Clinical and Practical **Psychopharmacology**

Fruit Juice, Organic Anion Transporting Polypeptides, and Drug Interactions in Psychiatry

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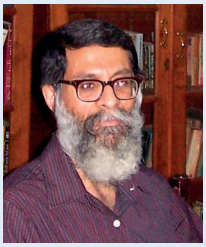

Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Organic anion transporting polypeptides (OATPs) are a group of membrane transport proteins that facilitate the influx of endogenous and exogenous substances across biological membranes. OATPs are found in enterocytes and hepatocytes and in brain, kidney, and other tissues. In enterocytes, OATPs facilitate the gastrointestinal absorption of certain orally administered drugs. Fruit juices such as grapefruit juice, orange juice, and apple juice contain substances that are OATP inhibitors. These fruit juices diminish the gastrointestinal absorption of certain antiallergen, antibiotic, antihypertensive, and β-blocker drugs. While there is no evidence, so far, that OATP inhibition affects the absorption of psychotropic medications, there is no room for complacency because the field is still nascent and because the necessary studies have not been conducted. Patients should therefore err on the side of caution, taking their medications at least 4 hours distant from fruit juice intake. Doing so is especially desirable with grapefruit juice, orange juice, and apple juice; with commercial fruit juices in which OATP-inhibiting substances are likely to be present in higher concentrations; with calcium-fortified fruit juices; and with medications such as atenolol and fexofenadine, the absorption of which is substantially diminished by concurrent fruit juice intake.

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Clinical Question

Apple juice and orange juice are popular beverages. Could drinking apple or orange juice regularly, or taking medications with these beverages instead of with water, result in clinically significant food-drug interactions in patients receiving psychotropic medications?

Fruit Juices: Benefits and Risks

Fruit juices contain vitamins, antioxidants, electrolytes, trace elements, and other nutrients that are associated with potential health benefits; for example, constituents with anti-inflammatory, antioxidant, antiobesity, antidiabetic, and antitumoral properties have been identified in pomegranate juice.[1,2] This may explain why fruit juice intake is associated with clinically relevant gains in observational studies; for example, the regular intake of fruit and vegetable juice may delay the onset of Alzheimer's disease.[3]

Apples are traditionally associated with large health benefits, as implied by the proverb "An apple a day keeps the doctor away." In vitro, in vivo, and even clinical data on the antioxidant, antiproliferative, and cell signaling effects of apple juice suggest the possibility of benefits related to cognitive decline of normal aging, diabetes, weight management, bone health, pulmonary function, and gastrointestinal function.[4] Orange juice is similarly associated with health benefits. For example, orange juice reduces low-density lipoprotein cholesterol levels[5] and may have favorable effects on bone health.[6] Anti-inflammatory, antioxidant, cytoprotective, antigenotoxic, and antitumoral constituents have been identified in orange juice.[7]

Consumption of fruit juice is also associated with health concerns; for example, a meta-analysis of cohort studies showed that the regular intake of sugar-sweetened (but not 100% natural) fruit juice increased the risk of diabetes mellitus.[8] Additionally, many fruit juices contain substances that can cause drug interactions. In this regard, grapefruit juice–drug interactions involving cytochrome P450 (CYP)3A4 are well known,[9] and pomegranate juice–drug interactions were recently examined in this column.[10] The present article examines how fruit juice intake may influence the bioavailability of orally administered medications.

Fruit Juice and Organic Anion Transporting Polypeptides

Organic anion transporting polypeptides (OATPs) are membrane transport proteins that facilitate the sodium-dependent influx of endogenous and exogenous substances across biological membranes.[11] There are 11 human OATPs, subdivided into 6 families (Table 1). These OATPs are found in the intestinal wall, where they facilitate the absorption of drugs into circulation; in liver cells, where they facilitate the absorption of drugs into the hepatocytes so that the drugs can be metabolized; and in other tissues, such as the heart, kidney, and brain, as well.[11,12]

Grapefruit, orange, apple, and other fruit juices contain substances such as naringin, hesperidin, phloridzin, phloretin, and quercetin that

Clinical Points

- Apple and citrus fruit juices have been shown to diminish the intestinal absorption of drugs such as fexofenadine, montelukast, ciprofloxacin, aliskiren, atenolol, celiprolol, and talinolol.
- Other than the well-known interaction between grapefruit juice and CYP3A4 substrates, there are no published studies, so far, on the effect of fruit juice on the intestinal absorption of psychotropic medications.
- Patients should ideally err on the side of caution and take their medications at least 4 hours distant from fruit juice intake. This is particularly desirable if patients drink commercial and calcium-fortified fruit juices.

separately and together inhibit various OATPs[13]; these are present in greater concentration in commercial fruit juice than in freshly squeezed fruit juice.[11] The implication is that fresh or homemade fruit juice is less likely to inhibit drug absorption than commercial fruit juice.

