Practical Applications of MedWatch Updates

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The speakers have no conflict of interest to declare.

Objectives

- Discuss the MedWatch Program and future safety initiatives (P, T)
- Describe the content of recently issued MedWatch Safety Alerts (P, T)
- Apply specific MedWatch information to simulated patient cases (P)
- Utilize specific MedWatch Alert information to develop or modify policy and guidelines (P)
- Demonstrate how to navigate safety information on the FDA website (P, T)

Overview

- Speaker #1 (Jen Phillips)
  - Introduction
- Speaker #2 (Kim Janicek)
  - Review of regadenoson (Lexiscan) and Adenosine (Adenoscan)
  - Review of rosiglitazone (Avandia)
  - Review of sodium phosphate products
- Speaker #3 (Jen Phillips)
  - Discussion

Introduction

- MedWatch is an on-line database of FDA safety alerts for drugs, devices, biologics, and dietary supplements.
- Many safety alerts are issued for drugs and biological products each year.
  - A total of 83 issued in 2013
- Staying up-to-date on safety information is challenging!

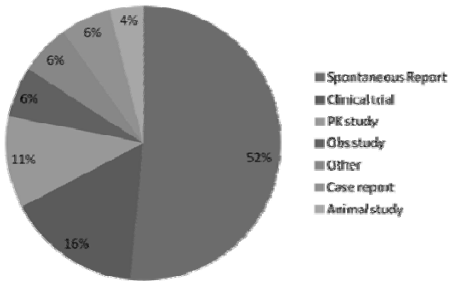
Sources of Safety Information

- Clinical trials
- Post-marketing surveillance
  - Industry reporting
    - Required to report all ADRs.
  - Voluntary reporting
    - Consumers and healthcare professionals
  - Adverse Event Reporting System (AERS)
    - Computerized database of ADRs
- Other strategies

FDA Safety Actions

- Changes to product labeling
  - Changes to contraindications, warnings, precautions
- Recall
  - Removal of certain lots of the product due to quality issues
- Drug withdrawal from the market
  - Change in approval status

Evidence Sources for Labeling Changes



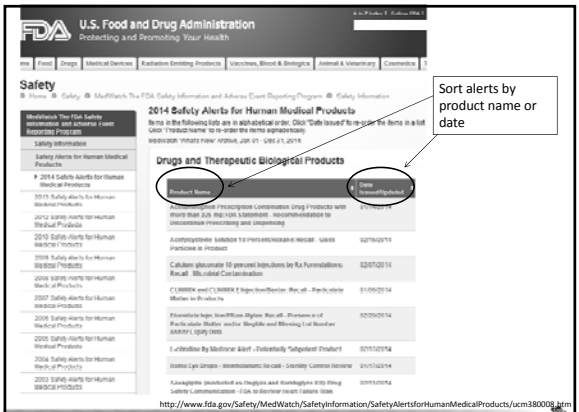
Pharmacoepidemiol Drug Saf 2013; 3: 302-5.

Navigating the MedWatch Site

- Active Learning Demonstration
  - http://www.fda.gov/Safety/MedWatch/default.htm
  - Links to safety alerts and drug safety communications
  - Links to drug safety labeling changes
  - MedWatch Learn
  - Subscription options
  - Reporting events

Drug Safety Communications

- Purpose
  - Provide actionable information to patients and healthcare professionals on new safety information
- Sections
  - Safety Announcement
  - Additional Information for Patients
  - Additional Information for Healthcare Professionals
  - Data Summary



http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm380008.htm

Drug Safety Communications

http://www.accessdata.fda.gov/scripts/MedWatchLearn/

MedWatch Learn

- Interactive tutorial on how to report problems to the FDA
  - Students
  - Healthcare professionals
  - Consumers
- Includes interactive case studies

Subscription Options

- Listservs
  - Hyperlinked summaries of the MedWatch alerts
- Twitter
  - @FDAMedWatch
- RSS feeds
  - Alerts delivered to your webpage or desktop

Reporting Events

- Can submit reports of ***serious*** adverse effects or quality problems related to:
  - Prescription or OTC products
  - Biologics
  - Medical devices
  - Nutritional products
    - Dietary supplements, infant formulas, medical food
  - Cosmetics
  - Food/beverages

