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FOOD CONSUMPTION IN RELATION TO DRUG CONSUMPTION: ITS INTERACTIONS

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ABSTRACT

Introduction: Food-drug interactions are unknown in many cases by health professionals, which modifies their therapeutic action. **Objectives:** To provide sufficient information on the interactions that occur when administering a food when the patient is taking a drug and to prevent it from their joint consumption has clinical significance. **Material and method:** A literature review was carried out in the Medline (pubmed) databases, in the Pubmed and Scielo databases. The only filter used was language, searching only articles written in Spanish and English. All types of studies have been included except AMI with alcohol. **Results:** Out of a total of 285 articles, a total of 133 have been included in this review. Of them, 39 describe the main AMI that decrease the therapeutic effect of drugs due to various mechanisms of action and 28 the main AMI that increase the effect. drug therapy. Food-drug interactions can be inhibitors or enhancers of the therapeutic action of drugs, in many cases, these interactions can lead to the administered drug becoming toxic or, on the contrary, not exerting the expected therapeutic effect. **Discussion:** It is a subject of great study but health professionals who have a low degree of knowledge of AMI to guarantee a better therapeutic treatment. **Conclusion:** The fact that there is an interaction is not always negative and can sometimes be used for the benefit of therapy. To quickly reach high therapeutic levels, medications must be administered outside of meals with a glass of water. On the contrary, if the drugs cause gastric irritation or if you want to delay their action or achieve lower plasma levels, the drugs should be administered with food.

KEYWORDS: Interactions, foods, medications.

INTRODUCTION

Adverse drug effects and iatrogenic diseases are one of the main causes of mortality and morbidity in patients. The number of these due to drug-food interactions is not exactly known, and they receive adequate attention when their effects are clinically significant. Interactions between drugs and nutrients lead to the appearance of adverse effects due to the joint intake of both. Generally, they are associated with negative effects, although it is important to note that the interactions will not always be negative and that sometimes they can be used even for the benefit of therapy. They are considered important when the therapeutic effect and / or toxicity of the drug is modified requiring dose adjustment or change of drug when adverse effects or lack of pharmacological activity occurs. In the administration of medications, it is food that interacts the most, however this interaction is not usually of clinical importance.

The consequences of these interactions are very diverse both in the type of interaction and in the intensity and range, from a decrease in the therapeutic effect due to the presence of foods that will reduce the action of the drugs, to interactions in which the drug inhibits the action of nutrients in food (Figure 1).[1]

An interaction is considered to be of clinical importance when the pharmacological and / or toxic effect of the drug varies, such that it may not cause the expected therapeutic effect or even cause toxicity.

The first descriptions of these interactions date back to the 20th century, referring to the effects produced by drugs on the disposition of nutrients[2] indicated that laxative mineral oils, such as paraffin, could reduce or inhibit the absorption of fat-soluble vitamins. Later studies by Curtis and Balmer, in 1939[3] confirmed the previous hypothesis. In the 1940s and 1950s, the ability of some drugs to cause malnutrition was observed. For

example, the pyridoxine deficiency induced by isoniazid or the inhibitory activity of some isoenzymes of cytochrome P450 produced by grapefruit and discovered by chance in 1991.[4]

Figure 1: Food-drug interactions.

The most serious cases that helped to draw attention to these interactions were those that occurred after 1963, described by Blackwell and others, who studied hypertensive crises due to the interaction of monoamine oxidase inhibitors (MAOIs) with biogenic amines such as tyramine. It was called the cheese syndrome because one of the first cases was a patient taking an MAOI and it occurred after the consumption of this food.[5,6]

-Factors that will influence the incidence and magnitude of interactions.

• Different chemical characteristics within the same therapeutic group: there are differences between the different physical-chemical characteristics of drugs, thus this also marks the therapeutic margin, since drugs whose therapeutic margin is narrow tend to have greater clinical relevance.[7]

• Type of drug formulation: solutions and suspensions are less susceptible to interacting with food since their mobility in the gastrointestinal tract is greater, enteric-coated tablets and retard forms remain in the body longer and therefore are longer. susceptible to interact.[7]

• Amount, composition and time when food is eaten. The period between food and the administration of medications also influences, as well as the quantity and composition of meals, especially if they are rich in fat, protein and fiber.[8]

• Severity of the disease: the existence of diseases also modifies the pharmacological response, thus when there is a kidney or liver disorder, the toxicity of the drug due to its accumulation is greater.[9]

• Inter- and intra-patient variability: nutritional status, age, pathologies and interindividual differences such as the amount of metabolic enzymes. For example, in elderly patients the number of drugs consumed is greater, this makes the chances of interactions greater, in addition, their metabolic capacity is decreased and the adsorption mechanisms of the drug may be altered, likewise the child population has a lower development of the mechanisms of detoxification, and the population that has different eating habits such as weight loss or vegetarian diets also has greater interactions, obesity or self-medication also affect these interactions.[7,10]

- Populations susceptible to food-drug interactions

It is essential to take precautions in the case of the elderly since they may have different responses due to their inability to inactivate or eliminate some medications due to presenting some type of pathology, thus the population self-medicated or with chronic treatments are more susceptible to errors in medication and to suffer a greater number of interactions.[9]

• Geriatric population: In the geriatric population, pharmacological and drug-nutritional interactions do not present fundamental differences from those of the rest of the population, although interactions between food and drugs are more clinically important. The main reason is due to the high consumption of drugs, an alteration in their absorption, metabolization and excretion; as well as because they present a greater risk of nutritional deficits and a greater incidence of non-compliance and medication errors.

• Self-medicating population: The main reason is that self-medication presents a risk factor for adverse effects to occur when food interacts consumed with medications. It can also be due to incorrect administration guidelines.

• Patients with chronic treatments: Taking several medications a day, as in the case of hypertension, heart failure, diabetes or transplant recipients makes this population group have a higher risk of AMI.

• Patients with special diets: Some patients have specific dietary guidelines, for example weight loss, vegetarian or low or high in salt. This group is susceptible because drugs sometimes have to be taken with food or dietary fat is needed for adequate absorption.[11]

• Patients who consume medicinal plants: Interactions with food of the active principles contained in medicinal plants have been less studied than with chemical drugs. However, the consumption of medicinal plants by the population is very important, in the United States it is estimated 30-40% and, in most cases without a prescription. An example is the medicinal plant St. John's wort [12], it is used with great frequency by patients with depression, its pharmacological action occurs because it is an enzymatic inducer of metabolism through cytochrome P4503A4, and has led to important interactions with medications such as cyclosporine, indinavir, and others.[2]

• Patients who consume supplements / dietary supplements.

Likewise, soy is another vegetable that will interact with certain medications such as tamoxifen, (a drug with antiestrogenic activity in the treatment of breast cancer), or toremifene, the interaction is due to phytoestrogens, it is a flavonoid, mainly isoflavone, It acts as an inhibitory antagonist of the isoenzymes CYP1A2 and CYP2C9.

Other supplements that will produce drug interactions are for example garlic, ginseng, ephedra and ginkgo.[2]

- Types of interactions

An interaction between a nutrient and a drug is defined as.[8]

• Modification of the effects of nutrients by the previous or simultaneous administration of a medicine.

• The modification of the effects of a medicine by the previous or simultaneous administration of a nutrient.

In some cases the interaction is bidirectional, however there is always, therefore, a drug or nutrient whose action is altered and another or others that act as inducers of the interaction.

Interactions between drugs and foods can be classified according to which of the substrates will modify their function or behavior in the presence of the other.[11]

• Food-drug interactions (AMI): food or its components can modify the bioavailability of a drug, its pharmacokinetics (branch of pharmacology that studies the processes that a drug undergoes when it passes through the body or its pharmacodynamics (branch of pharmacology that studies the mechanisms of action of drugs and the physiological and biochemical effects they produce in the body).[13]

• Drug-food interactions (AMI): drugs can alter the absorption, metabolism or excretion of nutrients, as well as nutritional status.

The drugs most frequently associated with these interactions are.

• Medicines with a narrow therapeutic margin: their therapeutic dose is close to the toxic one such as warfarin, phenytoin, digoxin, lithium, antihypertensive or OAC.

• Drugs that have a steep dose-effect curve: small changes in doses generate large changes in effects.

• Drugs that need to maintain a stable plasma concentration to be effective, such as antibiotics, the efficacy of which may be compromised if plasma levels are not maintained above a minimum inhibitory concentration for the duration of treatment.

