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Dietary fiber and its interaction with drugs

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Abstract

As the intake of purified dietary fibers is increasing in the society, it is necessary to know how these fibers interact with simultaneously administered drugs, in order to ensure adequate therapeutic effects, minimizing the risk for adverse effects. This paper reviews the literature on the interactions between different types of purified fibers and several drugs.

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LA FIBRA DIETÉTICA Y SU INTERACCIÓN CON LOS FÁRMACOS

Resumen

El uso, cada vez más frecuente, de distintos tipos de fibra dietética en la población hace necesario conocer cómo interaccionan dichas fibras con los fármacos empleados simultáneamente, para garantizar un adecuado efecto terapéutico y minimizar la posibilidad de aparición de efectos adversos. En el presente trabajo se revisan las publicaciones relativas a las interacciones entre distintos tipos de fibras dietéticas purificadas y fármacos.

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Palabras clave: *Fibra dietética. Fármacos. Interacción.*

The bioavailability of orally administered drugs depends on the processes of absorption and plasma clearance, which can be affected by the presence of certain dietary components in the gastrointestinal tract.[1,2]

The information on the effect of food on drug absorption has increased during the past recent years. Nevertheless, it is not easy to assess to what extent they contribute to changes in the bioavailability of drugs, in treatment failures and toxicity. Thus, small changes in bioavailability may be clinically unimportant in the case of drugs with wide therapeutic index, but can have serious consequences particularly with drugs that have low therapeutic index or steep-dose response curves.[1-4]

It has been shown that food can decrease, delay, increase or accelerate the absorption of different drugs. Food can influence the absorption of drugs by different mechanisms. Thus, during digestion, the increase of splanchnic blood flow tends to *enhance the absorption* of the medicinal product, as the intestinal absorption depends on blood flow at the absorption site.[1]

On the other hand, food can also *decrease the absorption* of drugs by several mechanisms, such as altered gastric emptying rate resulting from food intake, the relatively rapid movement through the intestines as a result of increased peristalsis and/or alteration of the enterohepatic circulation.[1-3] In addition, food can act as a physical barrier, thereby preventing drug access to the absorptive surface of the gastrointestinal mucosa.[4-6]

Several papers reviewed the influence of different food components on the Pharmacokinetics and / or the clinical effect of several drugs.[7-12] The present paper reviews the literature concerning interactions between drugs and different types of purified dietary fibers (for an extensive information about dietary fiber see Rojas[13] and Escudero y González[14]).

The increasing intake of purified fibers in the treatment of diseases such as diabetes, hypercholesterolemia, chronic constipation or obesity, makes it necessary to know how these fibers interact with drugs used simultaneously in the treatment of these diseases. However, these studies are scarce, and their results variable. Most studies suggest that fiber interacts with drugs, while others did not find any interaction.

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Interactions with drugs acting on the nervous system

In 1990, it was reported that when a patient being treated with lithium ingested ispaghula husk (2 teaspoons daily), blood levels of the drug decreased (48%), recovering the normal blood values after ispaghula husk was discontinued.[15] Similar results were obtained in another study, that showed that this fiber reduced the absorption of lithium (in this case 14%), in 6 healthy volunteers.[16]

In 1992, it was observed that, after commencing a high fiber diet (different fiber supplements), 3 patients became refractory to treatment with tricyclic antidepressants (amitriptyline, doxepin and imipramine), coinciding with a decrease in the serum levels of these drugs. The removal of fiber intake led to the recovery of the normal serum levels of the antidepressants and the clinical improvement of the patients.[17]

On the other hand, a study conducted in 4 healthy volunteers concluded that the ingestion of a single dose of 200 mg of carbamazepine and 3.5 g of ispaghula husk resulted in subclinical concentrations of the drug and the reduced bioavailability of the compound was attributed to the fiber.[18]

