPD were analyzed for demography of patients and pFDI. Freely available Drug Interaction Checker on Internet was used to analyze pFDI. Interactions were classified major, moderate, and minor according to severity and by their mechanism as pharmacokinetic or pharmacodynamic types. Statistical analysis was done using appropriate Microsoft Excel.

Result: A total of 300 prescriptions were collected from study site; from those, 253 prescriptions were included in our study. From these, 128 (50.59%) were from male patients and 125 (49.41%) from female patients. The number of drugs prescribed to the individual patient was 4.4 ± 1.48 (range, 2–12). The frequency of pFDI per patient was 0.97 ± 1.03 (range, 0–5). The number of pFDI increased with increase in the age of patients and the number of drugs prescribed. Among 253 patients, 149 (59%) patients showed at least one pFDI, and 104 (41%) patients did not show pFDI. Among 243 pFDIs, 26 (10.69%) were pharmacodynamic and 217 (89.30%) pharmacokinetic types. In this study, four (1.65%) interactions were major, while those with moderate and minor severities accounted for 173 (71.19%) and 66 (27.16%), respectively.

Conclusion: In this study, it was found that most of pFDIs were pharmacokinetic in nature and of moderate severity. Physician should be aware of significant food-drug interaction with food consumed by local community.

KEY WORDS: Potential food-drug interaction (pFDI), pharmacokinetic food-drug interaction, pharmacodynamic food-drug interaction, grapefruit juice

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Introduction

In our society, there is a great misbelief that natural products are always safe. But, sometimes food and herbs may interact with medicine, which can cause failure of drug therapy or produce serious side effects in patients. Nowadays, polypharmacy in diabetes, hypertension, and other diseases make patients prone to food-drug interaction.[1]

Food-drug interaction can affect either pharmacodynamics or pharmacokinetics of drugs. Few examples of pharmacokinetics interactions are: Digoxin is a well-known medicine used in heart failure patient and its absorption from gastrointestinal tract is affected by dietary fibers. The absorption of alendronate, a drug used in osteoporosis, is significantly affected by food. Broad spectrum antibiotic tetracycline's absorption is affected by dairy products. Various flavonoids in grapefruit juice (GFJ) inhibit metabolism of a large number of drugs and produce serious interactions. Food such as pickled fish, aged cheese, beer, and red wine contain high concentrations of tyramine, which produce hypertensive crisis in patients on nonselective monoamine oxidase inhibitors.[2] Lithium and sodium compete for tubular reabsorption; so, high salt diet increases excretion of lithium.[3] Pharmacodynamic interaction is seen with green leafy vegetables such as broccoli and spinach, which have high contents of vitamin K that can affect action of warfarin.[4]

Elderly patients may be at a greater risk for food-drug interactions, because they typically consume more medications for their chronic medical conditions. A study of drug-nutrient interactions in long-term care facilities found a significant relationship between the number of medications consumed and the number of drug-nutrient interactions for which a resident was at risk.[5]

There are few review articles available on significant food-drug interactions.[6,7] If we are aware of such potential food drug interactions (pFDIs) in our patients, then it can be of great help for rational drug therapy. So, this study was planned with the aim of detecting pFDIs in Medicine outpatient department (OPD) patients. Moreover, this study can be useful to advise patients who are prone to develop food-drug interactions.

Materials and Methods

This was a cross-sectional, observational study and was conducted among the patients attending Medicine OPD of a tertiary-care teaching hospital in Valsad, Gujarat, India. This study was started after obtaining ethical clearance from the institutional ethics committee. The study period was from July 2013 to September 2013, during which the data were collected. Patients visiting Medicine OPD for treatment were included in the study after written informed consent. Patients who refused to give consent were excluded from the study. Only one prescription from each patient during his/her visit in the OPD during the study period was included. Information about patient's demographic profile, diagnosis, and information about prescribed drugs were collected. The data were analyzed by using the online freely available Food-Drug Interaction Checker.[8] This interaction checker provides infor mation about pFDIs with prescribed drugs. It also informs about its severity, management, and monitoring parameters with scientific references. Statistical analysis was done using appropriate statistical software (MS Excel).

Classification of Potential Food-Drug Interaction

1. According to the mechanism, pFDIs were classified as: (a) pharmacokinetic and (b) pharmacodynamic.
2. According to severity, pFDIs were classified as: (1) major, the effects are potentially life-threatening or capable of causing permanent damage; (2) moderate, the effects may cause deterioration in patient's clinical status and additional treatment or extension of hospital stay; and (3) minor, the effects are usually mild. Consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome.
3. Pharmacokinetic pFDIs were further classified as either increase/decrease in: (a) absorption, (b) distribution, (c) metabolism, and (d) excretion.
4. Pharmacodynamic pFDIs were further classified as: (a) synergistic or (b) antagonistic.

