Clinical Analysis of Adverse Drug Reactions

Christine Chamberlain, Pharm.D., BCPS
Clinical Center Pharmacy Department
National Institutes of Health
February 2012

Objectives
- Define adverse drug reactions
- Discuss epidemiology and classification of ADRs
- Describe basic methods to detect, evaluate, and document ADRs
- FDA changes for ADR detection
- FDA adverse drug reaction initiatives

Definition - WHO
- WHO
  • response to a drug that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function
  • Purposely excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

Definition - FDA
- Adverse drug reaction according to the U.S. Food and Drug Administration (FDA)
  • Any undesirable experience associated with the use of a medical product in a patient.

Adverse Drug Events
Adapted from Bates et al.

Pharmacovigilance
- The science of adverse drug reactions
- detection, assessment, understanding and prevention of adverse effects
- Regulatory agencies, pharmaceutical companies and individual healthcare providers enact a system
Epidemiology of ADRs

- substantial morbidity and mortality
- estimates of incidence vary with study methods, population, and ADR definition
- 4th to 6th leading cause of death among hospitalized patients
- 6.7% incidence of serious ADRs
- 0.3% to 7% of all hospital admissions
- annual dollar costs in the billions


Epidemiology

- 82% of American adults take at least one medication and 29% take five or more
- 700,000 emergency department visits and 120,000 hospitalizations are due to ADEs annually
- $3.5 billion is spent on extra medical costs of ADEs annually
- At least 40% of costs of ambulatory (non-hospital settings) ADEs are estimated to be preventable

Increase in Adverse Drug Events

- Development of new medications
- Discovery of new uses for older medications
- Aging American population
- Increase in the use of medications for disease prevention
- Increased coverage for prescription medications

Classification

- Onset
- Severity
- Type

Classification

- Onset of event:
  - Acute
    - within 60 minutes
    - Anaphylactic shock, bronchoconstriction
  - Sub-acute
    - 1 to 24 hours
    - Rash, serum sickness, abx associated colitis
  - Latent
    - > 2 days
    - Eczematous eruptions, tardive dyskinesia

Classification - Severity

Severity of reaction:
- Mild
  - bothersome but requires no change in therapy
  - Metallic taste with metronidazole
- Moderate
  - requires change in therapy, additional treatment, hospitalization
  - Amphotericin induced hypokalemia
- Severe
  - disabling or life-threatening
  - QT interval prolongation, kidney failure
FDA Defines Serious ADR

- Result in death
- Life-threatening
- Require hospitalization
- Prolong hospitalization
- Cause disability
- Cause congenital anomalies
- Require intervention to prevent permanent injury

Classification - Severity

**Type A**
- Extension of pharmacologic effect
- Often predictable and dose dependent
- Responsible for at least two-thirds of ADRs
- E.g., propranolol and heart block, anticholinergics and dry mouth

**Type B**
- Idiosyncratic or immunologic reactions
- Rare and unpredictable
- E.g., chloramphenicol and aplastic anemia
- Rash caused by beta lactam antibiotics

Classification

<table>
<thead>
<tr>
<th>IMMUNE REACTION</th>
<th>MECHANISM</th>
<th>CLINICAL MANIFESTATION</th>
<th>TIMING OF REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (IgE mediated)</td>
<td>Drug-IgE binding to mast cells, release of histamine, inflammatory mediators</td>
<td>Urticaria, angioedema, bronchospasm, pruritis</td>
<td>Minutes to hours after exposure</td>
</tr>
<tr>
<td>Type II (cytotoxic)</td>
<td>Specific IgG or IgM antibodies directed at drug-hapten coated cells</td>
<td>Hemolytic anemia, neutropenia, thrombocytopenia</td>
<td>Variable</td>
</tr>
<tr>
<td>Type III (immune complex)</td>
<td>Tissue deposition of drug-antibody complexes with complement activation, inflammatory</td>
<td>Serum sickness, fever, rash, arthralgia, lymphadenopathy, urticaria, vasculitis</td>
<td>1-3 weeks after exposure</td>
</tr>
<tr>
<td>Type IV (delayed hypersensitivity)</td>
<td>MHC presentation of drug molecules on T cells, cytokine and inflammatory release</td>
<td>Allergic contact dermatitis, maculopapular rash</td>
<td>2 to 7 days after cutaneous drug exposure</td>
</tr>
</tbody>
</table>

