Clinical Analysis of Adverse Drug Reactions

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Objectives

- Define adverse drug reactions
- Discuss epidemiology and classification of ADRs – discussed in previous lecture
- 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

Adverse Drug Event: preventable or unpredicted medication event—harm to patient

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
Classification

- Onset
- Severity
- Type

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

Classification - Severity

- Minor
- Moderate
- Serious
- Serious life-threatening
- Serious lethal
FDA Defines Serious ADE

- Result in death
- Life-threatening
- Hospitalization (new or prolonged)
- Disability or incapacity
- Congenital anomaly, birth defect
- Other: require intervention to prevent any of the above

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

Common Causes of ADRs

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

*account for 69% of fatal ADRs
**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
- Decision Support systems
  - Physician order entry, pharm info system
### 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

**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?

Preliminary Assessment

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

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**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

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**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

Pertinent Medication Factors

- 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

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
• Definite
• Probable
• Possible
• Doubtful
To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</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>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4. Did the adverse reaction appear when the drug was withhold?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could have caused the reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6. Did the reaction improve when a placebo was given?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7. Was the drug detected in the blood or other fluids in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8. Did the adverse reaction occur when the dose was increased, or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</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>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total Score: 8

Naranjo ADR Probability Classification

<table>
<thead>
<tr>
<th>Score</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Definite</td>
</tr>
<tr>
<td>5-8</td>
<td>Probable</td>
</tr>
<tr>
<td>1-4</td>
<td>Possible</td>
</tr>
<tr>
<td>0</td>
<td>Doubtful</td>
</tr>
</tbody>
</table>

Assessing ADR Risk

- Review drug labels
  - DailyMed, Drugs@FDA
- Safety Alerts – FDA, international
- Published literature (case reports, reviews, clinical trials)
- Drug information resources
  - NLM – Livertox
  - Micromedex

Evaluating a Publication for ADRs

- Are adverse events actually reported?
- Passive or active surveillance used to identify AE?
- Is a validated checklist available?
- Are pre-specified objective endpoints reported?
- Are patient withdrawals because of adverse events reported?
- Are AE reported in the abstract, methods, and results section?
- Discussion includes a balanced discussion of harms and benefits?
- Is there external validity?


[11]
**Minimizing and Managing ADRS**

- 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, phytonadione, 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 3500A Reporting Form

https://www.accessdata.fda.gov/scripts/medwatch
MedWatch Direct Reports

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

Post-marketing Adverse Events

FAERS

- FAERS (FDA Adverse Event Reporting System) database for drugs and biologics
  • Adverse event reports
  • Medication error reports
- Replaced AERS on September 10, 2012.
- FDA will use FAERS for regulatory compliance, and to monitor for adverse events and medication errors that might occur with CDER and CBER regulated products.
Reports Received and Reports Entered into AERS by Year

Reports Received and Reports Entered into FAERS/AERS by Year

Office of Surveillance & Epidemiology

Office of Medication Error Prevention & Risk Management (OEMFRM)

Office of Medication Error Prevention & Analysis (OEMEPA)

Office of Risk Management (ORMR)

Division of Medication Error Prevention & Analysis (DMEPA)

Division of Risk Management (DRMR)

Division of Epidemiology I and II (DEPI I and II)

Division of Pharmacovigilance I and II (DPV I and II)
Division of Pharmacovigilance

- Evaluate the safety of drug and biologic products
- Advance public health by detecting and analyzing safety signals from all available data sources, utilizing evidence-based methods
- Recommend appropriate regulatory actions, including labeling changes, REMS, etc.
- Communicate related safety information

FDA Drug Safety Communications

- FDA provides easy access to important drug safety information
- Risk of Progressive Multifocal Leukoencephalopathy (PML) with the use of Tysabri (natalizumab) and increases with number of infusions
  - 31 confirmed cases of PML received by the FDA as of January 21, 2010
  - Additional information for patients and prescribers provided on website
  - This information will be included on the drug label and patient Medication Guide
  - Limited distribution prescribing system is in place

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
- 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
Sample of Victoza® Medication Guide

- 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.
  - For a list of Medication guides:
    http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm

How to get FDA Drug Safety Alerts

- FDA Drug Safety Newsletter
yen/defualt.htm

- MedWatch Safety Alerts
  - http://www.fda.gov/Safety/MedWatch/ucm1684
22.htm

- FDA Patient Safety News
  - Video news show for health professionals
ocs/psn/index.cfm

- MedWatch reporting:
  - http://www.fda.gov/Safety/MedWatch/ucm3359
23.htm

Questions ???