PHARMACOLOGICAL EFFECTS OF GRAPEFRUIT JUICE WITH MEDICATIONS (Part 1 of 2)

Grapefruit or grapefruit juice has been shown to affect the metabolism of many medications, increasing the risk of toxicity and adverse events. Characteristics of oral medications that may interact with grapefruit include extensive metabolism through the intestinal cytochrome P450 3A4 (CYP3A4) system, low bioavailability, and a narrow therapeutic index. Grapefruit juice interacts through the intestinal CYP3A4 system and can inhibit the concentration for 24–72hrs. Not an exclusive list of medications that may interact with grapefruit. Caution should be taken by both patient and physician and monitor adverse reactions when taking medications that may interact with grapefruit or juice.

Generic	Brand	Clinical Implications of Co-administration with Grapefruit or Grapefruit Juice
ANTI-INFECTIVES		
erythromycin	**Ery-Tab, Eryped, E.E.S.**	Inhibits CYP3A4-mediated metabolism resulting in increased erythromycin bioavailability.
maraviroc	**Selzentry**	May increase plasma concentrations of maraviroc and should be avoided.
praziquantel	**Biltricide**	1.6-fold increase in the C_{max} and a 1.9-fold increase in the AUC of praziquantel. The effect of this increase on the efficacy and safety of praziquantel has not been systemically evaluated.
primaquine phosphate	**Primaquine**	Increases bioavailability of primaquine resulting in increased adverse effects. Avoid co-administration.
rilpivirine	**Edurant**	May increase plasma concentrations of rilpivirine and should be avoided.
CARDIOVASCULAR AGENTS		
amiodarone	—	Inhibits CYP3A4-mediated metabolism of oral amiodarone resulting in increased plasma levels of amiodarone. Avoid co-administration.
apixaban	**Eliquis**	May moderately inhibit CYP3A4-mediated metabolism of apixaban. If co-administration is necessary, use with caution.
atorvastatin	**Lipitor**	Inhibits CYP3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2L/day).
clopidogrel	**Plavix**	May impair the efficacy of clopidogrel. Avoid co-administration.
dofetilide	**Tikosyn**	Inhibitor of the CYP3A4 isoenzyme, thus could increase systemic dofetilide exposure. If co-administration is necessary, use with caution.
dronedarone	**Multaq**	Moderate inhibitor of CYP3A, results in a 3-fold increase in dronedarone exposure and a 2.5-fold increase in C_{max}. Avoid co-administration.
eplerenone	**Inspra**	May increase plasma concentrations of eplerenone resulting in hyperkalemia and serious arrhythmias.
felodipine	—	2-fold increase in felodipine AUC and C_{max} with no prolongation of half-life. Avoid co-administration prior to and during treatment.
lovastatin	—	Inhibits CYP3A4 and can increase plasma concentrations of lovastatin. Avoid co-administration.
nifedipine	**Procardia**	2-fold increase in nifedipine AUC and C_{max} with no change in half-life. Avoid co-administration.
nisoldipine	**Sular**	3-fold increase in nisoldipine C_{max} and 2-fold increase in nisoldipine AUC. Avoid co-administration.
simvastatin	**Zocor**	Inhibits CYP3A4 and can increase plasma concentrations of simvastatin and may increase risk of myopathy. Avoid co-administration.
verapamil	**Verelan**	May significantly increase concentrations of verapamil. Increased S-and R-verapamil AUC0-12 by 36% and 28%, respectively. Steady state C_{max} and C_{min} of S-verapamil increased by 57% and 16.7%, respectively compared to control. C_{max} and C_{min} of R-verapamil increased by 40% and 13%, respectively. No clinical consequences expected.
ticagrelor	**Brilinta**	Increases ticagrelor exposure by more than 2-fold, resulting to an enhanced and prolonged antiplatelet effect.
IMMUNOSUPPRESSANTS		
cyclosporine	**Neoral**	Affects metabolism and increases blood concentrations of cyclosporine. Avoid co-administration.
everolimus	**Zortress**	Inhibits CYP3A4 and P-gp activity and should therefore be avoided.
sirolimus	**Rapamune**	Reduces CYP3A4-mediated drug metabolism and must not be taken with or used for dilution of sirolimus.
tacrolimus	**Prograf**	Inhibits CYP3A-mediated metabolism resulting in increased tacrolimus whole blood trough concentrations. Avoid co-administration.

