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categories: Administration errors may result for accidental under or over dosing or from the use of inaccurate or outdated guidelines.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 also a quantal response curve that relates the % of population with a unwanted effect (TD0 toxic dose) to the effective dose % (EDn). Usually this will be 1%, therefore the certain safety factor (and therefore therapeutic window) is the range from TD0/ED1.

**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 cholinesteras 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 overview. **Drug interactions** are discussed above.

### 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 - midazolam, fentanyl), CYP2C9 - warfarin, CYP2C19 - diazepams and Omeprazole.
- **Plasma Cholinesterase** - responsible for the breakdown of sux in plasma, an autosomal recessive trait, leading to prolonged duration of action.

**Acetylation**

- **Glucose-6-Phosphate Dehydrogenase** required in the pentose phosphate pathway which leads to restoring glutathione levels required to combat H2O2 released by the plasma Cholinesterase.

**Primary effects**

- **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 plasma Cholinesterase.

**Secondary effects**

- **Anaphylaxis** - A group of disorders characterised by excessive build up of the precursors of heme. These precursors, porphyrinogens are excrated 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.

**Classification of Adverse Drug Reactions**

- Administration errors
- Intolerance
- Idiosyncrasy
- Anaphylaxis/anaphylactoid
- Direct organ toxicity
- Secondary effects
- Drug effects

### 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 oxidents. 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 excrated 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 overwheels 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 (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% or 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)

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