Clinical Pharmacology of ADRs

20 April 2015
Meyler Course
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Scientific Assessor
Quiz

1. An adverse drug reaction is every unwanted effect occurring during a treatment. ✔️ ✗
2. Dose-dependant adverse drug reactions are most of the time not serious. ✔️ ✗
3. Whether an adverse drug reaction occurs, depends on individual sensitivity. ✔️ ✗
4. There is always a pharmacological explanation available for an adverse drug reaction. ✔️ ✗
5. Based on risk factors it is predictable which patients will develop an adverse drug reaction. ✔️ ✗
Learning objectives

• Be able to apply the pathophysiologic principles that underlie the occurrence of side effects such as pharmacological effects and patient-related effects.

• Characterizing adverse drug reaction according to the knowledge of side effects according to different formats
  - Applying the classification in the A / B category classification of adverse events.
  - Having knowledge of aspects which play a role in the development of side effects.

• Discuss which patients have an increased risk for developing side effects.
Outline

- Concept definition
- Pharmacological classification
- Risk factors
Classification of ADRs
ADR

Primary

Related to known mechanism

Secondary

Usually occurring in other organ systems, but can be explained from clinical pharmacology
# Pharmacologically explainable ADRs

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>Toxicity</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical</td>
<td>Phenytoin</td>
<td>Phenytoin toxicity (ataxia, nystagmus, etc)</td>
<td>Increase in bioavailability as a result of a change in formulation</td>
</tr>
<tr>
<td>Pharmacokinetic (can involve absorption, distribution, metabolism and excretion)</td>
<td>Digoxin</td>
<td>Digoxin toxicity (nausea, arrhythmias, etc)</td>
<td>Decreased elimination if renal function is impaired</td>
</tr>
<tr>
<td>Pharmacodynamic</td>
<td>Indomethacin</td>
<td>Left ventricular failure</td>
<td>Water and sodium retention</td>
</tr>
<tr>
<td>Genetic</td>
<td>Nortriptyline</td>
<td>Confusion</td>
<td>Reduced hepatic elimination as a result of a deficiency of CYP2D6</td>
</tr>
<tr>
<td>Drug-drug interactions (can involve any of the above processes)</td>
<td>Lithium-nonsteroidal anti-inflammatory drugs</td>
<td>Lithium toxicity</td>
<td>Inhibition of excretion of lithium</td>
</tr>
</tbody>
</table>

M. Pirmohamed, University of Liverpool
Classification of ADRs
Type A-G
1) A - F(G) classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(augmented)</td>
<td>Pharmacological effect</td>
<td>Withdrawal or dose reduction</td>
</tr>
<tr>
<td></td>
<td>Dose related</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Predictable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low mortality</td>
<td></td>
</tr>
<tr>
<td>B(izard)</td>
<td>Rare</td>
<td>Withdrawal; avoid in the future</td>
</tr>
<tr>
<td></td>
<td>Unpredictable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High mortality</td>
<td></td>
</tr>
<tr>
<td>C(hronic)</td>
<td>Rare</td>
<td>Withdrawal (longer period) or</td>
</tr>
<tr>
<td></td>
<td>Cumulative dose</td>
<td>dose reduction</td>
</tr>
<tr>
<td>D(elayed)</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mostly dose related, sometimes only after withdrawal</td>
<td></td>
</tr>
<tr>
<td>E(nd of use)</td>
<td>Rare or unpredictable</td>
<td>Restart and tapering</td>
</tr>
<tr>
<td></td>
<td>Rapidly after withdrawal</td>
<td></td>
</tr>
<tr>
<td>F ailure)</td>
<td>Frequent</td>
<td>Dose increase</td>
</tr>
<tr>
<td></td>
<td>Dose related; result of interactions</td>
<td>Effect comedication</td>
</tr>
<tr>
<td>G(eneric)</td>
<td>Farmacokinetic of -dynamic</td>
<td>Dosis adjustment or withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and avoidance</td>
</tr>
</tbody>
</table>

Type A/B reactions

A “Augmented”
- Pharmacological effect
- Dose dependent
- Occurs frequently
- Often detected in clinical trials

B “Bizarre”
- Idiosyncratic
- Rare
- Serious
- Not detected in clinical trials

Type A drug related reaction

- Dose dependent
- Reversible
- Disappears after dose reduction or cessation of therapy
- Rechallenge often positive
Type B reaction

- Not dose dependent
- Sensibilisation may be needed
- Reduction of dose often no effect on ADR
- Treatment is often needed
- Dechallenge positive
Patient: type B

- Allergic / immunological reactions
  - Anaphylaxis, various skin images
  - Blood count abnormalities
  - Immune-complex disease
  - Contact-allergy (ointment, eye drops)

- Other patient-related factors
  - Genetic factors
Examples type B reactions

Blood: serious blood disorders
Liver: hepatitis
Kidney: nephritis
Long: pneumonia, alveolitis
Skin: urticaria, angioedema, anaphylaxis
Other type of reactions

• Type C  Chronic reaction
• Type D  Delayed type
• Type E  Withdrawal reaction
• Type F  Failure of therapy
Sharp distinction?