A beneficial interaction was documented with an insoluble fibre and levodopa, a drug used for the treatment of Parkinson's disease. Consumption, for two months, of a dietary supplement fiber (bran of wheat, pectin and dimethylpolyoxylhexane; 28 g) with the usual dose of levodopa (525 mg daily) led to an elevation of levodopa plasma levels, especially at 30 and 60 minutes after oral intake. Also, in all patients, the severity of constipation improved significantly, as well as motor coordination. The authors suggested that this was due to the acceleration of drug absorption by shortened gastric emptying and increased gastrointestinal motility caused by the consumption of dietary fiber.[19]

One of the most frequent autonomic disorders in Parkinson's patients is constipation. Fiber therapy could be employed to reduce the symptoms of gastrointestinal motility disorders because fiber intake regulates stool transit in the small and in the large intestine. However, it is important to know if fiber administration could modify levodopa concentrations, because the onset of dyskinesias is related with the pharmacokinetics of the compound. In this way, an experimental study was carried out in rabbits to evaluate the influence of *Plantago ovata* husk in the pharmacokinetics of levodopa after a single administration of the drugs. Levodopa was administered alone at a dose of 20 mg/kg and with carbidopa (5 mg/kg), as it is usual in daily treatment. Fiber was given immediately before levodopa administration at two different doses: 100 mg/kg and 400 mg/kg. Fiber administration can reduce severity of dopamine mediated gastrointestinal and cardiovascular adverse effects by providing lower levodopa maximum concentrations (C_{max}) and also provide a more uniform response by maintaining plasma concentrations in a narrower range, when levodopa was administered alone[20] and in the presence of carbidopa.[21] A further study was carried out using repeated doses (during 7 and 14 days), and it was found that there was an improvement in the extent of levodopa absorbed with higher final concentrations and that levodopa elimination was slower with the administration of *Plantago ovata* husk.[22]

Other studies, however, could not demonstrate an interaction. Thus, it was shown that when 6.8 g of ispaghula husk were ingested with 1000 mg of carbamazepine the absorption of the compound did not change.[23]

Another study evaluated the influence of citrus pectin (14 g) on the Pharmacokinetics of valproic acid (500 mg; single dose) in healthy individuals.[24] These authors indicated that the fiber did not affect the absorption rate nor the amount of drug absorbed.

Interactions with lipid lowering drugs

In 29 hypercholesterolemic patients, gemfibrozil was administered alone (900-1,200 mg/day) or with guar gum (15 g/day) and it was observed that this combined therapy resulted in a higher lipid-lowering effect as compared to the effect of each separate compound. After 3 months of therapy, the decreases in total and LDL cholesterol levels were, respectively, 27 and 39% (combination therapy) and 14 and 10% (when using gemfibrozil alone). Furthermore, the HDL/LDL ratio was increased by 95 and 72%, respectively.[25]

In other studies, the interaction between dietary fiber and ion exchange resins (bile acid sequestrants) was investigated. Thus, one study[26] compared the efficacy of ispaghula husk (5 g), cholestipol (5 g) and combination of both (ispaghula Husk: 2.5 g + cholestipol: 2.5 g) to reduce cholesterol levels in 121 patients (with moderate hypercholesterolemia) treated 3 times daily during a period of 10 weeks. Higher decreases in cholesterol were achieved with the combination therapy (18.2% compared with 6.1 and 10.6%, respectively, for the fiber and the drug alone). According to the authors, this would result in a lower dose of the drug, and, consequently, in less adverse effects, as it could be constipation. Moreover, in cholesterol-fed hamsters, greater decreases in LDL cholesterol levels were found in animals receiving cholestyramine (1%) with psyllium (4%) than in hamsters that received the drug alone (55 and 33%, respectively). [27]

