

Adverse Drug Reactions (ADRs) – immune-mediated versus pharmacological

The Drug Information Service at Christchurch Hospital answers over fifty questions each month from health professionals asking about adverse drug reactions (ADRs). Frequently, the enquirer is interested in the potential risks of causing a similar adverse reaction if they prescribe an agent from the same or similar class. This decision is influenced largely by whether the ADR was immune-mediated or pharmacologically-mediated.

ADR classification

The World Health Organisation definition of an ADR is, “any response to a drug that is noxious and unintended, and that occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function”.

Broadly, ADRs can be categorised as:

- **Type A:** where A stands for “augmented” response
ie: a pharmacologically-mediated response
- **Type B:** where B stands for “bizarre” response
ie: usually an immune-mediated response

This system is a useful tool to assist health professionals determine whether it is reasonable to prescribe a drug for a patient from a class that has previously produced an ADR in that patient. Consider the table below:

	Type A	Type B
Pharmacologically predictable?	yes	no
Dose-dependent?	yes	no
Incidence	high	low
Morbidity	variable	variable
Mortality	low	high
Rechallenge?	↓ dose	no

When a patient has an ADR that is predictable from its pharmacological effect (Type A), generally the drug may be recommenced relatively safely at a reduced dose. Even if the low dose is still not tolerated and treatment subsequently stopped, a life-threatening reaction due to rechallenge is unlikely. Examples of pharmacologically-mediated ADRs are respiratory depression with opioid analgesics, or tachycardia with salbutamol.

When a patient has an ADR that is NOT predictable from its pharmacological effect (Type B) the mechanism is frequently immune-mediated. While these ADRs are more rare, they are more often associated with life-threatening symptoms. Rechallenge is generally not recommended. The most florid example of this is anaphylaxis.

Anaphylactic versus anaphylactoid drug reactions

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death, most commonly from hypoxaemia due to intractable bronchospasm, upper airway oedema, or cardiovascular collapse. Anaphylaxis results from activation of IgE bound to mast cells and basophils causing release of histamine and other inflammatory mediators (a Type B reaction).

Any immediate reaction that resembles anaphylaxis, but is non-IgE mediated, is referred to as anaphylactoid. In clinical practice, they are indistinguishable. However, while anaphylactic reactions which are always Type B, anaphylactoid reactions may be either Type B or Type A. Knowing that a reaction is ‘anaphylactoid’ is therefore not informative when considering rechallenge.

Risk versus benefit of rechallenge

Where possible, it is preferable to use an alternative treatment option where one exists, as while an ADR may not be severe from a medical perspective, it may still cause considerable morbidity. When considering whether it may be reasonable to recommence a drug that has been associated with an ADR (or commence a drug from a similar class), consider the risk versus benefit in each individual case.

Where a patient with a Type A ADR may derive considerable benefit from the causal drug class, rechallenge with a smaller dose may be reasonably safe (eg. in renal dysfunction with gentamicin). As these ADRs are an extension of the mechanism of action of the drug, other drugs with the same mechanism of action are likely to cause a similar ADR at higher concentrations.

In contrast, when the ADR is Type B, rechallenge with a drug that is chemically similar is likely to cause a similar reaction even in small doses (eg. urticaria with penicillins). These adverse effects are due to antibodies recognising the chemical structure of the drug.

Sometimes it is difficult to determine whether the ADR is Type A or B. Examples are:

- exacerbation of asthma induced by aspirin (which blocks prostaglandin synthesis, resulting in increased leukotrienes, which have bronchoconstrictor activity).
- angioedema associated with angiotensin-converting enzyme inhibitors (due to increased bradykinin)

In these situations, the symptoms appear “allergic” but the mechanism is pharmacological (Type A) in most patients. However, these examples also illustrate that in some patients with Type A ADRs, the risks of rechallenge may still outweigh the benefits.

Summary

- Where the reaction is not severe and Type A, rechallenge with a smaller dose may be reasonable.
- Where the reaction is severe and/or Type B, we recommend specialist advice before rechallenge.