Unfortunately not

- Tendinitis with fluoroquinolones (norfloxacin, ciprofloxacin)
  Toxic or immunological?

- Toxic hepatitis
  Often, auto-immune component after initial hepatocellular damage
Classification ADRs

Steven Johnson syndrome in allopurinol.

Type ?
Classification ADRs

Mydriasis in amitriptyline.

Type ?
Classification ADRs

Suppression of the adrenal cortex (HPA-axis) in corticosteroids.
Classification of ADRs
DTOS
Another classification

Education and debate

Joining the DoTS: new approach to classifying adverse drug reactions
Jeffrey K Aronson, Robin E Ferner

A new classification system for adverse drug reactions based on time course and susceptibility as well as dose responsiveness should improve drug development and management of adverse reactions

- D  Dose relatedness
- T  Time relatedness
- S  Susceptibility
Dose relatedness

• Effects of medicines are based on interactions between chemical substances, to which law of mass action is applicable.

• Even for immunological disorders like
  - Hay Fever!
  - Other type B reactions
Dose relatedness

Alternative classification relates to reactions that occur in

- Supra-therapeutic doses (toxic dose)
- Standard therapeutic doses (collateral effects)
- Subtherapeutic doses (allergic reactions)
Dose-response curve for allergic reaction in susceptible patients.

"Type B" curve for the analgesic effect of morphine.

"Type A" curve for the depressive effect of morphine on respiration.

Margin of safety.

Dose of drug: low to high.
Time relatedness

- Time-independent reactions can occur at any time; independent of the duration of the treatment
  - Whenever dosage is changed
  - When pharmacological response alters due to other causes
Timing

• Time dependent reactions

1. Rapid reactions only when a drug is administered rapidly
   • Red man syndrome on vancomycin
   • Rapid injection of adrenaline

2. First dose reaction. In particular, at first dose, not necessarily herafter
   • Hypotension ACE inhibitors
Timing

3. Early reaction.
   • Early in treatment but then disappears through adaptation
   • Example: nitrate-dependent headache

4. Intermediate reaction.
   • Occurs after a few days
   • 5th day rash with antibiotics
   • Type III allergic reactions like nephritis with penicillins
Timing

5. Late reaction. The risk of the onset of the side effect increases with time.
   • Osteoporosis in use of corticosteroids
   • Tardive dyskinesia at dopamine agonists (withdrawal reactions like myocardial infarction after discontinuation of β-blockers)

6. Delayed reaction.
   • Especially after prolonged use or repeated exposure
   • Increased risk of breast carcinoma after the use of estrogens in menopause
Graphs showing how probability of adverse drug reaction (y axis) might vary with variations in time after administration (x axis, arbitrary units) and dose (z axis, arbitrary units) in people with high, medium, and low susceptibility having an adverse effect of intermediate type.
Individual susceptibility

- Risks of an adverse reaction depends on various factors such as
  - Age
  - Sex
  - Renal function
  - Hepatic function
  - Exogenous factors
Table 1 Sources of altered susceptibility to adverse drug reactions

<table>
<thead>
<tr>
<th>Source of susceptibility</th>
<th>Examples</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Porphyria</td>
<td>Screen for abnormalities; avoid specific drugs</td>
</tr>
<tr>
<td></td>
<td>Succinylcholine sensitivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignant hyperthermia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP isozyme polymorphisms</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Neonates (chloramphenicol&lt;sup&gt;15&lt;/sup&gt;)</td>
<td>Adjust doses according to age</td>
</tr>
<tr>
<td></td>
<td>Elderly people (hypnotics&lt;sup&gt;16&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Alcohol intoxication</td>
<td>Use different doses in men and women</td>
</tr>
<tr>
<td></td>
<td>Mefloquine, neuropsychiatric effects&lt;sup&gt;17&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiotensin converting enzyme inhibitors, cough</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lupus-like syndrome&lt;sup&gt;18&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Physiology altered</td>
<td>Phenytion in pregnancy&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Alter dose or avoid</td>
</tr>
<tr>
<td>Exogenous factors</td>
<td>Drug interactions</td>
<td>Alter dose or avoid co-administration</td>
</tr>
<tr>
<td></td>
<td>Interactions with food (eg grapefruit juice with drugs cleared by CYP3A4&lt;sup&gt;20&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Renal insufficiency (eg lithium&lt;sup&gt;21&lt;/sup&gt;)</td>
<td>Screen for abnormalities; avoid specific drugs; use reduced doses</td>
</tr>
<tr>
<td></td>
<td>Hepatic cirrhosis (eg morphine&lt;sup&gt;22&lt;/sup&gt;)</td>
<td></td>
</tr>
</tbody>
</table>
Risk factors
Dosis sola facit *venenum*,

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy."

