Side Effects and Adverse Drug Reactions.

Abstract

In this article in the series of ‘bite sized’ pharmacology, we will look at the pharmacological aspects surrounding side effects of drugs, adverse drug reactions and the key differences between the two. We will also touch on the concept of drug ‘allergy’ and its meaning from a pharmacological perspective. Using examples this article will illustrate common and rare side effects and discuss how side effects are classified and how the data is gathered to achieve this. The article will then go on to examine the main types of Adverse Drug Reactions (ADRs) and give examples of each highlighting for Type A when a side effect becomes and adverse effect. Exercises will be provided to help you apply this knowledge to your prescribing practice.

Side Effects

The occurrence of side-effects to dugs is a common effect. Some are minor, transient and can be tolerated by the patient, but some are more troublesome or severe and can lead to n-compliance with medicine regimens. No drug is completely free from side-effects. Information and education to your patients about actual and about potential side-effects is essential in prescribing. This means that the prescriber must have a knowledge and understanding of side effects related to the medications in their area of practice.

Some side-effects can be severe and may even become adverse for the patient. It is therefore vital to inform patients, at the point of prescribing or review, that if they experience any side-effects and they are concerned or it seems to be particularly troublesome they should seek advice at once.

The British National Formulary (BNF) lists side effects of drugs in order of their frequency of occurrence, where known, and alphabetically. The frequency of side effects is set according to

table 1.

Frequency	Occurrence
Very Common	Occurs more than 1 in 10 administrations of a drug
Common	Occurs between 1 in 10 and 1 in 100 administrations of a drug
Uncommon	Occurs between 1 in 100 and 1 in 1000 administrations of a drug
Rare	Occurs between than 1 in 1000 and 1 in 10000 administrations of a drug
Very Rare	Occurs less than 1 in 10000 administrations of a drug
Frequency Not Known	N/A

Table 1 – Side Effect Frequency

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out, for a drug class from your area of practice the range and frequency of side effects attributed to that drug or the class of drug it belongs to and relate the rating of side effects to your own experience of encountering side effects.

Pharmacovigilance- How Side Effect Information is gathered

Pharmacovigilance is the study relating to the detection, assessment, understanding and prevention of adverse drug effects. The origin of the word is a combination of the Greek *pharmakon*, 'drug' and the Latin *vigilare*, 'to keep awake or alert, to keep watch' (Barber and Robertson 2015). As prescribers we should be concerned with side-effects of medicines that may be intolerable by our patients or cause them to have adverse effects which may lead to non-compliance. Pharmacovigilance involves collecting, monitoring, researching, assessing and evaluating information from health care providers and patients on the adverse effects of medications with a view to:

- identifying new information about medicines to inform prescribing practice;
- preventing harm to patients.

This is done through the Yellow Card Scheme which we shall now look at in more detail.

https://yellowcard.mhra.gov.uk/

The Yellow Card

The yellow card scheme is an important tool to assist the Medicines and Healthcare Products Regulatory Agency (MHRA) monitor the safety of the medicines, healthcare products, devices and vaccines on the market in the UK.

Even if it is only a *suspicion* that a medicine or combination of medicines have caused a side-effect, patients and health professionals should send the MHRA a yellow card. Yellow card reports on suspected side-effects are evaluated, together with other sources of information such as clinical trial data, medical literature or data from international medicines regulators, to pinpoint previously unidentified safety issues or concerns (MHRA 2017).

Adverse Reaction

An adverse drug reaction (ADR) (sometimes called an adverse drug event – ADE) is a reaction that is always unwanted or intolerant to the patient. This differs from a side effect which may be beneficial or able to be tolerated.

