

Let's Keep an Eye on Food-Drug Interaction

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Abstract

The interference between food and drugs is known for ages and it is part of the basic curriculum in the faculties of pharmacy. Still we can state that this problem is more complex as daily meals are very different in size and composition. We address some examples in this article and point out that the problem is in generalization. Due to several influencing parameters in drug pharmacokinetics as well as pharmacodynamics the prediction of food-drug interactions is very difficult. It is essential to understand that interaction is usually just a potential that will come true (ie. appears in perceivable and clinically significant manner) when all above mentioned circumstances are wrong.

Keywords: Drug; Food; Interaction; Pharmacokinetics; Pharmacodynamics

Introduction

Counselling drug-drug interactions is a daily task of pharmacists as patients expect guiding in taking their medicine. Drug-drug interaction is a fairly simple situation because in this case mutual activities of one well defined molecule and an other also familiar molecule are studied with well established methods of chemistry, pharmacology (*in vitro* and *in vivo* experiments) and clinical pharmacology (human studies). Study the interaction of three-four or more drugs is much more complex task therefore such studies are scarcely seen in the scientific literature. The interference between food and drugs is known for ages and it is part of the basic curriculum in the faculties of pharmacy. Still we can state that this problem is more complex as daily meals are very different in size and composition. Most textbooks for medical doctors as well as for pharmacists contain short description of the top 5 to 10 food-drug interactions but there are problems with these examples, too. First of all since we eat food and not food components. And in most cases the amount of a food component in the food is not fixed moreover the ingested dose is also very different. Thus one can just approximately predict the effect of food on drugs. However in certain cases this can be of significance as well. In this minireview we will address some main points of the topic.

General Overview

Nutrient components of food can basically affect drug effects in 3 ways: via incompatibilities, via pharmacokinetics and pharmacodynamics.

a) In case of incompatibility (special form of interaction) the any component of food stuff and the medicine molecule binds together and results in an insoluble compound. The classical example is here the calcium content of dairy products and tetracyclines. In this case the antimicrobial tetracycline can not be absorbed and is not able to express its systemic antibacterial effect [1]. Similar - clinically relevant - interaction has been detected between the dairy products and bivalent/trivalent cation contained dietary supplements and ciprofloxacin and cefuroxime. Here should be mentioned that bioaccessibility is a very important parameter in drug effects: it is the fraction of compounds that is released from pharmaceutical dosage form (and also from food products!) and is available for absorption. Incompatibilities (inclusive food-induced incompatibilities) often hinder the bioaccessibility [2]. Nevertheless on the whole, real incompatibilities are rare with food products.

b) The pharmacokinetic interactions are, in contrast, the most abundant interactions. This type of interactions can be positive and negative as well. It means food components can enhance or hinder the movement of medical molecules in the body during

the phase of Absorption, Transport, Metabolism And Excretion (ADME). In case of oral drug administration absorption and metabolism (biotransformation) are the main targets of food-born kinetic interactions. Cytochrome P 450 enzymes (predominant phase-I enzymes present in the intestinal system, the liver and many other organs) are the most often affected by exogenic agents found in the food and plant-derived beverages, as well. The maximum plasma concentration (C_{max}), the time to reach the maximum plasma concentration (T_{max}) and the area under the concentration-time curve (AUC) are the main parameters to describe pharmacokinetic behaviour of a compound. AUC is often referred to as Bioavailability (BA) because AUC actually quantifies the BA. Bioavailability means the proportion of drug or food-component that can be utilized for restoring (medicine) or keeping (food) the normal (healthy) body functions [3].

c) Pharmacodynamic interactions are visualized as influenced drug action. They usually disturb drug molecule-drug receptor binding but recently more and more mechanism of action reveal genomic background, ie. gene-expression and production of receptor-proteins are influenced consequently too much or too few receptors are present to develop drug action. Classical example is warfarin, that antagonize the action of vitamin-K (originated from food). Vitamin K (VK) derivate vitamin K hydroquinone (VKH_2) is an essential component of the blood-clotting cascade (coagulation). In a well-balanced patient the dose of warfarine and the concentrations of VK and VKH_2 are in harmony that ensure the blockade of blood clot formation. Should we give extra vitamin-K into this system (as food-supplement or VK-containing vegetables like kale, spinach, broccoly, sauerkraut, etc.), the balance is lost and coagulation will come into overweight nsequently thrombus occurs. In some cases pharmacodynamic and pharmacokinetic interactions are present side by side, and the situation is more complex.

