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Revisión

# Interactions between antihypertensive drugs and food

B. Jáuregui-Garrido<sup>1</sup> and I. Jáuregui-Lobera<sup>2</sup>

<sup>1</sup>Department of Cardiology. University Hospital Virgen del Rocío. Seville. Spain. <sup>2</sup>Bromatology and Nutrition. Pablo de Olavide University. Seville. Spain.

## 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 antihypertensive drugs, altering their therapeutic efficacy and causing toxic effects. The aim of this study was to conduct a review of available data about interactions between antihypertensive agents and food.

**Methods:** The purpose of this review was to report an update of main findings with respect to the interactions between food and antihypertensive drugs by way of a search conducted in PubMed, which yielded a total of 236 articles initially.

**Results:** After excluding different articles, which were not focusing on the specific objective, the main results refer to interactions between antihypertensive drugs and food (in general) as well as between antihypertensive agents and grapefruit juice.

**Discussion:** Food may affect the bioavailability of antihypertensive drugs and this should be carefully considered. Advising patients to remove the grapefruit juice from their diet when treatment with these drugs seems to be the best recommendation. Given these interactions and the associated potential adverse effects the anamnesis must include detailed information about the specific eating habits of the patients.

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Key words: Antihypertensive drugs. Food-drugs interactions. Grapefruit juice. Diet.

## INTERACCIONES ENTRE FÁRMACOS ANTIHIPERTENSIVOS 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 antihipertensivos, alterando su eficacia terapéutica y causando efectos tóxicos. El objetivo de este estudio fue realizar una revisión de los datos disponibles acerca de las interacciones entre los fármacos antihipertensivos y los alimentos.

**Métodos:** El objetivo de esta revisión fue proporcionar una puesta al día sobre los principales resultados con respecto a las interacciones entre alimentos y fármacos antihipertensivos mediante una búsqueda realizada en PubMed, que dio lugar inicialmente a un total de 236 artículos.

**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 y entre dichos fármacos y el zumo de pomelo.

**Discusión:** Los alimentos pueden afectar a la biodisponibilidad de los fármacos antihipertensivos y ello debe ser considerado cuidadosamente. Advertir a los pacientes que supriman el zumo de pomelo en su dieta cuando están en tratamiento con estos fármacos parece la mejor recomendación. Dadas estas interacciones y sus potenciales efectos adversos, la anamnesis debe incluir información detallada sobre los hábitos alimentarios de los pacientes.

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Palabras clave: Fármacos antihipertensivos. Interacciones entre alimentos y medicamentos. Zumo de pomelo. Dieta.

## Abbreviations

ACE: Angiotensin-converting enzyme.

ARBs: Angiotensin II receptor blockers.

**Correspondence:** I. Jáuregui-Lobera.  
Bromatology and Nutrition.  
Pablo de Olavide University.  
Virgen del Monte, 31.  
41011 Seville. Spain.  
E-mail: igjl@upo.es / ij@tcasvilla.com

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AT1 receptor: Angiotensin 1 receptor.

AUC: Area under the curve (Area under the plasma concentration time curve).

BA: Bioavailability.

BP: Blood pressure.

C<sub>max</sub>: Maximum plasma concentration.

cGMP: cyclic guanosine monophosphate.

CYP: Cytochrome P450 gene family.

DASH: Dietary Approach to Stop Hypertension.

DBP: Diastolic blood pressure.

HT: Hypertension.

IP3: Inositol triphosphate.

NaCl: Sodium chloride, common salt.

OAT: Organic anion transporter.

OCT: Organic cation transporter.

P-gp: P-glycoprotein.

SBP: Systolic blood pressure.

$t_{1/2}$ : Drug elimination half-life.

$t_{max}$ : Time after administration of a drug when the maximum plasma concentration is reached.