Common Causes of ADRs

- Antibiotics
- Antineoplastics*
- Anticoagulants
- Cardiovascular drugs*
- Hypoglycemics
- Antihypertensives
- NSAID/Analgesics
- Diagnostic agents
- CNS drugs*

*Account for 69% of fatal ADRs

Body Systems Commonly Involved

- Hematologic
- CNS
- Dermatologic/Allergic
- Metabolic
- Cardiovascular
- Gastrointestinal
- Renal/Genitourinary
- Respiratory
- Sensory

ADR Risk Factors

- Age (children and elderly)
- Multiple medications
- Multiple co-morbid conditions
- Inappropriate medication prescribing, use, or monitoring
- End-organ dysfunction
- Altered physiology
- Prior history of ADRs
- Extent (dose) and duration of exposure
- Genetic predisposition
**ADR Detection**

- Subjective report
  - patient complaint
- Objective report:
  - direct observation of event
  - abnormal findings
    » physical exam
    » laboratory test
    » diagnostic procedure

**ADR Detection**

- Medication order screening
  • abrupt medication discontinuation
  • abrupt dosage reduction
  • orders for “tracer” or “trigger” substances
  • orders for special tests or serum drug concentrations
- Spontaneous reporting
- Medication utilization review
  • Computerized screening
  • Chart review and concurrent audits

**ADR Detection in Clinical Trials**

- Methods
  • Standard laboratory tests
  • Diagnostic tests
  • Complete history and physical
  • Adverse drug event questionnaire
    » Extensive checklist of symptoms categorized by body system
    » Review-of-systems approach
    » Qualitative and quantitative

**ADR Detection in Clinical Trials**

Limitations
- exposure limited to few individuals
  » rare and unusual ADRs not detected
- exposure is often short-term
  » latent ADRs missed
- external validity
  » may exclude children, elderly, women of child-bearing age; and patients with severe form of disease, multiple co-morbidities, and those taking multiple medications

**ADR Reporting in Clinical Trials 21 CFR 312**

- Changes to safety information reporting during clinical trials began in March 2011 and enforcement on September 28, 2011
- Clarifies definitions (Adverse Event, Suspected Adverse Reaction, Adverse Reaction)
- Suspected adverse reaction
  • Evidence suggesting a relationship with the study drug
- Revised requirements for expedited reporting

**IND Safety Reporting Issues**

- Adverse events that were likely to have been a manifestation of the underlying disease
- Adverse events that commonly occurred in the study population
- Adverse events that were study endpoints
**Preliminary Assessment**

- Preliminary description of event:
  - Who, what, when, where, how?
  - Who is involved?
  - What is the most likely causative agent?
    - Is this an exacerbation of a pre-existing condition?
    - Alternative explanations / differential diagnosis
  - When did the event take place?
  - Where did the event occur?
  - How has the event been managed thus far?

- Determination of urgency:
  - What is the patient’s current clinical status?
  - How severe is the reaction?

- Appropriate triage:
  - Acute (ER, ICU, Poison Control)

**Detailed Description of Event**

- History of present illness
- Signs / Symptoms:
  - Provoking or palliative factors
  - Quality (character or intensity)
  - Response to treatment,
  - Severity / extent, Site (location)
  - Temporal relationship (onset, duration, frequency)
  - Other associated signs and symptoms

**Pertinent Patient/Disease Factors**

- Demographics
  - age, race, ethnicity, gender, height, weight
- Medical history and physical exam
  - Concurrent conditions or special circumstances
    - e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding
  - Recent procedures or surgeries and any resultant complications
    - e.g., contrast material, radiation treatment, hypotension, shock, renal insufficiency

- Pertinent Patient/Disease Factors
  - End-organ function
  - Review of systems
  - Laboratory tests and diagnostics
  - Social history
    - tobacco, alcohol, substance abuse, physical activity, environmental or occupational hazards or exposures
  - Pertinent family history
  - Nutritional status
    - special diets, malnutrition, weight loss

**Pertinent Medication Factors**

- Medication history
  - Prescription medications
  - Non-prescription medications
  - Alternative and investigational therapies
  - Medication use within previous 6 months
  - Allergies or intolerances
  - History of medication reactions
  - Adherence to prescribed regimens
  - Cumulative medication dosages
## Pertinent Medication Factors

