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Review Article

ANTIMICROBIAL DRUG ADMINISTRATION AND FOOD TIMINGS: CLINICO-PHARMACOLOGICAL CONSIDERATIONS

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ABSTRACT: Food may alter the extent or rate of absorption through various mechanisms, but not all pharmacokinetic effects are clinically relevant. Understanding the possible clinical implications of taking a drug with or without a meal is important for achieving its quality use. Although the effect of food is not clinically important for many drugs, there are food-drug interactions which may have adverse consequences. These interactions can be avoided by taking the medicines with consideration of the time of taking meals.

Key words: Antimicrobial drugs, Food timings, Pharmacokinetic effects, Food-drug interactions.

INTRODUCTION

Should the medicine is to be taken with food or without food? This is a very common question propounded by patients initiated on a new therapy. Factors influencing drug administration with regard to food or meal timings include, pharmacokinetics, drug efficacy, improving patient outcomes by minimizing gastrointestinal intolerance.To obtain optimum clinical benefit, it is very important to obtain a suitable synergy between pharmacokinetics and pharmacodynamics of drugs (Grannell 2019). Pharmacokinetics deals with what the body acts with drug whereas pharmacodynamics deals with what drugs do with the body (Palleria *et al*. 2013). To get optimum results with antibiotics, we need a better understanding of their pharmacokinetics and pharmacodynamics. When to administer antibiotics in relationship to the food timing? To answer this question we have to go through the pharmacokinetics of the drug specially focusing on the drug absorption.

ABSORPTION OF DRUGS AND FOOD INTAKE

Absorption is defined as movement of drugs from its site of administration to a compartment where it needs to present to produce desired action (Caldwell *et al*. 1995). Clinicians are more accustomed with the term 'Bioavailability' than 'Absorption'. Bioavailability is defined as the fraction of drug that reaches to its site of action or a biological fluid from which the drug has access to its site of action (Mayersohn 1987). Food interferes with bioavailability of the drug. Antibiotic dosage timing with relationship with food is thus important for its bioavailability. In general, a drug's bioavailability will be more if we administer it in empty stomach. However, some exceptions exist (Melander 1978). But the problem is with gastrointestinal adverse effects which can yet be reduced if we administer it after giving food. Food-drug interaction may lead to decrease the effectiveness of the drug, increase the intensity and incidence of adverse drug reaction and occurrence of new side effects (Alomar 2014). The present review discusses few antimicrobials and their varied behaviour based on food timings.

Sulfonamides

This group of drugs is absorbed rapidly from the gastrointestinal tract (almost 70-100%), except locally acting sulfonamides. Within 30 min of oral intake these drugs can be found in urine (Levison and Levison 2009). This group of drugs does not cause much food-drug interaction but as there is a chance of crystalluria, patient needs adequate hydration. Sulfamethoxazole and Sulfadiazine are two most commonly used sulfonamide antimicrobial agents. For sulfadiazine it is mandatory to

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maintain at least 1200 ml of urine output in adults otherwise need $NaHCO_3$ co-administration to prevent crystalluria.

Trimethoprim

In high dose it may increase serum potassium level. Special caution is hence required in renal compromised patients, concomitant hyperkalemic drug users and patients with hyperkalemia. Potassium rich foods should better be avoided in patients on high dose of trimethoprim (Perazella 1997). Though trimethoprim impairs phenylalanine metabolism, in clinical practice it has been seen to be insignificant in phenylketonuric patients if they are on appropriate dietary restriction (high protein foods, such as dairy products, meat, fish, chicken, eggs, beans, and nuts) (MacDonald *et al*. 2020).

Fluoroquinolones

Food does not impair oral absorption of fluoroquinolones but may delay the time to peak serum concentrations (Levison and Levison 2009). Ciprofloxacin, moxifloxacin and levofloxacin can be taken before or after food. Levofloxacin oral solution would be taken one hour before food or two hours after food. Oral absorption of fluoroquinolones is decreased by the presence of divalent (calcium rich food likes cheese, milk, yogurt, dark leafy vegetable etc.) and trivalent cations. Aluminium, calcium, magnesium, iron rich foods decrease the bioavailability of fluoroquinolones. Therefore, oral fluoroquinolones should be taken 2 hours before or 4 hours after any products containing these cations (Levison and Levison 2009). Fluoroquinolones increase the concentration of caffeine in the blood and enhance stimulation of CNS, an effect generally observed in heavy coffee users. It is thus better to avoid caffeine containing drinks like coffee, soda, and chocolate in patients taking fluoroquinolones (Lubasch *et al*. 2000). Caution should be exercised while administering in professional athletes. Apart from high risk of adverse tendon injury outcomes, fluoroquinolones may increase the concentration of caffeine in their blood as they take plenty of caffeine containing health drinks. Thus the chance of dope test positivity surfaces if one takes fluroquinolones and caffeine concomitantly. It is always better to take fluroquinolones without food if it is not producing gastrointestinal side effects.

Nitrofurantoin

Nitrofurantoin, a rapid and almost completely absorbed drug from gastrointestinal tract has no significant drug food interaction. As it causes gastrointestinal adverse effects it is advised to be consumed after meal. Urine alkalinizer reduces the antimicrobial effect of nitrofurantoin. Intake of alkali mixture is better to be avoided (Yang *et al*. 2014). To minimize the gastrointestinal adverse effects macrocrystalline preparations are better choices.

Penicillin V and other oral penicillins (dicloxacillin, ampicillin and amoxicillin)

Presence of food hampers absorption of all penicillins. Except amoxicillin, all other oral penicillins are better to administer 1-2 hours prior or 2-4 hours after taking food.