## Introduction

Hypertension (HT), which is defined as a chronic elevation of systolic and/or diastolic blood pressure (BP), is in all probability the most common chronic disease today. The main clinical significance of HT, which is not a disease in the usual sense of the word, lies on the future risk of vascular disease. Apart from various causes of HT, the most frequent case is the essential HT (up to 95%).<sup>1,2</sup>

In the regulation of BP, there are different involving factors (sympathetic nervous system, kidney, hormonal systems), one of them being the composition of the diet. Thus, sodium, potassium, magnesium, lipids and total energy intake influence the control of BP.<sup>3</sup> In the largest international study on the relationship between sodium and BP (INTERSALT),<sup>4</sup> the analysis of more than 10,000 participants showed that a variation of 100 mmol sodium intake modified the systolic BP (SBP) 2.2 mmHg, being lower the effect on diastolic BP (DBP). As for diet, one of the most relevant studies (DASH: Dietary Approaches to Stop Hypertension)<sup>5</sup> showed that BP levels decreased with a diet low in saturated fat, cholesterol and total fat and high in fruits, vegetables and skimmed or semi-skimmed milk, that is a diet rich in magnesium, calcium, potassium, protein and fibre. In a later study (DASH-sodium),<sup>6</sup> it was observed that with any level of sodium, the greatest reduction in BP was achieved with the DASH diet and even better with a sodium intake of only 1,500 mg of sodium per day.

Regarding the treatment of HT, it is correct when its continued efficacy is proven and it has minimal side effects. The goal is to achieve and maintain a SBP below 140 mmHg and a DBP below 90 mmHg.<sup>7</sup> Apart from general measures of treatment (stress management, moderate salt restriction, regular exercise and moderate reduction of other risk factors)<sup>8</sup> there is a full arsenal of antihypertensive drugs: diuretics, alpha and beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and others such as sodium nitroprusside, monoxidine, hydralazine and minoxidil.

With regard to the bioavailability (BA) of antihypertensive drugs, it is noted the importance of the cytochrome P450, a family of enzymes (encoded by the gene CYP) located in the liver and gastrointestinal tract, which represents the major source of metabolic activity for the phase I reactions. Regarding the use of other drugs and food intake, it is remarkable the presence of inducers

and inhibitors of the CYP system, so the association of antihypertensive drugs with other drugs and/or food which use the CYP for their metabolism may be toxic. Together with CYP, it should be noted, due to its metabolic importance, the P-glycoprotein (P-gp), a family of membrane transporters located in the brush border of the enterocytes' membranes. In addition to mobilizing endogenous substances, the P-gp mobilizes certain drugs including some antihypertensive drugs.<sup>9-11</sup>

Drug interactions are defined as any alteration, pharmacokinetics and/or pharmacodynamics, produced by different substances, other drug treatments, dietary factors and habits such as drinking and smoking.<sup>12</sup> These interactions may affect the antihypertensive drugs, modifying their therapeutic efficacy and the adverse effects.

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

## Method

The review was conducted through a PubMed search. The initial search term was "Interactions between antihypertensive drugs and food," which resulted in a total of 337 articles. Later, other specific searches were performed, by entering "Interactions between loop diuretics and food", "Interactions between calcium channel blockers and food", "Interactions between ACE inhibitors and food", "Interactions between ARBs and food", "Interactions between hydralazine and food" and "Interactions between grapefruit juice and antihypertensive agents". Having excluded the repeated articles, a total of 236 articles were considered. Then those that did not make specific reference to the object of the review were rejected. 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 food and diuretics*

