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CMIRPS SCDPIM
Canadian Medication Incident Reporting and Prevention System
Système canadien de déclaration et de prévention des incidents médicamenteux

TransPhIR from CPhIR

Connecting you to safe medication practices

Safety Alerts: Preventable Drug-Drug Interactions

- Challenges in preventing drug-drug interactions
- Evaluating the clinical significance of drug-drug interactions
- Selected pharmacoepidemiological studies on drug-drug interactions with increased risk of hospitalization

Did you know ...

Some drug-drug interactions, based on pharmacoepidemiological studies, have shown an increased risk of potential hospitalization in the geriatric population.

Summary of selected pharmacoepidemiological studies on drug-drug interactions can be found in Table 1.

Introduction

Drug interactions are pharmacokinetic or pharmacodynamic influences of drugs on each other, which can result, beside desired effects, in reduced effectiveness or increased toxicity. [1] It is estimated that drug interactions cause up to 2.8% of hospital admissions [2] and they can lead to serious adverse patient outcomes. The following tragic incident is an example:

> *A 46-year-old patient was provided with a "starter" medication kit for HIV PEP, containing Kaletra (lopinavir and ritonavir) and Combivir (zidovudine and lamivudine), by a hospital emergency department. The patient's regular medications were noted as venlafaxine, amitriptyline, bupropion, hormone replacement therapy, and fentanyl patch 100 mcg/h. Approximately 4 days after initiation of PEP, the patient was noted to be very drowsy and needed to be frequently wakened. The patient went to lie down and some time later that evening was found unresponsive. Resuscitation attempts were not successful. Based on post-mortem examination and serum drug levels, the cause of death was determined to be fentanyl toxicity due to an interaction with Kaletra.* [3]

Challenges in Preventing Drug-Drug Interactions

Drug-drug interactions are, in theory, largely preventable. In most cases there are a number of therapeutic alternatives available so that a significant drug-drug interaction can be avoided. In practice, however, recognition and detection of drug-drug interactions by clinicians is not optimal. For instance, a study of 263 physicians who practiced at a large southern California Veterans Affairs health care system, only 54 percent of contraindicated drug-drug interactions was recognized. [4] A potential cause for this situation is the continually increasing number of drug interactions, making it virtually impossible for the health care practitioners to keep up with new knowledge.

A solution to the over reliance on human memory in drug interaction detection is the development of computerized drug interaction detection systems; however, studies evaluating pharmacy computerized drug interaction detection systems identify opportunities for improvement. For example, a study evaluating pharmacy computerized drug interaction systems found that such systems may fail to detect up to a third of drug-drug interactions while frequently alerting pharmacists to trivial issues. [5]

What's New

ISMP Canada has developed a one-page documentation form for pharmacists to communicate with the prescriber regarding these drug-drug interactions. We are currently looking for pharmacies to pilot test this new intervention tool; if you are interested, please contact ISMP Canada at cphir@ismp-canada.org

Evaluating the Clinical Significance of Drug-Drug Interactions

One of the fundamental reasons for the lack of sensitivity and specificity of computerized drug interaction systems is the lack of high quality evidence evaluating the clinical significance of drug interactions. An exciting development in this field had been the growing body of research studies filling this gap. By utilizing pharmacoepidemiologic methods and the linkage of several databases (such as the Ontario Drug Benefit prescription claims database), these studies clearly demonstrated a significant association between specific drug-drug interactions and hospitalization with adverse event such as digoxin toxicity, hypoglycemia, hyperkalemia and recurrent myocardial infarctions. [6, 7] It is very important that health care practitioners be aware of these studies and systematically incorporate them in practice so that these serious drug interactions can be prevented.

Table 1 summarizes the pharmacoepidemiological studies in Ontario with drug-drug interaction pairs that have been shown to increase the rate of hospitalizations in the elderly population.

Conclusion

Drug-drug interactions (DDIs) represent a potentially serious problem for patients that can result in preventable adverse drug events and consumption of scarce healthcare resources. There has been a growing body of high quality studies demonstrating an increase in hospitalization with specific drug-drug interaction pairs. Healthcare practitioners are encouraged to familiarize themselves with these drug-drug interaction pairs so that these clinically significant drug interactions can be prevented.

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ISMP Canada Community Pharmacy Incident Reporting (CPhIR) Program is a national, voluntary medication incident and 'near miss' reporting program founded for the purpose of sharing the learning and experiences from medication incidents. ISMP Canada guarantees confidentiality and security of information received. Implementation of preventative strategies and system safeguards to decrease the risk for error-induced injury and thereby promote medication safety in healthcare is our collaborative goal.

Table 1. 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		Study Population	Drug Toxicity/ Adverse Event	Possible mechanism of action	Comments
Continuous Medication	Added Medication				
Glyburide[1]	Trimethoprim-sulfamethoxazole (TMP-SMX)	Older than 66 years treated with glyburide. A total of 909 cases.	Hypoglycemia	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.	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	Older than 66 years treated with digoxin. A total of 1051 cases. A total of 51896 controls.	Digoxin toxicity	Clarithromycin inhibits P-glycoprotein which leads to decreased renal clearance of digoxin.	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.
Angiotensin-Converting Enzyme Inhibitors (ACEIs)[1]	Potassium-sparing diuretics (amiloride, triamterene, or spironolactone)	Older than 66 years treated with an ACEI. A total of 523 cases. A total of 25807 controls.	Hyperkalemia	ACEIs and potassium sparing diuretics both increase serum potassium levels. When used together they may precipitate hyperkalemia.	The concomitant use of ACEIs and potassium sparring diuretics was associated with an increased risk of hospitalization due to hyperkalemia in the elderly. Juurlink et al. estimated that patients who were hospitalized due to hyperkalemia while using ACEIs are 20 times more likely to have been treated by potassium sparring diuretics.
Lithium[2]	ACEIs or loop diuretics	Older than 66 years treated with lithium. A total of 413 cases and 1651 controls.	Lithium toxicity	ACEIs reduce glomerular perfusion via inhibition of angiotensin II.	Concomitant use of lithium and ACEIs or loop diuretics was associated with increased risk of hospitalization due to lithium toxicities in the elderly. Juurlink et al. estimated that patients who were hospitalized due to lithium toxicity while using lithium are 2 times more likely to have been treated by ACEIs or loop diuretics.

