

Revisión

Interactions between antiarrhythmic drugs and food

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Abstract

Objective: A drug interaction is defined as any alteration, pharmacokinetics and/or pharmacodynamics, produced by different substances, other drug treatments, dietary factors and habits such as drinking and smoking. These interactions can affect the antiarrhythmic drugs, altering their therapeutic efficacy and adverse effects. The aim of this study was to conduct a review of available data about interactions between antiarrhythmic drugs and food.

Methods: The purpose of this review was to report an update of the existing literature data on the main findings with respect to food and antiarrhythmic drugs interactions by means of a search conducted in PubMed, which yielded a total of 250 articles initially.

Results: After excluding different articles which were not focusing on the specific objective, the main results refer to interactions among antiarrhythmic drugs and food in general, grapefruit juice, and others like fibre or medicinal plants.

Discussion: Food may affect the bioavailability of antiarrhythmic drugs and in some specific cases (dairy products, rich-in-protein diets, grapefruit juice), this should be carefully considered. The best recommendation seems to advise patients to remove the grapefruit juice from their diet when treatment with these drugs. Fibre should be separated from taking these drugs and regarding medicinal plants and given their increased use, the anamnesis must include information about its use, the reason for that use and what types of plants are used, all in order to give the corresponding recommendations.

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Key words: *Antiarrhythmic drugs. Food-drugs interactions. Grapefruit juice. Medicinal plants. Fibre. Diet.*

INTERACCIONES ENTRE FÁRMACOS ANTIARRÍTMICOS Y ALIMENTOS

Resumen

Objetivo: La interacción de medicamentos se define como cualquier alteración, farmacocinética y/o farmacodinámica, producida por diferentes sustancias, otros tratamientos, factores dietéticos y hábitos como beber y fumar. Estas interacciones pueden afectar a los fármacos antiarrítmicos, alterando su eficacia terapéutica y sus efectos adversos. El objetivo de este estudio fue realizar una revisión de los datos disponibles acerca de las interacciones entre los fármacos antiarrítmicos y los alimentos.

Métodos: El objetivo de esta revisión fue realizar una actualización de los datos de la literatura existente sobre los principales resultados con respecto a las interacciones entre alimentos y fármacos antiarrítmicos por medio de una búsqueda realizada en PubMed, que arrojó un total de 250 artículos inicialmente.

Resultados: Tras la exclusión de diferentes artículos que no estaban centrados en el objetivo específico, los resultados principales se refieren a las interacciones entre los fármacos antiarrítmicos y alimentos en general, el zumo de pomelo y otros como plantas medicinales o fibra.

Discusión: Los alimentos pueden afectar a la biodisponibilidad de los fármacos antiarrítmicos y en algunos casos específicos (productos lácteos, dietas ricas en proteínas, zumo de pomelo), este aspecto debe ser considerado cuidadosamente. La mejor recomendación parece ser que los pacientes supriman el zumo de pomelo en su dieta cuando están en tratamiento con estos fármacos. La fibra debería ser separada de la toma de estos medicamentos y en relación con las plantas medicinales y dado su creciente uso, la anamnesis debería incluir información sobre dicho uso y la razón del mismo, y qué tipo de plantas se utilizan, todo ello con el fin de dar las recomendaciones correspondientes.

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Palabras clave: *Fármacos antiarrítmicos. Interacciones entre alimentos y medicamentos. Zumo de pomelo. Plantas medicinales. Fibra. Dieta.*

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Introduction

Cardiac arrhythmias are one of the leading causes of morbidity and mortality in developed countries with a constant presence in medical practices, often urgently and associated with cases of sudden death. Typically, however, is that patients consult by symptoms resulting from arrhythmia and required therapeutic interventions.¹

Antiarrhythmic drugs (AD) are substances capable of interrupting an arrhythmia, preventing its recurrence or mitigating its clinical consequences, through its effects on automaticity and conduction in cardiac tissues. Antiarrhythmic drugs are potent modifiers of the hearth electrical properties for their effects on the ion exchange through the cells' membranes (directly or through its action on β -adrenergic, muscarinic or adenosine receptors). This modifying ability makes AD have a therapeutic window to be considered in order to prevent that AD become producers of arrhythmias.¹

