

Drug Administration and Grapefruit Juice

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The following is an overview of drug administration and grapefruit juice consumption. This information is not intended to present a comprehensive review; the reader is therefore encouraged to seek additional and confirmatory information.

Recently, drug interactions with grapefruit juice have received considerable attention. The selection of drugs presented in the following table is based on information contained in product monographs in the *CPS* and on information cited in reputable references. The table outlines pharmacokinetic and pharmacodynamic effects of concurrent grapefruit juice and drug administration known to date as well as management options. It should not be assumed that the drugs in the table should never be taken concomitantly with grapefruit juice or that drugs not appearing in the table do not interact.

Studies have shown that grapefruit juice acts as an inhibitor of intestinal isoenzymes. In particular, grapefruit juice inhibits intestinal CYP 3A4-mediated metabolism which is believed to be responsible for grapefruit juice effects. There appears to be a prolonged inhibitory effect of grapefruit juice on intestinal CYP 3A4-mediated metabolism, therefore, separating the dose of the drug from ingestion of grapefruit juice may not prevent an interaction. Enzyme inhibition by grapefruit juice has been shown to increase the serum concentration of drugs with high first-pass metabolism. Although most studies have used grapefruit juice prepared from frozen concentrate, all forms of grapefruit (fresh juice and whole fruit included) have the potential to affect intestinal CYP 3A4.

The exact grapefruit juice constituent responsible for this enzyme inhibition has not yet been conclusively identified. While sweet orange juice does not appear to cause the same interaction, sour (Seville) orange juice has similar enzyme inhibitory effects. The quantity of grapefruit juice

consumed is important to consider, since as little as 250 mL can cause significant inhibition of CYP 3A4.

The clinical significance of the interaction is determined by the grapefruit juice-induced change in drug bioavailability relative to the therapeutic range for the individual drug (i.e., drugs with a wide therapeutic index may be less affected than drugs with a narrow therapeutic index) and the individual's susceptibility (e.g., patients with hepatic insufficiency or pre-existing medical conditions). Most of the reported studies of interactions with grapefruit juice are from single-dose studies in healthy volunteers. Repeated dosing of grapefruit juice may increase the effect of many drugs.

Little or no effect is observed when usual amounts of grapefruit juice are ingested concomitantly with parenterally administered drugs (e.g., i.v. midazolam, nifedipine). Also, no interaction would be expected with the use of transdermal dosage forms (e.g., estradiol-17 β patch) since usual amounts of grapefruit juice have little effect on hepatic CYP 3A4. Large amounts of grapefruit juice administered under experimental conditions (e.g., 200 mL double-strength juice three times daily) have been shown to inhibit hepatic CYP 3A4.

If a drug is not listed in the table, there may be no information or inconclusive information known about the interaction (e.g., imipramine, verapamil). Also, drugs that have been studied and found not to interact have not been included. The recommendations in the table are not absolute. Interpretation of the information requires clinical judgement and evaluation of the interaction using other sources.

Table I—Drug Administration and Grapefruit Juice

Drug*	Grapefruit Juice Effect	Management
Amiodarone	<ul style="list-style-type: none"> Repeated doses of grapefruit juice markedly increase amiodarone levels. Evaluated in controlled studies in healthy volunteers; increased AUC and C_{max}. 	<ul style="list-style-type: none"> Avoid grapefruit juice; other juices not known to interact. If used in combination, monitor for adverse effects associated with increased serum levels of amiodarone (e.g., bradycardia, elevation of liver enzymes).
Atorvastatin	<ul style="list-style-type: none"> Grapefruit juice may increase plasma levels of HMG CoA reductase inhibitors metabolized by CYP 3A4. Atorvastatin appears to be affected to a lesser extent than lovastatin and simvastatin. 	<ul style="list-style-type: none"> Avoid consumption of grapefruit juice; other juices not known to interact. Consider choosing a HMG CoA reductase inhibitor not metabolized by CYP 3A4 (e.g., pravastatin and fluvastatin). If used in combination, monitor for adverse effects associated with increased serum levels of atorvastatin (e.g., myopathy, rhabdomyolysis).
Benzodiazepines, see diazepam, triazolam		
Budesonide	<ul style="list-style-type: none"> Substantial intake of grapefruit juice may increase systemic exposure to orally administered budesonide. The bioavailability of orally administered budesonide was approximately doubled in male subjects taking 600 mL of concentrated grapefruit juice per day for 4 days. 	<ul style="list-style-type: none"> Avoid consumption of grapefruit juice; other juices not known to interact. If used in combination, monitor for adverse effects associated with the use of glucocorticoids (e.g., hyperglycemia, Cushingoid features).
Buspiron	<ul style="list-style-type: none"> Repeated doses of grapefruit juice markedly increase buspiron serum concentration. 	<ul style="list-style-type: none"> Avoid grapefruit juice; other juices not known to interact. If used in combination, monitor for adverse effects associated with increased serum levels of buspiron (e.g., sedation and psychomotor impairment).
Calcium Channel Blockers, see felodipine, nifedipine, nimodipine		
Carbamazepine	<ul style="list-style-type: none"> May increase carbamazepine serum levels. Evaluated in small controlled study of epileptic patients; increased AUC, peak and trough concentrations. 	<ul style="list-style-type: none"> Avoid grapefruit juice; other juices not known to interact. If used in combination, monitor for signs of carbamazepine toxicity (e.g., drowsiness, dizziness, headache, unsteadiness on the feet, diplopia, nausea, vomiting).
Carvedilol	<ul style="list-style-type: none"> Can result in higher plasma levels of carvedilol due to reduced drug metabolism. Evaluated in controlled studies; increased area under curve (AUC). 	<ul style="list-style-type: none"> Evidence of this interaction is limited. If used in combination, monitor for adverse effects associated with increased serum levels of carvedilol (e.g., low blood pressure and bradycardia).
Clomipramine	<ul style="list-style-type: none"> May increase clomipramine serum levels. The interaction between grapefruit juice and other tricyclic antidepressants has not been established. 	<ul style="list-style-type: none"> Avoid consumption of grapefruit juice; other juices not known to interact. If used in combination, monitor for adverse effects associated with increased serum levels of clomipramine (e.g., drowsiness, hypotension, respiratory depression, cardiovascular disturbances, anticholinergic effects, agitation).