DRUG-INTERACTION PAIR		Study Population	Drug Toxicity/ Adverse Event	Possible mechanism of action	Comments
Continuous Medication	Added Medication				
Warfarin[3]	NSAIDs [(nonselective NSAIDs) or COX-2 Inhibitors (celecoxib and rofecoxib)]	Older than 66 years treated with warfarin. A total of 361 cases. A total of 1437 controls.	Upper GI hemorrhage	S-warfarin (active enantiomer) and NSAIDs are substrates for CYP 2C9. Both NSAIDs and warfarin can increase risk of GI bleeding.	Concomitant use of warfarin and NSAID or COX-2 inhibitor was associated with increased risk of upper GI hemorrhage in the elderly. Battistella et al. estimated that patients who were hospitalized due to an upper GI bleed while using warfarin were around 2 times more likely to have used an NSAID or COX-2 inhibitor within 90 days.
Digoxin[4]	Macrolide antibiotics	Over the age of 66 treated with digoxin. A total of 1659 cases. A total of 6439 control cases.	Digoxin toxicity	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.	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.
Clopidogrel[5]	Proton pump inhibitors (PPIs)	Over the age of 66 years treated with clopidogrel. A total of 734 cases. A total of 2057 controls.	Re-infarction	Clopidogrel is a pro-drug requiring activation by CYP 2C19. Omeprazole, lansoprazole and rabeprazole inhibit CYP 2C19 which leads to reduced anti-platelet action.	Concomitant use of clopideogrel and PPIs (except pantoprazole) is associated with increased risk of re-infarction in the elderly. Juurlink et al. report in patients who are hospitalized for a re-infarct and using clopidogrel are more likely to be using a PPI within 30 days. Pantoprazole was not associated with increased hospitalization.
ACEIs/Angiotensin Receptor Blockers (ARBs)[6]	TMP-SMX	Over the age of 66 years treated with ACEI or ARBs. A total of 369 cases. A total of 1417 controls.	Hyperkalemia	ACEIs and ARBs impair urinary potassium excretion. TMP reduces urinary potassium excretion.	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		Study Population	Drug Toxicity/ Adverse Event	Possible mechanism of action	Comments
Continuous Medication	Added Medication				
Warfarin[7]	TMP-SMX, ciprofloxacin	Over the age of 66 years treated with warfarin. A total of 2151 cases. A total of 10201 controls.	Hemorrhagic complications	TMP-SMX inhibits CYP 2C9. S-warfarin (active enantiomer) metabolized predominantly by CYP 2C9.	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.
Tamoxifen[8]	Paroxetine	2430 women over the age of 66 years treated with tamoxifen for breast cancer on concurrent treatment with a single SSRI.	Breast cancer mortality	Tamoxifen is a pro-drug metabolized by CYP 2D6 to the active endoxifen. Paroxetine is a potent CYP 2D6 inhibitor and may reduce the activation of tamoxifen.	Kelly et al. report paroxetine use during tamoxifen treatment increases breast cancer mortality. The median overlap time of tamoxifen and paroxetine treatment in this study was 41%. It is estimated that this level of overlap would result in one additional breast cancer death at 5 years for every 20 women treated. This is a retrospective cohort study.
Calcium channel blockers (CCBs) (verapamil, diltiazem, nifedipine, amlodipine, or felodipine)[9]	Macrolide antibiotics (erythromycin, clarithromycin, and azithromycin)	Over the age of 66 years treated with CCBs. A total of 7100 in cohort. A total of 176 cases.	Hypotension	Two macrolides, erythromycin and clarithromycin, inhibit CYP 3A4. Azithromycin does not inhibit CYP 3A4. Calcium channel blockers are CYP 3A4 substrates.	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.
Theophylline[10]	Ciprofloxacin	Over the age of 66 treated with theophylline. A total of 180 cases. A total of 9000 controls.	Theophylline toxicity	Theophylline is metabolized by CYP 1A2. Ciprofloxacin is a potent inhibitor of CYP 1A2. Ciprofloxacin is a commonly used antibiotic given to COPD patients.	Concomitant use of theophylline and ciprofloxacin may lead to an increased risk of hospitalization due to theophylline toxicity. Antoniou et al. estimated that patients hospitalized due to theophylline toxicity were 2 times more likely to have been treated with ciprofloxacin.

DRUG-INTERACTION PAIR		Study Population	Drug Toxicity/ Adverse Event	Possible mechanism of action	Comments
Continuous Medication	Added Medication				
Phenytoin[11]	TMP-SMX	Over the age of 66 years treated with phenytoin. A total of 796 cases. A total of 3148 controls.	Phenytoin toxicity	Phenytoin is metabolized by CYP 2C8. TMP-SMX is a potent CYP 2C8 inhibitor and may lead to increase in phenytoin level.	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[12]	TMP-SMX, Nitrofurantoin	Over the age of 66 years treated with spironolactone. A total of 248 cases (median age, 82 years). A total of 783 controls (median age, 81 years).	Hyperkalemia	Spironolactone and TMP-SMX both decrease urinary excretion of potassium.	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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