The simultaneous intake of food and some loop diuretics such as furosemide and bumetanide causes a decrease of the BA of these drugs, which in the case of furosemide seems to be very high (approximately 30%).<sup>13</sup> In a review, Bard et al. corroborated the existence of a decrease in the BA of loop diuretics when administered orally with food, although, only one study found a decrease in urinary excretion of these drugs after taken with food (such excretion is related to the threshold of the diuretic effectiveness)<sup>14</sup>. In rats with protein-calorie malnutrition, the BA of furosemide

significantly increased after oral administration, a fact attributable to a decrease in the metabolism of gastrointestinal and hepatic first step.<sup>15</sup> With respect to spironolactone and canrenone, its major active metabolite, food intake with simultaneous drug intake increases the BA of both drugs by increasing its absorption and possibly reducing the first pass metabolism.<sup>16,17</sup> This food intake also increases the BA of hydrochlorothiazide.<sup>18</sup> With respect to indapamide, a study has revealed that its administration in sustained release form is unaffected when taken with food.<sup>19</sup>

#### *Interactions between food and alpha- and beta-blockers*

Blockers of  $\alpha$ 1-adrenergic receptors causes a competitive and reversible blockage of those receptors, thus lessening or removing the actions of catecholamines mediated by way of the stimulation of those receptors. In regard to  $\beta$ -adrenergic blockers, these agents block competitively and reversibly the actions of catecholamines mediated by way of the stimulation of  $\beta$ -adrenergic receptors. Furthermore, some of these agents have vasodilator properties, which are associated with an increase in nitric oxide release or with the blocking of the  $\alpha$ -adrenergic receptors.<sup>20</sup>

With respect to doxazosin, the BA of a single dose of 8 mg by means of a controlled release gastrointestinal form under fasting conditions and after ingestion, and a single standard dose of 2 mg under fasting conditions have been studied comparatively. Under fasting conditions,  $C_{max}$  was similar for both presentations, with a BA of 75% in the case of the sustained release form with respect to the standard one. In the case of the sustained release form, an administration with fat-rich food leads to a  $C_{max}$  and AUC 31% and 18% higher respectively.<sup>21</sup>

Regarding indoramin, there are not any published studies with respect to its use as antihypertensive and possible drug-nutrients interactions. The same applies to prazosin from a clinical point of view.

Regarding urapidil, a pioneer study showed that food intake did not influence the BA of the drug when administered in tablet form. However, after administration by a sustained release formulation,  $C_{max}$  and  $t_{max}$  increased, whereas  $t_{1/2}$  decreased with food intake. Despite these differences, the AUC was not influenced by concomitant food intake in the case of sustained release form. In fasting, the AUC after administration of the sustained release form was 28% lower than after administration of the standard form, while food intake, with the sustained release capsule, eliminated such difference. Since the decreases of BP in hypertensive patients treated with urapidil are more pronounced in the inclined portion of the curve of serum concentration of the drug, maximizing that part of the curve, as is the case of administration of the sustained release capsule with breakfast, could be advantageous.<sup>22</sup>

In the case of prazosin, an animal experimental work has shown that its administration at the paraventricular

nucleus of the hypothalamus is able to reduce the SBP only in undernourished animals.<sup>23</sup> However, no studies concerning potential interactions between the drug and food in humans are developed.

With respect to beta-blockers, the BA of bevantolol, metoprolol when administered as sustained release form, propranolol when administered as sustained release form and timolol is not affected by the simultaneous ingestion of food.<sup>24-27</sup> In the case of acebutolol and diacetolol there is a decrease of BA when administered with food but without relevant clinical effects.<sup>28</sup> The BA of propranolol may be increased with simultaneous food intake and specifically with a high-in-protein diet. Nevertheless no relevant clinical effects have been reported.<sup>29</sup> Other diets (high-in-carbohydrates diet and low-in-protein diet) do not modify the BA of propranolol.<sup>29</sup> In addition, the simultaneous intake of propranolol and garlic increases the BA without causing clinical effects.<sup>30,31</sup> With respect to metoprolol, a high-in-protein diet seems to increase the BA but without relevant clinical effects.<sup>32</sup>

