



Important Drug Interactions



Grapefruit juice, St. John's wort and iron supplements are a few products that can have adverse reactions with prescription medications. Understanding the mechanism of drug interactions and encouraging patients to discuss self-initiated health maintenance can reduce the likelihood of such adverse effects.

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Drug interaction is a measurable modification in magnitude or duration of the action of one

drug by prior or concomitant administration of another substance, including prescription and non-prescription drugs, food or alcohol.

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The Scope of Drug Interactions

Polypharmacy is an inevitable consequence of attempts by physicians and other members of the health-care team to manage multiple and chronic diseases, especially among the elderly patient

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population. As a result of the common use of drugs as therapy, the potential for interactions is almost certain. This complicates determining the cause of symptoms often reported by patients.

The potential for drug-drug interactions is enormous. Assuming the physician may prescribe 600 drugs, there are 179,700 possible combinations for the prescription of any two of them, 35,820,200 possible combinations for the prescription of any three of them, and 5,346,164,850 possible combinations for the prescription of any four of them. Obviously, it is impossible to know all possible drug interactions that may occur under these circumstances. As a further complication, we are becoming increasingly aware of drug-food interactions and drug interactions with herbal remedies, which are often patient-initiated without consultation with the physician. Drug interactions related to patient-initiated health maintenance is the focus of this article.

Three candidate substances involved in patient-initiated efforts to maintain health have been chosen to illustrate the potential for interactions with prescribed medications. They are: St. John's wort, grapefruit juice and iron supplements.

Drug Interactions With St. John's Wort

Formulations of this herbal preparation have been used for centuries. Only recently has there been a focus with modern scientific research methods to evaluate the long-standing claims of its efficacy as a therapeutic intervention and its potential for drug interactions. There is pharmacological evidence to support antibacterial, antiviral and antidepressant activities.¹ There is now reasonable evidence for the efficacy of St. John's wort in the management of mild to moderate depression, as compared to treatment with imipramine, and many patients initiate

Summary

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- The potential for drug-drug interactions is enormous. As a further complication, we are becoming increasingly aware of drug-food interactions and drug interactions with herbal remedies, which are often patient-initiated without consultation with a physician.
- Important drug interactions with St. John's wort include decreased bioavailability of digoxin, cyclosporine, protease inhibitors, oral contraceptives and, possibly, theophylline and amitriptyline.
- Grapefruit juice differs from other citrus fruits in that it contains inhibitors of not only the drug metabolizing enzyme isoform CYP3A4, but also the intestinal P-glycoprotein transporter. The effects of grapefruit juice last at least 24 hours and are maximal after the first glass. Daily ingestion of grapefruit juice, therefore, could be expected to enhance the accumulation of drugs ingested chronically and may lead to unexpected toxicity for drugs with a narrow therapeutic index.
- Iron supplements are commonly consumed by elderly patients as over-the-counter preparations, and ferrous sulfate is often prescribed by physicians. Iron has long been known to decrease the bioavailability of tetracycline drugs, but interactions with other commonly prescribed drug treatments is less well appreciated.

therapy with this herbal remedy without seeking medical advice.^{2,3} St. John's wort has not been proven effective, however, for the management of major depression.⁴

Until recently, it was claimed this remedy was safer than modern conventional prescribed treatments for depression. With increased research, however, the use of St. John's wort is being shown as associated with an increasing number of drug interactions that may be clinically important.