Problems with the Appreciation of Food-Drug and Drug-Food Interactions

Food-drug and drug-food interference do exist. Some of the interferences will result in pharmacological interaction, ie. the participating molecules (both exogenous and endogenous) will influence their biological action. In case of food where there are a lot of micro- and macromolecules present within one „unit”, the actions are as good as unpredictable. Actual variety (quality) and quantity of ingredients will define the result and, these parameters are dependent in case of fruits and vegetables on breed, soil, climate, season, storage, processing etc . At times we know the interaction-

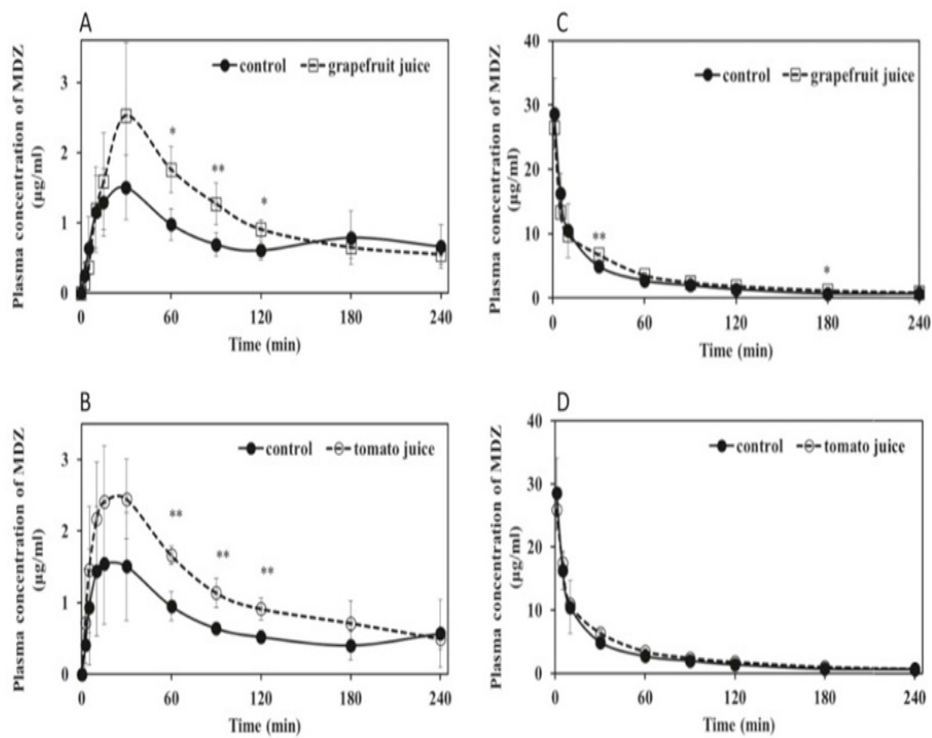
potential of the ingredients but we are far enough from full mapping of the pharmacological potentials of the ingredients. The point is to understand that interaction is usually just a potential that will come true (ie. appears in perceivable and clinically significant manner) when all above mentioned circumstances are wrong.

Practical Examples to be Considered

Pharmacokinetic interactions are among the most often experienced influence of food and food compounds on drugs. Their impact is, however very different. Biotransformation of drug molecules is the main way of detoxification, which is usually coupled with the declining of drug effect. But there are - in smaller proportion - certain medications (called prodrugs) where the metabolism resulted in more effective drug, too.

Food-induced modifications in drug action are as already mentioned difficult to predict. In certain cases the effect of food-ingredients were discovered and more or less tested. Such examples are part of basic curriculum, however the examples might be misleading or give unsubstantiated feeling of safety. Let's take some examples.