#### *Interactions between food and calcium-channel blockers*

These antihypertensive agents are drugs that reduce the tone of vascular smooth muscle and produce peripheral and coronary vasodilation, improving the coronary flow and reducing vascular resistance. There are three groups: a) dihydropyridine derivatives (nifedipine, amlodipine, nicardipine, felodipine, nisoldipine, barnidipine and isradipine), b) derived from phenylalkylamines (verapamil) and c) derived from benzodiazepines (diltiazem).<sup>20</sup>

Felodipine has a delayed absorption when administered by sustained release forms along with food, which is attributed to increased drug retention in the stomach.<sup>33</sup>

With respect to verapamil, a more rapid absorption by using a generic drug compared with the reference drug has been found when taken with food and using sustained release forms. In addition, an absence of BA changes in verapamil has been reported by taking it with rich-in-protein foods.<sup>34,35</sup> 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.<sup>36</sup>

With respect to nisoldipine, at the time of maximum plasma concentration the additional decrease in BP relative to baseline due to the food effect seems to be about 7-15% for DBP and 3-9% for DBP.<sup>37</sup> Considering nisoldipine coat-core, the concomitant use of other drugs, which may produce marked induction or inhibition of CYP3A4 is contraindicated. The concomitant intake of the coat-core tablet with high-fat, high-calorie foods results in an increase in the maximum plasma concentrations of nisoldipine. This "food-effect" can be avoided by administration of the coat-core tablet up to 30 minutes before the intake of food.<sup>38</sup>

The pharmacokinetic properties of barnidipine are unaffected by food.<sup>9</sup>

With regard to the salt, it is known that a high intake of common salt (NaCl) plays a fundamental role in the development and maintenance of HT.<sup>40,41</sup> Nevertheless, the antihypertensive effect of felodipine, a calcium channel blocker with natriuretic properties, is maintained during high salt intake, at least when given at the maximal antihypertensive dose.<sup>42</sup> Isradipine, another calcium channel blocker, decreases the sitting SBP and the sitting DBP during a high salt diet with a lowest effect during the salt restriction diets.<sup>43</sup> With respect to sodium restriction, it must be noted that calcium antagonists may have better efficacy when prescribed to salt-replete hypertensive persons.<sup>44</sup>

#### *Interactions between food and angiotensin-converting enzyme (ACE) inhibitors*

They are agents that act by blocking one of the steps in the formation of angiotensin II, a key effector of the renin-angiotensin-aldosterone system. ACE inhibitors are one of several groups of drugs capable of interfering with the renin-angiotensin-aldosterone system, others being inhibitors of renin and AT1 receptor blockers. ACE inhibitors inhibit competitively the angiotensin-converting enzyme.<sup>20</sup>

ACE inhibitors constitute a heterogeneous group of agents with pharmacologic, pharmacokinetic and therapeutic differences among them.<sup>45</sup> With respect to the classification, three groups are usually distinguished based on the existence of a sulfhydryl-, carboxyl- or phosphinyl-group.<sup>46</sup> In general, there are not any relevant food-drug interactions described for these agents.

Thus, food seems not to affect the BA of lisinopril.<sup>47,48</sup> With respect to captopril, the co-administration of food or antacids with this agent has been shown to diminish the BA of the latter and decrease its clearance, respectively. Nevertheless the decreased BA of captopril when taken with meals does not significantly alter clinical responses to the drug.<sup>49,50</sup>

Considering enalapril, its BA is not modified when taken with meals<sup>51</sup> and benazepril can be taken any time of day, with or without food, this not being relevant for its BA.<sup>52</sup>

Benazepril is rapidly converted to benazeprilat and despite foods delaying slightly the absorption of the first, the BA of the latter is not modified.<sup>53</sup> The absorption of quinapril is unaffected by food. Peak serum concentrations of quinapril and quinaprilat are achieved within one and two hours, respectively.<sup>54</sup>

Moexiprilat, the active metabolite of moexipril, has shown an extended duration of action owing to a long terminal pharmacokinetic half-life and produces a persistent ACE inhibition. Although the pharmacokinetic is partly influenced by food intake, ACE inhibition is not affected. This might be explained by a second compartment directly related to the ACE which is less prone to

food effects and the reaching of a ceiling in the sigmoidal concentration-effect curve, even with the lower  $C_{max}$  concentrations associated with the postprandial state.<sup>55</sup>