Result

A total of 300 prescriptions were randomly collected during the study period from Medicine OPD. Of those, 253 prescriptions were included, and others were removed because of illegible writing. Among 253 prescriptions, 128 (50.59%) were from male patients, and 125 (49.41%) were from female patients. The mean age of patients in our study was 43.50 ± 15.63 years. The most common diagnosis of patients was hypertension (19.41%), followed by upper respiratory tract infection (14.29%) and diabetes (11.36%).

Potential Food-Drug Interactions

On evaluation, the number of drugs prescribed to the individual patient was 4.4 ± 1.48 (range, 2–12). The frequency of pFDI per patient was 0.97 ± 1.03 (range, 0–5). Among 253 patients, 149 (59%) patients showed at least one pFDI, and 104 (41%) patients did not show pFDI. A direct correlation was observed between the age of the patient and the number of pFDI ($r = 0.38$, $P < 0.01$), between the age of the patient and the number of drugs prescribed ($r = 0.18$, $P < 0.01$), and between the number of drugs prescribed and the number of pFDI ($r = 0.58$, $P < 0.01$). Few commonly observed pFDIs in our study are shown in Table 1.

Classification of pFDI

The pFDIs seen in our study were classified based on their mechanisms such as pharmacodynamic or pharmacokinetic. Among 243 pFDIs, 26 (10.69%) were pharmacodynamic and 217 (89.30%) pharmacokinetic types [Figure 1]. The severity of pFDI was classified as major, moderate, and minor. Of the 243 pFDIs, the majority were of moderate severity. In our study, four (1.65%) interactions were major, while those with moderate and minor severity accounted for 173 (71.19%) and 66 (27.16%), respectively [Figure 2].

Table 1: Commonly observed potential food drug interactions (pFDIs)

Drug	Food	Total pFDI
Atenolol	Orange juice	47
Amlodipine	Grapefruit juice	34
Ferrous sulfate	Ascorbic acid	31
Alprazolam	Grapefruit juice	31
Atorvastatin	Grapefruit juice/oat bran/pectin	25
Theophylline	Caffeine	12
Enalapril	Potassium	11
Propranolol	High protein food	11
Aluminum hydroxide	Citrate containing food	4

Table 2: Common CYP450 microsomal enzymes involved in pFDI

Enzyme	Drug	Food	No. of pFDI	Total pFDI
CYP3A4	Amlodipine	Grapefruit juice	34	79
	Alprazolam	Grapefruit juice	31	
	Losartan	Grapefruit juice	7	
	Ergotamine	Grapefruit juice	3	
	Albendazole	Grapefruit juice	2	
	Lumefantrine	Grapefruit juice	2	
CYP1A2	Theophylline	Caffeine	12	12
CYP3A5	Atorvastatin	Grapefruit juice	25	25

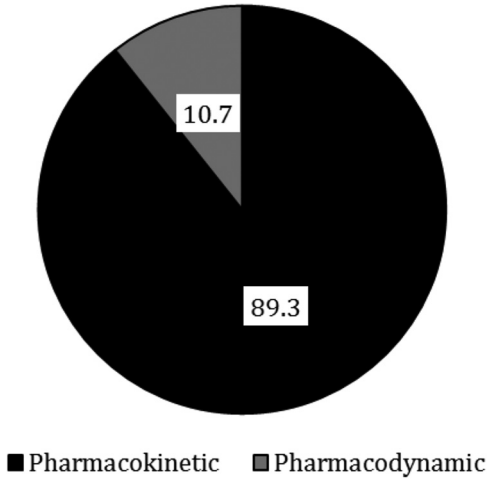

Figure 1: Classification of pFDI (according to mechanism).

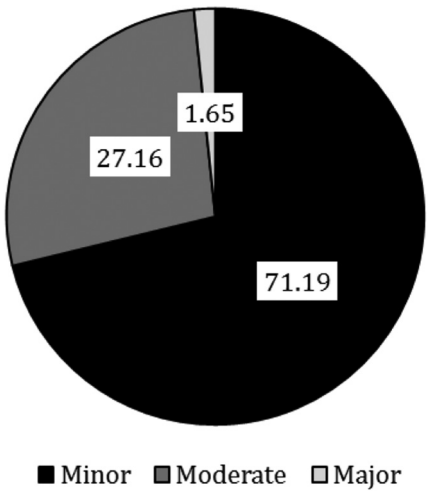

Figure 2: Classification of pFDI (according to severity).