Reporting Events

- What ***not*** to report to MedWatch
  - Vaccines
    - Report to Vaccine Adverse Event Reporting System (VAERS)
    - https://vaers.hhs.gov/esub/step1
  - Investigational drugs
    - Refer to study protocol for contact person
  - Veterinary Medicine Products
    - http://www.fda.gov/animalveterinary/safetyhealth/reportaproblem/ucm055305.htm

Recent FDA Alerts

- Regadenoson (Lexiscan) and adenosine (Adenoscan): 11-20-13
- Rosiglitazone (Avandia): 11-25-13
- Sodium Phosphate Products: 1-6-14

Regadenoson and Adenosine

Regadenoson and Adenosine

JG is a 69 year old Caucasian male scheduled to undergo an elective hip replacement. Prior to surgery, a cardiac clearance is required. JG's cardiologist contacts you regarding a recent alert he heard that was issued by the FDA about nuclear stress agents.

The physician is asking for further clarification of the alert and a recommendation from you on what he should do.

Regadenoson and Adenosine

- Basis of alert:
  - Medical literature
  - Spontaneous reports (FAERS)
- Current status:
  - Avoid use in patients with
    - Signs or symptoms of unstable angina
    - Cardiovascular instability
  - Unable to discern a difference between regadenoson and adenosine

http://www.fda.gov/Drugs/DrugSafety/ucm375654.htm

Regadenoson and Adenosine: Literature

- In 4 published studies, no increase in CV events were noted with regadenoson vs. adenosine
- There are 2 case reports of MI reported in the medical literature for regadenoson
- There are 4 case reports of MI in the literature for dipyridamole and 4 case reports for adenosine

http://www.fda.gov/Drugs/DrugSafety/ucm375654.htm

Regadenoson and Adenosine: Spontaneous Reports

- The FDA Adverse Event Reporting System (FAERS) database search
  - 6/24/08 – 4/10/13 for regadenoson
  - 5/18/95 – 4/10/13 for adenosine

	Death	MI
Regadenoson	29	26
Adenoscan	27	6

http://www.fda.gov/Drugs/DrugSafety/ucm375654.htm

Regadenoson and Adenosine: Spontaneous Reports

- Timing of deaths or MIs were not always specified in reports
  - When reported, events tended to occur within 6 hours of administration
- A few deaths occurred when regadenoson or adenosine were administered with exercise stress testing
  - Not FDA approved indication

http://www.fda.gov/Drugs/DrugSafety/ucm375654.htm

Back to the case…

JG is a 69 year old Caucasian male scheduled to undergo an elective hip replacement. Prior to surgery, a cardiac clearance is required. JG's cardiologist contacts you regarding a recent alert he heard that was issued by the FDA about nuclear stress agents.

The physician is asking for further clarification of the alert and a recommendation from you on what he should do.

Regadenoson and Adenosine: Interactive Application

Some more info on JG:

Ht: 5'10" , **Wt**: 225 lbs

Allergies: NKDA

PMH: Hypertension, Diabetes Mellitus, Gout, Multiple Sclerosis, Osteoarthritis, Renal Insufficiency

SH: Occasional ETOH use, smokes 1-2 cigars per week. Retired, lives at home with wife

Cardiologist Note: Recent travel to Europe with a moderate amount of walking. Patient reports that after eating, would experience "chest tightness" that was relieved by rest. Episodes lasted less than 5 minutes and typically were precipitated by a large meal.

Interactive Application

- Form groups of 3-5
- Review case and FDA alert on the FDA website
- What would you recommend?
  - Is it safe for this patient to receive regadenoson?
  - Is it safe for this patient to receive adenosine?
  - If not, what would you recommend instead?

Rosiglitazone (Avandia)

Rosiglitazone: Historical Perspective

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm376683.htm

Rosiglitazone

- FDA Safety Announcement
  - Use of rosiglitazone-containing products does *not* increase the risk of heart attack compared to standard drugs used to treat type 2 diabetes mellitus (i.e., metformin and sulfonylureas)
- Basis of Alert:
  - Meta-analysis of trials and observational studies (2010)
    - RECORD Trial
  - Expert Re-evaluation of data conducted by Duke Clinical Research Institute (DCRI)

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm376683.htm

Rosiglitazone

- Current Status:
  - Distribution no longer restricted
  - Health care professionals, pharmacies and patients no longer required to enroll in REMS
  - Prescribing information and medication guide updated

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm376683.htm

Rosiglitazone: Interactive Application

- Form groups of 3-5
- Review information found in the handouts at your table and the safety information listed on the FDA website.
- Make your recommendation, including rationale, to the Pharmacy and Therapeutics Committee as to the formulary status of rosiglitazone
  - ADD rosiglitazone to formulary?
  - Do NOT ADD rosiglitazone to formulary?
  - ADD with restrictions?