In general the BA of ACE inhibitors may be reduced by concomitant food or antacids, which may slow gastric emptying and raise gastric pH.<sup>56</sup> In the case of nifedipine, a low-fat (high-carbohydrate) meal slows the rate but does not alter the extent of nifedipine absorption. Insofar as certain side effects may be related to the high peak plasma levels associated with rapid absorption, administration with meals might serve to reduce the incidence of such effects. For the majority of patients on routine maintenance therapeutic regimens, nifedipine capsules may be administered without regard to food intake.<sup>57</sup>

#### *Interactions between food and angiotensin II receptor blockers (ARBs)*

Angiotensin II receptor blockers (ARBs) represent a class of effective and well tolerated orally active antihypertensive agents. The ARBs specifically block the interaction of angiotensin II at the AT1 receptor, thereby relaxing smooth muscle, increasing salt and water excretion, reducing plasma volume, and decreasing cellular hypertrophy. After oral administration, the ARBs are rapidly absorbed (time for peak plasma levels = 0.5-4 h) but they have a wide range of BA (from a low of 13% for eprosartan to a high of 60-80% for irbesartan). In general, food does not influence the BA, except for valsartan (a reduction of 40-50%) and eprosartan (increase).<sup>58</sup> The fact that most ARBs do not interact with food makes its oral administration very straightforward for this class of agents. Several of the ARBs, irbesartan and losartan, are metabolized by cytochrome P450 (CYP), and are therefore subject to potential drug-drug interactions with other drugs that alter CYP activity.<sup>59</sup> Despite the absence of general relevant effects of food intake on ARBs BA, foods retard the absorption and decrease the  $C_{max}$  of losartan (5-10%) and telmisartan (10-20%). In addition, foods decrease the BA,  $C_{max}$  and AUC (3,5%) of valsartan, although plasmatic concentrations are similar to those reached without food within the next eight hours. On the contrary, high-fat foods increase  $C_{max}$  and AUC of eprosartan (80% and 55%, respectively).<sup>60</sup>

Irbesartan is a specific AT1 receptor antagonist with rapid oral BA (peak plasma concentrations occurring at 1.5-2 h after administration) and a long half-life (11-15 h) that provides 24-h BP control with a single daily dose. The maximal BP fall occurs between 3 and 6 h after the dose. This antihypertensive agent is relatively unaffected by food or drugs.<sup>61,62</sup>

#### *Interactions between food and hydralazines*

Hydralazine acts directly on arteriolar smooth muscle, where it activates the guanylyl-cyclase and increases the



levels of intracellular cyclic-guanosine 3'-5'-monophosphate (cGMP). It also inhibits the release of calcium from the sarcoplasmic reticulum induced by inositol-1,4,5-triphosphate (IP3). The result is a decrease in intravascular calcium concentration, which leads to a reduction of the peripheral vascular resistances and BP, whereas venous tone is nearly unmodified.<sup>20</sup>

Hydralazine has been widely used in combination with other antihypertensive agents, particularly beta-blockers and diuretics. One of the main reasons for this combination relates to the pharmacological effects of hydralazine, such as fluid retention and reflex tachycardia. The logic behind the inclusion of a diuretic is the elimination of fluid retention, while the beta-blocker would control the tachycardia.<sup>63</sup> In a former study about the pharmacokinetics of hydralazine, the AUC and  $C_{max}$  values were much higher under the fasted and enteral infusion conditions than under the standard breakfast or enteral bolus conditions, indicating that the absorption and/or disposition kinetics of hydralazine may be altered by food. In addition the rate of administration, but not necessarily the physical form, of the nutrients appeared to be a significant factor to determine the magnitude of the food effect.<sup>64</sup>