(continued)

PHARMACOLOGICAL EFFECTS OF GRAPEFRUIT JUICE WITH MEDICATIONS (Part 2 of 2)

Generic	Brand	Clinical Implications of Co-administration with Grapefruit or Grapefruit Juice
ONCOLOGY AGENTS		
axitinib	**Inlyta**	May increase plasma concentrations of axitinib and should be avoided.
crizotinib	**Xalkori**	May increase plasma concentrations of crizotinib and should be avoided.
dasatinib	**Sprycel**	May increase plasma concentrations of dasatinib and should be avoided.
erlotinib	**Tarceva**	May increase plasma concentrations of erlotinib and should be avoided.
everolimus	**Afinitor**	May increase exposures of everolimus and should be avoided.
lapatanib	**Tykerb**	May increase plasma concentrations of lapatinib and should be avoided.
nilotinib	**Tasigna**	May increase plasma concentrations of nilotinib and should be avoided.
pazopanib	**Votrient**	May increase plasma concentrations of pazopanib and should be avoided.
ruxolitinib	**Jakafi**	The recommended starting dose of ruxolitinib is 10mg twice daily for patients with a platelet count $\geq 100 \times 10^9$/L. Concurrent administration of ruxolitinib should be avoided in patients with platelet counts $< 100 \times 10^9$/L.
sunitinib	**Sutent**	May increase plasma concentrations of sunitinib and should be avoided.
vandetanib	**Caprelsa**	May increase plasma concentrations of vandetanib and should be avoided.
vemurafenib	**Zelboraf**	May increase plasma concentrations of vemurafenib and should be avoided.
PAIN MEDICATIONS		
dihydroergotamine mesylate	—	A potential risk for serious toxicity (including vasospasm) exists.
ergotamine tartrate + caffeine	—	A potential risk for serious toxicity (including vasospasm) exists.
fentanyl (oral)	**Fentora**	May result in a potentially dangerous increase in plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression.
oxycodone	**Oxycontin**	May result in a potentially dangerous increase in plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression.
PSYCHOTROPIC AGENTS		
buspirone	—	4.3 fold increase in C_{max}; 9.2 fold increase in AUC. Avoid drinking large amounts (200mL double-strength 3 times daily) of grapefruit juice.
lurasidone	**Latuda**	May increase plasma concentrations of lurasidone resulting in increased adverse effects.
pimozide	—	Inhibits CYP3A4-mediated metabolism of pimozide. Avoid co-administration.
quetiapine	**Seroquel**	May increase plasma concentrations of quetiapine resulting in increased adverse effects.
triazolam	**Halcion**	Increases the C_{max} of triazolam by 25%, increases AUC by 48%, and increases half-life by 18%. Avoid co-administration.
ziprasidone	**Geodon**	May increase plasma concentrations of ziprasidone resulting in increased adverse effects.
UROLOGIC AGENTS		
tadalafil	**Cialis**	Likely increases of tadalafil exposure.
vardenafil	—	Increased systemic concentration of vardenafil. Avoid co-administration.
OTHERS		
budesonide	**Entocort EC**	After extensive intake of grapefruit juice, the systemic exposure for oral budesonide increased about 2 times. Ingestion of grapefruit or grapefruit juice should be avoided.
cilostazol	—	Increase in the C_{max} of cilostazol by ~ 50%, but has no effect on AUC. Avoid or reduce dose to 50mg with co-administration.
colchicine	**Colcrys**	Increases the risk of colchicine-induced toxic effects; significant increase in colchicine plasma concentration is anticipated. Grapefruit and grapefruit juice should not be consumed during colchicine treatment.
dextromethorphan	**Robitussin**	Increases bioavailability of dextromethorphan resulting in increased adverse effects.
fexofenadine	**Allegra**	May reduce bioavailability and exposure of fexofenadine. In a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Take with water.
ivacaftor	**Kalydeco**	Co-administration may increase exposure of ivacaftor. Grapefruit or Seville oranges should be avoided during treatment.
tolvaptan	**Samsca**	Co-administration results in a 1.8-fold increase in exposure to tolvaptan.

REFERENCES

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