Surveillance for Liver Toxicity After Marketing

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Predicting Serious Drug-Induced Liver Injury in Patients
Who Gets It? Who Doesn’t? Why?
Hyattsville, MD
The opinions expressed in this lecture are those of the presenter, and do not necessarily represent the views of the US Food and Drug Administration or the US Government.

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Goals of Drug Safety Surveillance

• To identify previously unknown drug-related adverse events
• To learn more about known drug-related adverse events
• To learn more about how drugs are used in ways that may not promote safe use
• The method you use depends on what you are trying to learn
• To communicate findings about drug safety
Historically….

- Individual case safety reports were the main source of drug safety information
  - Good for rare events that are usually the result of drug or toxin exposure
    - Acute liver failure
    - Stevens-Johnson Syndrome
    - Torsades de pointes
- Most drug withdrawals and major safety actions are related to one of these events
Qualities of a Good Case Report

• What makes a good case report?
  – Description of the event
  – Suspected product(s) and concomitant treatment details
  – Patient characteristics, medical history, treatment history
  – Documentation of the diagnosis
  – Clinical course and outcomes
  – Treatment and lab values at baseline, during therapy, and after therapy
  – Response to dechallenge and rechallenge
  – Any other relevant information

• This takes time

Passive Surveillance - Challenges

- Case reports, as a whole, often lack important clinical details
- Need to involve stakeholders
- Need refinement of signal detection methods, as numbers of reports increase
- Can this be automated?
Percentage of safety-related label changes in the United States by data source - 2010
Today....

• Large databases are available for drug safety studies
• We can detect much more subtle adverse drug effects including increases in relatively common events
  – Common in the population
  – Manifestation of the disease being treated
Active Surveillance

• Actively looking
• Can be:
  – Disease-based
  – Drug-based
  – Setting-based
• Can use large healthcare databases for surveillance
Sentinel Initiative

• FDA initiative
• Use large databases from multiple sources
• Cover a large number of lives
  – 25 million in 2010
  – 100 million in 2012
• Two components:
  – Mini-Sentinel
  – Federal Partners Collaboration
Active Surveillance - Challenges

**Governance**

- What are the keys to a successful public-private partnership?

**Data**

- Which types of data? administrative claims, electronic health records
- Which sources? healthcare providers, insurers, data aggregators

**Performance**

- What are appropriate analyses for:
  - hypothesis generating?
  - hypothesis strengthening?

**Architecture**

- What is the appropriate infrastructure:
  - hardware?
  - software?
  - processes?
  - policies?

**Methods**

- How to maintain collaborations and engage research community?

**Technology**

- What are best practices for protecting data?

**Feasibility**

- What are viable data access models:
  - centralized?
  - distributed?
Building Safety Into Drug Development

- **Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation**
  - Quantitative data analysis
  - Individual case analysis
  - Analysis of signals

- **Guidance for Industry: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs**
  - Thorough QT/QTc studies
  - Interpretation of ECG data in clinical trials

- **Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes**
  - Appropriate design of Phase 2/3 trials to assess cardiovascular risk
  - Methods for meta-analysis
  - Criteria for pre-approval and post-approval testing
Thank you