Review

Top 10 Prescribed Drugs:
Important Interactions

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Presented at the University of Saskatchewan's 4th Annual Peter and Anna Zbeetnoff Memorial Drug Therapy Decision-Making Conference, Saskatoon, Saskatchewan, March 2007.

With more drugs and drug combinations being used than ever before, the potential for adverse effects due to interaction is also increasing. The actual incidence of clinically significant interaction has not been determined but it is known to be a factor in many ER visits and hospital admissions. Patient groups at higher risk of serious interaction effects include:

- those taking three or more drugs,
- psychiatric patients,
- the elderly,
- patients under the care of multiple physicians and
- patients who fill prescriptions at more than one pharmacy.

The following are examples of interactions involving last year's top 10 prescribed drugs.

Atorvastatin and macrolides

Atorvastatin and macrolides interact via the inhibition of cytochrome P450 3A4 and p-glycoprotein by macrolide antibiotics. This results in elevated atorvastatin serum levels and an increased risk of adverse reactions, such as myopathy and rhabdomyolysis. Erythromycin has the strongest inhibitory activity, clarithromycin has a moderate effect and azithromycin has little or no effect.

Management

Manage this drug interaction by:

- using azithromycin or antibiotics from an alternate class,
- discontinuing atorvastatin for the duration of antibiotic therapy, or by
- switching from atorvastatin to a "statin" less likely to interact, such as:
  - pravastatin,
  - rosuvastatin or
  - fluvastatin.

Be aware of…

Possible cases of an interaction that have been reported with pravastatin; one case report of rhabdomyolysis as a cause was associated with azithromycin plus lovastatin.[1]

Caution those patients on any "statin" plus macrolide combination to watch for signs of myopathy.

Levothyroxine and calcium

The calcium binds to levothyroxine, decreasing the amount of levothyroxine available for absorption in the gut. Although the effect is insignificant for most people, there are case reports of elevated thyroid stimulating hormone and symptoms of hypothyroidism.

Management

Patients should be counselled to take levothyroxine at the same time each day in relation to meals and calcium supplements so that any interaction effect will be adjusted for when titrating the levothyroxine dose. Ideally, levothyroxine should be taken on an empty stomach and at least one hour before or four hours after the ingestion of calcium supplements.

Consider the possibility of interaction between levothyroxine and calcium when previously stable patients exhibit signs/symptoms of hypothyroidism.

Other potential interactants

Calcium-fortified orange juices, bottled waters, some cereals and breads have the potential to interact with levothyroxine, as do meal replacements (*e.g.*, nutritional energy drinks), iron, magnesium and possibly zinc supplements.

Ideally, levothyroxine should be taken on an empty stomach and at least one hour before or four hours after the ingestion of calcium supplements.

Ramipril and potassium-sparing diuretics

The combination of ACE inhibitors and potassium-sparing diuretics is often beneficial for patients with congestive heart failure. Both of these drug classes, however, have the potential to increase potassium levels which can progress to severe hyperkalemia and life-threatening cardiac arrythmias. Elderly, renally-impaired and diabetic patients are at higher risk.

Management

To avoid this interaction effect, the combination of ACE inhibitors and the potassium-sparing diuretics, amiloride or triamterene is not recommended. Doses of spironolactone with ACE inhibitors should be limited to ≤ 25 mg.

Regular monitoring of serum potassium is essential and extra vigilance is required for high-risk patients.

Did you know...?

Elderly patients on ACE inhibitors hospitalized with hyperkalemia are 20 times more likely than control patients (without hyperkalemia) to have received a potassium-sparing diuretic.[2]

Amlodipine and alcohol

Alcohol is reported to increase serum levels of nifedipine (inhibited metabolism) and felodipine (increased bioavailability), but it appears to have no significant effect on amlodipine pharmacokinetics.[3] However, patients who combine amlodipine and alcohol are still susceptible to the pharmacodynamic effects of interaction, which are:

- Acutely - an increased likelihood of orthostatic hypotension
- Long-term - decreased antihypertensive effect when ≥ 30 gm of alcohol daily (two drinks) are ingested on a regular basis

Management

According to the 2006 Canadian Hypertension Education Program Guidelines, to avoid the pharmacodynamic effects of alcohol and amlodipine, consumption should be limited to less than two standard drinks daily, < 14 drinks per week for men and less than nine drinks per week for women. Patients should be made aware of the potential for exaggerated hypotensive effect with alcohol.

Did you know...?

Moderate alcohol intake in men with hypertension is associated with a decreased risk of MI, but not mortality.[4]

Elderly patients on ACE inhibitors hospitalized with hyperkalemia are 20 times more likely to have received a potassium-sparing diuretic.