As with the administration of several drugs together, the potential for interactions increases, the interaction with nutrients will not be the same within the same therapeutic group since they may have totally different characteristics depending on the type of food. The interaction can be positive, that is, it increases the therapeutic effect of the drug or negative, in this case the therapeutic effect of the drug is less or there may even be no interaction. For example, in the case of isoniazid, it has the function of inhibiting the metabolism of various drugs and nutrients, producing clinically significant interactions in some patients.[8]

Another factor that will affect is the formulation of the drug, which can have a very relevant clinical effect, such as modified release formulations that, having the same active principle as those with normal release, can have a different interaction profile.

On the other hand, food in its quantity and composition, as well as the moment in which it is ingested with respect to taking medications can also influence the appearance of interactions, so for example iron compounds have to be taken in fasting, it is necessary to take into account the fasting conditions when taking various medications, the absence of food intake for at least 1 hour before and 2 hours after taking the medication can be considered as fasting.[8]

There are several ways to classify food-drug interactions. In principle, a classification can be established based on which of the two substrates is the one whose action is modified by the presence of another (Table 1). That is why there are two possibilities, on the one hand the IAM, and on the other the IMA.

Table 1 summarizes the interactions between foods and medications.

Food-Medicine (AMI)

Nonspecific effects caused by the presence of food in the gastrointestinal tract Effects of a specific component of the food Effects derived from a significant imbalance (increase or decrease) of some component of the diet.

Medicine-Food (IMA)

Direct interaction between a nutrient and the drug.

Effects caused by the drug on organic physiological functions

Table 1: Interactions between food and drugs.[14]

-Drug-food interactions (IMA)

Certain medications can influence the normal use of nutrients, compromising nutritional status, either through a direct interaction between the two or through effects on the physiological functions of the body caused by the medication.

These effects include.[2]

• Anti-nutrient effect.

• Poor digestion and / or poor absorption.

• Changes in metabolic use.

• Urinary hyperexcretion of vitamins and / or trace elements.

• Hypercatabolism of nutrients.

• Catabolic stress with weight loss.

• Decreased intake due to loss of appetite.

• These types of interactions are important in patients with chronic or very long treatments and in patients with malnutrition. An example of this type of interaction is the deficiency of vitamin B6 in prolonged treatment with the tuberculostatic isoniazid.

• Also included in this category are those drugs that affect appetite, both increasing it (psychotropic) and decreasing it (amphetamines); or that affect taste, reducing its sensitivity (hypogeusia) or producing unpleasant taste sensations (dysgeusia).[15]

-Food-drug interactions (AMI).

These interactions are the true object of this work and are due to alterations in the therapeutic activity of drugs due to food; being able to increase the effect, decrease it, delay it or alter it qualitatively. In this way, and due to AMI, the drug would not fulfill its function.[11]

This type of interaction is produced by.
• Nonspecific effects due to the presence of food in the gastrointestinal tract.
• Specific effects of a specific component of food.
• Effects due to a nutritional imbalance.

Most drugs are taken orally and together with food, although these or their components can influence their bioavailability and therapeutic activity. Due to this characteristic, they sometimes have to be taken on an empty stomach or with a glass of water.
According to their mechanism, these interactions can be divided into.

a) Physico-chemical or "in vitro" interactions.
Generally, there is a decrease in the amount of drug absorbed without interfering with physiological processes in the body. Their interaction mechanisms are.[8]
• Formation of insoluble precipitates with some component of the food. One of the examples on this occasion would be the case of tetracyclines and their interaction with milk, which leads to the formation of an insoluble precipitate between the drug and calcium and which causes underdosing.
• Adsorption of the drug to a component of the diet, mainly to fiber and pectins. In this way, the drug accesses the intestinal surface with greater difficulty and, therefore, its bioavailability decreases.
• Increased solubility of the drug due to some component of the diet, such as fat. It is due to the potentiating effect of food on gastrointestinal secretions, such as bile salts that facilitate the dissolution of fat-soluble drugs and their absorption.
• Gastrointestinal pH modifications. The stability of drugs is altered at acidic pH or variations in the degree of dissociation.
• Redox mechanism, such as the reducing nature of ascorbic acid present in foods rich in vitamin C, which facilitates the transformation of Fe3 + into Fe2+, and therefore, favors the absorption of iron.

b) Pharmacokinetic interactions.
They are the most frequent interactions and those that occur in the stages that the drug follows in the body (LADME: release, adsorption, distribution, metabolism and excretion) modifying its concentration and, as a result, increasing, reducing or delaying its therapeutic activity.[15]
• Release: The disintegration rate of a drug depends on physiological conditions such as pH, motility or gastrointestinal secretions; which, in turn, can be modified with food intake.
• Absorption**:** It is the most frequent mechanism in pharmacokinetic interactions, although the clinical importance is not very significant, except for some exceptions or drugs with a narrow therapeutic margin.

Food can cause.
- A stiffening of the gastric emptying.
- Stimulate intestinal motility.
- Increasing gastrointestinal secretions.
- Modifying the presystemic clearance of drugs at the hepatic level.

An alteration of the absorption rate can occur by modifying the maximum concentration, which is important if a rapid effect is needed (analgesics) or in drugs with a very short half-life. A change in the total amount absorbed can also be achieved by altering the stable concentration of the drug.[8]

Another interaction is due to the drug using the same transport system as the nutrient, such as levodopa and amino acids.[8]

There are no general guidelines on whether to take the drugs with food or not, so each case should be evaluated, taking into account that there are drugs that irritate the gastrointestinal mucosa and to alleviate it they should be ingested with food. However, in general, joint intake with milk, coffee, tea and fiber or mineral supplements should be avoided.
• Distribution: When the drug reaches the bloodstream there are two different mechanisms of interaction:
-Displacement of the drug by a nutrient in its binding to plasma proteins: (hyperprotein diets) or by mobilization of fats (prolonged fasting).
-Deficiency of plasma proteins due to malnutrition.[8]

This results in a greater amount of free medicine, which is what exerts the pharmacological effect, and therefore its activity will increase. If they have a narrow therapeutic window, there may be risks of toxicity.
• Metabolism: In this stage, the drugs are transformed into water-soluble substances to be eliminated via the kidneys through a series of enzymatic reactions.
-Non-synthetic: oxidation and reduction.
-Synthetic: conjugation with endogenous molecules.

The liver is the main metabolic organ, but these isoenzymes can be in various tissues; For example, CYP3A4, which is the most abundant isoenzyme of cytochrome P450 and responsible for the biotransformation of more than 50% of drugs, is found in high concentration in the mucosa of the small intestine. Because of this, medications taken by mouth are more likely to have these types of interactions.

These interactions have the greatest clinical impact and occur because[8]
• Food provides substrates for conjugation reactions.
• Food induces or inhibits enzyme systems.

• Food causes changes in splenic-liver blood flow.
Enzyme inducers, such as polycyclic aromatic hydrocarbons from grilled foods or indole compounds from crucifers, increase the rate of metabolism of drugs, leading to a decrease in therapeutic effect, which makes them ineffective; while enzyme inhibitors, such as phenolic compounds in grapefruit juice, lead to a more sustained pharmacological effect, increasing the risk of overdose.
• Excretion: The major route of elimination of drugs is the kidney and its main modulator, the pH of the urine, which can be modified by food. These can be acidifying or alkalizing of the urine, which will depend on the acidity or basicity of the ashes of the food, that is, on its mineral composition.[8]

Acidifiers (acid ash): meat, fish and shellfish, eggs, and cereals and derivatives.

Alkalinizers (basic ashes): milk and derivatives, vegetables, legumes (except lentils), nuts and fruits (except plum and blueberries).

Another type of interaction in this phase is due to a competitive effect between the drug and the food in tubular reabsorption, as is the case of salt and lithium salts.

c) Pharmacodynamic interactions
These interactions are rare and can occur at drug receptors, that is, on the action of the drug; or by functional synergies and alteration in cellular transport systems. Some of the main drug interactions described are.[16]
Agonists: enhance the action.
Antagonists: decrease or inhibit the action.
Other types of interactions have been described, such as in the case of vitamin K, present in broad-leaf vegetables, lentils, beans, etc. And its effect with coumarin anticoagulants (warfarin, acenocoumarol). Likewise, the interaction of caffeinated beverages (coffee, tea) and neuroleptics (haloperidol).[14]

OBJECTIVES

The objective is to study the interactions between foods and medicines in order that their joint use is correct and both exert their effect.
• Give an overview of the different interactions between foods and drugs that may be relevant, classifying them according to group therapeutic.
• Describe the mechanism by which these interactions occur, as well as deepen their knowledge.
• Provide information on the consequences of the simultaneous administration of food-medicine.
• Provide documentation-based advice on how best to best co-administer food-drug, if possible.
• Pretend to serve as a guide when scheduling a treatment.
• Serve as a basis for the development of guidelines or protocols to be followed to detect and prevent food-drug interactions in the daily practice of health professionals.