Another work evaluated the interaction between lovastatin, a cholesterol-lowering agent, and pectin, a fiber with known efficacy in lowering the LDL fraction of cholesterol. For a period of 4 four weeks, provided 15 g of pectin were administered daily to 3 patients that were ingesting 80 mg of lovastatin daily, and it was found that LDL levels increased 12, 52 and 58%, respectively. In all patients, LDL levels, measured 4 weeks after discontinuing the ingestion of the fiber, were similar to the pretreatment values. These results were explained by the capacity of pectin to reduce the intestinal absorption of lovastatin.[28]

Interactions with oral hypoglycaemic agents

Shima et al.[29] determined, during a of 6 hour period, the plasma concentration of sulphonylurea in 9 healthy volunteers who took 2.5 mg of glibenclamide together with 3.9 g of glucomannan, comparing the data obtained with the values found in the same individuals, who received the same dose of the hypoglycaemic agent, but not the fiber. The ingestion of glucomannan lowered (50%) the plasma concentration of glibenclamide at 30, 60, 90, 120 and 150 minutes. The authors suggested that glucomannan may influence the intestinal absorption of glibenclamide, diminishing the bioavailability of the drug.

In a later study,[30] the influence of a different fiber (guar gum) on the Pharmacokinetics of metformin, another hypoglycaemic drug, was evaluated. Thus, 10 g of guar gum were coadministered with 1.7 g of metformin to 6 healthy volunteers. It was shown that the absorption of the drug was delayed and that metformin plasma levels (determined during 6 hours) were lower (40%) compared with the administration of the compound alone (0.66 and 1.03 mg / ml, respectively). The investigators concluded that this combined intake could lead to a decrease in antihyperglycemic action of metformin.

Other authors, however, found no interaction between dietary fiber and hypoglycemic agents. Thus, in a study conducted in 10 healthy persons that received a single dose of 2.5 mg glipizide alone or with 4.75 g of guar gum, it was indicated that neither the $AUC_{0\text{-}8\,h}$ of the drug, nor the insulin and glucose levels (calculated during 3 hours after ingestion) differed between the two experimental protocols. The authors stated that this fiber does not deteriorate the absorption of glipizide and this lack of effect was attributed to the complete absorption of the drug.[31]

In addition, this fiber (guar gum, 5 g) ingested with glibenclamide (3.5 mg) did not interfere with the absorption of the drug in 9 diabetic patients.[32]

Interactions with drugs acting on the cardiovascular system

In a study conducted in 10 healthy volunteers that were given digoxin with guar gum, it was demonstrated that the fiber reduced the absorption of digoxin by, approximately, 16%.[33]

In another study,[34] in 16 healthy volunteers, the intake of 11 g of wheat bran with 0.4 mg of digoxin decreased $AUC_{0\text{-}24\,h}$ of the drug about 7%, but did not modified the values of C_{max}, t_{max}, or the amount detected in urine during 24 hours. Given these findings, it was suggested that this reduction would not be clinically important. Similar results were obtained in another trial[35] that determined the steady state concentrations of digoxin in 30 elderly patients that received the drug for 4 weeks, alone or with fiber (wheat bran or ispaghula husk). The addition of wheat bran lowered digoxin plasma levels (at 2 weeks but not at 4 weeks), although the concentrations remained within the therapeutic range. With ispaghula husk, no interference was observed.

Fassihi et al.[36] investigated the influence of an insoluble fiber (cellulose aqueous dispersion, 15 g) on the oral absorption of theophylline (200 mg), administered to 4 four healthy volunteers, and concluded that there was no interaction between both compounds.

Interactions with hormones

In 1993, it was reported that the intake of different fiber supplements (oat bran, soy fiber and ispaghula husk) decreased the bioavailability of levothyroxine in 13 hypothyroid patients, through a mechanism involving nonspecific adsorption of the drug to the fibers. Increased intake of dietary fiber may account for the need for larger than expected doses of this drug.[37]

Chiu and Sherman[38] measured the absorption of levothyroxine (600 g) with and without the simultaneous ingestion of ispaghula husk (3.4 g). After finding that the amount of drug absorbed, during the first 6 hours after ingestion, decreased only 9%, they concluded that this fiber is not lokely to cause malabsorption of levothyroxine.