Venlafaxine and "triptans"

The combination of venlafaxine and "triptans" (*i.e.*, sumatriptan, zolmitriptan, naratriptan, *etc.*) can result in excess serotonergic activity, increasing the risk of serotonin syndrome, a rare, but potentially serious condition involving:

- Autonomic hyperactivity:
  - Fever
  - Diarrhea
- Mental status changes:
  - Agitation
  - Incoherent speech
  - Delirium
- Neuromuscular abnormalities:
  - Incoordination
  - Tremors
  - Rigidity

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Management

Patients should be counselled on particular symptoms of concern and the need for immediate medical attention if any of the above symptoms occur.

The risk increases when therapy with venlafaxine is initiated, when the dose of venlafaxine or the "triptan" is increased and if the patient is using additional drugs with serotonergic activity. The actual incidence of an interaction between venlafaxine and "triptans" appears to be low but vigilance is required given the potential severity of the reaction.

FDA alert

In July 2006, the FDA issued an alert based on seven reported cases of serotonin syndrome involving selective serotonin or serotonin-norepinephrine reuptake inhibitors and the use of "triptans." Thirteen patients were admitted to hospital and two of these cases were life-threatening.[5]

Low-dose ASA and ibuprofen

Ibuprofen use may counteract the beneficial CV effect of ASA by inhibiting ASA binding to platelets.

Management

Acetaminophen should be substituted for ibuprofen. For occasional use, ibuprofen may be taken at least 30 minutes after the regular ASA dose and not less than eight hours before the next scheduled dose of ASA.

NSAIDs less likely to interact with ASA are diclofenac or naproxen.

Did you know...?

Platelet function tests suggest an interaction between 400 mg of ibuprofen and low-dose ASA,[6] but the significance has not been evaluated in reliable outcome studies.

Pantoprazole and nutrients

An increased gastric pH may decrease absorption of calcium (resulting in an increased risk of fracture), vitamin B12 (resulting in megaloblastic anemia and neuropathy) and may possibly impair iron absorption.

Management

PPIs are recommended at the lowest effective dose and should only be used when needed.

Treating physicians should ensure that those patients who must take a PPI to suppress the amount of acid in their stomachs do receive the recommended amounts of calcium and vitamin D from their diet and supplements. It may be necessary to recommend a daily multivitamin, though iron supplements are not required unless the patient is iron deficient.

Consider periodic vitamin B12 level checks for patients considered to be at higher risk (*e.g.*, potential strict vegetarians, alcoholics and the elderly).

PPIs and risk of hip fracture

An observational study reported a statistically significant increase in overall fracture rate in those taking PPIs. This risk increased with high-dose PPIs and a longer duration of PPI therapy. The actual individual risk appears to be minimal (number needed to harm = 1,200 elderly adults/year).[7]

Acetaminophen/codeine and CYP2D6 inhibitors

CYP2D6 inhibitors (*e.g.*, fluoxetine, paroxetine, hydroxychloroquine, propafenone, terbinafine) prevent the hepatic conversion of codeine to morphine, reducing or nullifying the analgesic effect of codeine.

Management

Try an alternate analgesic for patients on 2D6 inhibitors and discourage the use of OTC codeine combinations.

Monitor patients

Monitor patients who are discontinuing 2D6 inhibitors, as these individuals are at risk of toxicity due to increased morphine levels.

Salbutamol and thiazide diuretics

High doses of inhaled ß-agonists in combination with thiazide diuretics can result in hypokalemia and cardiac arrhythmias.

Management

Be aware of interaction potential, though no action on the part of the GP is usually required (*i.e.*, hypokalemia induced by salbutamol is

generally transient). Monitor serum potassium levels in patients with risk factors such as frequent use of salbutamol, high doses of diuretic, renal impairment and during illnesses causing vomiting, diarrhea, and dehydration (exacerbate potassium loss).

Extra caution required

Extra caution is required in those with severe asthma, chronic obstructive pulmonary disorder (the effect is potentiated with concurrent therapy with theophylline and corticosteroids and with hypoxia) and ischemic heart disease (hypokalemia may affect response to digoxin, antiarrythmics and may generate arrhythmias).

Identifying and monitoring those patients at high-risk for adverse effects resulting from interaction is the shared responsibility of physicians and pharmacists.

Furosemide and NSAIDs

NSAIDs decrease prostaglandin synthesis, renal blood flow and diuresis as well as antagonize the diuretic and the antihypertensive effect of furosemide while increasing the risk of nephropathy.

Management

BP should be regularly monitored and patients should be encouraged to report sudden weight gain, decreased urine output and increased edema.

Consider...

Carefully consider the risk vs. benefit of this combination of medications in patients at higher risk (*i.e.*, the elderly, those with congestive heart failure, renal insufficiency and cirrhosis).

Conclusion

Drug interactions can cause unnecessary patient suffering and expense to the healthcare system. The likelihood of clinically significant interaction is largely dependent on the individual patient situation. Identifying and monitoring those patients at high-risk for adverse effects resulting from interaction is the shared responsibility of physicians and pharmacists. There are many good resources available, both electronic and hard copy. For more obscure or complex situations, specialists in pharmacology or drug information services can be consulted.

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