Pharmacokinetic Interaction

Of the 217 pharmacokinetic pFDIs found, four (1.84%) were major, 147 (67.74%) moderate, and 66 (30.41%) minor severities. From these, 217 pharmacokinetic pFDIs, 53.51% were affecting absorption (12.41% increase and 87.59% decrease absorption), 41.78% were reducing metabolism, and 4.69% were decreasing excretion [Figure 3]. Few commonly responsible CYP450 microsomal enzymes affecting metabolism in pFDI in our study were mentioned in Table 2. In our study, CYP3A4 (followed by CYP3A5 and CYP1A2) was a commonly responsible microsomal enzyme for pFDI. The most common pharmacokinetic pFDI observed in our study was between atenolol and orange juice, which reduces absorption of atenolol.

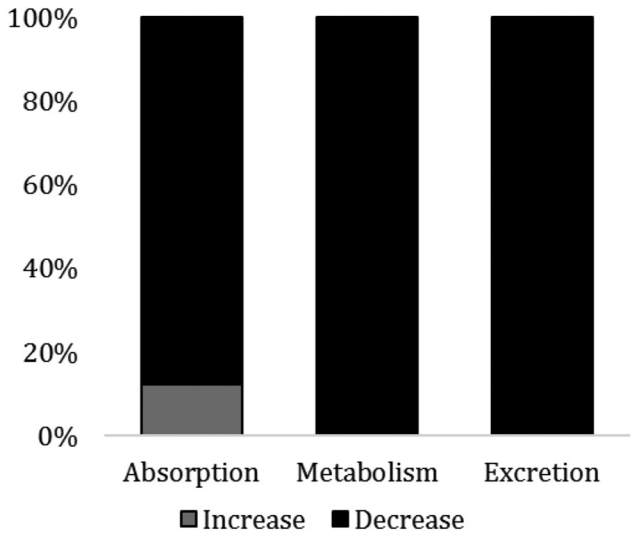

Figure 3: Mechanism responsible for pharmacokinetic pFDI.

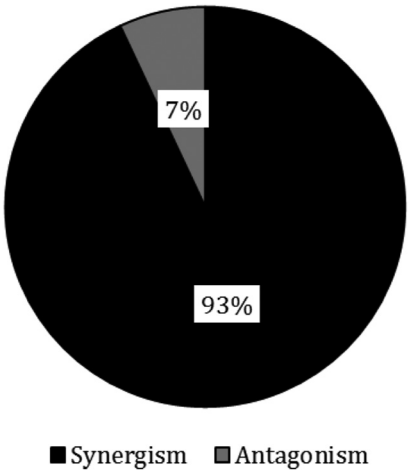

Figure 4: Mechanism responsible for pharmacodynamic pFDI.

Pharmacodynamic Interactions

Among these 26 pharmacodynamic pFDIs, all were moderate in severities. Moreover, most of them were synergistic (97%) in nature; very few were antagonistic (7%) in nature [Figure 4]. The most common pharmacodynamic pFDI was between enalapril and high content potassium foods.

Discussion

Diet and lifestyle sometimes show significant impact on drug. Drug-food interaction may be accidental and mostly because of lack of awareness on physician's part. Some commonly used herbs, fruits, and alcohol may cause failure of drug therapy and serious side effects.

In this study, it was found that 59% patients were prone to develop various types of food-drug interactions, and incidence of pFDI was approximately one per patient in this study. The number of drugs prescribed per patient was 4.4, which was lower than other studies.[9,10] There was a direct correlation found between age of patients and numbers of drugs prescribed; similar results were found in other studies.[11] Similar linear correlation was found between number of drugs prescribed and number of pFDI in this study. With increase in age of patient, there was similar increase in prescribed drugs, which may be the reason for increase in number of pFDIs.

