Clinical Analysis of Adverse Drug Reactions

Karim Anton Calis, Pharm.D., M.P.H.
National Institutes of Health

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Objectives

- Define adverse drug reactions
- Discuss epidemiology and classification of ADRs
- Describe basic methods to detect, evaluate, and document ADRs
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.

- excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors.
Adverse Drug Events

Adapted from Bates et al.

Adverse Drug Events (ME & ADR)

Medication Errors (preventable)

Adverse Drug Event: preventable or unpredicted medication event---with harm to patient
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
- 30% to 60% are preventable

Classification

- Onset
- Severity
- Type
Onset of event:

- **Acute**
  » within 60 minutes
- **Sub-acute**
  » 1 to 24 hours
- **Latent**
  » > 2 days
Severity of reaction:

- **Mild**
  - bothersome but requires no change in therapy

- **Moderate**
  - requires change in therapy, additional treatment, hospitalization

- **Severe**
  - disabling or life-threatening
Classification - Severity

- FDA Serious ADR
  - Result in death
  - Life-threatening
  - Require hospitalization
  - Prolong hospitalization
  - Cause disability
  - Cause congenital anomalies
  - Require intervention to prevent permanent injury
• 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
Classification

• Type C
  » associated with long-term use
  » involves dose accumulation
  » e.g., phenacetin and interstitial nephritis or antimalarials and ocular toxicity
• Type D
  » delayed effects (dose independent)
  » Carcinogenicity (e.g., immunosuppressants)
  » Teratogenicity (e.g., fetal hydantoin syndrome)
Classification

- Types of allergic reactions
  - Type I - immediate, anaphylactic (IgE)
    » e.g., anaphylaxis with penicillins
  - Type II - cytotoxic antibody (IgG, IgM)
    » e.g., methyldopa and hemolytic anemia
  - Type III - serum sickness (IgG, IgM)
    » antigen-antibody complex
    » e.g., procainamide-induced lupus
  - Type IV - delayed hypersensitivity (T cell)
    » e.g., contact dermatitis
Classification - Type

Reportable

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

Reportable

- Hypersensitivity
  - Life-threatening
  - Cause disability
  - Idiosyncratic
  - Secondary to Drug interactions

- Unexpected detrimental effect
- Drug intolerance
- Any ADR with investigational drug
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 Frequency by Drug Use

- **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
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
  » 3000 patients at risk are needed to detect ADR with incidence of 1/1000 with 95% certainty

• 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
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
PQRSTA Acronym
Detailed Description of Event

- History of present illness
- Signs / Symptoms: PQRSTA
  - Provoking or palliative factors
  - Quality (character or intensity)
  - Response to treatment, Radiation, Reports in literature
  - Severity / extent, Site (location)
  - Temporal relationship (onset, duration, frequency)
  - 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
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
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 Reactions
• 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
To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous <em>conclusive</em> reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></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></td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a <em>specific</em> antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse reactions appear when the drug was readministered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></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>
<td></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></td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in <em>any</em> previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Total Score __________

Total Score                  ADR Probability Classification

9  Highly Probable
5-8  Probable
1-4  Possible
0  Doubtful
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, 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
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