MATERIAL AND METHODS

The bibliographic search was carried out in the Medline information banks (PubMed) in the Pubmed and Scielo databases. The following search strategy was used based on MeSH terms: food-drugs interactions, drug-nutrient interaction, hypnotic, neuroleptics, anxiolytics, benzodiazeoines, antiepileptics, antidepressants, dopaminergic agonists, anticholinergics, antihistamines, curarmatory, analgesics, anti-inflammatory, anti-inflammatory, hypotensives, cardiotonics, antiarrhythmics, adrenergic antagonists, antiulcer, anticholinergics, antithyroid, sex hormones, corticosteroids, oral hypoglucemic agents, antiasthmatics, brochoodilators, antibiotics, antimicrobials, antimalarial drgs, amoebicides, anthelmintics, tuberculostatic, antivirals, diuretics, antiplatelet agents, coronary vasodilators, anticoagulants, calcium channel, blockers, mineral supplements, cytostatic, antineoplastic, toco-gynecological drugs, hipolipidemic and immunosupressants. The different concepts were combined by means of the Boolean AND and OR operations.

The search provided the starting information to delve into the different interactions by performing specific searches for each therapeutic group. A total of 285 articles were initially obtained, the vast majority in Medline, those articles in which the described interaction was repeated and did not clearly specify what type of interaction the drug suffered when administered with food were discarded.[17-19]

Of the 285 initial articles, 133 were selected, from which the necessary information has been extracted.

The only filter used was language, searching only articles written in Spanish and English.

No additional filter was included such as age, publication date, etc., in order not to miss any described interaction. The bibliographic search has been done without date restriction from the origins to March 2018.

Among the exclusion criteria of the present review, those articles that repeated the interaction already described or did not provide any new data were discarded. In addition, those who analyzed AMI with alcohol were excluded, since it is one of the broadest interactions, being outside the objective of this study.

RESULTS

Food-drug interactions have been divided into two types.
1. Inhibitors of the pharmacological effect of the drug.
2. Enhancers of the pharmacological effect of the drug.

In turn, they have been classified according to the food with which the different drugs interact.

Foods/nutrients of interest in drug absorption

Table 2 shows the results indicating the author together with the bibliographic reference, year of publication, population on which the study is carried out, food involved in the interaction, nutrient that the food contains responsible for the pharmacological interaction, drugs with which the food interacts and the interaction observed, as it is difficult to quantify this last section, has defined as.

-Normal interaction: one that implies that it is not convenient to take the drug with the food studied but there is no clinical relevance.

-Low interaction: it is one in which there is interaction between the drug and the food but both can be taken together without any problem.

-High interaction: It is advisable not to consume food with the medicine at the same time, since there is clinical relevance in the therapeutic effect of the medicine.

-Very high interaction: The food and the medicine cannot be consumed together, since the pharmacological interaction is very dangerous and can even cause the death of the patient.

Table 2 describes the main AMI obtained in the literature, observing a total of 39 studies that describe the main interactions of food with different drugs, which decrease their therapeutic effect due to various mechanisms of action.[20]

The pharmacological activity of these drugs is diminished when they are administered together with certain specific foods in some cases, or simply by the administration of the drug with food, not on an empty stomach.

Among the studies carried out in animals is a study in rats that describes the interaction when administering nuts in patients treated with phenobarbital, due to the pyridoxine contained in nuts, the pharmacological effect of phenobarbital decreases.[21]

While some authors observed that there were important interactions between coffee and tea with many medications, reducing their effect when administered to the population without any distinction, among them are interactions with fluphenazine, haloperidol, clonazepam, diazepam, triazolam, zopiclone, salts of dipyridamole lithium, iron salts and zinc salts. In all cases, the recommendation would be not to administer it jointly, although the interaction that exists is not of excessive clinical importance. Other authors highlight, for example, the interaction of folic acid with phenytoin, since we consider it to be of a high level due to the clinical importance of this interaction and it should be noted never to administer together.

Other important interactions that stand out would be fluphenazine with oranges or kiwis due to its vitamin content, lithium salts when the patient consumes a diet rich in sodium, or paracetamol when a diet rich in carbohydrates is consumed, or antipurine that interacts with food when the protein content of the diet is high. The same is true of theophylline retard if it is administered with any food.

Among the interactions without clinical importance found are alclofenac when administered with food or zidovudine when administered with diets rich in lipids.

Finally, note the interaction of cyclosporine when drinking red wine, although it should be noted that its clinical importance is not noteworthy.

Table 2: Food-drug interactions that impair drug absorption.

Author	Study data	Food involved	Nutrient	Medicine	Interaction Observed
Kulhanek F. " y cols" 1981 (23)	Población diana	Café	CAFEINA	FLUFENAZINA	Normal
Kulak F. " y cols" 1981 (23)	Población general	Café	CAFEINA	HALOPERIDOL	Normal
Mattila MJ. "y	Población general	Café	CAFEÍNA	DIAZEPAM	Normal

cols" 1983 (24)					
Mattila MJ. "y cols" 1983 (24)	Población general	Café	CAFEINA	CLONAZEPAM	Normal
Mattila MJ. "y cols" 1983 (24)	Población general	Café	CAFEINA	TRIAZOLAM	Normal
Mattila MJ. "y cols" 1983 (24)	Población general	Café	CAFEINA	ZOPICLONA	Normal
Mester R. "y cols" 1995 (25)	Población general	Café	CAFEINA	SALES DE LITIO	Normal
Smits P. "y cols" 1991 (27)	Población general	Café	CAFEINA	DIPIRIDAMOL	Normal
Disler PB "y cols" 1975 (28)	Población general	Café	CAFEINA	SALES DE HIERRO	Normal
Pécoud A "y cols" 1975 (299)	Población general	Café	CAFEINA	SALES DE ZINC	Alta
Kulhanek F. " y cols" 1981 (23)	Población diana	Te	TEINA	FLUFENAZINA	Normal
Kulak F. " y cols" 1981 (23)	Población general	Te	TEINA	HALOPERIDOL	Normal
Mattila MJ. "y cols" 1983 (24)	Población general	Té	TEINA	DIAZEPAM	Normal
Mattila MJ. "y cols" 1983 (24)	Población general	Té	TEINA	CLONAZEPAM	Normal
Cook BL. "y cols" 1985 (26)	Población general	TE	TEINA	SALES DE LITIO	Alta
Smits P. "y cols" 1991 (27)	Población general	Té	TEINA	DIPIRIDAMOL	Normal
Disler PB "y cols" 1975 (28)	Población general	Té	TEINA	SALES DE HIERRO	Normal
Hansson, O. "y cols" 1976 (22)	Ratas	Frutos secos	PIRIDOXINA	FENOBARBITAL	Normal
Hansson O. " y cols" 1976 (22)	Población general	Dieta	PIRIDOXINA	FENITOINA	Normal
Bhagavan HN " y cols" 1983 (30)	Población diana	Dieta	PIRIDOXINA	LEVODOPA	Normal
Johansson	Población general	Dieta	PROTEINAS	FENITOINA	Normal

O "y cols" 1983 (31)					
Bianchine JR "y cols" 1976 (32) Gillespie NG "y cols" 1973 (33)	Población diana	Dieta	PROTEINAS	LEVODOPA	Normal
Anderson KE "y cols" 1979 (35) Kappas A "y cols" 1976 (36)	Población general	Dieta	PROTEINAS	ANTIPIRINA	Alta
Kappas A "y cols" 1978 (37)	Población general	Carne	PROTEINAS	ANTIPIRINA	
Kappas A "y cols" 1978 (37)	Población general	Carnes	PROTEINAS	TEOFILINA	Normal
Björn-Rasmussen E "y cols" 1974 (38) Callender ST "y cols" 1971 (39)	Población general	Dieta	PROTEINAS	SALES DE HIERRO	Baja
Stewart DE "y cols" 1992 (41)	Población general	Salvado de trigo, copos avena	FIBRA	DOXEPINA	Normal
Stewart DE "y cols" 1992 (41)	Población general	Salvado de trigo, copos avena	FIBRA	DESIPRAMINA	Normal
Björn-Rasmussen E "y cols" 1974 (38) Callender ST "y cols" 1971 (39)	Población general	Dieta	FIBRA	SALES DE HIERRO	Baja
Ralston AJ "y cols" 1970 (42) Reynolds EH " y cols" 1973 (43)	Población General Población general	Dieta	AC FOLICO	FENITOINA	Alta
Kappas A "y cols" 1978 (37)	Población general	Carne	BRASA	ANTIPIRINA	
Conney AH "y cols" 1976 (44) Pantuck EJ "y cols" 1976 (45)	Población general	Alimentos	BRASA	FENACETINA	Normal
Kappas A "y cols" 1976 (36)	Población general	Alimentos	BRASAS	ANTIPIRINA	Normal

