

When drugs are given together the pharmacological response may be additive (1+1=2), synergistic (1+1>2) or antagonistic (1+1<2). It is possible to represent this quantitative relationship using an isobole shown adjacent. In this case midazolam (y axis) is added to morphine (x axis). Using the isobole we can see that the result is supra-additive (synergistic), both drugs have a reduction in their ED₅₀ therefore they have increased potency. Isoboles do not describe qualitative interactions.

Table 9.2 Mechanisms of drug interaction

Pharmaceutical interactions (i.e. in vitro interactions)

Chemical or physical incompatibility

Pharmacokinetic interactions

Interference with absorption

Change in gastrointestinal pH and motility

Binding and chelation of drugs

Toxic effects on gastrointestinal tract

Change in regional blood flow

Drug distribution (plasma protein-binding displacement)

Drug elimination

Drug metabolism

Stimulation

Inhibition

Changes in hepatic blood flow

Interference with biliary excretion and enterohepatic circulation

Modification of renal excretion

Competition for active renal tubular secretion

Changes in urinary pH

Pharmacodynamic interactions

Competition for same receptors

Action on the same physiological system

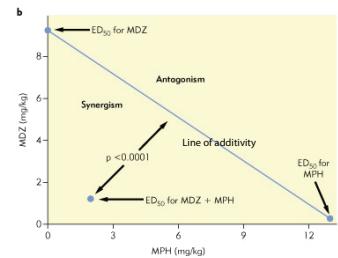
Modification of conditions at the site of action

There are three main **mechanisms of drug interaction**.

Pharmaceutical interactions often occur before a drug is given to the patient. Chemical interactions can occur because of acid base rxns, oxidation-reduction, salt formation, hydrolysis, or epimerization (change in the conformation of a compound). An example is thiopental and rocuronium forming a precipitate due to change in pH.

Pharmacokinetic interactions may influence the absorption, distribution and the elimination. Absorption may be influenced by changing the gastrointestinal pH and motility (opiates), intraluminal binding or chelation, changing regional blood flow (peripheral vasoconstrictors), inhibition or stimulation of first pass metabolism (ketoconazole inhibits CYP3A4 which leads to 16-fold increase in oral midazolam). Likewise, drug metabolism may be induced or inhibited due to drug interaction greatly influencing elimination. The CYP450 enzymes are again very important in this process. St John Wort is a potent inhibitor of CYP3A4 leading to potentially hazardous interactions with the substrates of this enzyme.

Pharmacodynamic interactions although pharmacokinetic interactions are very well studied and significant in specific circumstances, it is the pharmacodynamic that have greater significance in anaesthesia. The concurrent use of drugs acting at the same site or on the same physiological system can have increased or decreased effect. The most common example is drugs acting on the CNS. Inhalational anaesthetics have an additive effect. Interactions between benzodiazepines and opiates is synergistic (as shown above). Volatile anaesthetics potentiate the effects of neuromuscular blockade.



An **adverse drug reaction (ADR)** can be considered as any potentially harmful untoward outcome of therapeutic drug administration. The unwanted outcome may be a side effect of the drug, an exaggeration of the therapeutic effect, failure of therapeutic effect or a totally unexpected effect. ADR may be classified into the adjacent categories; **Administration errors** may result for accidental under or over dosing or from the use of inaccurate or outdated guidelines. When a patient gets the correct intended dose and has a ADR but is within a unimodal population variation or response, the phenomenon is usually termed a **drug intolerance**. Although the therapeutic index (ED₅₀/LD₅₀) is often referred to it is not always clinically useful in describing drug intolerance. For this reason the certain safety factor may be more useful. This is also a quantal response curve that relates the % of population with a unwanted effect (TD% toxic dose) to the effective dose % (ED%).

Usually this will be 1%, therefore the certain safety factor (and therefore therapeutic window) is the range from TD₀₁/ED₉₉.