The mostly cited example for influencing pharmacokinetics by food is the grapefruit juice. Since 1989 we know that this juice (more precisely some of its ingredient) is an enzyme inductor that enhances metabolism of drugs being substrates of cytochrome-P450 (CYP) enzymes. Often mentioned results are the increased C_{max} , time to action and AUC of drugs used for blood pressure control, hypnotics, antihistamines, etc. The fact, that eg. tomato juice can produce similar effect, is not really known and distributed in the public. A recent study of Ohkubo et al. [3] demonstrates that tomato juice is as strong inhibitor as the grapefruit juice (Figure 1/AB.), whereupon pharmacological effect of the midazolam increases, first of all due to the increased T_{max} and AUC. The referred study also demonstrate using different routes of administration (intraduodenal vs. intravenous) that the inhibition takes place in the intestinally located CYP-450 isoenzymes (mainly CYP 3A4) not in the liver (Figure 1/CD). Furthermore a figure of an other study performed by Watson et al. [4] depict the interactions of colchicine and grape fruit or orange juice (Figure 2). One can see that Sevilla orange juice is more potent inhibitor of biotransformation via CYP3A4 than grape fruit juice. Continuing the examples of grapefruit juice, one should not forget about the differences of virtually similar products. In fact the qualitative and quantitative composition of the food product determines the biological effect. The study of Goosen [5] displays well the CYP3A4 inhibitory activity of the grapefruit juice depending on the bergamottin-content (Figure 3).



Figures 1(A-D): Effect of Grape Fruit Juice and Tomato Juice on Plasma Concentration of Midazolam after Intraduodenal (1A And 1B) and Intravenous (1C And 1D) Administration. Figure Originated from Reference [3].

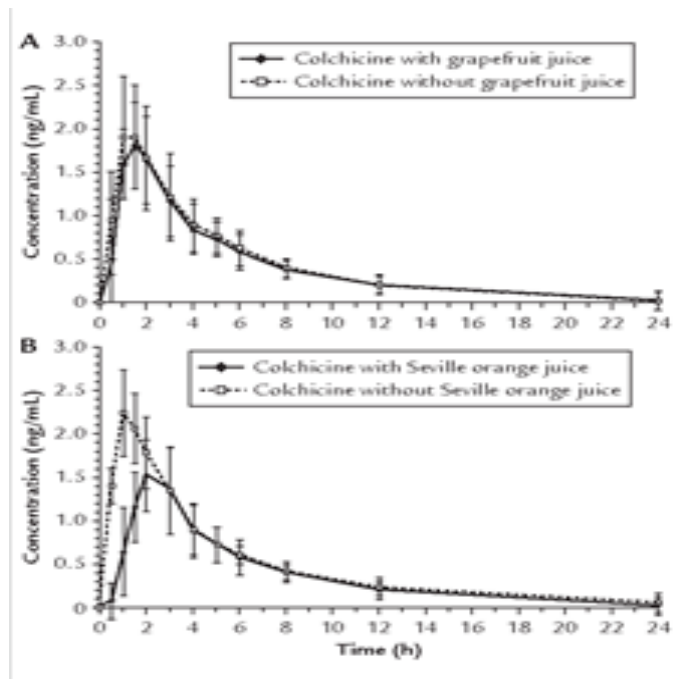


Figure 2: Effect of Grape Fruit (2A) and Seville Orange Juices on Colchicine Plasma Concentration. Original Figure Stems from Reference [4].

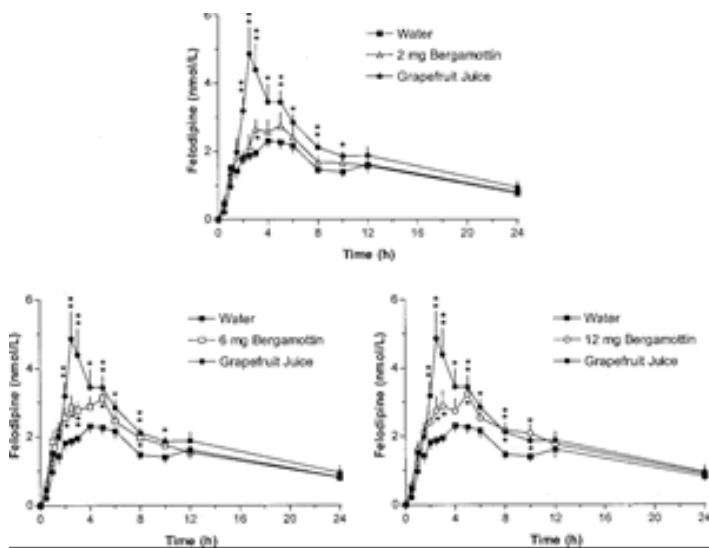


Figure 3: Effect of Bergamottin-Content on the Felodipine Serum Concentration Original Figure Stems from Reference [5].