Antiarrhythmic drugs are divided into sodium channel blockers of intermediate, fast and slow kinetic (IA, IB and IC), beta-receptor inhibitors (II), potassium channel blockers (III), calcium channel blockers (IV), digoxin and adenosine.² Actual plasma concentration of the AD is relatively important, because low concentrations can exert a therapeutic effect or toxic, being much more important to consider the response of the patient and the specific arrhythmia. The margin between therapeutic and toxic threshold of the AD is quite narrow, which can lead to serious complications in drug concentrations that only slightly exceed the necessary amount to produce therapeutic effects. Therefore a proper dosage and the knowledge of its pharmacokinetic characteristics are very important.³

In relation to the bioavailability of the AD it is necessary to emphasize the importance of cytochrome P450 (CYP), a family of enzymes located in the liver and gastrointestinal tract, which represents the major source of metabolic activity for the phase I reactions. Among the up-to-date 30 known isoforms of CYP, those with the most cardiovascular interest are CYP3A, CYP2D6, CYP1A2, CYP2C19 and CYP2C9. With regards to the use of other drugs and food intake, the presence of CYP inducers and CYP inhibitors is remarkable, so the association of AD with other drugs and/or foods that use the CYP for their metabolism can be toxic. Both CYP3A and CYP1A2 are highly variable in their expression in the general population. CYP enzyme activity has a Gaussian distribution in the population, with a majority of individuals with intermediate activity and a minority with very low or very high activities. Besides CYP, P-glycoprotein (P-gp), a family of membrane transporters, which is located in the brush border of the enterocytes membrane, should be noted, due to its metabolic importance. In addition to mobilizing endogenous substances, the P-gp mobilizes certain drugs including some AD.^{4,6}

A drug interaction is defined as any alteration, pharmacokinetics and/or pharmacodynamics, produced by different substances, other drug treatments, dietary factors and habits such as drinking and smoking.⁷ These interactions can affect the AD, altering their therapeutic efficacy and adverse effects.

The aim of this study was to conduct a review of available data about interactions between AD and food.

Method

The review was conducted through a PubMed search. The initial search term was "Interactions between antiarrhythmic drugs and food," which resulted in a total of 244 articles. Later, a specific search was performed, by entering "Interactions between... (name of specific drugs)... and food," and including acebutolol, amiodarone, atenolol, bidisomide, celiprolol, digoxin, diprafenone, disopyramide, dronedarone, felodipine, metoprolol, penticainide, procainamide, propranolol, ramipril, talinolol, timolol, and verapamil. Thus six additional articles were obtained that were not among those found with the initial search. As a result, we obtained a total of 250 articles, excluding those that do not make specific reference to the object of the review. Articles without an abstract were also excluded. With respect to case reports and letters, because of the scarcity of articles focusing specifically on a subject, some of them were considered. Apart from the articles included after the search, some other articles and/or chapters were considered due to its relevance.

Results

Interactions between AD and food in general

Among the documented food-AD interactions associated with lidocaine, a group-IB drug, with locking action on the sodium channel, a fast kinetic and which acts without affecting or shortening the action potential duration (APD) must be noted. Lidocaine has a high hepatic first pass effect, so its bioavailability is increased when taken with food. Elvin et al., showed that the hepatic clearance of lidocaine increased from 1,245 to 1,477 ml/min after food ingestion. It was also found that the intake did not influence the drug protein transport (the free fraction was 0.305 ± 0.027 in the case of participants after fasting and 0.321 ± 0.042 after food intake). The authors concluded that increased hepatic clearance was stimulated by the hepatic blood flow after food ingestion. The result was the saturation of the enzymes responsible for this clearance with increased bioavailability of the drug when taken orally with food.⁸

In the case of propafenone, an increased bioavailability related with food intake has been described.

This group-IC AD, with locking action of the sodium channel, slow kinetic and does not affect or lengthens the APD, has a similar structure to propranolol and an important first-pass metabolism.⁹⁻¹¹ In this regard, two different phenotypes are considered, being known as slow and fast metabolizers.¹² Comparing the bioavailability of propafenone taken after fasting or after food intake, Axelson et al., noted that the maximum plasma concentration increased and was reached before with food. Excluding cases of slow metabolizers, the increase in the area under the curve (AUC) reached 147% after food ingestion with breakfast. In slow metabolizers the bioavailability was not affected.¹³ The difference lies in the effect of a higher blood flow related with food intake. In the case of slow metabolizers, the slow hepatic metabolism makes the result similar with or without food, most of the drug reaching the circulation without being metabolized in the liver.

