Adverse Medicine Reactions

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Learning goals

• Define adverse drug reaction
• Understand mechanisms and classification of adverse drug reactions
• Know some important examples
• Appreciate how adverse drug reactions can be prevented
• Know where to source information for prescribers about adverse drug reactions

Adverse Drug Reactions

Definition:
A noxious or unintended response to a drug, which occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of diseases or for the modification of physiological function.

Significance:
• Common (9-28% of hospitalised patients)
• Associated with long-term disability and death.
Adverse Drug Interactions: Classification

- **Type A (Augmented pharmacological effect)**
  Related to the main pharmacological action of the drug, or cytotoxicity of the drug or metabolites
- **Type B (Bizarre)**
  Unrelated to the main pharmacological action of the drug
- **Type C (Chronic effects)**
  Adverse effects associated with long-term therapy
- **Type D (Delayed effects)**
  Effects appearing along time after treatment
- **Type E (End of treatment effects)**
  Withdrawal reactions
- **Type F (Failure of treatment)**

Type A Adverse Drug Reactions

- Related to the main pharmacological action of a drug or the cytotoxic action of the drug or its metabolites
- Predictable
- Dose-related
  - eg. bleeding with warfarin
  - hypoglycaemia with insulin
  - confusion and drowsiness with nortriptyline

Type A Adverse Drug Reaction

**Cytotoxicity:**

- Drug or reactive metabolites may directly damage cells
- Form covalent bonds or alter target molecules by non-convavalent interaction
- Hepatic metabolism generates high levels of metabolites in the liver → hepatotoxicity
- Polar drugs/metabolites are concentrated within the nephron → nephrotoxicity
Type A Adverse Drug Reactions

Clinical example: Paracetamol Hepatotoxicity:
- converted by hepatic CYPs to toxic alkylating intermediate*
- metabolite inactivated by conjugation to reduced glutathione
- in overdose, glutathione is rapidly depleted
- excess metabolite binds covalently to liver macromolecules causing cell damage and acute hepatic necrosis
- prevented by N-acetylcysteine that facilitates glutathione synthesis

*N-acetyl-p-benzoquinimine (NABQ1)

Type A Adverse Drug Reactions

Clinical example: Gentamicin nephrotoxicity:
- Aminoglycoside antibacterial ribosomal protein synthesis inhibitor
- Excreted unchanged in urine by glomerular filtration
- Cytotoxic at high concentrations to proximal renal tubules causing nephrotoxicity
- Gentamicin dose needs to be adjusted according to blood level monitoring and renal function

Type B Adverse Drug Reactions

- Bizarre
- Not related to the main pharmacological action of a drug
- not predictable
- not dose related
- allergic reactions or pharmacogenetic variability
Adverse Drug Reactions

**Allergic Reactions:**
- initial exposure and sensitisation
- allergic reaction occurs on repeated exposure
- symptoms and signs resemble allergic disease eg. acute hypersensitivity, skin rash, haematological reaction
- antibiotics, non-steroidal anti-inflammatory drugs, radio-contrast agents, anaesthetic agents

Type B Adverse Drug Reactions

**Clinical example: Benzylpenicillin Allergy:**
- skin rash 1:10; anaphylaxis 1:5000; death 1:50,000
- antibodies directed to penicilloyl-protein complex or penicillin polymers
- many types of allergic reaction
  - eg. acute anaphylaxis
  - haemolytic anaemia
  - serum sickness
  - rash

Type B Adverse Drug Reactions

**Clinical example: Carbamazepine Skin Reaction:**
- Sodium channel blocker used for epilepsy
- Occasional life-threatening severe skin reactions
  - Stevens-Johnson syndrome, Toxic Epidermal Necrolysis
  - Blistering and peeling of skin leading to dehydration, sepsis, multiple organ failure and death
  - Immune-mediated adverse drug reactions
  - Genetic susceptibility among those with HLA-B*1502 allele
### Type C Adverse Drug Reactions (Chronic effects of Long-Term Therapy)

- Long-term treatment may alter receptor expression and/or tissue sensitivity to drugs
- adverse drug reactions can occur during therapy or after withdrawal of the drug

### Type C Adverse Drug Reaction (Chronic effect)

- Clinical example: haloperidol-induced dyskinesia
- Dopamine receptor antagonist used for psychosis
- Tardive dyskinesia - Late neurological syndrome associated with long-term anti-psychotic use that persists after cessation of treatment
- Involuntary movements of the lips, jaw and tongue
- Possibly due to compensatory increase in dopaminergic system

### Type E Adverse Drug Reaction (End of treatment effect) Withdrawal Reactions

- Withdrawal reaction
- Abrupt cessation of treatment can cause symptoms because of the unopposed change in receptor expression or tissue sensitivity
- Clinical example: dexamethasone-induced adrenocorticoid insufficiency
- acute adrenocorticoid insufficiency upon sudden withdrawal of dexamethasone due to adrenal atrophy
- Dexamethasone must be gradually reduced and withdrawn to allow return of adrenocorticoid function
### Type D (Delayed) Adverse Drug Reactions

#### Carcinogenesis
Drug may cause cause by:

a) causing mutations by covalently modifying DNA in growth regulatory proto-oncogenes or tumour suppressor genes, or;

b) by promoting cell proliferation

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#### Delayed ADR due to Carcinogenesis

- Clinical example: Doxorubicin (topoisomerase inhibitor) or Cyclophosphamide (DNA binder) induced secondary cancers
- Both common components of combination chemotherapy
- Both mutagenic and carcinogenic
- Secondary cancers presenting after a long delay after treatment, most commonly acute myelogenous leukaemia
- Survivors of childhood cancer >10 times increase risk of secondary cancer for 30 years after initial treatment compared to normal population

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#### Teratogenicity:
- fetal malformations
- damage resulting from drugs prescribed during pregnancy
- Clinical example: doxycycline-induced tooth discoloration and malformation
  - Antibacterial ribosomal protein synthesis inhibitor
  - Disposition of doxycycline in growing bones and teeth by binding calcium causes tooth staining and hypoplasia in unborn child
Adverse Drug Reactions

Risk Factors:

- fetus or neonatal
- elderly
- previous drug reactions
- liver or kidney disease
- number of drugs given

Adverse Drug Reaction Monitoring

Some important adverse reactions are not recognised before approval for marketing.

Post-marketing monitoring aims to detect serious or unexpected adverse drug reactions.

New Zealand:
- Voluntary reporting of serious or unexpected reactions or interactions
- Intensive Medicines Monitoring Programme

Summary

- adverse drug reactions are unwanted effects of drugs
- they can arise via mechanisms related (Type A) or unrelated (Type B) to the main mechanism of action of the drug
- adverse drug reactions are predicted and therefore can often be anticipated
- monitoring programs aim to identify significant adverse drug reactions after marketing
Short answer question example

- An 87 year old NZ European woman is brought to Emergency Dept by ambulance. She is unconscious and was found on the floor by a cleaner. The ambulance officer noted she was taking glipizide.
- What is the main mechanism of action of glipizide?
- What is the main clinical use of glipizide?
- What Type A (Augmented pharmacological effect) adverse drug reaction would be expected from glipizide?