Bleiweiss H "y cols" 1970 (47)	Población general	Dieta	SODIO	SALES DE LITIO	concentración: normal
Pearce L. "y cols" 1981 (49)	Población diana	Dieta	L-METIONINA	LEVODOPA	Normal
Deahl M. "y cols" 1989 (50)	Población diana	Nueces de betel	ARECOLINA	PROCICLIDINA	Normal
Pantuck EJ "y cols" 1979 (46)	Población general	Dieta	CRUCÍFERAS	ANTIPIRINA	Normal
McGilvera y IJ "y cols" 1972 (51)	Población general	Dieta	CH (pectinas)	PARACETAMOL	Alta
Bot LUS 2.0 (19)	Población general	Dieta	GRASAS	ESTAVUDINA	Normal
Carver PL "y cols" 1999 (54)	Población general	Dieta	GRASAS	INDINAVIR	Normal
Hollister A. "y cols" 1994 (55)	Población general	Grasa	LIPIDOS	ZIDOVUDINA	Baja
Hansten PD 2003 (56)	Población general	Harinas integrales	FITATOS	SALES DE ZINC	Normal
Björn-Rasmussen E "y cols" 1974 (38)	Población general	Dieta	FOSFATOS	SALES DE HIERRO	Baja
Callender ST "y cols" 1971 (39)					
Pécoud A. "y cols" 1975 (29)	Población general	Leche	FOSFATOS	SALES DEZINC	Alta
Pécoud A. "y cols" 1975 (29)	Población general	Leche	CALCIO	SALES DEZINC	Alta
Tsunoda SM "y cols" 2001 (61)	Población general	Vino tinto	TANINOS	CICLOSPORINAS	Normal

The consumption of tea or coffee in patients treated with fluphenazine orally can reduce the effect of the drug by forming an insoluble complex between the drug and the components of tea or coffee infusions, leading to less absorption of the drug. This has been proven in "in vitro" work with different tea or coffee extracts and fluphenazine solutions.[23] Therefore, it seems advisable to avoid the consumption of tea or coffee infusions in patients treated with this medicine. Likewise, the effects of haloperidol in oral form can be diminished with the consumption of tea or coffee infusions by forming a insoluble complex between the drug and extractive substances from said infusions.[23] It is therefore advisable to avoid the joint consumption of infusions such as tea or coffee with medications such as fluphenazine or haloperidol.

Likewise, the ingestion of caffeine, and to a lesser extent theophylline, can reduce the sedative effects of diazepam and clonazepam.[24] On the other hand, caffeine opposes the effects of triazolam and zopiclone, since they have opposite effects.[24] The mechanism of action by which these drug interactions occur is not clear, although it is probably due to the blockade of adenosine receptors.

Excessive consumption of caffeinated beverages can also reduce serum lithium concentrations.[25] The mechanism of action of this interaction is not clear, but it is known that the exact way in which caffeine affects the excretion of lithium is at the level of the renal tubules. Also the joint ingestion of theophylline with lithium salts reduces the plasma concentrations of the drug and, therefore, patients can suffer relapses when taking them together.[26]

Caffeine and theophylline, derived from xanthine, can interfere in the scintigraphy with dipyridamole labeled with thallium 201, inhibiting the hemodynamic response to its infusion, acting as competitive antagonists of the adenosine that is involved in the mechanism of action of dipyridamole. Similarly, theophylline can reduce some pharmacological effects of dipyridamole.[27]

Another interaction is due to the intake of iron salts together with tea or coffee infusions, since these and the tannins of said infusions form insoluble, non-absorbable complexes in the intestine, reducing the bioavailability of iron, so taking joint of both infusions with iron salts.[28]

In the case of zinc salts, it has also been found that it interacts with coffee since it appreciably reduces the absorption of the drug. Due to this, coffee intake should be avoided until a few hours after the administration of zinc salts..[29]

As regards pyridoxine, its interaction with phenobarbital has been described, this interaction is related to the consumption of high doses of pyridoxine since it has been proven that serum levels of the drug are decreased in patients taking phenobarbital. The mechanism of action in this case is apparently due to the fact that pyridoxine is part of the enzymatic system responsible for the biotransformation of phenobarbital. Such an interaction will hardly occur with a normal diet in which sufficiently high pyridoxine levels would not be achieved.[22]

It has also been shown that serum levels of phenytoin are reduced when taking high doses of pyridoxine because the latter is part of the enzyme system responsible for biotransformation of the drug.[22] Accordingly, it is necessary to control the intake of pyridoxine, being difficult to reach such high levels with a normal diet in which the concentration of pyridoxine is not so high.
Pyridoxine has been reported to interfere with the desired and unwanted effects of levodopa in the treatment of Parkinson's. There is a decrease in the therapeutic efficacy of the drug; the mechanism of action by which it has been postulated that this interaction is due is that pyridoxine increases the metabolism of the drug, reducing its concentration in the brain.[30]

Another study highlights the importance of protein content in the diet since it affects drugs such as phenytoin, decreasing its absorption.[31] Because of this, the composition of the diet must be taken into account in patients treated with phenytoin.

Another of the interactions observed and in some way related to the previous one is manifested by the joint intake of levodopa and foods rich in protein. The mechanism of action this time is at the level of drug absorption, which is diminished by the consumption of proteins at the same time as levodopa. The reason is that levodopa competes, for its intestinal absorption mechanism, with amino acids from the diet, especially neutral ones. However, due to its emetic and irritative properties, it is advisable to administer levodopa together with meals, but its protein content must be taken into account, since, as indicated, it can reduce its absorption. In any case, the amount of protein ingested must be controlled and fixed in order to establish an adequate dose of the medication, avoiding that there is a great variation in protein intake that could alter the treatment guidelines with levodopa.[32, 33]

The administration of antipyrine to individuals who consume a large amount of protein results in their biological half-life being significantly reduced when compared to other low-protein diets. This has its origin in the influence of proteins and carbohydrates on the hepatic oxidative system, especially cytochromes P450 and P448, proving that certain medications stimulate the activity of these systems and that certain types of foods also do (always that are rich in protein); on the contrary, carbohydrates act inversely due to the so-called "glucose effect" but to a very high degree less than proteins.[34,35,36] Due to these interactions, protein intake must be taken into account in antipyrine treatments, both to prevent a decrease in the pharmacological response due to a diet rich in protein, and due to the premature appearance of side effects due to the consumption of a diet low in protein. said nutrient. For this reason, the importance of diet control in patients treated with antipyrine.

Co-administration of theophylline with a protein-rich diet has also been observed to significantly decrease the biological half-life of the drug. Again it has its origin in the influence that it exerts, both proteins and carbohydrates, in the hepatic oxidative microsomal system; Proteins stimulate the pharmacological activity of theophylline and carbohydrates inhibit it, known as the "glucose effect." As a consequence, the protein content in the diet must be taken into account, both to prevent a decrease in the therapeutic response and due to the premature appearance of adverse effects.[37]

The administration of iron salts on an empty stomach can cause severe gastrointestinal irritation, so to alleviate the symptoms it is advisable to always take them with food.

However, foods in general, and especially foods with significant amounts of fiber, phosphates, or proteins, lead to a reduction in the bioavailability of iron salts. This is

because these substances form insoluble complexes with iron that are not absorbed by the body.[38, 39, 40]

Likewise, the intake of a diet rich in fiber (wheat bran, oat flakes, etc.) can decrease the serum concentrations of doxepin and desipramine.[41] In this case, the literature does not specify the mechanism of action by which this interaction occurs.

The absorption of phenobarbital is delayed and / or decreased if it is taken simultaneously with food. This interaction occurs mainly in the small intestine of the body and when food is present, the speed of gastric emptying is delayed, in this way the time it takes for the drug to reach its absorption points is prolonged.

