Clinical Importance of Drug-Drug Interactions Involving Antidiabetic Drugs

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Overview

- Health Service Research: Pharmacoepidemiology
- Study of the use and effects of medical products in populations
- DDIs are alterations of the activity of one drug (Object drug) caused by the presence of another drug (Precipitant drug)
- Sources of DDIs: Pharmacokinetics (PK) & or Pharmacodynamics (PD) mechanisms
- PK mechanism through CYP enzymes are most abundant.\(^1\)
- \(~50\%\) of all drugs used in clinical practice are metabolized by CYP3A4\(^1\)

\(^1\) JAMA 2003;289(9):1107-1116
Definition

- Precipitant Drug: the drug that causes the interaction

- Object Drug: the drug that is affected by the interaction
Sources of DDIs

http://www.themednote.com/2011/07/10/pharmacodynamics-vs-pharmacokinetics/#.UB81waN6t8E
DDI Focus

Drug metabolite

Direct Route to kidneys

To urine

liver

CYP450

transporter
Physiology of Glucose control

Dietary intake: consume food (carbs, etc.)

Food broken down into simple molecules like glucose

Levels of glucose rises in the blood

Insulin in blood binds to cells in the body triggering uptake of glucose

Uptake of glucose by pancreatic cells triggers insulin release

As glucose circulates some is transported to pancreatic beta cells

Type 2 diabetes

Type 1 diabetes
Objective

• To develop a series of biologically based hypothesis about clinically important Drug-Drug interactions (DDIs) involving antidiabetic drugs.
SIGNIFICANCE

- DDIs cause at least 13% of adverse drug events (ADEs) in older adults & nearly 3% of all hospital admissions in well established DDIs.
- Burden increases with polypharmacy & baby-boomer population
- 70% of respondents from a 2002 public opinion poll indicated that if hospitalized they would be “concerned about receiving two or more medication that interact in a negative way”

JAMA 2003;289(9):1107-1116
Clinical pharmacology & therapeutics;2012;Vol91(5):771-3
Rx Medications Used in the Past Month by US Residents age ≥ 65 (2005-08)

Methodology

**STUDY DESIGN**
- Researched drug databases to identify DDIs with antidiabetics
- Peer reviewed the identified DDIs to determine their clinical significance

**STUDY CONDUCT**
- Conduct *in vitro, invivo, in silico, in populo* (epidemiologic) studies
- Identify clinical outcomes & significance of the suggested DDIs
Metformin + PPIs

Rabeprazole potent inhibitor of all 3 OCTs omeza,panto,lansoprazone inhibit OCT2->OCT1 or 3
GLIMEPRIDE + STATINS/FIBRATES

Inhibitors:
- Fenofibrates
- Fluvastatin
- Lovastatin
- Gemfibrozil

Liver Cell

Metabolites of neteglinide are primarily excreted via urine

http://www.pharmgkb.org/pathway/PA154423659
Repaglinide + statins, fibrates

http://www.pharmgkb.org/pathway/PA153627759
Lesson Learned

- Mechanism of DDIs
- Process of research design
- Significance of pharmacoepi studies
Conclusion

- DDIs & ADEs
  - Biological basis
  - Clinical importance
  - Optimal strategies to ↓↓ AEs of DDIs

Important Implications for Public health & Clinical care
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