OTC Sodium Phosphate Products

Sodium Phosphate OTC Products

- History:
  - Previous alert issued in 2008 warned against use of high-dose oral sodium products prior to colonoscopy
- Current Alert:
  - Use of ≥ 1 dose in 24 hours can cause serious complications including acute kidney injury, arrhythmias, or death
  - Do not use oral in children ≤ 5 years or rectal in children ≤ 2 years without consulting healthcare provider

http://www.fda.gov/Drugs/DrugSafety/ucm380757.htm

Sodium Phosphate OTC Products

- Current Alert (cont.)
  - Use with caution in patients:
    - Older than 55 years of age
    - Kidney disease
    - Bowel inflammation or obstruction
    - Heart or kidney failure
    - Taking certain medications (ACEI, ARB, or NSAIDs)

http://www.fda.gov/Drugs/DrugSafety/ucm380757.htm

Sodium Phosphate OTC products

- Basis of Alert
  - FAERS database from 1969-2012 and Medical Literature 1957-August 2013
    - 54 cases of serious adverse events
      - 10 FAERS
      - 44 published case reports
- Reported Events:
  - Dehydration and/or electrolyte disturbances (Ca, Na, Phos)
  - Fatalities
    - 12/25 adults
    - 1/29 pediatric cases

http://www.fda.gov/Drugs/DrugSafety/ucm380757.htm

Sodium Phosphate OTC products

- Most complications occurred with
  - A single, larger than recommended dose - OR -
  - Multiple doses per day
- Individuals at higher risk for adverse events:
  - Young children
  - ≥ 55 years of age
  - Dehydration
  - Kidney disease, bowel obstruction, bowel inflammation
  - Concomitant use of ACEI, ARB, or NSAIDs

http://www.fda.gov/Drugs/DrugSafety/ucm380757.htm

Sodium Phsopahte: Patient Case

- BP is a 4 year old male with constipation s/p hernia repair surgery and post-op opioid usage for pain control in PACU. Patient is now being discharged home. PMH includes chronic constipation and chronic ear infections with recent bilateral tympanostomy tube insertion. Current medications include a daily peds MVI, daily peds fiber supplement and ibuprofen 10 mg/kg for pain control. Wt: 42 lbs
- Mother would like to know if it is OK to use Fleets pediatric enema to manage patient's constipation.

Sodium Phosphate: Interactive Application

- Form groups of 3-5
- Review patient case and information found on the FDA MedWatch website.
- Make your recommendation on the appropriateness of using sodium phosphate in this patient.
  - If appropriate, what dose and product would you recommend?
  - If not appropriate, what other product would you recommend?

Other Recent FDA Safety Alerts

Recent Alerts

- FDA evaluating risk of stroke, heart attack and death with FDA approved testosterone products *(issued 1/31/14)*
  - Alert issued based on two observational studies
  - No label changes at this time
- FDA to review heart failure risks with saxagliptin *(issued 2/11/14)*
  - Alert issued based on a single, randomized placebo controlled trial (n=16,492)
  - No label changes at this time
  - FDA requested clinical trial data from the manufacturer

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm384225.htm
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm385471.htm

What is the impact of FDA Drug Risk Communications?

Impact of FDA Communications

- Systematic review (2012)
  - Reviewed 49 published studies from 1990-2010
  - Data sources
    - Medical/pharmacy claims
    - Surveys/focus groups
    - Medical records
    - Prescribing audits
    - Vital statistics
  - Analyzed the impact of FDA risk communications on drug utilization, health care services, and health outcomes
  - Analyzed intended and unintended consequences

Dusetzina SB, et al. Med Care 2012;50:466-78.

Impact of FDA Communications

Type	Result	Examples
Increased monitoring	No evidence of a large or sustained impact	Anti-psychotics: glucose Troglitazone: LFTs
Drug-drug interactions	Clinical practice responds slowly; multiple alerts required	Cisapride, terfenadine, tramadol
Sub-population	"Spill-over" effect to unintended sub-populations	Telithromycin Atypical anti-psychotics
General Caution	Varied impact on clinical practice	Rosiglitazone LABAs

Dusetzina SB, et al. Med Care 2012;50:466-78.