Another reason why the absorption of phenobarbital is also decreased is because being in contact with gastric juices for longer, its degradation is favored. As a result, the drug should be taken one hour before or two hours after meals. Experimentation in rats corroborates the mechanism of action of this pharmacological interaction since it has been shown that there are differences in the amount and speed of drug absorption, depending on whether the animal is fasting or not.[21]

An interaction observed with phenytoin is produced by folic acid, since in people treated with this drug and who take high doses of folic acid, serum phenytoin levels may decrease, even reaching below the therapeutic threshold, the because of this decrease in the concentrations of the drug is in its mechanism of action since it increases the metabolism of the drug. Therefore, the intake of folic acid in the diet should be controlled to avoid possible alterations in phenytoin treatment, although it is really difficult to achieve levels high enough with a normal diet for this to occur.[42, 43]

Another described interaction of phenytoin occurs with food intake in general, especially due to the effects of carbohydrates that increase its absorption and the effects of proteins that decrease it.[31] Because of this, the composition of the diet must be taken into account in patients treated with phenytoin as previously noted.

Experimental studies have shown that a moderate intake of grilled meat or grilled foods can significantly reduce the plasma half-life values of antipyrine, in this case the mechanism of action of the interaction is that the liver metabolism is increased. oxidative caused by the ingestion of these foods that contain high amounts of polycyclic hydrocarbons. These substances act as enzyme inducers on the hepatic microsomal system (cytochrome P450), increasing the hepatic clearance of antipyrine.[37] For this reason, during treatment with this medicine, food cooked on the grill should be dispensed with.

Grilled foods also decrease the bioavailability of phenacetin if ingested for very long periods of time, so they should be avoided in the diet of an individual treated with this drug.[44,45]

Experimental studies have shown that a short period of ingestion of moderate amounts of grilled food is sufficient to significantly shorten the plasma half-life values for theophylline due to increased hepatic oxidation. This effect is produced by polycyclic hydrocarbons that act as enzyme inducers on the hepatic microsomal system, increasing the metabolic clearance of the drug. In this case, it does not seem necessary to take special precautions, although during treatment with theophylline it is always advisable to dispense with grilled cooking in the daily diet.[36]

Another interaction found in the antipyrine literature is carried out with crucifers if they are ingested regularly, in this case the mechanism of action is that it increases their metabolism, this is due to the ability of these vegetables to increase the activity of the liver and intestinal microsomal enzymes.[46]

Likewise, the habitual intake of crucifers reduces blood levels of phenacetin by increasing plasma concentrations of N-acetyl-p-aminophenol (paracetamol), its main metabolite and active substance; it is therefore important to take into account the eating habits of the patient treated with phenacetin.[46]

Treatment with lithium carbonate involves taking into account the amount of sodium in the diet because sodium facilitates the renal elimination of lithium, preventing its tubular reabsorption.

If the sodium intake is rich, there will be an excessive elimination of lithium and its therapeutic effect will be reduced, while if it is poor, intoxication may occur.[47,48] Consequently, the patient's eating habits must be known, especially salt intake, adjusting the dose of the drug based on the usual diet.

In patients treated with levodopa, it was observed that when large doses of Lmethionine were ingested together, the presence of gait disturbances, bradykinesia, tremor and rigidity occurred.

Therefore, it should be recommended to avoid the intake of high amounts of L-methionine in patients with Parkinson's.[49] The anticholinergic effects in patients treated with procyclidine are counteracted by chewing areca (betel nuts), since it contains arecoline, which provide a cholinergic action.[50]

The joint intake of paracetamol and food in general causes a delay in the absorption of the drug, maintaining more sustained plasma levels, but the mechanism of action is because gastric emptying is delayed. Therefore, as it is not a drug that produces gastric irritation and there is practically no difference in serum levels whether

or not it is ingested with food, it would not be necessary for its intake to coincide with the intake of these.[51]

On the other hand, it has been shown that diets rich in carbohydrates (especially pectins) significantly delay the absorption of paracetamol orally, not only because of the delay in the gastric emptying rate, but also because the pectins hinder the solubilization of the drug by being very viscous and absorb part of it. In this case, if a rapid analgesic effect is desired, a diet rich in carbohydrates may be contraindicated, while if what is of interest is a prolonged action, a diet rich in carbohydrates could be useful.[52,53] A high-fat meal reduces and delays the time to reach peak plasma concentrations of paracetamol, but does not change the body's systemic exposure to the drug compared to the fasting state. However, it would be convenient that for optimal absorption of paracetamol it should be taken on an empty stomach, therefore it should be taken at least one hour before eating food. If this is not possible, the literature suggests that it be taken with a light meal.[19]

Food in general decreases the absorption of indinavir. Fatty food is the one that is related to a greater variation in the bioavailability of the drug, probably due to the delay in the rate of gastric emptying. Its administration is recommended 1 hour before or 2 hours after meals or only with light and low-fat meals. The mechanism of action by which this delay in the gastric emptying rate of the drug occurs is not really known what it is, there are no clinical studies that can demonstrate the exact mechanism by which this gastric emptying occurs.[54]

A diet high in lipids moderately reduces the rate of absorption of zidovudine. In this case, the mechanism by which the food-drug interaction occurs is not well established. There are no data in the literature on the mechanism of action by which this interaction of lipids with zidovudine occurs. It is therefore recommended as a precautionary measure when a patient is being treated with zidovudine that it be administered fasting whenever possible.[55]

Foods rich in phytates, especially wholemeal flours, phosphates, calcium or other precipitating agents decrease the absorption of zinc, if they are taken together or immediately afterwards. Therefore, the intake of zinc salts with foods with high amounts of these substances such as wholemeal flours, milk and dairy derivatives should be avoided to avoid this pharmacological interaction.[29,56]

Ingesting food, milk or grapefruit juice (but not orange) and cyclosporine together increases the bioavailability of the drug and its maximum serum concentration.[57,58,59,60] The mechanism of action of this pharmacological interaction is well defined in the literature, since grapefruit juice is one of the foods with which drugs interact the most, and it is due to the fact that cyclosporine is metabolized by the CYP3A4 enzyme and therefore its concentration increases. It should be noted that cyclosporine is one of the few drugs that, when interacting with grapefruit juice, reduces its pharmacological action, since in most cases the interaction with grapefruit juice produces an increase in the pharmacological effect of the drug.

The administration of cyclosporine when drinking red wine leads to a reduction in its bioavailability and its maximum plasma concentration.[61] In this case, the mechanism of action of said drug interaction is not well understood.

Table 3 describes the main AMI obtained in the literature, observing a total of 28 studies that describe the main interactions of food with different drugs, which increase their therapeutic effect by various mechanisms of action.

It indicates the author along with the bibliographic reference, year of publication, population on which the study is carried out, food involved in the drug interaction, nutrient that the food contains responsible for the drug interaction, drugs with which the food interacts and observed interaction, as it is difficult to quantify this last section, has been defined as.
-Normal interaction: one that implies that it is not convenient to take the drug with the food studied but there is no clinical relevance.
-Low interaction: it is one in which there is interaction between the drug and the food but both can be taken together without any problem.
-High interaction: It is advisable not to consume food with the medicine at the same time, since there is clinical relevance in the therapeutic effect of the medicine.
-Very high interaction: The food and the medicine cannot be consumed together, since the pharmacological interaction is very dangerous and can even cause the death of the patient. The interactions of grapefruit juice with numerous drugs are highlighted, all of them in a positive sense, and in many cases interactions with high clinical interest such as that which occurs when it is administered together with carbamazepine, astemizole, halofrantine, albendazole, felodipine and nisoldipine. Very important are the interactions of grapefruit juice with terfenadine, simvastatins and lovastatins since they have great clinical importance. Unimportant interactions with grapefruit juice are: tacrolimus, saquinavir, nicardipine, nifedipine, or digoxin. Lastly, several positive interactions with lipids have been found and are drugs such as halofrantine, albendazole and saquinavir. With milk there is an important positive interaction and it is with cyclosporine.

Table 3: Food-drug interactions that favor drug absorption.