With respect to diprafenone, a group-IC AD without specific beta-antagonist action, Koytchev et al., reported an increase of 50% in bioavailability when taking the drug with food, the effect being similar in fast and slow metabolizers.¹⁴ With regard to flecainide, another group-IC AD, approximately 27% is eliminated in urine unchanged. In this regard, urinary elimination decreases with urine alkalinizing diets.¹⁵ It must also be noted that a lower absorption of flecainide with the intake of milk has been observed, with a consequent increased risk of toxicity after removing milk from the diet.¹⁶ Respecting to food in general and the use of antacids such as aluminum hydroxide, it does not seem to affect the bioavailability of flecainide (oral or intravenous).¹⁷

Penticainide, another group-IC AD, taken with food does not appear to affect bioavailability,¹⁸ as occurs with procainamide, a group-IA AD.¹⁹ Studies with disopyramide and bidisomide, group-I AD, show that while the former does not change its bioavailability, the second is affected significantly when administered with food, finding which has been linked to the different absorption of the drug depending on the intestinal tract region. Specifically, the permeability of bidisomide is lower, especially in the ileum, and its absorption appears to be inhibited by the presence of glycine, and glycine-glycine and glycine-proline dipeptides.²⁰⁻²²

Among beta-blockers (group-II), bevantolol bioavailability is not affected when administered with food,²³ whereas the absorption and the maximum concentration (C_{max}) of acebutolol and its major metabolite, diacetolol, are slightly decreased but without clinical significance.²⁴ Metoprolol is one of the AD that its bioavailability is increased when administered with a high-protein diet. Amino acids reduce the maximum rate of elimination (V_{max}) of metoprolol and its metabolites α -hydroxy-metoprolol and O-dimethyl-metoprolol, thereby increasing their bioavailability. The enzymatic inhibition caused by the amino acids (reduction of first-pass metabolism) as well as a limita-

tion of co-substrate (NADPH or oxygen) have been invoked as possible mechanisms involved.²⁵ With respect to metoprolol, neither bioavailability nor absorption are affected when using sustained release forms.²⁶ In regard to propranolol, with the use of sustained release forms its bioavailability is not affected.²⁷ This AD does seem exhibit differences in its bioavailability depending on diet composition. Thus, a rich-in-proteins diet substantially increases the bioavailability due to the amino acids inhibitory action on the liver enzymatic system,²⁸ whereas high-in-carbohydrates diets and poor-in-protein diets do not appear to affect bioavailability. In studies with artificial membranes, maltooligosaccharides delay the transport of propranolol and pectines produce a similar effect by decreasing its esterification.^{29,30} Furthermore, the exposure to food (seeing and smelling it but without intaking it), both in animal and human studies, has shown to be able to increase the bioavailability of propranolol.³¹ Regardless of a specific composition of the diet, it has been noted that the administration of propranolol simultaneously with food may increase its bioavailability by up to 50% due to saturation of first-pass system. However, comparing the effect of an experimental oral, intra-arterial or portal (thus bridging the intestinal barrier) administration of glucose, some interaction glucose-propranolol before the liver step has been observed.³² Finally, on the basis of its potential antiarrhythmic effects, also in animal experiments, it has been suggested that garlic (*Allium sativum*) may increase the bioavailability of propranolol.^{33,34} Finally, the bioavailability of timolol seems to not be affected when administered with food.³⁵ Some interactions between beta-blockers and food are shown in table I.

