Adverse drug reactions

Dr. Mark Haworth MBChB DA MRCA

Types of drug reaction

- The appearance of known side effects to a drug e.g. respiratory depression following the administration of opioid analgesics
- Pharmacodynamic drug interactions
- Pharmacokinetic drug interactions
- Allergic reactions

Pharmacodynamic interactions

Interactions between drugs that have similar or opposite effects leading to the potentiation of or the antagonism of the effects of these drugs. e.g. enhanced sedative effect of benzodiazepine drugs when taken with alcohol.

Pharmacokinetic interactions

- Occur when one drug alters how the body deals with another, thus altering the amount of drug available to exert its effect.
- These reactions are of several types.

Pharmacokinetic interactions

- Affecting absorption

Rate of absorption or total amount absorbed can both be altered. Not a problem with intravenous therapy.

- Changes in protein binding

Most drugs are loosely bound to plasma proteins. One drug can displace another from these proteins thereby increasing its proportion free to diffuse from its site of action. This only produces a clinical effect with extensively bound drugs. e.g. potentiation of warfarin effect by sulphonamide antibiotics.

Pharmacokinetic interactions

- Affecting metabolism

Increased liver enzyme activity as a result of administration of some drugs (e.g. barbiturates) can result in increased metabolism of other drugs (e.g. warfarin) and hence reduce their effect.

- Affecting renal excretion

Some drugs compete for the same mechanism of elimination via the kidneys resulting in delayed excretion and thence an increased effect (e.g. probenicid reduces the renal excretion of penicillin).

Increased risk of drug interactions

- Elderly
- Impaired renal function
- Impaired liver function
- Malnutrition
- Polypharmacy

DRUG ALLERGY

- **Types of severe drug reaction**
- Anapylactic reactions e.g. to penicillin, latex
- Anaphylactoid reactions e.g. to radiological contrast
- **Chemical mediators of severe drug reactions**
- **Clinical presentation of severe drug reactions**
- **Management of severe drug reactions**

Anaphylactic reactions

- **Previous exposure to antigen**
- **Antigen introduced into body**
  - **GIT e.g. oral antibiotics**
  - **Skin e.g. wasp stings**
  - **IM e.g. antibiotics**
  - **IV e.g. anaesthetics**
- **Antigen combines with circulating antibody to form a hapten complex**
- **Hapten complex binds with antibodies on white blood cells (plasma cells and basophils)**
- **White blood cell release chemical mediators**

Anaphylactoid reactions

- Previous exposure to the antigen not necessary
- Antigen combines directly with antibodies on white blood cells
- White blood cells release chemical mediators
- Chemical mediators produce clinical effects

Chemical mediators of allergic reactions

- Histamine - acts on H receptors in blood vessels, skin, gut, platelets, lungs to produce clinical effects
- Prostaglandins - act on receptors in blood vessels, skin, gut etc.
- Chemotactic factors - attract more white blood cells acting as an amplifier

Clinical presentation - Severe allergic reactions

- **Increased permeability of blood vessels resulting in tissue oedema and swelling. Occurs especially around face, neck and larynx. (Angioneurotic oedema)**
- **Bronchoconstriction leading to wheezing and hypoxia. (Acute asthma)**
- **Blood vessel dilatation leading to hypotension, reduced cardiac output, tachycardia, cardiac ischaemia, tissue ischaemia.**
- **Urticarial (blistering) or erythematous (red) rashes.**

Treatment priorities in severe allergic reactions

- Withdraw stimulus
- Airway
- Breathing
- Circulation

Treatment schedule - Severe allergic reactions

- Give oxygen - high flow 100%
- Head down tilt
- The development of angioneurotic oedema of the larynx or acute airflow obstruction secondary to bronchospasm may necessitate endotracheal intubation and artificial ventilation.
- Wide bore vascular access ie 16Ch or 14Ch canula with rapid i.v. fluid replacement. Initially 1000ml of colloid solution (Haemaccel or PPF)
- Intravenous adrenaline, initially 1 to 5ml of 1:10,000 to oppose the bronchoconstriction and vasodilatation initiated by the mediators released from white blood cells.

Further management

- Refractory bronchospasm may require treatment with nebulised or intravenous bronchodilators. (Salbutamol)
- Continuing circulatory failure may require treatment with infusions of inotropic drugs (Dopamine, Adrenaline) and monitoring of circulatory performance with central venous line or Swan Ganz catheter.
- Treatment with antihistamine drugs is of doubtful value since they may, by themselves, produce hypotension and make the situation worse. May be useful later in the treatment of urticarial rashes. (piriton 10mg i.v.)
- The benefit of the use of high doses of intravenous steroids has not been proven.

Further management

All patients having suffered a severe allergic reaction must be admitted to a high dependancy or intensive care area where close monitoring is possible and the appropriate treatment initiated should there be a recurrence of symptoms.

Untreated, severe allergic reactions will lead to cardio-respiratory collapse and death, maybe within a few minutes. Delay in treatment may result in irreversible organ damage leading to death or severe disability.