Author	Study data	Food involved	Nutrient	Medicine	Interaction Observed
Garg SK "y cols" 1998 (63)	Población general	Zumo de pomelo	Bioflavonoides	CARBAMAZEPINA	Alta
Benton RE "y cols" 1996 (64) Clifford CO "y cols" 1997 (65)	Población general	Zumo de pomelo	Bioflavonoides	TERFENADINA	Muy alta
Bailey DG "y cols" 1998 (66)	Población general	Zumo de pomelo	Bioflavonoides	ASTEMIZOL	Alta
Parker RB "y cols" 2003 (74)	Población general	Zumo de pomelo	Bioflavonoides	DIAZEPAM	Normal
Parker RB "y cols" 2003 (74)	Población general	Zumo de pomelo	Bioflavonoides	DIGOXINA	Normal
Charbit B "y cols" 2002 (70)	Población general	Zumo de pomelo	Bioflavonoides	HALOFRANTINA	Alta
Nagy J "y cols" 2002 (72)	Población general	Zumo de pomelo	Bioflavonoides	ALBENDAZOL	Alta
Kupfersch midt HH "y cols" 1998 (75)	Población general	Zumo de pomelo	Bioflavonoides	SAQUINAVIR	Normal
Lundahl J "y cols" 1995 (76)	Población general	ZUMO DE POMELO	Bioflavonoides	FELODIPINO	Alta
Bailey DG "y cols" 1993 (78)	Población general	ZUMO DE POMELO	Bioflavonoides	NISOLDIPINO	Alta
Bailey DG "y cols" 1993 (78)	Población general	ZUMO DE POMELO	Bioflavonoides	NICARDIPINO	Normal
Bayley DG "y cols" 1991 (77)	Población general	ZUMO DE POMELO	Bioflavonoides	NIFEDIPINO	Normal
Bailey DG "y cols" 1993 (78)	Población general	ZUMO DE POMELO	Bioflavonoides	NIMODIPINO	Normal
Bailey DG "y cols" 1993 (78)	Población general	ZUMO DE POMELO	Bioflavonoides	NITRENDIPINO	Normal
Min DI "y cols" 1996 (81)	Población general	Zumo de pomelo	Bioflavonoides	QUINIDINA	Normal
Kantola T "y cols" 1998 (82)	Población general	Zumo de pomelo	Bioflavonoides	LOVASTATINA	Muy alta

Lilja JJ "y cols" 1998 (83)	Población general	Zumo de pomelo	Bioflavonoides	SIMVASTATINA	Muy alta
Ducharme MP "y cols" 1993 (59) Ku YM "y cols" 1998 (60)	Población general	Zumo de pomelo	Bioflavonoides	CICLOSPORINA	Normal
Michelangelo V "y cols" 2001 (91)	Población general	Zumo de pomelo	Bioflavonoides	TACROLIMUS	Normal
Raaska K "y cols" 2004 (84)	Población general	Café	CAFEINA	CLOZAPINA	Alta
Thithapandha A "y cols" 1989 (88) Yoovathaworn "y cols" 1986 (89)	Población general	Café	CAFEINA	AC ACETILSALICILICO	Normal
Anderson JR "y cols" 1981 (90)	Población general	Café	CAFEINA	ERGOTAMINA	Normal
Hamilton-Smith "y cols" 1976 (73)	Población general		VITAMINA D	DIGOXINA	Muy alta Normal
Kaufman a G 1984 (92)	Población general	Frutos secos	Piridoxina	AMIODARONA	Alta
Elvin AT "y cols" 1981 (93)	Población general		Proteinas	LIDOCAINA	Alta
Milton KA "y cols" 1989 (69)	Población general	Comidas grasas	LIPIDOS	HALOFRANTINA	Alta
Homeida M "y cols" 1994 (71)	Población general	Grasas	LIPIDOS	ALBENDAZOL	Normal
Bot PLUS (19)	Población general	Grasas	LIPIDOS	SAQUINAVIR	Normal
Gupta SK "y cols" 1989 (58)	Población general	Leche	CALCIO	CICLOSPOPRINA	Normal

The joint intake of carbamazepine with food in general increases its bioavailability, the mechanism of action by which this drug interaction occurs is because there is an increase in the solubility of carbamazepine in the gastrointestinal tract due to increased secretion of juices. gallstones caused by food. However, it is not necessary

to take special measures or modify the drug administration regimen.[62]

Grapefruit juice increases carbamazepine concentrations because it inhibits the CYP3A4 isoenzyme of cytochrome P450, which is responsible for metabolizing the drug.

Due to this, if the consumption of grapefruit juice is occasional, it is recommended to stop taking it, while if it is constant, it would be necessary to adjust the dose of the drug.[63]

The ingestion of terfenadine and grapefruit juice produces an accumulation of the drug, probably due to the inhibition of cytochrome P450 involved in its metabolism, increasing the risk of cardiotoxicity and the possibility of arrhythmias. For this reason, the literature recommends avoiding taking this juice during treatment with terfenadine.[64, 65]

The ingestion of astemizole and grapefruit juice also produces in this case an accumulation of the drug, probably due to inhibition of the CYP3A4 isoenzyme of cytochrome P450 involved in the metabolism of astemizole, thus increasing the risk of drug toxicity. It is therefore recommended to avoid the intake of grapefruit juice during treatment with astemizole.[66]

The influence of joint ingestion of food in general and diazepam has been observed whether it is administered orally or intravenously. In the case of the oral route, the absorption rate of the drug is decreased while its bioavailability is increased due to a non-specific effect of the food of delaying the gastric emptying rate, which ultimately favors greater absorption. On the other hand, if it is administered intravenously with a close intake of food, the serum levels of the drug will be higher than those obtained if the patient were fasting, probably due to changes in the distribution pattern of the drug in the body when ingesting the drugs. Food.[67, 68]

Eating high-fat foods together with halofrantine increases peak plasma concentrations of the drug, leading to an increased risk of arrhythmias. Therefore, halofrantine should never be taken with food.[69] the studies found detail that this is due to the fact that fatty foods can reduce the presystemic metabolism of halofrantine.

The same effects occur if halofrantine is administered with grapefruit juice, so that taking a high-fat meal together increases the absorption of albendazole. Its systemic absorption is low, so it is recommended to always take it with food.[71]

Ingesting grapefruit juice increases the absorption of albendazole, but reduces its half-life, which could be harmful to the patient.[72]

Another described interaction is due to vitamin D and digoxin. An excessive increase of this in the diet can lead to an abnormally high concentration of calcium in the blood plasma and if at the same time treatment with digoxin is being received, these very high levels of calcium can increase its side effects and toxicity. medication, even affecting the life of the patient. This is because the calcium cation is a depressant of the sodium and potassium pump of the heart tissue, blocking repolarization and thus enhancing the effect of digoxin. However, a balanced diet will hardly lead the patient to this situation. Two cases are cited in which after administering a dose intramuscular digitalis and intravenous calcium (without specifying dose) the patients died.[73]

The intake of grapefruit juice together with digoxin does not usually modify the maximum serum concentrations or increases them slightly, except in some exceptions in which patients may present more significant increases.[74] This appears to be due to increased intestinal absorption of digoxin due to inhibition of P protein-mediated transport by grapefruit juice, although it should be noted that this theory about the mechanism of action of this interaction has been questioned.

Administration of saquinavir with a high-lipid diet increases its bioavailability due to its increased solubility. Thus, in certain cases its administration with food is recommended.[19] On the other hand, its bioavailability also increases when administered with grapefruit juice[75] because the CYP3A4 isoenzyme of cytochrome P450 is involved in its metabolism. Administration in this case together with grapefruit juice may be adequate.

The administration of felodipine and nisoldipine with grapefruit juice greatly increases their bioavailability, altering their hemodynamic effects. Because of this, it is recommended not to ingest these drugs with grapefruit juice. An increase in the bioavailability of nicardipine, nifedipine, nimodipine, nitrendipine has also been observed, although in these the pharmacological effect in healthy individuals has been less. The mechanism of action is not clearly defined in this case.[76,77,78]

It has been observed that alkalizing foods, such as grapefruit juice or other citrus fruits, cause an increase in the pH of the urine in such a way that the proportion of non-ionized quinidine increases, which can be reabsorbed at the level of the renal tubule, thus maintaining more sustained levels in the blood, with a longer duration of the therapeutic effect. It is not necessary to take special measures in this case as long as the intake of alkalizing foods is not exaggerated.[79,80,81]

Grapefruit juice significantly increases peak plasma concentrations of lovastatin and simvastatin, which carries an increased risk of toxicity; so they should not be taken together. The mechanism of action of this

interaction is produced by reduction of metabolism due to the inhibition of isoenzine CYP3A4 of cytochrome P450.[82,83]

Caffeine increases plasma concentrations of clozapine by inhibiting cytochrome P450.

This results in an increased risk of undesirable adverse effects; although it is very difficult to reach them if the drug levels are monitored correctly and provided that the caffeine supply is moderate and stable.[84]

It has been observed that the degree of absorption of acetylsalicylic acid is greater when it is administered with a relatively large amount of water, than when it is administered alone or with solid food; however, this also favors a faster elimination of the drug with a decrease in its plasma half-life. As for food, it has been proven that the intake of solid foods before taking acetylsalicylic acid, reduces its plasma levels; however, in the overall process the bioavailability is greater when / it is administered with food than when it is taken on an empty stomach. Due to this, the administration with solid food will give lower but more sustained levels, while if it is ingested with liquids it is because a faster analgesic response is required. In addition, due to the irritative action of the gastric mucosa of the drug, it is advisable to administer it with solid food or with a glass of water.[85,86,87]

It has also been observed that the bioavailability of acetylsalicylic acid is moderately increased by the action of caffeine, as well as its absorption rate and plasma concentration, through a pharmacokinetic mechanism.[88,89]

Caffeine increases the action of ergotamine since it increases its oral and rectal absorption by causing vasodilation and increased intestinal blood flow, and vasoconstriction of the extra and intracranial vessels.[90]

Ingesting food, milk or grapefruit juice (but not orange) and cyclosporine together increases the bioavailability of the drug and its maximum serum concentration.[57,58,59,60]

This is because cyclosporine is metabolized by the CYP3A4 isoenzine of cytochrome P450 and therefore its concentrations increase.