- **Medication**
  - Indication, dose, diluent, volume
- **Administration**
  - Route, method, site, schedule, rate, duration
- **Formulation**
  - Pharmaceutical excipients
    - e.g., colorings, flavorings, preservatives
  - Other components
    - e.g., DEHP, latex
- **Pharmacology**
- Pharmacokinetics (LADME)
- Pharmacodynamics
- **Adverse effect profiles**
- **Interactions**
  - drug-drug
  - drug-nutrient
  - drug-lab test interference
- Cross-allergenicity or cross-reactivity

## ADR Information

- Incidence and prevalence
- Mechanism and pathogenesis
- Clinical presentation and diagnosis
- Time course
- Dose relationship
- Reversibility
- Cross-reactivity/Cross-allergenicity
- Treatment and prognosis

## ADR Information Resources

- **Tertiary**
  - Reference books
    - Medical and pharmacotherapy textbooks
    - Package inserts, PDR, AHFS, USPDI
  - Specialized ADR resources
    - Meyler’s Side Effects of Drugs
    - Textbook of Adverse Drug Reactions
  - Drug interactions resources
    - Micromedex databases (e.g., TOMES, POISINDEX, DRUGDEX)
  - Review articles

- **Secondary**
  - MEDLARS databases (e.g., Medline, Toxline, Cancerline, Toxnet)
  - Excerpta Medica’s Embase
  - International Pharmaceutical Abstracts
  - Current Contents
  - Biological Abstracts (Biosis)
  - Science Citation Index
  - Clin-Alert and Reaction
  - Scopus

- **Primary**
  - Spontaneous reports or unpublished data
    - FDA
    - Manufacturer
  - Anecdotal and descriptive reports
    - Case reports, case series
  - Observational studies
    - Case-control, cross-sectional, cohort
  - Experimental and other studies
    - Clinical trials
    - Meta-analyses
Causality Assessment

- Prior reports of reaction
- Temporal relationship
- De-challenge
- Re-challenge
- Dose-response relationship
- Alternative etiologies
- Objective confirmation
- Past history of reaction to same or similar medication

Examples of causality algorithms
- Kramer
- Naranjo and Jones

Causality outcomes
- Highly probable
- Probable
- Possible
- Doubtful

Causality Assessment

Naranjo ADR Probability Scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there prior reports of reaction to this medication?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>4. Did the adverse reaction appear when the drug was reinstituted?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>5. Are there other causes (other than the drug) that could have caused the reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>6. Did the reaction improve when a placebo was given?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>7. Was the drug detected in the patient’s blood (or other fluids) in toxic concentrations?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>10. Did the adverse event improve by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
</tbody>
</table>

Total Score


Management Options

- Discontinue the offending agent if:
  - it can be safely stopped
  - the event is life-threatening or intolerable
  - there is a reasonable alternative
  - continuing the medication will further exacerbate the patient’s condition

- Continue the medication (modified as needed) if:
  - it is medically necessary
  - there is no reasonable alternative
  - the problem is mild and will resolve with time

Management Options

- Discontinue non-essential medications
- Administer appropriate treatment
  - e.g., atropine, benztropine, dextrose, antihistamines, epinephrine, naloxone, phenytoin, phytodnolone, protamine, sodium polystyrene sulfonate, digibind, flumazenil, corticosteroids, glucagon
- Provide supportive or palliative care
  - e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics
- Consider rechallenge or desensitization

Follow-up and Re-evaluation

- Patient’s progress
- Course of event
- Delayed reactions
- Response to treatment
- Specific monitoring parameters
Reporting ADRs

**Reportable**
- All significant or unusual adverse drug reactions as well as unanticipated or novel events that are suspected to be drug related

**Reportable**
- Hypersensitivity
- Life-threatening
- Cause disability
- Idiosyncratic
- Secondary to Drug interactions
- Unexpected detrimental effect
- Drug intolerance
- Any ADR with investigational drug

Documentation and Reporting

- Medical record
  - Description
  - Management
  - Outcome
- Reporting responsibility
  - JCAHO-mandated reporting programs
  - Food and Drug Administration
    - post-marketing surveillance
    - particular interest in serious reactions involving new chemical entities
  - Pharmaceutical manufacturers
  - Publishing in the medical literature

Components of an ADR Report

- Product name and manufacturer
- Patient demographics
- Description of adverse event and outcome
- Date of onset
- Drug start and stop dates/times
- Dose, frequency, and method
- Relevant lab test results or other objective evidence
- De-challenge and re-challenge information
- Confounding variables