Regarding dronedarone, a multichannel blocker AD (benzofuran derivative of amiodarone), it has been noted that strong CYP3A4 inhibitors may increase its C_{max} while CYP3A4 inducers reduce its concentration.³⁶ With regard to amiodarone (a group-III AD,

Table I
Some interactions between beta-blockers and food

Drug	Food	Bioavailability	Clinical effect
Acebutolol	General	Decrease	No
Bevantolol	General	No changes	No
Diacetolol	General	Decrease	No
Metoprolol (SR)	General	No changes	No
Metoprolol	HPD	Increase	?
Propranolol	General	Increase	?
Propranolol	HPD	Increase	?
Propranolol	HCHD, LPD	No changes	No
Propranolol (SR)	General	No changes	No
Propranolol	Garlic	Increase	?
Timolol	General	No changes	No

HCHD: High-in-carbohydrates diet; HPD: High-in-protein diet; LPD: Low-in-protein diet; SR: Sustained release.

potassium channel blocker), an experimental high-fat meal does not affect the intestinal presystemic formation of desmetilamiodarone, its active metabolite.³⁷

Felodipine (a group-IV AD, calcium channel blocker) has a delayed absorption when administered by sustained release forms along with food, which is attributed to increased drug retention in the stomach.³⁸ With respect to verapamil (a group-IV AD, calcium channel blocker), a more rapid absorption by using generic drug compared with the reference drug has been found when taken with food and using sustained release forms. In addition, an absence of bioavailability changes in verapamil has been reported by taking it with rich-in-protein foods.^{39,40} The use of sustained release capsules compared with the dispersion of the content of the capsules in food has not shown significant differences on the pharmacokinetics neither of verapamil nor of norverapamil.⁴¹

With respect to digoxin (AD with inhibitory action on Na⁺/K⁺ ATPase), a pioneer work of Greenblatt et al., reported that its bioavailability could vary with respect to food, among other factors.⁴² The comparative study between digoxin and beta-methyl-digoxin (BMD) shows a higher peak serum concentration after fasting than after food intake, but this difference is significant only in the case of BMD.⁴³ The relevance of this effect was subsequently confirmed in another comparative analysis, which showed a lower peak serum concentration of BMD when administered after breakfast compared with under fasting or thirty minutes before breakfast.⁴⁴

Interactions between grapefruit juice and AD

By chance in 1989, Bailey et al., studying the influence of ethanol on the effects of felodipine and using grapefruit juice as a vehicle to mask the taste of ethanol, found that plasma drug concentrations were much higher than expected.⁴⁵ Years later, Bailey et al., indicated that grapefruit juice acted by inhibiting the drug presystemic metabolism mediated by CYP, particularly the isoform CYP3A4 in the bowel. They added that people with higher levels of CYP3A4 with liver failure and with clinical situations that predispose to increase the effects and toxicity of drugs would be more likely to suffer from the interaction of grapefruit juice with administered drugs.⁴⁶ The characteristic of grapefruit juice is to act on intestinal CYP3A4, which metabolizes more than 60% of commonly prescribed drugs, drug transporter proteins (such as P-gp) and transporter proteins of organic cations, all in the intestine. The hepatic CYP3A4 appears to not be inhibited and, on the other hand, the above-mentioned P-gp would be inhibited.⁴⁷ However, with regard to this latter mechanism, the intake of grapefruit juice with drugs effectively inhibits P-gp, but the habitual intake of grapefruit juice could increase the expression of P-gp.⁴⁸ On the other hand, flavonoids (some of them like

naringin and quercetin are present in grapefruit juice) may interfere with the P-gp not only at the binding site but also inhibiting OCT (organic cation transporter) and OAT (organic anion transporter) transport systems of the basal membrane of intestinal epithelium.^{49,50} The bioactive components of grapefruit juice are the flavonoids (flavanones, flavones, flavonols, anthocyanins), along with limonoid aglycones, glycosides, furanocoumarins (bergamottin, dihydroxybergamottin), ascorbic acid, folic acid, glucaric or saccharic acid, carotenoids, pectin and potassium. Traditionally, drug interactions have been attributed to furanocoumarins.^{47,51,52}

With regard to cardiovascular pharmacology, the fact that inactivation of CYP3A4 is irreversible, it occurs when taking 200-300 ml, and the effect of increasing the bioavailability of the drugs can occur even after 24 hours of the intake are particularly relevant.⁵³ However, action at level of CYP is not the only one caused by the components of grapefruit juice. One of the effects of naringenin, another flavonoid of grapefruit juice, seems to be to increase the inhibitory action of the potassium channel blockers AD by an inhibitory action at hERG (human-ether-a-go-go-related gene) level.⁵⁴

Considering the AD, grapefruit juice could enhance the toxicity of amiodarone, quinidine, disopyramide and propafenone.⁵⁴ With respect to interactions, none has been described for group-I AD except the above-mentioned for propafenone in terms of increased toxicity.