Grapefruit juice can increase peak serum concentrations of tacrolimus.[91]

The mechanism of action is not entirely known but it seems likely that it is due to the inhibition of its metabolism by some component of grapefruit. The literature suggests that grapefruit juice should be avoided during treatment with tacrolimus. Pyridoxine prevents photosensitization in patients treated with amiodarone, without altering the desired effects of the drug in any way. This photosensitization is due to the fact that amiodarone inhibits, as a side effect, the formation of melanin in the skin. Therefore, a diet low in this vitamin should be avoided when the patient is being treated with amiodarone.[92]

Oral administration of lidocaine with a meal rich in protein significantly increases the bioavailability of the drug due to a reduction in liver clearance, which reduces the first-pass effects, which are very marked for this drug.

Decreased liver clearance is due to increased splanchnic blood flow caused by protein intake. On the contrary, if the administration of lidocaine is intravenous, this increase in splanchnic flow produces a decrease in its bioavailability.

As a consequence, it is advisable to take oral lidocaine with food to improve bioavailability; while if it is administered intravenously, the intake close to the time of administration would not be recommended.[93]

Among all the AMI found in the review of the 285 articles, and of the 133 articles selected, many and very diverse interactions can be found when administering food with certain drugs and therefore modifying their therapeutic effect.

From the results obtained, the interaction of numerous drugs with a food that is grapefruit juice can be highlighted above all. For this reason, it is very interesting to emphasize the interaction of grapefruit juice in a more specific way.

Grapefruit is also known by the name of pamplemusa. This fruit is used fresh, due to its fiber rich in pectin that is mainly found in the white layer just under the skin and between the segments and the juice, with a high content of vitamin C. Citrus juices, especially juice grapefruit and orange are important sources of flavonoids, folate and vitamin C, for which various studies have considered their role in cardiovascular health.

The number of published studies on food-drug interactions has increased dramatically throughout the 1990s, and many of these investigations have yielded serious and unpredictable results.[94] The discovery that grapefruit juice can greatly increase the oral bioavailability of certain drugs came after an unexpected observation during a study analyzing the interaction between felodipine and ethanol in which grapefruit juice was used to mask the taste of ethanol. The results of the study showed that grapefruit juice works by reducing the presystemic metabolism of felodipine. Subsequently, it was known that the appearance of clinically relevant interactions through this mechanism with a large number of drugs is very likely.[8,66]

Grapefruit juice represents one of the most significant examples of food-drug interactions that occur in

metabolism. It has been shown to inhibit the metabolic activity of the cytochrome P450 isoenzyme CYP3A4 in the intestinal wall with almost no effect on hepatic CYP3A4, leading to an increase in the concentration of various drugs. The magnitude of the interaction is sometimes so great that a five-fold increase in oral absorption of a drug can be achieved.[66]

The mechanism of this interaction appears even more complicated, since in the human small intestine, CYP3A4 and P-glycoprotein form a coupled system to reduce xenotoxic exposure. Drug molecules that "escape" from the first extraction by intestinal CYP3A4 enzymes and are absorbed by epithelial cells can be excreted back into the intestinal lumen by GP, which is located on the brush border of the intestinal wall and also carries CYP3A4 substrates, re-exposing them to intestinal parad metabolism several times.[95]

This interaction may be clinically relevant, especially in drugs with a narrow therapeutic index, elderly patients or those with liver failure[66], and there is the possibility of serious interactions that affect multiple systems. Thus, cisapride, terfenadine, astemizole or pimozide can cause a prolongation of the QT interval of the electrocardiogram, but if it is administered with a CYP3A4 inhibitor such as grapefruit juice, this effect can occur with much greater probability.[96] Other serious interactions can occur when administering grapefruit with statins since it increases the risk of rhabdomyolysis that is described for these drugs.[83]

Finally, the articles on the interactions of those drugs with foods have not been included in the tables in which neither the food with which the drug or the nutrient interacted was specified in any case, however it is considered appropriate to detail in a way More schematized these interactions and include them in the results of this study.

In this way, there are studies in which it is detailed that food reduces the absorption rate of diclofenac but does not have a significant effect on its degree of absorption. Due to this, it is recommended to take it with food in order to avoid gastrointestinal discomfort.[97]

Food slows the absorption rate of ibuprofen but does not have a significant effect on its degree of absorption.[98] It is recommended to take it with food to avoid gastrointestinal discomfort. Food delays gastric emptying so the rate of absorption is often affected but not the degree of absorption of NSAIDs in general.

Food delays the rate of ketoprofen, and therefore the maximum plasma concentration, and the degree of absorption of ketoprofen.[99] It is recommended to take it with food to avoid gastrointestinal discomfort.

It has been observed that when indomethacin is administered with food, in some cases its peak plasma concentration can be delayed and reduced. On the other hand, this avoids gastric irritation produced by this drug.[100]

The joint intake of food with penicillamine causes a decrease in bioavailability, the rate of absorption remaining constant, while the amount absorbed is lower since a smaller proportion of the drug reaches the absorption sites. Therefore, it would be advisable to take it on an empty stomach.[101,102]

The bioavailability of penicillamine is also diminished by the presence of appreciable amounts of iron in the gastrointestinal tract, since a penicillamine-iron chelate is formed that cannot be absorbed.[101,102]

The ingestion of piroxicam with food causes a delay in the appearance of maximum serum levels, without affecting its total absorption; although it is not necessary to take special measures.[103]

Food can reduce the absorption of captopril although it appears to be of no clinical relevance.

However, it is recommended to take an hour before or two after meals.[104]

Food reduces the conversion of perindopril to perindropilat. It is recommended that the drug be ingested before consuming food.[105]

Sotalol absorption is reduced by joint food intake, so it is recommended to take the drug between meals.[106]

Administration of lansoprazole with food moderately reduces its bioavailability, however, this does not occur with omeprazole. Therefore, lansoprazole should be taken in the morning before eating any food.[107]

Giving propantheline with food causes a decrease in the anticholinergic effects of the drug. For best efficacy, it should be administered at least two hours before meals.[108]

Taking propylthiouracil with food may have a small and unsystematic influence on its absorption. Given the irregularity of the interaction, it is convenient to individually monitor the patients who may present it.[109]

Likewise, the joint intake of hydrocortisone with food delays its absorption. It is not recommended to take any special measures but it is suggested to follow the same administration schedule to maintain therapeutic levels.[110]

Oral administration of ampicillin with food produces a decrease in bioavailability, delaying the absorption of the drug and reducing its peak plasma concentrations. Therefore, ampicillin should not be taken with food for

optimal absorption, but should be administered one hour before or two hours after meals.[111, 112]

Co-administering cephalosporins with food causes a delay, and in some cases a decrease in their absorption. No special precautions are necessary except if absorption is seriously impaired, as with cephradine. In studies carried out with this type of cephalosporin, in pre- and postprandial conditions, it was observed that the serum level curve indicated a significant delay (one hour) and a reduction (approximately 50%) in the absorption of the drug administered in the postprandial state.[113,114]

The serum concentrations of hetacillin, obtained when the drug is administered orally with food, are lower than those corresponding to its intake in the fasting state, because food delays and reduces the absorption of the antibiotic. Because of this, oral administration of hetacillin is advised at times away from meals.[115]

The reduction of the bioavailability of lincomycin when administered with food has been proven since it is acid labile and therefore inactivated in the stomach, due to the low pH values of the medium. Food stimulates gastric secretions, slows gastric emptying and thus favors the breakdown of the drug. It is recommended to take the common drug a glass of water on an empty stomach, or one hour before meals or two after.[116]

The absorption of oxacillin and the other isoxazolylpenicillins is reduced if it is taken with food. This is apparently because these drugs are acid-labile and therefore break down in the stomach. An increase in acid secretions or a delay in gastric emptying produced by food increases the proportion of the altered drug. Therefore, to obtain optimal absorption, they should not be administered with meals.[117]