In a former study, the peak blood hydralazine levels were reduced by food after both hydralazine and slow-release hydralazine, by 69 and 66%, respectively. Time to peak blood hydralazine concentration was delayed significantly with the slow-release form and a statistically significant food-related reduction of area under blood hydralazine concentration versus time curves (AUC) only with hydralazine (by 44%) was observed. The AUC for slow-release hydralazine was decreased only 29% by food. Authors concluded that hydralazine should be taken at a consistent time with respect to meals,<sup>65</sup> thus confirming another previous study.<sup>66</sup>

With respect to endralazine, comparing a dose of 5 mg and 10 mg after a standard breakfast, in the case of 5 mg the peak endralazine concentration averaged 57.5% lower and the AUC decreased significantly by 49.9%, whereas after 10 mg the postprandial peak level and the AUC were 82.9% and 64.7%, lower. In the 5 mg study the mean arterial BP was decreased by 30 mmHg in the fasting subjects and by 21 mmHg in the postprandial group. For the 10 mg dose the corresponding values were 35 and 24 mmHg. The BP lowering effect was only weakly correlated with the food-related reduction in the plasma endralazine levels. The results suggested that endralazine has a similar kinetic interaction with food as that found for hydralazine.<sup>67</sup>

#### *Interactions between antihypertensive agents and grapefruit juice*

In 1998, Bailey et al., indicated that grapefruit juice acted by inhibiting the drug pre-systemic metabolism mediated by CYP, particularly the isoform CYP3A4 in the bowel. In addition, they reported 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.<sup>68</sup> Grapefruit juice acts 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 (OCT), 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.<sup>69</sup> It must be noted that 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.<sup>70</sup> 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 and organic anion transporter (OAT), transport systems of the basal membrane of intestinal epithelium.<sup>71,72</sup> Grapefruit juice has different bioactive components such as flavonoids (flavanones, flavones, flavonols, anthocyanins), 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.<sup>69,73,74</sup> Inactivation of CYP3A4 seems to be irreversible, it occurs when taking 200-300 ml, and the effect of increasing the BA of the drugs, that may occur even after 24 hours of the intake, are particularly relevant.<sup>75</sup>

After having described an increase in the levels of the dihydropyridine calcium channel antagonists felodipine and nifedipine when taken with grapefruit juice,<sup>76</sup> different drugs in this antihypertensive group have been seen to interact with grapefruit juice. Thus, amlodipine, azelnidipine, benidipine, cilnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine and pranidipine. The result of the interaction is an enhancement of plasma concentration of these drugs.<sup>77-88</sup> With respect to barnidipine, minor increases in its availability may occur with concomitant use of alcohol or grapefruit juice, but these are unlikely to have clinical relevance.<sup>39</sup> Paine et al. have reported in an experimental design that furanocoumarins are the active ingredients of grapefruit juice responsible for enhancing the systemic exposure of felodipine and probably other CYP3A4 substrates that undergo extensive intestinal first-pass metabolism.<sup>89</sup> It has been suggested that felodipine-grapefruit juice interaction should be taken into account among elderly people<sup>90</sup> and that taking grapefruit juice should be separated by at least 2-3 days of the drug intake.<sup>91</sup> In addition, the existence of interindividual variability in the effect of that interaction has been noted<sup>92</sup> and also the fact that among calcium channel blockers felodipine is the one with the clearest interaction.<sup>93</sup> Finally, with respect to felodipine, one of the most recent studies concludes that previous research may have overestimated the effect of that interaction.<sup>94</sup>

In other cases, the interaction between grapefruit juice and some drugs causes a reduction of  $C_{max}$ , AUC and  $t_{1/2}$ . This is the case of aliskiren, a renin inhibitor.<sup>95</sup>

Amlodipine seems to not be affected by the concomitant intake of grapefruit juice.<sup>96</sup>