Among the group-II AD (beta-blockers), talinolol absorption is modified by an inhibitory action of naringin on the P-gp and the OAT system.⁵⁵ The most potent inhibitor of talinolol among the components of grapefruit juice is 6'7'-epoxy-bergamottin, followed by 6'7'-dihydroxybergamottin and bergamottin. In regard to other components, naringenine causes a more potent inhibition than naringin.⁵⁶ After the intake of a glass of grapefruit juice a reduced bioavailability of talinolol has been found as occurs with the repeated intake. The parameters affected are AUC, maximum plasmatic concentration and urinary excretion values.⁵⁷ However, the inhibitory action on the P-gp would result in an increased bioavailability.⁵⁸ With respect to acebutolol and its major metabolite, diacetolol, the intake of grapefruit juice slightly decreases plasma concentrations by interfering with intestinal absorption, without significant clinical manifestations.⁵⁹

In regard to group-III AD, grapefruit juice completely inhibits the production of N-desetilamiodarone, a product of the metabolic action of CYP3A on amiodarone, increasing the AUC and Cmax by 50 and 84% respectively, resulting in a consequent increased risk of toxicity.^{51,53,60}

Experimentally, different effects of grapefruit juice on verapamil (group-IV AD) have been observed depending on the time of intake, thus leading to plasma concentrations changes.⁶¹ However, clinical studies show a clear increase in AUC and Cmax when administering verapamil along with grapefruit juice,^{62,63}

although a previous study had shown no changes in bioavailability.⁶⁴ There are several studies on interaction between felodipine and grapefruit juice, highlighting one of the most recent that concludes that previous studies may have overestimated the effect of that interaction.⁶⁵ In the case of felodipine, an interaction at level of CYP3A4 caused by furanocoumarins of grapefruit juice (e.g., bergamotone, 6'7'-dihydroxybergamottin and naringin) with a possible role for CYP3A5 is assumed.⁶⁶⁻⁶⁹ It has been suggested that this interaction should be taken into account among elderly people⁷⁰ and that taking grapefruit juice should be separated by at least 2-3 days of the drug intake.⁷¹ In addition, the existence of interindividual variability in the effect of that interaction has been noted⁷² and also the fact that among calcium channel blockers felodipine is the one with the clearest interaction.⁷³

With regard to digoxin, the inhibition of P-gp by the grapefruit juice appears to have no significant effect.^{74,75}

Other interactions

Considering orange juice, hesperidin, one of its flavonoids, would be responsible for a lower intestinal absorption of celiprolol.⁷⁶ A moderate interference between the orange juice and absorption of atenolol has also been reported.⁷⁷ Differently, the bioavailability of celiprolol diminishes when taken along with orange juice by possible mechanisms related to pH variations and changes in the function of the transporters in the intestine.⁷⁸ The bitter Seville orange juice has an interaction with felodipine similar to grapefruit juice (inactivation of intestinal CYP3A4), but without any action at P-gp level.⁷⁹ In a comparative study with grapefruit juice and lime juice, it was concluded that interaction with felodipine is not caused by an inhibitory action on CYP3A4 bergamotone.⁸⁰ Bitter orange hesperidin increases the bioavailability of verapamil by interference at the intestinal outflow level.⁸¹

In an experimental study with digoxin, it was found that piperine (the main component of black pepper) inhibits P-gp and CYP3A4, an enzyme which could affect plasma drug concentrations especially when administered orally.⁸²

Regarding ramipril, an antihypertensive with antiarrhythmic effect, it has been found experimentally that in combination with felodipine and with a low salt diet (or potassium or magnesium alternative salts) a greater beneficial cardiovascular effect is achieved.⁸³

It is worth mentioning possible interactions with the use of various plants. For example, St. John's Wort (*Hypericum perforatum*) reduces the AUC and C_{max} of digoxin while Echinacea does not alter the pharmacokinetics of the drug.⁸⁴ The effect of St John's Wort increases when taking it longer with a decrease in AUC and C_{max} probably by induction of P-gp.⁸⁵ Milk thistle (*Silybum marianum*) and black cohosh (*Cimifuga racemosa*) do not appear to substantially affect the bioavailability of digoxin.⁸⁶