In this study, the most common pFDI was between atenolol and orange juice, of moderate severity, which reduced absorption. There are few studies that showed food-drug interaction with antihypertensive drugs. Studies mentioned that antihypertensive drugs can be benefited from sodium restricted diet.[12] The intestinal absorption of celiprolol (beta-blocker) is inhibited when it is taken with orange juice. Hesperidin, present in orange juice, is responsible for the decreased absorption of celiprolol.[7] Licorice extract, common ingredient of dietary supplement, contains glycyrrhizin and glycyrrhetinic acid and can cause potent inhibition of 11-beta hydroxysteroid dehydrogenase. Thus, it increases mineralocorticoid activity, which can affect antihypertensive drugs action.[13] Studies showed that a daily consumption of glycyrrhizic acid of 95 mg or more caused an increase in blood pressure.[14] Another common interaction was seen between amlodipine and GFJ, of minor severity, which was synergistic in nature. Studies showed that GFJ can produce various food-drug interactions. GFJ can inhibit P-glycoprotein activity, and it can inhibit various CYP3A microsomal enzymes.[15,16] Furanocoumarins and active bioflavonoids present in GFJ are also inhibitors of organic anion transport proteins (OATP), and, when ingested concomitantly, can reduce the oral bioavailability of the OATP substrate, fexofenadine.[17] Various flavonoids present in GFJ are identified as esterase inhibitors, of which kaempferol and naringenin are shown to mediate pharmacokinetic drug interaction with most of the calcium channel antagonist and the statin groups of drugs such as enalapril and lovastatin due to their capability of esterase inhibition.[18] The overall exposure of some drugs can be increased by more than fivefold when taken with GFJ and increase the risk of adverse effects.[15] Result shows pFDI between Ferrous sulfate and foods containing ascorbic acid. This is because ascorbic acid helps in absorption of iron. In this study, it was observed that interaction between alprazolam and GFJ was moderate in severity. Study mentioned that GFJ is contraindicated in patients taking psychotropic drugs, and doctor should advice about it to patients.[19] The pFDI with atorvastatin and GFJ (moderate severity), oat bran, and pectin was also observed. Concomitant administration of statins with food may alter statin pharmacokinetics or pharmacodynamics, increasing the risk of adverse reactions such as myopathy or rhabdomyolysis or reducing their pharmacological action. Consumption of pectin or oat bran together with lovastatin reduces absorption of the drug, while alcohol intake does not appear to affect the efficacy and safety of fluvastatin treatment.[20] Another commonly observed interaction is between theophylline and caffeine (moderate severity).

High fat meal increase and carbohydrate meal reduce absorption of theophylline. Eating or drinking large amounts of foods and beverages that contain caffeine (e.g., chocolate, colas, coffee, and tea) should be avoided as theophylline is a xanthine derivative, and these substances also contain xanthine. Hence, consuming large amounts of these substances while taking theophylline increases the risk of drug toxicity.[7] GFJ also produces interaction with theophylline and reduces its absorption.[21] There was an interaction observed between propranolol and high protein diet (moderate severity). A study mentioned propranolol serum levels may be increased if taken with rich protein food. A change in diet from high carbohydrates/low protein to low carbohydrate/high protein may result in increased oral clearance.[22] In this study, the major pFDI was found between aluminum hydroxide of antacid and citrate-containing foods. One study mentioned that concomitant administration of aluminum-containing product such as antacids with citrate-containing food increase absorption of aluminum and increase serum concentration of aluminum 4.6–50 folds, which produce serious side effects. Patients with renal insufficiency were prone to develop hyperaluminemia and encephalopathy. Patients with renal failure or on hemodialysis may also be at risk from soft drinks and effervescent dispersible drug formulation that contain high concentration of citrate or citric acid.[23]

The result in this study showed that most of pFDIs were because of pharmacokinetic interaction and moderate severity. Pharmacokinetic interactions were mostly affecting bioavailability of drugs, followed by affecting drug metabolism and excretion of drugs. Few studies mentioned pFDI affecting absorption of drug because of chelating agent in food or physiological response of body to food, which increase or decrease gastric acid secretion.[24,25] Among pFDI affecting metabolism of drugs in our study, majority affect CYP3A4 enzyme, followed by CYP3A5 and CYP1A2. That was because CYP3A4 enzyme is the most common microsomal enzyme involved in drug metabolism. The most common pFDI affecting CYP450 enzyme was amlodipine interaction with GFJ, which reduces metabolism of amlodipine. Various studies showed that GFJ can inhibit CYP3A activity.[26] Furanocoumarins present in GFJ inhibit the intestinal CYP3A4 and have been shown to increase the oral bioavailability of medications that are CYP3A4 substrates such as felodipine, midazolam, and cyclosporine and raise their concentrations above toxic levels.[27]

In this study, most of the pharmacodynamic interactions were synergistic in nature; only very few were antagonistic in nature. Commonly seen pharmacodynamic interaction was with enalapril and high potassium-containing food. The reason for that is enalapril can cause hyperkalemia, which produce synergistic action with potassium-containing food.

Limitation

There are a few limitations of this study. This study was cross-sectional, observational type, but prospective study can be planned in future for in-depth understanding of the topic with more sample size.

Conclusion

In this study, overall incidence of pFDI in Medicine OPD patients was 59%. The majority of pFDIs was pharmacokinetic in nature and showed moderate severity. GFJ was found prone to produce various food-drug interactions in our study. So, foods which can produce food-drug interaction should be avoided, and patients should be properly informed about such interaction. Prescribing doctors should be well aware about food-drug interaction with locally used foods. Seminar can be organized about local food-drug interactions.

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