Idiosyncrasy is an abnormal reactivity to a chemical that is peculiar to a given individual. The idiosyncratic is usually related to pharmacogenetic disorders. These have been identified in drug metabolism (acetylation, cytochrome P450 variants, plasma cholinesterase variants), inability to compensate for drug effects (G6PD deficiency, acute porphyrias), and in the drug effects themselves (Malignant Hyperthermia). **Allergy** is an immune mediated ADR discussed in greater detail below. Specific **secondary effects** and **organ toxicity** are discussed in the system specific overviews. **Drug interactions** are discussed above.

Classification of Adverse Drug Reactions

Administration errors

Intolerance

Idiosyncrasy

Anaphylaxis/anaphylactoid

Direct organ toxicity

Secondary effects

Drug effects

Idiosyncrasy

Drug metabolism

Acetylator status - one of the phase II metabolised N-acetyltransferase exists in fast or slow forms (60% slow in caucasians, only 20% in asians) leading to increased side effects in the slow metabolisers. Drugs implicated include isoniazid, hydralazine, nitrazepam.

CYP450 variants - CYP2D6 - involved in metabolism of 25% of drugs. 6% of caucasians and 1% of asians have reduced activity. Drugs implicated include; Beta-blockers (metoprolol, propanolol), antiarythmics (flecainide, amiodarone), antidepressants (most TCAs and SSRIs), and neuroleptics CYP3A4-5 - 6% caucasians have reduced activity (drugs - midazolam, fentanyl), CYP2C9 - warfarin, CYP2C19 - diazepam and Omeprazole.

Plasma Cholinesterase - responsible for the breakdown of sux in plasma, an autosomal recessive trait, leading to prolonged duration of action.

Inability to compensate for drug effects

Glucose-6-Phosphate Dehydrogenase required in the pentose phosphate pathway which leads to restoring glutathione levels required to combat H₂O₂ released by the cell in the presence of oxidants. Therefore highly oxidant drugs like chloramphenicol, primaquine, may lead to haemolytic anaemia

The Porphyrias - A group of disorders characterised by excessive build up of the precursors of heme. These precursors porphyrinogens are excreted in the urine where they are exposed to light and air to convert to purple coloured porphyrins. Usually this is regulated by inhibition of ALA synthetase. Some drugs such as propofol may upregulate this enzyme.

The drug effects themselves

Malignant Hyperthermia is an autosomal dominant condition which susceptible individuals have a defect in skeletal muscle intracellular regulation. Under most circumstances homeostatic mechanisms compensate for increased calcium turnover, but the potent inhalational anaesthetics and sux cause a massive acceleration of calcium release which overwhelms the compensatory mechanisms. The massive Ca release leads to increased muscle activity and metabolism. Oxygen supply can not match the demand and CO₂, lactate and heat builds up. The other feature of MH is rhabdomyolysis. Mutations of the skeletal muscle ryanodine receptor gene (RYR1) lead to the susceptibility to the condition.

Allergic reactions to drugs administered IV are acute hypersensitivity reactions. By definition these occur on the second or subsequent exposure to an allergen. It is recognised that more than 50% of patients who have anaphylactic-like (anaphylactoid) responses are during their first exposure. The **anaphylaxis results from IgE mediated mast cell degranulation** and release of mainly histamine and vasoactive amines but also proteases (tryptase) and lipid derived mediators (such as leukotrienes and prostaglandins). **Anaphylactoid reactions occur through complement pathways or direct drug action on mast cells** and result in similar outcomes although anaphylactoid reactions may be more dose dependent. Latex sensitivity is increasingly becoming a problem in anaesthesia with 20-50% of reactions due to this precipitant. The reactions tend to occur after 30-60 minutes whereas drug reactions typically occur within minutes. Chlorhexidine is also increasingly associated with severe systemic rxns.

Therapeutic drug monitoring. Given the multiple factors that alter drug disposition, measurement of the concentration in body fluids can assist in individualizing therapy with selected drugs. Determination of the concentration of a drug is particularly useful when well-defined criteria are met:

1. A demonstrated relationship exists between the concentration of drug in plasma and the desired therapeutic effect or the toxic effect to be avoided.
2. There is sufficient variability in plasma level that the level cannot be predicted from the dose alone.
3. The drug produces effects, intended or unwanted, that are difficult to monitor.
4. The concentration required to produce the therapeutic effect is close to the level that causes toxicity (narrow therapeutic window)