Adverse Drug Reactions (ADRs)

Outline

1. What are Adverse Drug Reactions (ADRs)?
2. How important are ADRs and are they preventable?
3. What are the classifications and mechanisms of ADRs?
4. Adverse-Drug Events
5. Evaluate the various types of ADRs using clinical examples

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At the end of the lecture, you should begin to think of patient’s safety, and be able to:

1. **Differentiate the underlying mechanisms** for Type A and Type B ADRs

2. **Recognize important examples** of Type A and Type B ADRs

3. **Apply** the knowledge of ADRs to clinical scenarios
Prince: cause of death

http://www.ashp.org/DocLibrary/Bookstore/P2418-Chapter1.aspx
Adverse Drug Reactions (ADRs)

WHO definition: An adverse reaction is any response to a drug that is noxious and unintended, and that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease.

(Excluding overdose, drug abuse, and medication errors)
Clinical and economic burden of adverse drug reactions

**J Pharmacol Pharmacother.** 2013 Dec; 4(Suppl1): S73–S77

Adverse drug reactions (ADRs) are unwanted drug effects that have considerable economic as well as clinical costs as they often lead to hospital admission, prolongation of hospital stay and emergency department visits.

**ADRs accounts for**
- 30% of hospital admissions in the USA and Canada
- 20% of admissions in Australia
- 11% of admissions in Europe

5.2% of ADRs in children lead to hospitalization up to 40% in pediatric patients can be life-threatening or fatal.

Up to 36% of emergency department visits in older adults are due to drug-related causes.

[link](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853675/)
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ADRs are of great concern to drug regulatory authority in all countries because of the issues of:

SAFETY, EFFICACY and QUALITY

How do we gather ADRs information?

- From Pre-clinical phase I studies
- From Clinical trial Phase I to Phase III
- Post marketing surveillance
- Spontaneous reports of suspected ADRs
  - continuous monitoring of drugs after issuance of license is necessary
Incidence of ADRs in Hospitalized Patients: A Meta-analysis of Prospective Studies


**Objective.**—To estimate incidence of serious and fatal ADRs in hospital patients.

**Data Synthesis.**—ADRs: fourth to sixth leading cause of death.

**Conclusions.**—ADRs represent an important clinical issue.

[http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4168391/]
Incidence of fatal ADRs: a population study

Fatal ADRs: 3% of all deaths in the general population.

Haemorrhage: 2/3 of the Fatal ADRs, antithrombotic agents are implicated in more than half of the suspected Fatal ADRs.
Conclusion: ADRs are a significant public health problem in our health care system. For the 12 millions Medicare patients admitted to US hospitals, ADRs were projected to cause 3000 deaths

Up to 50% of ADRs are preventable, more attention to their detection and management is warranted
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Adverse Drug Reactions (ADRs)
Classifications of ADRs

According to Rawlins and Thompson (1998)

Type A

Predictable

Type B

Unpredictable

idiosyncratic

immunological (classified as Type I - IV hypersensitivity)
What are the mechanisms of ADRs?
Type A (Predictable ADRs)

ADRs related to Pharmacological actions of drug

Dose-related, recognized as possible ADRs during clinical trials (account for ~2/3 of ADRs)

• ADRs as unwanted or excessive Pharmacological effects
Examples of Type A, Predictable ADRs

Unwanted or excessive Pharmacological effects

• Bleeding ...........
• Sedation ...........
• Hypoglycemic coma ......
• Tremors ..................
• Respiratory depression .......
Examples of Type A, Predictable ADRs

Unwanted or excessive Pharmacological effects

• Bleeding ........... anticoagulant (warfarin), antiplatelet drugs
• Sedation ........... anti-anxiety drug, (diazepam)
• Hypoglycemic coma ...... insulin
• Tremors ...................... \( \beta_2 \) agonists (salbutamol)
• Respiratory depression ....... morphine

How to prevent ADRs?
### Example of Type A, Predictable ADRs

#### Mechanism of the ADRs of Gentamicin

<table>
<thead>
<tr>
<th><strong>Ototoxic</strong></th>
<th><strong>Nephrotoxic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>toxic to the sensory cells of the inner ear, sometimes causing complete hearing loss</td>
<td>inhibit protein synthesis in renal cells, causes necrosis of cells in the proximal tubule, resulting in acute tubular necrosis, can lead to acute renal failure</td>
</tr>
<tr>
<td>usually if taken at high doses or for prolonged periods of time,</td>
<td>if multiple doses accumulate over a course of treatment,</td>
</tr>
</tbody>
</table>
Symptoms of gentamicin ADRs

• Balance difficulty
• Hearing loss
• Ringing in the ears
Type A

Predictable

Type B

Unpredictable

idiosyncratic

immunological (classified as Type I - IV hypersensitivity)
Unpredictable (Type B) ADRs

Idiosyncratic (often linked to genetic anomalies)

• Glucose-6-phosphate dehydrogenase (G6PD) deficiency --- hemolysis with maloprim (antimalarial)

• Acetylator polymorphism – slow acetylator --- peripheral neuropathy with isoniazid (anti-TB)
Drug itself or its metabolites can act as a hapten by interacting with protein to become immunogenic.
Characteristics of an immunogenic response are:

- Prior exposure
- May be delayed in onset
- Can occur with subsequent low doses
- Reactions conform to immunogenic responses, Type I, II, III and IV
Types of hypersensitivity/allergic reactions to drugs

Type I, II and III are antibody-mediated reactions while Type IV is cell mediated

**FIGURE 25.1** Mechanisms of hypersensitivity reactions. *Type I*: Antigens bind to antibodies on mast cells causing degranulation and release of histamine and other mediators. *Type II*: Antibodies attach to cell-surface antigens, causing activation of complement or other effector cells (neutrophils, K-lymphocytes, etc.) and resulting in cell damage and cell death. *Type III*: Antigen-antibody complexes are deposited in tissue. *Type IV*: T-cells are sensitized to a specific antigen thereby causing lymphokine release. (Reproduced with permission from Young LR, Wurtzbacher JD, Blankenship CS. Am J Manag Care 1997;3:1884–906.)