Paracelsus (1493-1541).
Pharmacokinetics in children

Formsulation

Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children
Drug therapy in young children

Tan et al. MJA 2003
Adverse drug reactions in children

• Different patterns compared to adults

• Sometimes higher frequency
  - Liver failure and valproate
  - Stevens Johnson Syndrome and lamotrigine

• Alterations in pharmacokinetics and pharmacodynamics
Pharmacokinetics: absorption

• Acidity of stomach higher due to buffering of milk
  - Less absorbed: i.e. phenobarbital, phenytoin, carbamazepin, indinavir
  - Increased absorption: doxapram

• Gastric emptying rate
  - Decreased in newborn
  - Increased in toddlers and children

• Absorption through skin: caution needed
Pharmacokinetics: distribution

• Depends on i.e. Lipid solubility, ionization and protein binding

• In children:
  - Percentage of fat (newborns, 15% → puberty, similar to adults)
  - Extracellular volume (45% newborns; 15% adults)
  - Protein binding in newborn lower
Metabolism: biotransformation liver

• Activity CYP450 system is low
• Glucuronidation still slow
  - Chloramphenicol → gray-baby syndrome
• Acetylation reduced
  - Isoniazid more toxic

• Intrauterine enzyme induction (i.e. Anticonvulsants)
• Drug delivery at childbirth
  - i.e. Mother i.v. Diazepam → ‘floppy infant syndrome’
Metabolism

• Not fully developed: drugs may have longer $t_{1/2}$

• Excretion by liver

• Kidney
  - Glomerular filtration fully developed at 2.5-5 months
  - Tubular function fully developed at 7 months
Pharmacodynamics

• Increased or decreased sensitivity
• Antihistamines: central stimulating effects
• Benzodiazepines: paradoxal effects
• Ketotifen: aggressive/hyperactive behaviour
• Cyclosporine: High immunosuppressive response
• Effect of growth and development
Promoting safety of medicines for children

Guideline WHO, September 2007

‘Pharmacovigilance and medicine safety issues in children are relevant to everyone who has an interest in and cares about the health of children’
Elderly
Drug therapy in the elderly

- Aging process differs among individuals
- Aging of various tissues may differ (within individuals)
- Multiple morbidity
- Polypharmacy (interactions)
- Long term use of drugs
- Compliance
- Practical problems
ADRs in elderly

6% of all hospital admissions are preventable

Table 5. Frequency of Adverse Drug Events by Drug Class*

<table>
<thead>
<tr>
<th>Prescription Drug Class</th>
<th>Overall (N = 1523)</th>
<th>Preventable (n = 421)</th>
<th>Nonpreventable (n = 1102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>396 (26.0)</td>
<td>103 (24.5)</td>
<td>293 (26.6)</td>
</tr>
<tr>
<td>Antibiotics/anti-infectives</td>
<td>224 (14.7)</td>
<td>13 (3.1)</td>
<td>211 (19.1)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>203 (13.3)</td>
<td>93 (22.1)</td>
<td>110 (10.0)</td>
</tr>
<tr>
<td>Nonopioid analgesics</td>
<td>180 (11.8)</td>
<td>65 (15.4)</td>
<td>115 (10.4)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>121 (7.9)</td>
<td>43 (10.2)</td>
<td>78 (7.1)</td>
</tr>
<tr>
<td>Hypoglycemics</td>
<td>103 (6.8)</td>
<td>46 (10.9)</td>
<td>57 (5.2)</td>
</tr>
<tr>
<td>Steroids</td>
<td>80 (5.3)</td>
<td>11 (2.6)</td>
<td>69 (6.3)</td>
</tr>
</tbody>
</table>