Table II
Some interactions between herbs and antiarrhythmic drugs

Herb	Drug	Effect
<i>Hypericum perforatum</i>	Digoxin	Decrease in BA
<i>Equinácea</i>	Digoxin	No changes in BA
<i>Silybum marianum</i>	Digoxin	No changes in BA
<i>Cimifuga racemosa</i>	Digoxin	No changes in BA
<i>Cassia y Rhamnus purshiana</i>	Digoxin	Potassium decrease, Toxicity increase
<i>Glycyrrhiza glabra</i>	Digoxin	Potassium decrease, Sodium retention Effect/toxicity increase
<i>Eleutherococcus senticosus</i>	Digoxin	Plasmatic levels increase
<i>Crataegus monogyma</i>	Digitalis	Sinergism
<i>Ginkgo biloba</i>	Nicardipine	Interaction with CYP3A2

BA: Bioavailability; CYP3A2: 3A2 isoform of cytochrome P450.

Similarly, licorice (*Glycyrrhiza glabra*), by passing glycyrrhizin to glycyrrhetic acid (by hydrolysis and the action of intestinal beta-glucuronidase) may increase the effect of digoxin due to an effect of sodium retention and potassium depletion.⁸⁹ In addition, Siberian ginseng (*Eleutherococcus senticosus*) can cause elevated levels of digoxin^{90,91} and hawthorn (*Crataegus monogyma*) show synergy with digitalis.^{92,93} Regarding nicardipine, an interaction with the use of ginkgo (*Ginkgo biloba*) by induction of CYP3A2 isoform has been experimentally.⁹⁴ Some interactions between herbs and AD are shown in table II.

With regard to caffeine, a study has shown interaction with the use of adenosine used in the detection of coronary artery disease. Therefore, the use of medications, beverages or foods containing caffeine should be known in advance.⁹⁵

Consumption of honey from the genus *Rhododendron*, with a toxin called grayanotoxin, has resulted in a reported case of complete atrioventricular block alongside taking verapamil.⁹⁶

With respect to fibre, studies have focused on possible interactions with digoxin, having observed a reduction (6-7%) in its absorption after the administration of capsules of digoxin along with a fibre supplement, this having no clinical significance. In addition, it appears that the administration of more or less water volume does not affect the drug bioavailability.^{97,98} In geriatric patients, the possible effect of wheat bran and *Plantago ovate-Plantago isphagula* has been studied, concluding that there are not relevant changes in digoxin bioavailability.⁹⁹

In relation to vitamins, there are some controversial results. Thus, the photosensitizing action of amio-

darone is well known, and it has been reported that pyridoxine could prevent such effect. Nevertheless, it has also been noted that pyridoxine could aggravate that effect.¹⁰⁰⁻¹⁰² Furthermore, administration of 2 g of ascorbic acid affects the absorption and first pass metabolism of propranolol, producing a decrease in C_{max}, and the time to reach it, as well as a decrease of AUC, although with no clinical significance.¹⁰³

Discussion

Antiarrhythmic drugs are an essential part of medical treatment of cardiovascular disease and the response to them may vary among patients as well as in each individual patient, with potentially serious consequences. This is influenced by the interactions, either drug-drug or drug-food. Taking various and very different drugs is common and it is obvious that food shall be accompanied by the taking thereof. Sometimes that coincidence is required (for example, adherence could be improved), but occasionally may cause potentially dangerous interactions.⁵⁰

The bioavailability and effectiveness of the AD is determined mainly by the metabolism of these agents, specifically by the enzymatic system known as cytochrome P450 (CYP), among whose isoenzymes, CYP3A4 contributes to the inactivation and removal of 50-60% of drugs.^{45,104-106} This enzyme is localized at the level of epithelial cells of the small intestine (70%) as well as in the liver (30%), so that the passage of the drugs will result in the corresponding enzymatic action or first pass oxidative metabolism.¹⁰⁷ An amount of unaltered drug will undergo into the systemic circulation, in relation to the dose administered orally, which will depend on how much this enzymatic action is avoided. In any situation where the usual bioavailability is increased by a greater passage of drug into the systemic circulation, the chance of side effects and toxicity will be increased, especially for those drugs with a narrow therapeutic window. In other cases, it is not an increased blood flow which modifies the bioavailability, but an action on the CYP3A4 by means of an irreversible and inhibitory interaction at the intestinal level. Inhibition of CYP3A4 by certain foods will interfere the correct metabolism of the drug in question with a resulting increase in AUC. On the other hand, some changes in bioavailability will depend on the food action inhibiting P-gp transporter that returns a certain amount of the drug into the intestinal lumen. The inhibition of this binding protein will cause an increase in the amount of drug absorbed. Finally the action on the transport systems of organic anions and cations (OAT, OCT) have been involved in some interactions. If the P-gp returns part of the drugs into the intestinal lumen, the above-mentioned transport systems act contrary. Thus a food that selectively inhibits, for example, P-gp and OAT would cause the effect of increasing bioavailability of a drug and, secondly, its decrease.⁴⁵