Cephalosporin

Cefaclor concentration is decreased if taken with food, but there are no significant drug food interaction data with other cephalosporins (cefixime, cefpodoxime, cefuroxime and cephalexin) (McLachlan and Ramzan 2006).

Tetracyclines

Percentage of absorption after oral administration of tetracycline is 60-80%, doxycycline is 95% and minocycline is 100% (Valentín *et al*. 2009). This drug would exert best outcome if given in empty stomach, one hour before meal and two hours after meal with one full glass of water. But if these drugs produce some gastrointestinal adverse effects it should be given after meals. Absorption of these drugs is impaired by the concomitant presence of divalent and trivalent cations like calcium, magnesium, iron, aluminium due to chelation of drugs with these cations and formation of insoluble compound (Valentín *et al*. 2009). Dairy products should not be used with tetracyclines. Minocycline and doxycycline are less affected by dairy products than tetracycline. Adverse drug reaction related to gastrointestinal tract like nausea, vomiting, loose motion can be minimized by administering food or carboxymethylcellulose along with the drug. But food should be devoid of divalent and trivalent cations (McLachlan and Ramzan 2006).

Macrolide

Erythromycin absorption is however less altered by food, though it's better to consume it in empty stomach. If gastrointestinal upset occurs, then it requires administration with low fat meals or snacks. Grapefruit juice increases its bioavailability. It is better to avoid concomitant use of erythromycin and grapefruit juice as it may potentiate dangerous drug-drug interaction with other drugs (Järvinen *et al*. 1992). Clarithromycin is

absorbed rapidly from the GI tract after oral administration, but due to first pass metabolism, bioavailability is less (60%). It can be given with or without food, but while administering extended release once daily preparation, it is better to administer clarithromycin with food to increase its bioavailability. Azithromycin is a rapidly absorbed and well tolerated macrolide. It is better to administer azithromycin one hour before or two-hours post meal (McMullan and Mostaghim 2015). Concomitant administration of divalent and trivalent cations like aluminium and magnesium may reduce peak serum drug concentration of azithromycin, but not its overall bioavailability (McMullan and Mostaghim 2015).

Clindamycin

It is well absorbed orally. Food in the stomach does not interact with its absorption. So, it can be administered irrespective of food timing.

Linezolid

Linezolid is well absorbed orally and may be given with or without food. Tyramine containing food should be restricted in patients receiving linezolid. Patients taking tyramine more than 100 mg per 24 hours and linezolid may experience serotonin syndrome, characterized by palpitations, headache, or hypertensive crisis. Tyramine is present in cheese, yogurt, beef or chicken liver, dry sausage (including genoa salami, hard salami, pepperoni, and lebanon bologna), caviar, dried or pickled herring, anchovies, meat extracts, avocados, bananas, canned figs, dried fruits (raisins, prunes), raspberries, overripe fruit, sauerkraut, soy beans and soy sauce, yeast extract (including brewer's yeast in large quantities), broad beans (fava) and excessive amounts of chocolate. Alcohol also should be avoided. Many alcoholic beverages like red wine contain tyramine. In patients taking both adrenergic and serotonergic agents (like SSRI), more vigilant approach should be taken to prevent serotonin syndrome (Manfredi 2006).

Antitubercular drugs

Ethambutol can be taken before or after food. Isoniazid, rifampicin and pyrazinamide should be taken in empty stomach with a full glass of water. For better compliance Revised National TB Control Program (RNTCP) prescribes all four anti tubercular drugs should be taken in empty stomach. Patient on antitubercular drugs should also restrict tyramine rich food as it may lead to serotonin syndrome (Kumar *et al*. 2017). Alcohol should be prohibited during antitubercular drug therapy because it may potentiate isoniazid related hepatotoxicity. Foods with histamine including skipjack, tuna, and other tropical fish interacts with isoniazid and produce headache, sweating, palpitations, flushing, and hypotension. Isoniazid is a potent inhibitor of histaminase. High histamine content of skipjack and the interference by isoniazid with the metabolism of the amine plays complementary actions to over produce histamine. Histamine rich foods should be avoided in patients receiving antitubercular drugs, especially isoniazid (Kumar *et al.* 2017).

Antiprotozoal drug

Metronidazole produces disulfiram-like reactions (abdominal distress, vomiting, flushing, or headache) if they drink alcohol during or within 3 days of therapy patients with this drug. Patients should thus be warned to avoid drinking alcohol during metronidazole therapy (Alonzo *et al*. 2019). Tinidazole, ornidazole, secnidazole also exhibit a similar type of disulfiram-like reaction. Satranidazole however, does not produce disulfiram-like reaction with alcohol. Metronidazole produces metallic taste and food does not impair its bioavailability, so it is better to administer it after meal (Ogata *et al*. 1986).

Antifungal agents

Fluconazole, itraconazole, posaconazole, voriconazole, griseofulvin, and terbinafine are commonly prescribed oral antifungals. Itraconazole works better if we administer it after a full meal (Lewis 2011). Posaconazole is advised to be taken with meals, within 20 minutes of eating a full meal, or with a liquid nutritional supplement. Voriconazole is better absorbed in empty stomach. Griseofulvin absorption increases when taken with fatty foods. It interacts with alcohol and causes palpitation, flushes (Lewis 2011).

CONCLUSION

Drug-food interaction is a very important factor to achieve optimum result. Prescriber should be regularly updated regarding their knowledge on appropriate drug timing and counsel the patients accordingly. To improve therapeutic outcomes, patients must thoroughly understand the appropriate timing of doses relative to food intake and time of day.

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