The joint intake of rifampicin with food decreases its maximum plasma concentration and its rate of absorption. The mechanism of action is unknown and it is recommended to ingest on an empty stomach (30 minutes before or 2 hours after meals in order to ensure rapid and complete absorption.[118,119]

The ingestion of food decreases the absorption rate of pyrazinamide, but not its magnitude, so it seems that it can be ingested without taking into account the meals.[120]

The administration of phenoxymethylpenicillin potassium orally with meals or shortly before or after them, causes a notable decrease in its bioavailability. Given that the absorption of penicillin takes place mainly in the duodenum and ileum and that penicillins are broken down in the stomach, due to the acidic pH and digestive enzymes, the presence of food, which increases these secretions and delays gastric emptying, will be a factor. important in reducing bioavailability. Because of this, it is recommended that the drug be taken at least one hour before meals or two hours after.[121]

The joint administration of tetracyclines with foods with a high content of divalent cations, especially calcium, can lead to a great decrease in the absorption of the antibiotic, due to the formation of insoluble complexes between them that are not absorbed. Other factors, such as gastrointestinal pH alteration, may also play a role. These drugs should be taken one hour before or two hours after meals, especially if the food to be eaten is rich in calcium or divalent metals.[122,123]

Food intake delays the absorption of ciprofloxacin, but does not reduce it.[124] Ciprofloxacin absorption is also reduced in enteral diets. They also cause a decrease in the maximum serum concentration of the drug. Antibacterial quinolones can form insoluble chelates with divalent ions, reducing their intestinal absorption. Preferably take it 1 hour before or 2 hours after meals.[125]

Food can decrease the degree of absorption of didanosine. It seems to be due to the fact that food delays gastric emptying and didanosine is exposed to prolonged contact with gastric acid which causes its degradation. It is therefore recommended to take it on an empty stomach.[126]

The absorption of fluorouracil is reduced if it is administered with food, as is the dilution rate in an acid medium, so there will be less availability of the drug for absorption. If the drug is taken orally, it may be advisable to take it between meals, always taking into account the influence of pH.[127]

The blood levels of methotrexate after oral administration, in the presence of food, are significantly lower than those obtained on an empty stomach. Food decreases the maximum plasma concentration of the drug and the total amount absorbed. Due to this, it should not be taken with meals since the adequate dosage is achieved by taking it on an empty stomach or with light meals.[128]

Eating food together with melphalan can decrease its absorption if it is administered orally, so it is recommended not to administer it with meals.[129]

Food taken together with temozolomide slightly reduces its maximum plasma concentration, so it is recommended to administer the drug without food.[19]

Food can reduce or delay the absorption of mercaptopurine. It appears that the cause is a delay in gastric emptying. It is recommended to administer on an empty stomach.[130]

The joint intake of hydrocortisone with food delays its absorption. It is not recommended to take any special

measures but it is suggested to follow the same administration schedule to maintain therapeutic levels.[131]

DISCUSSION

The importance of this work lies in the identification in a concrete and schematic way of the main interactions of food with drugs when they are administered jointly that are documented in the literature, with this in a global way it can be intuited if when a certain drug is administered, the patient who consumes it has suffered or may suffer a pharmacological interaction that alters the pharmacological effect of the drug when consuming certain foods. Simply in many cases by modifying the patient's diet without the need to modify the dosage of their medication, the desired therapeutic effect can be achieved.

As described above, it is considered that an interaction is in the negative sense when the food modifies the therapeutic effect of the drug, decreasing its pharmacological activity regardless of the mechanism of action by which this interaction occurs, which in many cases is unknown.

On the contrary, an interaction can be defined in a positive sense when the food modifies the therapeutic action of the drug, enhancing its pharmacological effect, also independently in this case of the mechanism of action by which this pharmacological interaction occurs.

Among the main foods that interact with drugs is coffee. There are 7 drugs that interact at the same time with coffee and tea in a negative sense and they are: 2 neuroleptics: fluphenazine and haloperidol, 2 benzodiazepines: diazepam and clonazepan, 1 antidepressant: lithium salts, 1 coronary vasodilator: dipyridamole and 1 mineral supplement: iron salts.

Grapefruit juice also stands out, with 18 drugs found to interact with: 1 antiepileptic: carbamazepine, 2 antihistamines: terfenadine and astemizole, 1 cardiotonic: digoxin, 1 antiarrhythmic: quinidine, 2 antimalarials: halofrantine and saquinavir, 1 anthelmintic: albendazole, 6 calcium channel blockers: felodipine, nisoldipine, nicardipine, nifedipine, nimodipine, and nitrendipine, 2 lipid-lowering drugs: lovastatin and simvastatin, 2 immunosuppressants: cyclosporine and tacrolimus, all of them in a positive sense.

There are 3 drugs that interact with grapefruit juice and fats at the same time and are: 1 antimalarial: halofrantine, 1 anthelmintic: albendazole and 1 antiviral: saquinavir, in all cases both interactions are positive.

Highlight the interest of the protein content of the diet when there is drug use since there are 8 interactions, 1 in a positive sense and 7 in a negative sense.

Highlight the grilled meats that present 3 interactions in a negative sense with drugs and the cruciferous that do so in a negative sense in 1 case.

Finally, it should be noted that the drug with which foods interact the most are iron salts, however these interactions in many cases are of no clinical interest, and the food that causes the most interactions is grapefruit juice, the vast majority in positive sense.

A review studied on the different interactions between foods and drugs that exist in the formulary highlights the importance of gastrointestinal pH in the absorption and bioavailability of drugs administered orally. Gastrointestinal pH is considered to be a very important factor that can significantly affect the absorption and oral bioavailability of the drug.[132] The effects of drugs on oral drug absorption can be achieved through direct and indirect mechanisms. For this reason, it considers that those foods that modify the gastrointestinal pH with greater intensity, acidic foods such as grapefruit juice, are responsible for a greater number of pharmacological interactions when administered together.

Another reviewed review highlights the importance of natural foods and plant supplements, increasingly important in the daily diet as staple foods, and their importance in AMI due to the content of bioactive ingredients in these foods. The interactions that occur are in many cases of a pharmacokinetic type: release, absorption, distribution, metabolism and excretion, as well as the interactions observed in the study work. As in the present work, the most clinically important interactions are those that occur in the metabolism of the drug and the observed effects can be beneficial and harmful, increasing or decreasing the therapeutic action of the drug administered jointly. Finally, like the present work, the importance of knowing and understanding the possible interactions between food and drugs and the specific results of said interactions is highlighted.[133]

Strengths and limitations

Among the strengths are the fact that no restriction of the year of publication has been made, with the aim of studying all the food-drug interactions that are described in the literature since the first journals began to describe the existing interactions between drugs. food and medicine. Another of the strengths of the present study is the nature of the design of the included studies, most of them being RCTs, which have been carried out under strict control conditions. On the other hand, the study has been carried out in all population groups, no group has been discriminated neither by age, nor by sex, nor by the existence of any pathology.

Taking into account the design of this work, it consists of an exhaustive review of the literature, but due to the timeframes it is not possible to have carried out a systematic review. One of the main limitations of the present work has been the exclusion of a food with

which a large number of drugs interact, such as alcohol, since there is a large volume of interactions, which would lead to another work with similar characteristics to the current one.

Another possible limitation has been that only published articles that are not indexed in online databases or that are published in books have been considered, so there may be a bias in relation to the sources consulted, as well as only including studies published in both English and Spanish.

Finally, it should be noted that the drugs studied are only of a chemical type, medicinal plants whose active principles also interact on numerous occasions with foods supplied together modifying their pharmacological activity have been excluded.

CONCLUSIONS

The number of AMI is very high and has been analyzed in the last decades with great exhaustiveness. AMI occurs through various mechanisms of action, both at the level of drug release, absorption, distribution, metabolism, and excretion. In many cases, the exact mechanism of action by which AMI occurs is not known.

However, it is considered necessary to verify and contrast many of the interactions described. On various occasions the observations or experiences made and the data obtained come from a small number of subjects. It seems that we do not always work with all the information that would be desirable, that is, with different population groups with various pathologies, so that the conclusions have a reasonable general value.

It has been proven that the fact that there is an interaction does not always hinder the action of the drug in a negative sense, sometimes AMI can be used to benefit therapeutics.

In general, in order for the drugs to reach high therapeutic levels, they should be administered outside of meals with a glass of water, as this achieves a higher gastric emptying speed.

In the event that those drugs that cause gastric irritation must be administered with food, they must also be administered with food if you want to delay their action or achieve lower plasma levels.

Among the main food-drug interactions detected are the interaction with grapefruit juice, coffee and tea.

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