Impact of FDA Communications

- Conclusions
  - Risk communications involving increased monitoring did not have a large or sustained impact on clinical practice.
  - Warnings appear to be implemented more quickly for new users vs. continuing users.
  - Most prescribers were aware of safety alerts, although not all agreed with them.
  - Warnings are more effective when they are specific and the messaging is reinforced over time.
  - With a projected increase in the amount of safety communications, continued assessment of their impact on clinical practice is needed.

Dusetzina SB, et al. Med Care 2012;50:466-78.

The Sentinel Initiative and Mini-Sentinel Pilot

Sentinel Initiative

- Food and Drug Administration Amendments Act of 2007
  - Required collaboration with public, academic, and private sectors
  - Collect, link, and analyze data from multiple electronic data sources
- Sentinel Initiative launched in 2008
  - Multi-year effort to create a national, electronic safety monitoring system
  - "Active" vs. "passive" surveillance
  - Goal: Data from 100,000,000 patients by July 2012
  - Mini-Sentinel Pilot in progress

http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM274548.pdf

Sentinel Initiative

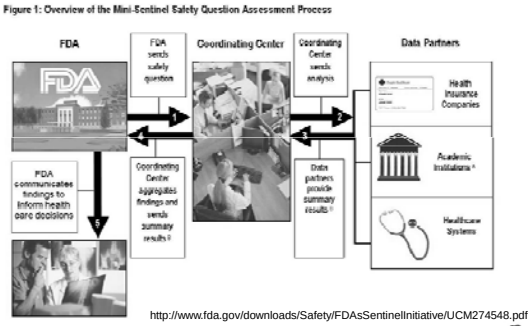
- Mini-Sentinel Pilot
  - Sophisticated statistical systems analyze patterns in defined patient populations (insurance claims, EHR)
  - Focuses on drugs, vaccines, biologics, and medical devices
  - Types of assessments
    - Exposure to medical products
    - Occurrence of diagnoses/medical procedure
    - Health outcomes based on exposure
    - Impact of FDA's regulatory actions or interventions

http://www.mini-sentinel.org/

Mini-Sentinel

- Allows for rapid response to FDA queries
  - Results to queries are in the public domain
- 18 partnering organizations as of 12/2012
  - 130,000,000 million individuals
- Being used in combination with data from other sources to help the FDA make decisions
- For more information:
  - http:///www.mini-sentinel.org

Mini-Sentinel Program



http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM274548.pdf

Mini Sentinel Controversies

- Results from the Mini-Sentinel program have contradicted published meta-analyses
- Example: dabigatran and bleeding risk
  - Meta-analysis
    - GI tract bleeding with dabigatran vs. warfarin
    - RR 1.41 [95% CI 1.29-1.55], p<0.001
  - Mini-Sentinel
    - Bleeding rate 1.6 with dabigatran (per 100,000 days at risk)
    - 3.5 with warfarin (per 100,000 days at risk)

JAMA Intern Med 2014;174(1):150-1

Summary

- Keeping up to date on safety information is a challenge
- Impact of risk communication on clinical practice is variable
- Future initiatives of the FDA may help capture impact on clinical practice in "real-time" but should be interpreted in the context of other data.

Questions and Comments?

Practical Applications of MedWatch Updates

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0121-0000-14-016-L05-P
0121-0000-14-016-L05-T

Learning Assessment Questions:

1. The evidence for most safety-related labeling changes comes from:
    a. Clinical trials
    b. Animal studies
    c. Spontaneous Reports

2. All of the following information should be reported to the FDA MedWatch program except:
    a. Serious adverse events related to the use of a newly approved drug
    b. Serious adverse events related to the use of an over-the-counter product
    c. Serious adverse events related to the use of a dietary supplement
    d. Serious adverse events related to the use of vaccines

3. Published analyses of bleeding associated with dabigatran from the Mini-Sentinel program correlate with findings from:
    a. Meta-analyses
    b. Clinical Trials
    c. Case reports
    d. None of the above

4. Based on a recent safety alert issued by the FDA, patients with signs or symptoms of (fill in the blank) _____ should not use adenosine or regadenoson.
    a. Unstable angina
    b. Renal insufficiency
    c. Constipation
    d. Gastroesophageal reflux disease

5. A recent safety alert issued by the FDA on rosiglitazone recommends which of the following?
    a. Removal of rosiglitazone distribution restrictions
    b. Creation of a REMS program for rosiglitazone
    c. Removal of rosiglitazone from the market