Institute for Safe Medication Practices Canada
L'Institut pour l'utilisation sécuritaire des médicaments du Canada

Canadian Foundation for Pharmacy

Drug Drug Interactions Pharmaceutical Opinion

Drug-drug Interactions in the Geriatric Population

Summary of Selected Pharmacoepidemiological Studies in Ontario (Nested Case-Control, Retrospective Cohort and Case Cross-Over Studies).*

DRUG-INTERACTION PAIR		DRUG TOXICITY/
Continuous	**Added Medication**	**Adverse Event**
Glyburide[1]	**Trimethoprim-sulfamethoxazole** (TMP-SMX)	**Hypoglycemia**

Possible mechanism of action:

- Sulfamethoxazole can directly cause pancreatic insulin release (at higher doses due to structural similarity to sulfonylurea) in patients with renal impairment.
- Sulfonamide antibiotics inhibit CYP 2C9. Glyburide is metabolized by CYP 2C9.

Comments:

- The concomitant use of TMP-SMX with glyburide was associated with increased risk of hospitalization due to hypoglycemia in the elderly.
- Juurlink et al. estimated that patients who were hospitalized due to hypoglycemia while using glyburide were around 6 times more likely to have been treated with TMP-SMX within 1 week.

Digoxin[1]	**Clarithromycin**	**Digoxin toxicity**

Possible mechanism of action:

- Clarithromycin inhibits P-glycoprotein which leads to decreased renal clearance of digoxin.

Comments:

- The concomitant use of clarithromycin and digoxin was associated with increased risk of hospitalization due to digoxin toxicity in the elderly.
- Juurlink et al. estimated that patients who were hosipitalized due to digoxin toxicities while using digoxin were around 12 times more likely to have been treated with clarithromycin.

Digoxin[2]	**Macrolide antibiotics** (erythromycin, clarithromycin, and azithromycin)	**Digoxin toxicity**

Possible mechanism of action:

- Macrolide antibiotics can reduce re-circulation of Digoxin by reducing *E. lentum* in the gut.
- Clarithromycin may inhibit P-glycoprotein-mediated tubular secretion of digoxin.

Comments:

- Concomitant use of digoxin and macrolide antibiotics may lead to increased risk of hospitalization in the elderly.
- Gomes et al. estimated that in patients who are hospitalized due to digoxin toxicity, are 15 times more likely to be taking clarithromycin and 4 times more likely to be taking azithromycin or erythromycin.

ACEIs/Angiotensin Receptor Blockers (ARBs)[3]	**TMP-SMX**	**Hyperkalemia**

Possible mechanism of action:

- ACEIs and ARBs impair urinary potassium excretion.
- TMP reduces urinary potassium excretion.

Comments:

- Concomitant use of TMP-SMX and ACEIs or ARBs is associated with increased risk of hospitalization due to hyperkalemia in the elderly.
- Antoniou et al. estimated in patients who are hospitalized for hyperkalemia and using ACEIs or ARBs are about 7 times more likely to have received TMP-SMX.

DRUG-INTERACTION PAIR: Continuous	DRUG-INTERACTION PAIR: Added Medication	DRUG TOXICITY/ Adverse Event
Warfarin[4]	**TMP-SMX, ciprofloxacin**	**Hemorrhagic complications**
Possible mechanism of action: • TMP-SMX inhibits CYP 2C9. S-warfarin (active enantiomer) metabolized predominantly by CYP 2C9.	**Comments:** • Concomitant use of TMP-SMX or ciprofloxacin with warfarin increases the risk of hospitalization due to hemorrhagic complications. • Fischer et al. estimated patients, who were hospitalized with hemorrhagic complications while using warfarin, are 3 times more likely to have been exposed to TMP-SMX and 2 times more likely to have been using ciprofloxacin.	
Calcium channel blockers (CCBs) (verapamil, diltiazem, nifedipine, amlodipine, or felodipine)[5]	**Macrolide antibiotics (erythromycin, clarithromycin, and azithromycin)**	**Hypotension**
Possible mechanism of action: • Two macrolides, erythromycin and clarithromycin, inhibit CYP 3A4. Azithromycin does not inhibit CYP 3A4. Calcium channel blockers are CYP 3A4 substrates.	**Comments:** • Concomitant use of CCBs and macrolide antibiotics are associated with increased risk of hospitalization due to hypotension. • Wright et al. found in patients who are admitted to hospital due to hypotension while using a CCB are more likely to have received clarithromycin or erythromycin prior to hospitalization. Azithromycin was not associated with hypotension. • This is a case cross-over study.	
Phenytoin[6]	**TMP-SMX**	**Phenytoin toxicity**
Possible mechanism of action: • Phenytoin is metabolized by CYP 2C8. TMP-SMX is a potent CYP 2C8 inhibitor and may lead to increase in phenytoin level.	**Comments:** • Concomitant use of phenytoin and TMP-SMX increases the risk of hospitalization due to phenytoin toxicity. • Antoniou et al. estimated patients who are hospitalized due to phenytoin toxicity are 2 times more likely to have received TMP-SMX within 30 days.	
Spironolactone[7]	**TMP-SMX, Nitrofurantoin**	**Hyperkalemia**
Possible mechanism of action: • Spironolactone and TMP-SMX both decrease urinary excretion of potassium.	**Comments:** • Concomitant use of TMP-SMX or nitrofurantoin with spironolactone has been associated with increased risk of hospitalization due to hyperkalemia. • Antoniou et al. estimated that patients hospitalized due to hyperkalemia while using spironolactone are 12 times more likely to have been using TMP-SMX and 2 times more likely to have been using nitrofurantoin.	

*The information in Table 1 was taken from the individual drug interaction studies and does not necessarily represent the opinion of ISMP Canada. Health care organizations are encouraged to critically appraise these studies to determine the applicability to their specific practice settings. (Updated April 24, 2013)

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