With respect to diltiazem, a single intake of grapefruit juice (250 ml) has been found to cause a slight but statistically significant increase in the systemic exposure of diltiazem. The inhibition of intestinal metabolism and/or P-gp efflux transport might be responsible for this effect.<sup>97</sup>

Considering verapamil, grapefruit juice significantly increases the AUC and the  $C_{max}$ . The increase in concentrations present for (R)- and (S)-enantiomers seems to be slightly greater for verapamil than for norverapamil.<sup>98</sup> In the study of Ho et al., it is demonstrated an interaction between verapamil and grapefruit juice, which is likely due to an inhibition of intestinal metabolism resulting in increased oral BA.<sup>99</sup> Nevertheless, certain controversy remains with respect to verapamil-grapefruit juice interaction due to the previous study of Zaidenstein et al., in which a single administration of grapefruit juice with short-acting verapamil had no significant effect on the pharmacokinetics of verapamil.<sup>100</sup>

With regard to angiotensin II receptor blockers, it must be noted that the AUC of losartan increased insignificantly when taken with grapefruit juice and the time to drug appearance in serum was prolonged. Grapefruit juice also caused a change in the pharmacokinetic properties of the pharmacologically active metabolite of losartan. The half-life of the metabolite as well as the mean retention time were significantly longer; however, the AUC was decreased. Losartan is thought to be primarily metabolized by CYP2C9, but the results of the study of Zaidenstein et al., show that grapefruit juice's effect on CYP3A4 in the gut is able to alter the pharmacokinetics of losartan.<sup>101</sup>

Among beta-blockers, talinolol absorption is modified by an inhibitory action of naringin on the P-gp and the OAT system.<sup>102</sup> The most potent inhibitor of talinolol among the components of grapefruit juice is 6'7'-epoxy-bergamottin, followed by 6'7'-dihydroxy-bergamottin and bergamottin. In regard to other components, naringenine causes a more potent inhibition than naringin.<sup>103</sup> After the intake of a glass of grapefruit juice a reduced BA of talinolol has been found as occurs with the repeated intake. The parameters affected are AUC, maximum plasmatic concentration and urinary excretion values.<sup>104</sup> However, the inhibitory action on the P-gp would result in an increased BA.<sup>105</sup> 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.<sup>106</sup> The reduced celiprolol concentrations when taken with grapefruit juice are probably caused by physicochemical factors that interfere with celiprolol absorption, although other mecha-

nisms cannot be excluded. It must be noted that the grapefruit juice-celiprolol interaction is probably of clinical relevance.<sup>107</sup>

## Other interactions

With respect to orange juice, hesperidin, one of its flavonoids, would be responsible for a lower intestinal absorption of celiprolol<sup>108</sup> and a moderate interference between the orange juice and the absorption of atenolol has also been reported.<sup>109</sup> Differently, the BA 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.<sup>110</sup> 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.<sup>111</sup> In a comparative study with grapefruit juice, lime juice and red wine, it was concluded that interaction with felodipine is not caused by an inhibitory action on CYP3A4 bergamottin.<sup>112</sup> Bitter orange hesperidin increases the BA of verapamil by interference at the intestinal outflow level.<sup>113</sup>

Peppermint oil, menthol, menthyl acetate, and ascorbyl palmitate have found to be moderately potent reversible inhibitors of in vitro CYP3A4 activity. As well as grapefruit juice, peppermint oil may increase the oral BA of felodipine by inhibition of CYP3A4-mediated presystemic drug metabolism. In the case of ascorbyl palmitate, it did not inhibit CYP3A4 activity in vivo.<sup>114</sup>

With respect to ramipril, 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.<sup>115</sup>

Regarding nicardipine, an interaction with the use of ginkgo (*Ginkgo biloba*) by induction of CYP3A2 isoform has been experimentally proven<sup>116</sup> and the 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.<sup>117</sup> In regard to vitamins, the administration of ascorbic acid seems to affect 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.<sup>118</sup>