These include decreased bioavailability of digoxin, cyclosporine, protease inhibitors, oral contraceptives and, possibly, theophylline and amitriptyline. Clinical consequences of these interactions may include reduced inotropic effect after the use of digoxin, increased risk of organ rejection with cyclosporine therapy, decreased suppression of human immunodeficiency virus (HIV) with protease inhibitor therapy and increased breakthrough bleeding in patients on low-dose estrogen oral contraceptives. Concomitant use of St. John's wort with selective serotonin reuptake inhibitor antidepressants can result in serotonin syndrome.⁵

A list of prescribed drugs currently known to have clinically important interactions with St. John's wort is presented in Table 1. Initially, the mechanism for this interaction was attributed to induction of the oxidative drug-metabolizing cytochrome P450 enzyme isoform CYP3A4.⁶ This is the most abundant form of cytochrome P450 in human liver tissue and its induction has implications for reducing the circulating concentration and, therefore, the efficacy, of many drugs administered to patients.⁷ This effect, however, does not explain the ability of St. John's wort preparations to reduce the bioavailability of digoxin.⁸ It is now known that this herbal remedy also induces the intestinal transporter P-glycoprotein/MDR1. This mechanism

Table 1

Prescribed Medication That Interacts With St. John's Wort

Amitriptyline
Cyclosporine
Digoxin
Nefazodone
Oral contraceptives
Paroxetine
Protease inhibitors
Theophylline

most likely explains the drug interaction with digoxin, since this transport system acts to reduce drug absorption across the intestinal epithelium.⁹ Some drugs are substrates for both the P-glycoprotein transporter and CYP3A4. Both mechanisms, therefore, could contribute to the reduced bioavailability of some orally-administered drugs. The contribution of P-glycoprotein to drug interactions with St. John's wort, however, is less firmly established by scientific data.

It is important to discuss with patients the potential of St. John's wort preparations to confound physician-prescribed medications. Patients should be advised against taking St. John's wort alongside prescription drugs. Patients also need to be reminded that they should discuss any self-initiated efforts at health maintenance with their physician to determine whether this activity may have undesired effects on their currently prescribed drug treatments.

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Table 2

Prescribed Medication That Interacts With Grapefruit Juice

Amiodarone
Buspirone
Carbamazepine
Clomipramine
Dihydropyridine calcium channel blockers
HMG-CoA reductase inhibitors
Immunosuppressants
Protease inhibitors

Drug Interactions With Grapefruit Juice

Drinking citrus fruit juice as part of a healthy diet is a widespread practice in North America. It is now appreciated, however, that grapefruit juice differs from other citrus fruits in that it contains inhibitors of not only the drug metabolizing enzyme isoform CYP3A4, but also the intestinal P-glycoprotein transporter.¹⁰ Initiation of daily ingestion of grapefruit juice, therefore, will have entirely different consequences with respect to drug interactions, as compared to St. John's wort.

The discovery of drug interactions with grapefruit juice was a chance observation first reported in studies with the calcium channel blocker, felodipine.¹¹ In this instance, the bioavailability of felodipine and, therefore, its concentration in the blood plasma, was greatly increased by the concurrent ingestion of grapefruit juice. The effects of grapefruit juice last at least 24 hours and the effect is maximal



after the first glass.¹² Daily ingestion of grapefruit juice, therefore, could be expected to enhance the accumulation of drugs ingested chronically and lead to unexpected toxicity for drugs with a narrow therapeutic index. Both flavonoids (naringin, naringenin, quercetin and kaempferol) and furanocoumarins (bergamottin and 6',7'-dihydrobergamottin) present in grapefruit have been implicated as responsible components in drug-grapefruit interactions, but it is not yet clear whether all of the components responsible for the interaction have been identified.¹³ Subsequent studies have shown grapefruit juice increases the bioavailability of most of the calcium channel blockers, many of the HMG-CoA reductase inhibitors, some protease inhibitors, cyclosporine, amiodarone, buspirone, sertraline, carbamazepine and ethinyl estradiol. A listing of known drug interactions with grapefruit juice is presented in Table 2. In these cases, the mechanism of the interaction is thought to be due to the inhibition of intestinal CYP3A4. Interaction with the P-glycoprotein transporter is complicated by the recent discovery of genetic variants that differ in frequency with ethnic origin of the patient.¹⁴ Clinical studies with digoxin, cyclosporine, fexofenadine and other substrates specific for the P-glycoprotein transporter have yielded variable results, supporting the hypothesis that enhanced intestinal P-glycoprotein activity will reduce drug bioavailability. The ultimate effect on P-glycoprotein by grapefruit juice remains to be determined from additional clinical studies.