(Bergamottin is a furanocoumarine-derivate typically present in grapefruit juice expressing strong inhibitory action on CYP 3A4.). Grapefruit juice augment colchicine intestinal absorption by inhibition of efflux transport rather than metabolizing enzymes. Similar effect has been discovered in case of grapefruit juice and aliskiren, too, but the interaction with felodipine results in potentially serious side-effects due to narrow therapeutic index of the drug [6,7]. Finally the polymorphism of the CYP450 system must be mentioned that basically influence all above mentioned metabolic reactions and explains majority of the inter-individual differences in these interactions [8].

All afore mentioned examples demonstrate that proper counseling on food-drug interactions needs a careful judgement of the participants as well as the circumstances.

2. Pharmacodynamic interactions appear in a wide variety in everyday life (vitamin K containing vegetables and warfarin-type anticoagulants, tiramin containing food and MAO inhibitor therapy, etc.) but most notable findings were recently registered in the field of molecular-pharmacology. Vitamin A can modulate lipid-metabolism of the mitochondria, vitamin B₆ influences Ca-channels in the cell membrane, acrylamides in french fries alter dopamine transporters, etc. Recently phytotherauectic agents affecting intestinal and hepatocellular transporters were summarized [9].

Fatty acids are main ingredients of food. By eating fatty food we take up several fatty acids that in original form or after conversion to other fatty acids will enter into the endogenous fatty acid metabolism. Arachidonic acid (C_{20:4}) which is in high proportion in chicken, duck, beef, eggs, etc. plays a pivotal

role in the biosynthesis of prostanoids. But the main part of metabolites of linoleic acid (C_{18:2}) present in canola and sunflower oils, is Arachidonic Acid (AA), too. The AA metabolism via transformation on lipoxygenase pathway results in leukotriens C₄, the cyclooxygenase pathway results in prostaglandines of groups G₂ and prostacyclin I₂ furthermore thromboxan A₂, finally biotransformation with the CYP-450 enzymes results (in part) in EETs (Epoxy-Eicosatrienoic Acids) and HETEs (Hydroxy-Eicosatetraenoic Acids), inclusive the 20-Hidroxy-Eicosatetraenic Acid (20-HETE) (Figure 4).

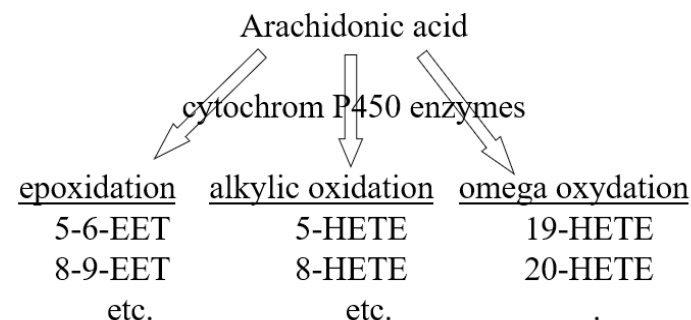


Figure 4: Cytochrom P450 Mediated Metabolic Pathway of Arachidonic Acid.

