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-convvalent 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 Hepatoxicity:
• 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-benzoquinonimine (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; anaphlaxis 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 by:

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

b) by promoting cell proliferation
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

Type D (Delayed) Adverse Drug Reactions

Teratogenicity:
- fetal malformations
- damage resulting from drugs prescribed during pregnancy
- Clinical example: doxycycline-induced tooth discolouration 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 reaction 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?