*The list of drugs in this table is not exhaustive. As more drugs in combination with grapefruit juice are studied, the list of interactions may change.

Table I—Drug Administration and Grapefruit Juice (*cont'd*)

Drug*	Grapefruit Juice Effect	Management
Cyclosporine	<ul style="list-style-type: none"> • May increase plasma levels of cyclosporine. • Evaluated in controlled studies; increased AUC and increased plasma concentration. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for symptoms of toxicity (e.g., nephrotoxicity, hepatotoxicity, increased immunosuppression). • Monitor cyclosporine effect particularly when grapefruit juice is initiated, discontinued or the interval between drug and grapefruit juice ingestion changes. • Lower doses of cyclosporine may be required.
Diazepam	<ul style="list-style-type: none"> • May increase diazepam levels. • Evaluated in controlled studies in healthy volunteers; increased AUC and C_{max}. 	<ul style="list-style-type: none"> • Clinical importance is unknown. • It is likely that some patients would be adversely affected especially those in whom diazepam levels are likely to be elevated (e.g., older individuals, those with liver impairment or concurrent use of other cytochrome P450-inhibitors). • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for increased sedation.
Erythromycin	<ul style="list-style-type: none"> • Grapefruit juice may increase serum concentrations of erythromycin. • Evaluated in an open crossover study in six healthy subjects; increased C_{max} and AUC. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for adverse effects that may be associated with erythromycin.
Ethinyl Estradiol	<ul style="list-style-type: none"> • Appears to increase serum concentrations of ethinyl estradiol. • Theoretically, grapefruit juice may affect the metabolism of other estrogens. 	<ul style="list-style-type: none"> • Clinical significance is not established. • Avoid consumption of grapefruit juice; other juices not known to interact. • If used in combination, suggest maintaining a consistent interval between drug and grapefruit juice ingestion when possible.
Felodipine	<ul style="list-style-type: none"> • Can increase plasma levels and intensify the clinical effects of some 1,4-dihydropyridine calcium channel blockers. • Can significantly increase plasma felodipine levels. • May be affected to a greater extent than other dihydropyridine calcium channel blockers. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for adverse effects associated with increased serum concentrations of felodipine (e.g., decreased diastolic blood pressure, increased heart rate, flushing, headache and lightheadedness).
HMG CoA reductase inhibitors, see atorvastatin, lovastatin, simvastatin		
Itraconazole	<ul style="list-style-type: none"> • May decrease itraconazole serum levels. • Evaluated in controlled study in healthy volunteers; decreased AUC and C_{max}. This effect has not been consistently shown in all studies. • May occur with ketoconazole but no data exists. 	<ul style="list-style-type: none"> • Avoid consumption of grapefruit juice. • If used in combination, monitor patient for loss of efficacy.
Lovastatin	<ul style="list-style-type: none"> • Repeated doses may result in increased lovastatin serum concentrations. • Simvastatin appears to be similarly affected by grapefruit juice; however, atorvastatin is not as greatly affected. 	<ul style="list-style-type: none"> • Avoid consumption of grapefruit juice; other juices not known to interact. • Consider choosing a HMG CoA reductase inhibitor not metabolized by CYP 3A4 (e.g., fluvastatin and pravastatin). • If used in combination, monitor for signs of adverse effects associated with increased serum concentrations of lovastatin (e.g., myopathy, rhabdomyolysis).
Methylprednisolone	<ul style="list-style-type: none"> • Grapefruit juice may increase serum concentrations and half-life of methylprednisolone. • Evaluated in a crossover study in ten healthy subjects; repeated administration of double-strength grapefruit juice increased AUC, C_{max} and half-life of methylprednisolone. Clinical significance unknown. The effect on half-life shown in this study is likely a function of the large doses of grapefruit juice administered. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for adverse effects that may be associated with the use of corticosteroids (e.g., hyperglycemia, Cushingoid features).
Nifedipine	<ul style="list-style-type: none"> • May lead to increased serum levels of nifedipine. • Evaluated in single dose controlled studies in healthy volunteers. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for signs of adverse effects associated with increased serum concentrations of nifedipine (e.g., decreased diastolic blood pressure, increased heart rate, flushing, headache and lightheadedness).
Nimodipine	<ul style="list-style-type: none"> • May increase plasma concentrations of nimodipine. • Pharmacokinetics after a single dose of grapefruit juice are altered. • Pharmacodynamic effects may be augmented. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for increased hypotensive effect and side effects such as headache.
Pimozide	<ul style="list-style-type: none"> • Can result in elevated levels due to decreased drug metabolism. • Elevated levels may enhance the risk of QT prolongation. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for signs of adverse effects associated with increased serum levels of pimozide (e.g., torsades de pointes, extrapyramidal symptoms, hypotension).
Protease inhibitors, see saquinavir		