Inhibiting CYP3A4 enzyme activity can have substantial pharmacokinetic and pharmacodynamic effects.¹⁵ For example, it is suspected that concomitant ingestion of HMG-CoA reductase

inhibitors with grapefruit juice could lead to an increased risk of rhabdomyolysis, due to drug accumulation. An alternative strategy, however, would be to prescribe pravastatin, a member of the statin drug class that is not significantly metabolized by CYP3A4. As a general principle, patients ingesting drugs with low bioavailability by the oral route should be encouraged to consume a fruit juice other than grapefruit juice.

Clinical research has demonstrated that ingesting grapefruit juice reduces intestinal CYP3A4 activity to a common low level in people who normally have a widely variable expression of this enzyme in the intestine.¹⁶ This interaction, therefore, could be used for some expensive drug treatments to reduce the required dose to maintain therapeutic concentra-

Table 3

Prescribed Medication That Interacts With Iron Supplements

Bisphosphonates
Captopril
Carbidopa
Cephalosporin antibiotics
Levodopa
Methyldopa
Penicillamine
Quinolone antibiotics
Tetracycline antibiotics
Thyroxine

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tions in the circulation. Studies are ongoing to determine the feasibility of such an approach to drug therapy for expensive agents having a high first-pass elimination after oral administration (*i.e.*, cyclosporine).

Drug Interactions With Iron Supplements

Iron supplements are commonly consumed by elderly patients as over-the-counter preparations, and ferrous sulfate is often prescribed by physicians.¹⁷ Iron has long been known to decrease the bioavailability of tetracycline drugs, but interactions with other commonly prescribed drug treatments is not as well appreciated.¹⁸

The mechanism of the interaction is reduced bioavailability of many concurrently administered drug treatments. Since iron has the capacity to bind six functional groups, a very small quantity is capable of binding a substantial number of drug molecules. Iron exists in two ionized states in the body — ferrous and ferric — having a double-positive and triple-positive charge, respectively. The ferric form binds more strongly to drug molecules. Although iron is usually administered in the ferrous form, it is readily converted to the ferric form in the gastrointestinal (GI) tract, and with greater efficiency at the higher pH of the duodenum.¹⁹

Physicians may be deceived by a sudden worsening of a patient's condition, which may, in fact, be related to reduced bioavailability of the prescribed drug therapy, rather than to progression of the pathophysiological process. Two clinically important examples are the lack of efficacy of replacement thyroxine when coingested with ferrous sulfate and the sudden loss of efficacy of sinemet in patients with Parkinson's disease who coingest an iron supplement.^{20,21} A listing of known drug interactions with iron is presented in

Table 3. Generally, these interactions may be expected to include the tetracycline antibiotics, many of the newer fluoroquinolones and catecholamine-containing drug molecules. Administering the iron-containing medication as much as two hours earlier still produced reduced bioavailability of the other candidate drug.¹⁸

The role of other metal micronutrients on drug bioavailability is less well understood, but there is evidence for the ability of zinc to reduce the bioavailability of ciprofloxacin, as well.²² This interaction could also occur by concurrent use of zinc lozenges with a prescribed fluoroquinolone.

As a general principle, physicians should discourage patients from ingesting multivitamins containing iron, ferrous sulfate or zinc lozenges with concurrently administered drug therapy of the types identified above.

Summary

In most situations, the risk of an important adverse drug interaction is small. There are, however, identifiable settings in which these interactions are more likely to occur. Recognizing these settings, understanding the mechanism of the interaction(s) and encouraging patients to discuss self-initiated health maintenance interventions should reduce the likelihood of these drug interactions. CME

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Suggested Readings

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