MedWatch Direct Reports

- Reports submitted directly to FDA through MedWatch by
  - Internet – on line reporting form
  - Mail or Fax
  - Telephone 1-800-FDA-1088

MEDWATCH 3500A Reporting Form

https://www.accessdata.fda.gov/scripts/medwatch
Post-marketing Adverse Events

- Patients, consumer and healthcare professionals
- Manufacturer
- FDA MedWatch
- FDA’s Adverse Event Reporting System database

Reports Received and Reports Entered into AERS by Year

- Analyzed computer excerpts from 33,068 reports
- Continued increase in reports – up 12% compared to Q2 2009
- Reports from manufacturers increased 24%
- Reports from consumers and health care professionals were 25% fewer

ISMP – QuarterWatch™ 2010 Quarter 2

ISMP – QuarterWatch™ 2010 Quarter 2

Risk Evaluation and Mitigation Strategy (REMS)

- Risk management plan that utilizes strategies that go beyond professional labeling to ensure drug benefits outweigh risks
- The FDA Amendments Act of 2007 (FDAAA) granted the FDA the authority to require the submission and implementation of a REMS
- REMS are designed to meet specific serious risk mitigation goals
REMS Considerations
- Does the product fill a significant unmet need?
- What is the magnitude of the risk?
- Do the data suggest ways to mitigate the risk?

REMS Components
- Medication Guide for patients
- Communication Plan for healthcare professionals
- Elements to Assure Safe Use (previously “restricted distribution”)
- Implementation system

Medication Guide Requirement
- Patient labeling could help prevent serious adverse events
- The product has serious risks that could affect a patient’s decision
- Patient adherence to directions is crucial to product effectiveness

Communication Plan
- If FDA determines a communication plan is needed, it can include:
  • Letters to healthcare providers
  • Disseminating information through professional societies about serious risk of the drug and any elements to assure safe use

Elements to Assure Safe Use
- Prescriber training or certification
- Certification of dispensers
- Drug administration limited to certain health care settings
- Documentation of safe use prior to dispensing
- Required monitoring of patients
- Enrollment of patients in a registry

REMS Example
Victoza® (Liraglutide)
- Goal is to inform providers of the risk of acute pancreatitis (including necrotizing pancreatitis) and potential risk of medullary thyroid carcinoma
- Medication guide will be dispensed with each prescription
- Communication Plan
  • Dear doctor letter
  • Direct mail letter each year x 3 yrs
  • Highlighted information for prescribers will be distributed by manufacturer representatives
Before taking Victoza, tell your healthcare provider if you have had:
- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels
  - These medical conditions can make you more likely to get pancreatitis in general. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking Victoza.
- While taking Victoza:
  - Stop taking Victoza and call your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. This type of pain may be a symptom of pancreatitis.

FDA Drug Safety Newsletter

MedWatch Safety Alerts

FDA Patient Safety News
- Video news show for health professionals

Future
- I-phone apps for MedWatch
- Hospital systems to report adrs directly to FDA
- FAERS – FDA Adverse Event Reporting System (enhanced analysis) for CDER and CBER
- Standardization of reporting to include data from Japan and Europe
- Federal Adverse Event Task Force (FAET)
- Innovative ways to increase reporting and identification of adverse drug reactions

Safety Reporting Portal
- Launched in May of 2010, testing phase
- FDA safety issues involving: Human or animal reportable foods
  - Animal drugs
  - Pet foods
- NIH safety issues involving: NIH gene-transfer research

Federal Adverse Event Reporting Portal
- Investigator
- Sponsor
- Manufacturer
- Veterinary
- Web site overview
- Victoza
- Physicians
- Patients
- Consumers
- Local
- DSMB
- IRB
- Institutional Database

Safety Reporting Portal
- The Safety Reporting Portal provides for the process of reporting product safety issues to the Food and Drug Administration (FDA) and other federal agencies. The portal is designed to enhance the submission of adverse event reports by providing a user-friendly interface. Reports can be submitted through this portal for various types of medical products, including drugs, biologics, medical devices, and dietary supplements. The portal also includes features such as data visualization and interactive maps to help users understand the information better. The portal is accessible through the FDA website, and users can register for an account to create and submit reports. The portal is updated regularly to improve usability and accuracy.
<table>
<thead>
<tr>
<th>Study Information</th>
<th>Study Name</th>
<th>Study Type</th>
<th>Study ID</th>
<th>Study Location</th>
<th>Study Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Questions ???