The first receptors of the last compounds were discovered last year by Garcia et al. [10] in the vascular system. Now we have one more explanation on the negative vascular effects of the n-6 fatty acids as 20-HETE exert direct vasoconstrictor effect as well as antagonize the vasodilaltator effect of nitric oxyde. 20-HETE also participate in the remodelling of vascular wall in hypertonic patients. But it should be known that CYP450 enzymes are targets of omega-3 fatty acids [11]. It means by modification of dietary intake of n-6/n-3 PUFA ratio people can influence the metabolism of several compounds running through CYP transformation. The alterations we can set up by diet in molecular level, influence the pharmacological action of drugs ordered for treatment of various illnesses. An other example: the substrates of eg. the multidrug-transporter P-glycoproteins are dozens of drugs including nifedipine, verapamil, clarithromycin, sertraline, paroxetine, omeprazole, esomeprazole etc. And the food that influences the drug action by alteration of this transport-system are garlic, green tea, curcumin, black pepper, etc. All these small pieces of information show how people can influence their own healt by selection of food.

Conclusion

In our days there are a lot of legends about the interactions between food and drugs. These chit-chats have some grounds but the knowledge behing are usually very sloppy. Generalization

about the interaction potential of food ingredients must be made with caution because large, strong studies are usually missing. To learn more about the reality further basic research is being done like recent discovery of the new metabolic pathway of arachidonic acid via CYP 450 system and the receptor of one of its metabolites 20-HETE. By the help of translational medicine these findings can be introduced into public health using the bench to bedside” concept. And randomized controlled clinical studies are also needed that determine clinical significance of particular food-drug interactions. Moreover studies must be made with wide range of well separated and/or standardized ingredients in order to draw exact conclusions from the results. This was the point in case of grapefruit juice when researchers revealed the multiple mechanism of interactions (various inhibition of the CYP450 enzymes in different locations and the inhibition of cell membrane transporters OATP, P-gp, etc.). On the other hand the complexity and quantity of food must be taken in account if effect of nutrients on drugs must be predicted. Let's keep in mind: keep an eye on potential food-drug interactions and eat accordingly.

References

1. Neuvonen PJ (1976) Interactions with the absorption of tetracyclines. *Drugs* 11: 45-54.
2. Rein MJ, Renouf M, Cruz-Hernandez C, Takkar SK, da Silva Pinto M, et al. (2012) Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. *Brit J Clin Pharmacol* 75: 588-602.
3. Ohkubo A, Chida T, Kikuchi H, Tsuda T, Sunaga K, et al. (2017) Effect of tomato juice on the pharmacokinetics of CYP3A4-substrate drugs. *Asian J Pharmaceut Sci* 12: 464-469.
4. Wason S, DiGiacinto JL, Davis MW (2012) Effects of grapefruit and Seville orange juices on the pharmacokinetic properties of colchicine in healthy subjects. *J Clin Ther* 34: 2161-2173.
5. Goosen TC, Cillié D, Bailey DG, Yu C, He K, et al. (2004) Bergamottin contribution to the grapefruit juice -felodipine interaction and disposition in humans. *Clin Pharmacol Ther* 76: 607-617.
6. Rabello S, Zhao S, Hariry S, Dahlke M, Alexander N, et al. (2011) Intestinal OATP1A2 inhibition as a potential mechanism for the effect of grapefruit juice on aliskiren pharmacokinetics in healthy subjects. *Eur J Clin Pharmacol* 68: 697-708.
7. Dahan A, Amidon GL (2009) Grapefruit juice and its constituents augment colchicine intestinal absorption: potential hazardous interaction and the role of P-glycoprotein. *Pharm Res* 26: 883-892.
8. Preissner SC, Hoffmann MF, Preissner R, Dunkel M, Gewiess A, et al. (2013) Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. *PLOS ONE* 8: e82562.
9. Murtaza G, Ullah N, Mukhtar F, Nwazish S, Muneer S, et al. (2017) Phytotherapeutics: the emerging role of intestinal and hepatocellular transporters in drug interactions with botanical supplements. *Molecules* 22: 1699.
10. Garcia V, Gilani A, Shkolnik B, Pandey V, Zhang FF, et al. (2017) 20-HETE signals through G-protein-coupled receptor GPR75 (Gq) to affect vascular function and trigger hypertension. *Circ Res* 120: 1776-1788.
11. Arnold C, Markovic M, Blossey K, Wallukat G, Fischer R, et al. (2010) Arachidonic acid-metabolizing cytochrome P450 enzymes are targets of ω -3 fatty acids. *J Biol Chem* 285: 32720-32733.