On the other hand, Fernández et al.[6] carried out a study in female rabbits, to evaluate if the pharmacokinetics of ethinyloestradiol (administered by the oral route at a dose of 1 mg/kg) was modified by the administration of two commercial fibers containing a high percentage of insoluble fiber [product A: wheat bran (76,5%), fruit fiber (12%) and guar gum (2%); product B: *Plantago ovata* seeds (65%) and *Plantago ovata* husk (2,2%)]. These authors showed that the extent of ethinyloestradiol absorbed decreased between 29% and 35%, respectively, when it was administered with product A and product B, respectively. No other absorption and elimination parameter was modified except C_{max}, which was lower in the presence of the 2 fibers. To explain the results, it was suggested that the fiber acts as a mechanical barrier that avoids the access of the compound to the intestinal surface, lowering its absorption and shortening the duration of action.

In a similar study, García et al.[39] evaluated the influence of 2 soluble fibers (guar gum and psyllium) on the pharmacokinetics of this estrogen, when they were administered together to female rabbits by the oral route. In this study, all animals received 1 mg/kg of ethinyloestradiol, alone in the control group and with 3.5 g of guar gum or psyllium in the other 2 groups. When guar gum was administered, the results were similar to those found in the previous study,[6] there was a decrease in AUC (35,6%) and in C_{max} (32,2%) without variations in t_{max} (time to reach the maximum concentration), suggesting that these fibers have a similar mechanism of action. When psyllium was administered, the extent of athinyloestradiol absorbed increased slightly (AUC was a 4,5% higher) and the rate of absorption was slower.

In a further study, these authors established the influence of glucomannan (1,5 g), a soluble fiber with a extraordinarily high water-holding capacity, forming highly viscous solutions when dissolved in water, in the oral bioavailability of ethinylestradiol, when administered to female rabbits in two different dosage forms: enteric capsules and dispersed in water. The administration of glucomannan dispersed in water caused a reduction in the extent of estrogen absorbed (C_{max} was 1.4 times lower and AUC 1.9 times lower) without modifying the rate of absorption. However, after the administration of fiber in enteric capsules, AUC and C_{max} are higher (4.1 and 7.8 times, respectively) than when the estrogen was administered alone and also there is a delay in t_{max} (20 min). The authors indicated that the changes in the pharmacokinetic parameters of ethinyloestradiol could be explained by a modification in the enzymes that metabolize this compound in the gastrointestinal tract or by an improvement in its transcellular absorption.[40]

Interactions with antimicrobial drugs and chemotherapeutic agents

On the other hand, in a study carried out with 10 healthy volunteers who simultaneously received penicillin and guar gum, it was found that the pharmacokinetic parameters representative of drug absorption were altered, with lower values of C_{max} and AUC (25 and 28%, respectively).[33]

A recent investigation, performed in 64 patients with uncomplicated diverticular disease that were given fiber (bran: 20 g/day for 14 days) and rifamixin (1200 mg/day) concluded that the administration of the drug improves the benefits of dietary fibre by preventing its bacterial degradation.[41]

The interaction between dietary fiber and methotrexate, a compound used in chemotherapy with known adverse toxic reactions, was also studied. Thus, diets enriched with soluble (pectin) and insoluble fiber (cellulose) were given to rats previously injected methotrexate. The addition of fiber did not lessen toxicity symptoms, such as anorexia or diarrhea.[42]

Other interactions

Finally, the influence of guar gum ingestion (15 g) on the absorption of paracetamol, hydrochlorothiazide and cimetidine (500, 50 and 300 mg, respectively) was studied in dogs. Both the rate and extent of paracetamol and hydrochlorothiazide absorption were significantly decreased with fiber consumption (reduction in C_{max} of 65 and 59% respectively, and AUC of 28 and 35% respectively). In the case of cimetidine significant differences were only detected in C_{max}, that decreased 62%.[43]

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