JAMA. 2003;289:1107-1116.
## Table 6. Frequency of Types of Adverse Drug Events*

<table>
<thead>
<tr>
<th>Type</th>
<th>Adverse Drug Events, No. (%)</th>
<th>Overall (N = 1523)</th>
<th>Preventable (n = 421)</th>
<th>Nonpreventable (n = 1102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
<td>336 (22.1)</td>
<td>89 (21.1)</td>
<td>247 (22.4)</td>
</tr>
<tr>
<td>Electrolyte/renal</td>
<td></td>
<td>255 (16.7)</td>
<td>112 (26.6)</td>
<td>143 (13.0)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td></td>
<td>194 (12.7)</td>
<td>67 (15.9)</td>
<td>127 (11.5)</td>
</tr>
<tr>
<td>Metabolic/endocrine</td>
<td></td>
<td>145 (9.5)</td>
<td>58 (13.8)</td>
<td>87 (7.9)</td>
</tr>
<tr>
<td>Dermatologic/allergic</td>
<td></td>
<td>120 (7.9)</td>
<td>9 (2.1)</td>
<td>111 (10.1)</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>91 (6.0)</td>
<td>2 (0.5)</td>
<td>89 (8.1)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td></td>
<td>83 (5.4)</td>
<td>12 (2.9)</td>
<td>71 (6.4)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td></td>
<td>75 (4.9)</td>
<td>36 (8.6)</td>
<td>39 (3.5)</td>
</tr>
<tr>
<td>Edema</td>
<td></td>
<td>72 (4.7)</td>
<td>6 (1.4)</td>
<td>66 (6.0)</td>
</tr>
<tr>
<td>Syncope/dizziness</td>
<td></td>
<td>72 (4.7)</td>
<td>20 (4.8)</td>
<td>52 (4.7)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>66 (4.3)</td>
<td>25 (5.9)</td>
<td>41 (3.7)</td>
</tr>
</tbody>
</table>

*JAMA. 2003;289:1107-1116.*
Changes in function when getting older

• Body composition
• Homeostasis e.g.
  - Temperature control
  - Orthostasis
  - Control of thirst
• Changes in tissues and organs (more vulnerable)
Pharmacokinetics: absorption

• Reduced motility of the oesophagus
  - Local irritation of tablets etc.
  - Irritation of bisphosfonates

• Slower gastric emptying

• Longer transit time intestine
Pharmacokinetics: distribution

• Decrease in muscle mass → decrease in lean body mass

• Lipophilic substances have greater distribution volume → plasma concentration initially low

• Hydrophilic substances have smaller distribution volume → higher toxicity and more side effects

• Albumin concentration hardly changes (but may be decreased by underlying disorders)
Elimination by liver

- Volume decreases, reduction of phase I reactions
  - Enzyme levels decreased
  - Especially CYP 1A2 and 3A4

- Reduction of blood flow hepatic artery and portal vein
  - Clearance of drugs with high first pass effect reduced
  - e.g. Propranolol 45%↓ and morphine 35%↓
Elimination by kidney

- In about 1/3 of the elderly no deterioration of renal function
- In 2/3 changes occur due to i.e.
  - Cortical area ↓
  - Number and density of glomeruli ↓
  - Length and volume of proximal tubuli ↓
  - Vascular changes
Kidney function and age

Stevens et al. NEJM. 2006;354 (23): 2473.
Pharmacodynamics

- Changes may occur in:
  - Receptor density
  - Receptor structure
  - Propagation of signals

- Sensitivity for various drugs
  - ↑ psychiatric drugs, opioids, dopamine agonists, parasympaticolytics
  - ↓ β-blockers and insulin
ADRs in elderly: risk of falling

• Balance is complex mechanism controlled by
  - Vestibular system
  - Vision
  - Proprioception
  - Muscle responses

• Falling may occur due to
  - Orthostatic effects (i.e. α- or β blocking agents)
  - Effect on EPS of muscle relaxants (i.e. Benzodiazepines)
ADRs in elderly: orthostatic effects

- Orthostatic effect may occur due to
  - Inadequate response due to vasodilatation
  - Reduction in function of baroreceptors
  - Insufficient fluid intake

- May occur due to
  - Use of α- or β blocking agents
  - Diuretics
  - Underlying acute illness
Psychoactive agents and falls

Table 1
Pooled OR for associations between use of various psychotropic medications from 40 nonrandomised controlled trials

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>1.48</td>
<td>1.23-1.77</td>
</tr>
<tr>
<td>Short-acting</td>
<td>1.44</td>
<td>1.09-1.90</td>
</tr>
<tr>
<td>Long-acting</td>
<td>1.32</td>
<td>0.98-1.77</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1.66</td>
<td>1.38-2.00</td>
</tr>
<tr>
<td>TCAs</td>
<td>1.51</td>
<td>1.14-2.00</td>
</tr>
<tr>
<td>SSRIs: low dose</td>
<td>1.50</td>
<td>1.30-1.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs: high dose</td>
<td>2.40</td>
<td>1.70-2.20</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>1.50</td>
<td>1.25-1.79</td>
</tr>
</tbody>
</table>

OR = odds ratio; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor.

ADRs in elderly: thermoregulation

• Problems in thermoregulation
  - Homeostasis for maintaining core temperature is changed
  - Ability to increase temperature (shivering) ↓
  - Risk for hypothermia/poikilothermia

• Antipsychotics may increase risk!
ADRs in elderly: cerebral function

- Loss of neurons and receptors for cholinergic transmission
- Additional neurologic disorders (i.e. stroke)
- Anticholinergic drugs may influence cerebral function to large extent
Thank you for your attention