Fruit Juice and OATP Substrates

Human OATPs were first discovered less than 2 decades ago,[12] which may explain why so few OATP substrates have so far been identified. Table 2 lists OATP substrates the absorption of which is known to be diminished by concurrent fruit juice intake. The decreased bioavailability of some of these substrates can be substantial; for example, 1 study found that drinking 600 mL of apple juice across 1.5 hours following drug administration reduced atenolol exposure by 58%, and drinking 1,200 mL of apple juice across 3 hours reduced atenolol exposure by 82%.[14]

In general, studies show that substrate absorption is diminished to a greater extent with larger quantity of juice intake and with greater proximity of juice intake to substrate intake. A 4-hour interval is recommended between juice and substrate intake because this is the duration for which OATP inhibition by fruit juice (especially apple and orange juice) has been shown to last.[11,15]

Interestingly, there are many OATP substrates the absorption of which is not significantly influenced by concurrent fruit juice intake (Table 3). This may be because OATPs may not play a large role in the absorption of some of these drugs. It may also be because that inhibition of certain OATPs can reduce the uptake of the drugs into hepatocytes, thereby diminishing their metabolism and thereby compensating for diminished gastrointestinal absorption, if any.[11]

Rosuvastatin, sotalol, and methotrexate are also OATP substrates.[11] However, there are no data, as yet, on whether or not their absorption is affected by fruit juice intake.

As already stated, the extent to which fruit juice interferes with drug absorption will depend on whether or not the drug is an OATP substrate and on the concentration of the fruit juice, the quantity of juice consumed, and the timing of juice intake relative to drug intake. Additionally, the OATP-inhibiting constituent concentration in fruit juice will depend on imponderables such as the fruit species, the geographic origin of the fruit, the season of harvesting, the fruit maturity at the time of juice extraction, and manufacturing and storage conditions[11]; therefore, all of these variables will also influence the degree to which drug absorption may be compromised by fruit juice intake.

The research on the subject is largely confined to OATP interactions with grapefruit juice, orange juice, and apple juice. There is no information on OATP interactions with other citrus fruit juices (eg, lemon juice) or other fruit juices (eg, pomegranate juice). It is likely that the subject has not been studied in these regards.

Table 1. Human Organic Anion Transporting Polypeptides and Their Tissue Distribution[a]

OATP1A2: Brain, kidney, liver, intestine
OATP1B1: Liver
OATP1B3: Liver
OATP1C1: Brain, testis, ciliary body
OATP2A1: Ubiquitous
OATP2B1: Liver, placenta, intestine, heart, skin
OATP3A1: Ubiquitous
OATP4A1: Ubiquitous
OATP4C1: Kidney
OATP5A1: Unknown
OATP6A1: Testis

[a]Based on Kalliokoski and Niemi.[12]

Table 2. Organic Anion Transporting Polypeptide Substrates the Absorption of Which May Be Diminished by Concurrent Fruit Juice Intake[a,b]

Antiallergens: fexofenadine, montelukast
Antibiotics: ciprofloxacin
Antihypertensives: aliskiren
β-blockers: atenolol, celiprolol, talinolol

[a]Studies conducted on grapefruit juice, apple juice, and orange juice.
[b]Based on Dolton et al.[11]

Table 3. Organic Anion Transporting Polypeptide Substrates the Absorption of Which Is Probably Uninfluenced by Concurrent Fruit Juice Intake[a,b]

Antibiotics: levofloxacin
Antidiabetics: glyburide, repaglinide
β-blockers: acebutolol
Hormones: thyroxine
Statins: pitavastatin, pravastatin

[a]Studies conducted on grapefruit juice, apple juice, and orange juice.
[b]Based on Dolton et al.[11]

OATP-Mediated Interactions: Relevance to Psychiatry

There seems to be no published literature, so far, on the relevance of OATP mechanisms to the pharmacokinetics of psychotropic drugs.[11,12,16] OATP1A2 and OATP1C1 are found in the brain; however, substrates of these transporters, listed in reviews,[12,16] do not include any psychotropic agent other than thyroxine. The importance of dosing thyroxine remote from the consumption of fruit juice has already been discussed in a previous article in this column.[17]

A search of the PubMed database (conducted on October 3 and 4, 2014) combining the search term *OATP* with

antipsychotic, antidepressant, benzodiazepine, and other psychotropic agents by class and by individual drug names yielded no relevant publications. There were also no relevant results with searches using the search terms *apple juice* and *orange juice* with *interactions*. This does not mean that OATPs are irrelevant to psychotropic drugs; it means, more likely, that the subject has not yet been studied.

Medical comorbidity is common in psychiatry, and some patients with major mental illness may be receiving drugs the absorption of which is diminished by fruit juice (Table 2). Physicians should then necessarily provide the guidance expressed in the concluding section of this article.

Fruit Juice and Non-OATP Interactions

This article has so far focused on OATP-related drug interactions in the context of grapefruit, orange, and apple juice. Readers are reminded about CYP3A4-related drug interactions with grapefruit juice, to which reference was made at the beginning of this article.[9] Similar concerns may apply to other citrus fruit as well; for example, CYP3A4 interactions may occur with Seville (sour) orange juice,[18] although evidence of clinically significant interactions remains to be published. Complicating the picture, grapefruit juice and perhaps orange juice, as well, contain ingredients that inhibit P-glycoprotein, an efflux transporter that also influences the intestinal absorption of drugs.[19,20] Finally, commercial juices are sometimes fortified with nutrients that are themselves capable of producing interactions; thus, calcium-fortified orange juice can reduce the bioavailability of fluoroquinolone antibiotics.[21–23]

Recommendations

Given the nascence of the field, the best guidance that can be provided to patients is to advise them to take their medications at least 4 hours distant from fruit juice intake. This guidance is particularly applicable to patients who use medications listed in Table 2 and those who drink significant quantities of grapefruit juice, apple juice, and orange juice, especially when these juices are commercially sourced (and when they are calcium-fortified) rather than prepared at home, directly from the fruit.

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