Type I:

antibody mediated hypersensitivity - Acute allergic reactions to stings, pollens, certain food, or drugs. The substance evokes release of IgE

IgE fixed to tissue mast cells and basophils

After interaction with antigen, the cells release potent mediators.

Localised: rhinitis, asthma, rash, urticaria

Generalised: anaphylactic shock

e.g. of drugs: penicillin, streptokinase…food
Type I:

Angioedema
Drug Allergy – case summary

- Pt admitted electively for minor surgery
- The doctor noted from the note that patient was allergic to Aspirin
- Same doctor ordered Synflex in the operating theater
- Patient noted to have acute periorbital swelling, blocked nose + watery eyes after he/she returned home and taken the Synflex.
Antibody-dependent cytolytic hypersensitivity – Reaction is directed at “foreign” host cells. Cells (eg. blood cells) can be made “foreign” by drugs.

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Drugs responsible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>carbamazepine, ticlopidine</td>
</tr>
<tr>
<td>Agranulocytosis, neutropenia</td>
<td>Carbamazepine, phenytoin, carbimazole, ganciclovir</td>
</tr>
<tr>
<td>Systemic- Drug induced SLE</td>
<td></td>
</tr>
</tbody>
</table>
### Analysis of ADR reports

#### E.g of drugs causing serious blood ADRs

<table>
<thead>
<tr>
<th>Description</th>
<th>Suspected active ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>agranulocytosis</td>
<td>Benzylpenicillin, <strong>carbamazepine</strong>, carbimazole, erythromycin, phenytoin, ticlopidine</td>
</tr>
<tr>
<td>pancytopenia</td>
<td>Amoxicillin, cloxacillin, methotrexate, phenytoin</td>
</tr>
<tr>
<td>leucopenia</td>
<td>Allopurinol, colchicine, sulfasalazine, ticlopidine</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>Amoxicillin, azathioprine, <strong>carbamazepine</strong>, clopidogrel, heparin, pentazocine,</td>
</tr>
</tbody>
</table>
Reactions due to elevated levels of antigen-antibody complexes. Complexes deposited in e.g. vascular endothelium to cause inflammatory responses/tissue injury (1-24 h) - serum sickness.

<table>
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<tr>
<th>ADRs</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Serum sickness syndrome</td>
<td>penicillins, NSAIDS</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>sulphonamides, carbamazepine</td>
</tr>
</tbody>
</table>
**Analysis of ADR reports**

E.g of drugs causing serious ADRs

<table>
<thead>
<tr>
<th>Description</th>
<th>Suspected active ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevens-Johnson, TEN</td>
<td>Acyclovir, allopurinol, amitriptyline, amoxicillin, carbamazepine (7), cotrimoxazole(6),</td>
</tr>
<tr>
<td></td>
<td>coamoxiclav (2), omeprazole(3), phenytoin(7)</td>
</tr>
</tbody>
</table>
Toxic Epidermal Necrolysis (TEN)  
immune-complex mediated

Stevens-Johnson syndrome (SJS)  
immune-complex–mediated

Both SJS and TEN are erythema multiforme. SJS (If <10% of body surface affected); TEN (>30% of body is affected). Mixed SJS/TEN when 10-30% body surface affected.

Sulphonamides (“sulpha” drugs) e.g. co-trimoxazole, most common cause

Pictures-from HSA, Adverse Drug Reaction News July 2004, - courtesy NSC
Type IV:

The reaction involves drug-sensitised T cells, which in response to antigen - release cytokines like lymphokines and interleukins.

e.g. latex gloves or drugs topically applied to the skin that cause contact dermatitis and photosensitivity

Manifestations: usually mild skin rash but may be fatal exfoliation, autoimmune diseases, fever.
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Adverse Drug Event

Any undesirable experience associated with use of a medical product in a patient: Includes ADRs and any other adverse events:

medication errors (prescribing, preparation, dispensing or administration), overdose, drug abuse
Medication Error - insulin

Incident: Actrapid 6 units was given to patient instead of Aspart 6 units ordered
Medication errors occurred before when these medication vials were not coloured. Pharmaceutical companies have since produced colour coded vials to minimize errors.
WARFARIN
- Containers are color coded to reflect color of warfarin tablet to avoid wrong
How to prevent or reduce the incidence of ADRs

• Knowledge and awareness of important ADRs of drugs that you are prescribing
• Ask questions about concurrent drug therapy
• Cautious with dose and duration of exposure
• Knowledge of drug-drug interactions
• Be aware of age of patient
• Be aware of patient’s disease states – organ dysfunction
WHO Collaborating Centre for International Drug Monitoring

The WHO Programme for International Drug Monitoring established in 1960s, (http://www.who-umc.org), Sweden has the world’s largest database of 3 million recorded cases of ADRs.
How to report incidence of ADRs

• Record patient’s drug medication history and known allergies

• Contact the local Medical Council to register the allergy of the individual. Some Medical association supplies bracelets and cards stating allergies

• Use information from local and International collaboration databases