## Conclusions

The response to antihypertensive agents may vary among patients as well as in each individual patient, with potentially serious consequences, this being influenced by some interactions, either drug-drug or drug-food. Taking various and very different drugs (antihypertensive and others) is common and 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.<sup>72</sup>

The BA and effectiveness of the antihypertensive drugs is determined mainly by the metabolism of these agents, specifically by the enzymatic system known as cytochrome P450 (CYP). The CYP system has different isoforms, CYP3A4 contributing to the inactivation and removal of 50-60% of drugs.<sup>119,120-122</sup> This isoform is localized in the 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.<sup>123</sup> 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 BA 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 BA, 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 with the correct metabolism of the drug in question with a resulting increase in AUC. On the other hand, some changes in BA 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 OAT and 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 BA of a drug and, secondly, its decrease.<sup>119</sup>

In view of the results some conclusions such as the following should be taken into account:

- The simultaneous intake of food and diuretics such as furosemide may cause a decrease of the BA of the diuretic. In the case of spironolactone and hydrochlorothiazide the BA may be increased.
- The  $C_{max}$  and AUC of doxazosin may be increased when taken with fat-rich foods.
- The administration of sustained release forms of urapidil with breakfast seems to be advantageous to achieve a better decrease of BP.
- Despite increasing the BA of propranolol when taken with a high-in-protein diet, that has not relevant clinical effects. The same applies to the use of garlic.
- Felodipine has a delayed absorption when administered by sustained release forms along with food due to more prolonged drug retention in the stomach.
- The increase of plasma concentration of nisoldipine coat-core when taken with high-fat, high-calorie foods can be avoided by administration of the drug up to 30 minutes before the intake of food.

- In general the BA of ACE inhibitors may be reduced by concomitant food or antacids, which may slow gastric emptying and raise gastric pH.

- Despite the absence of general relevant effects of food intake on the BA of ARBs, pharmacokinetics of losartan, telmisartan, valsartan and eprosartan may be changed when taken with food.

- Different studies have reported that pharmacokinetic parameters of hydralazine may be altered with food intake, so hydralazine should be taken at a consistent time with respect to meals. Similar interactions have been reported in the case of endralazine.

- The concomitant use of grapefruit juice enhances the plasma concentration of the following agents: azelnidipine, benidipine, cilnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nisoldipine, nimodipine, nitrendipine, and pranidipine. Amlodipine seems to not be affected by the simultaneous use of grapefruit juice.

- With respect to felodipine (one of the calcium channel blockers with the clearest interaction with grapefruit juice), taking grapefruit juice should be separated by at least 2-3 days of the drug intake. It must be noted that the bitter Sevilla orange juice has an interaction with felodipine similar to grapefruit juice.

- In the case of verapamil and the intake of grapefruit juice, certain controversy remains because despite increasing the AUC and the  $C_{max}$ , the study of Zaidenstein et al., had not reported significant effects on BA of verapamil when taken with grapefruit juice.

- With regard to talinolol, acebutolol and celiprolol, the simultaneous intake of grapefruit juice may reduce the BA but without relevant clinical effects.

Food may affect the BA of the antihypertensive agents and in some specific cases this should be carefully considered. Grapefruit juice is the food with the highest potentiality for interactions and toxicity associated with the intake of some antihypertensive agents as well as antiarrhythmic drugs.<sup>124</sup> Therefore, the best recommendation seems to advise patients to remove the grapefruit juice from their diet when cardiovascular treatments. 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.<sup>125</sup> Given the effect of grapefruit juice, even 24 hours after ingestion, changes in the BA of antihypertensive agents affected by the interaction and the consequent possible toxic effects should be taken into account by studying in detail the eating habits of patients with HT before the prescription of these drugs. Particular care should be taken into account in the elderly, so a proper separation of antihypertensive drugs and grapefruit juice should be considered. Other juices, like orange juice, should be taken into account when prescribing antihypertensive drugs.



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