Regarding the effect of the simultaneous intake of food and AD, while the pharmacokinetics of propafenone is affected only in fast metabolizers,¹³ in the case of diprafenone the increase of bioavailability would occur in all cases.¹⁴ With flecainide, the fact that milk decreases its absorption and alkalizing diets decrease its urinary excretion should be taken into account.^{5,16} Among beta-blockers, high-in-protein diets increase the bioavailability of propranolol and metoprolol^{25,26,28} (which does not occur when using sustained release forms). Felodipine administered as sustained release forms delays its absorption when given with food.³⁸ Finally, the serum concentration of beta-methyl-digoxin is reduced if given with food.^{43,44}

After consumption of grapefruit juice for about 5 days, a reduction of more than 60% of the content of CYP3A4 and CYP3A5 in the intestine has been observed, whereas hepatic CYP3A4 content remains unchanged as well as CYP3A5 in the colon and the intestinal content of CYP2D6 and CYP1A1. The fact that the reduction of intestinal content of CYP3A4 occurs only some hours after the ingestion may be relevant. Moreover, the allocation is not due to a simple competition for a substrate, but possibly accelerating the degradation of CYP3A4 by a mechanism of enzymatic inhibition. Therefore, the return of CYP3A4 activity requires a *de novo* enzymatic synthesis that would explain the prolonged effect of grapefruit juice intake.⁴⁶ With regard to grapefruit juice consumption in Spain, over 50% of consumers associate it with doing diets, especially women, and 16.4% use it frequently, especially between 56 and 65 years old. Half of those who take grapefruit do so at breakfast, usually without other foods, and almost 21% take it at mid-morning.¹⁰⁸ Given the effect of grapefruit juice, even 24 hours after ingestion, the increased bioavailability of the AD affected by the interaction and the consequent possible increase of toxicity should be taken into account by studying in detail the eating habits of patients with arrhythmias before the prescription of AD. Particular care should be taken into account in the elderly, so a proper separation of AD and grapefruit juice should be considered. Other juices, like orange juice, should be taken into account when prescribing AD, especially beta-blockers.⁷⁶⁻⁷⁹

With respect to the consumption of medicinal plants, it is noteworthy that Spain has increased the consumption dramatically over its possible therapeutic efficacy (sometimes demonstrated) and the mistaken belief about its safety.¹⁰⁹ This consumption, in most cases uncontrolled, is a potential source of interactions and toxic effects. In the case of drugs used in cardiovascular diseases, digoxin is of particular interest with respect to this type of interactions and the consequent potential adverse effects.⁸⁴⁻⁹¹ It is worth to mention that in a study on consumption of medicinal plants in Spain, 19.6% of those who were taking different medications were simultaneously using such plants, and 65% did so chronically, which facilitates interactions. Among the

consumers, a half use these plants by means of bulk products, which has also been associated with increased potential hazard.¹¹⁰

Food may affect the bioavailability of the AD and in some specific cases, such as dairy products and rich-in-protein diets, this should be carefully considered. Grapefruit juice, with unusual intake in Spain but very close to certain diets (aimed to loose weight), is the food with the highest potentiality for interactions and toxicity associated with the intake of some AD. Therefore, the best recommendation seems to advise patients to remove the grapefruit juice from their diet when treatment with AD. Fibre, which in some cases can affect bioavailability, should be separated from taking AD. Regarding medicinal plants and given its increased use, the anamnesis must include information about its use, the reason for that use and what type of plants are used, all in order to give the corresponding recommendations.

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