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Table I—Drug Administration and Grapefruit Juice (*cont'd*)

Drug*	Grapefruit Juice Effect	Management
Saquinavir	<ul style="list-style-type: none"> • Can increase absorption of saquinavir from hard gel capsules. Effect on soft gel capsules unknown, but may differ due to intrinsically better absorption from this formulation. • A decrease in AUC has been reported with indinavir; effect on ritonavir has not been studied. 	<ul style="list-style-type: none"> • Clinical significance is unknown.
Sertraline	<ul style="list-style-type: none"> • Grapefruit juice may increase serum concentrations of sertraline. • Evaluated in an open controlled study in five patients being treated for depression with 50-75 mg/day of sertraline; increased the mean trough concentration of sertraline. No subject was withdrawn from the study due to adverse effects or mood changes. Clinical significance unknown. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for adverse effects associated with increased serum levels of sertraline (e.g., insomnia or somnolence, tremor, dizziness).
Simvastatin	<ul style="list-style-type: none"> • May increase simvastatin serum concentrations. • Lovastatin bioavailability is similarly increased by grapefruit juice; however, atorvastatin is not as greatly affected. 	<ul style="list-style-type: none"> • Avoid consumption of grapefruit juice; other juices not known to interact. • Consider choosing a HMG CoA reductase inhibitor not metabolized by CYP 3A4 (e.g., fluvastatin and pravastatin). • If used in combination, monitor for signs of adverse effects associated with increased serum concentrations of simvastatin (e.g., myopathy, rhabdomyolysis).
Sirolimus	<ul style="list-style-type: none"> • Grapefruit juice may have the potential to increase sirolimus blood concentrations. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; the manufacturer of Rapamune® specifically recommends taking Rapamune® with either water or orange juice. • If used in combination, monitor for increased blood concentrations and for adverse effects associated with increased serum concentrations of sirolimus (e.g., thrombocytopenia, hyperlipidemia).
Tacrolimus	<ul style="list-style-type: none"> • May have the potential to increase tacrolimus blood concentrations. 	<ul style="list-style-type: none"> • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for increased blood levels and symptoms of toxicity (e.g., nephrotoxicity, hepatotoxicity, increased immunosuppression).
Triazolam	<ul style="list-style-type: none"> • May increase triazolam serum levels. • Evaluated in controlled studies in healthy volunteers; increased AUC and C_{max} and small increase in psychomotor impairment. 	<ul style="list-style-type: none"> • It is likely that some patients would be adversely affected especially those in whom triazolam levels are likely to be elevated (e.g., older individuals, those with liver impairment or concurrent use of other cytochrome P450-inhibitors). • Avoid grapefruit juice; other juices not known to interact. • If used in combination, monitor for increased sedation. Significant increase in drowsiness has been reported.

*The list of drugs in this table is not exhaustive. As more drugs in combination with grapefruit juice are studied, the list of interactions may change.

Selected References:

1. Ameer B, Weintraub A. Drug interactions with grapefruit juice. *Clin Pharmacokin* 1997; 33(2):103–21.
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4. Wichman K, ed. *New drugs/drug news: Drug interactions with grapefruit juice*. *Pharmacy Connection* 1999; 6(4):ii–iv.