The World Health Organization's (WHO) website gives definitions around adverse drug reactions as follows

Adverse drug reaction (ADR): A harmful effect suspected to be caused by a drug. This term has been used quite loosely to include all kinds of adverse events, many of which are not 'reactions' in the strict sense at all, and have not been subject to any assessment of causality. The term is properly reserved for late-stage analysis when the association between a medicine and an adverse effect has moved beyond 'unmeasurable' or 'uncertain'.
Adverse effect: A negative or harmful patient outcome that seems to be associated with treatment, including there being no effect at all.
Adverse event: Any negative or harmful occurrence that takes place during treatment that may or may not be associated with a medicine. *A fall could be such an event that may – or may not – have any association with a medicine.*

(WHO 2017- https://www.who-umc.org/safer-use-of-medicines/safer-use-of-medicines-the-basics/common-concepts-and-terms/)

ADRs can be classified according to their cause and there are many categories:

Type Name	Description of Effect
Type A	Augmented effects.
Type B	Bizarre effects.
Type C	Chronic effects.
Type D	Delayed effects.
Type E	End-of-treatment effects.
Type F	Failure of therapy.

Table 2 Types of ADR

The most common types of ADR are augmented and bizarre.

Type A: Augmented

The word augment means ‘to make bigger’ so a Type A reaction is where the reaction is an augmentation of the drug’s normal pharmacological action. This means we can often predict these reactions from our knowledge of the pharmacodynamic properties of a drug. If we know how our drugs work on a cellular level we can anticipate side effects and therefore warn our patients about side effects which they may then find augmented or become intolerable.

For example, a patient on an antihypertensive drug will expect the blood pressure to drop as the therapeutic action of the drug and may experience some light headedness initially after administration which usually passes, however, they may develop dizziness and fainting due to *too* great a lowering of their blood pressure. This could be categorised as adverse.

Patients on NSAIDs can develop gastric irritation due to the drug’s action on protective gastric mucous. These types of reactions are mainly dose dependent: the greater the dose of the drug, the higher the likelihood of adverse reaction. Patients should be warned to look for GI disturbances and report so they can be monitored as if this were to become augmented, the patient may experience gastric erosion, ulceration and potential gastric bleeding. Patients who need these medications long term or at high dose need to be prescribed gastric protection to minimise the risk of adverse reaction.

They are the most common ADRs but are associated with lower morbidity and mortality.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out, for a drug or drug class from your area of practice the range and frequency of side effects attributed to that drug or the class of drug it belongs to and relate these to any potential ADRs of Type A that may be foreseen.

Type B: Bizarre

This is where the reaction is wholly unexpected (or bizarre in nature) and could not be predicted from the pharmacodynamic properties of the drug. An example would be anaphylaxis to any drug, or a red pinprick rash with penicillin. We don't know the exact physiological or pharmacological mechanisms which lead to the reactions, but due to pharmacovigilance and reporting we may know that some drugs have a higher incidence of Type B reactions that others. These types of reactions are not dose dependent and can occur even at low starting doses. They are much rarer than Type A ADRs but are associated with a higher morbidity and mortality.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out, for a drug or drug class from your area of practice the number of serious side effects attributed to that drug or the class of drug it belongs to and relate these to any potential ADRs of Type B that may have been encountered.

The significance of an adverse drug reaction to the patient depends on many factors and can determine how prescribers respond to any reaction reported or detected

If a patient reports an ADR there are a variety of responses the prescriber can take. These could include:

- stopping the drug altogether or reducing the dose if type A is suspected
- switching to an alternative drug with a differing pharmacodynamic profile but same end effect (antibiotics are a common example here).

The ADR should always be recorded in the patient's notes and discussed with other prescribers for that patient where appropriate. Poor management of ADRs can lead to problems

with patients adhering to their medication regimens, even if Type A and deemed less serious so this is an important aspect of care and documentation for the prescriber.

Type B ADRs can be more serious than Type A and often require prompt and rapid action on behalf of the person detecting who may or may not be the original prescriber. The drug suspected of causing this reaction should be withheld and the original prescriber informed immediately. This means many NMPs are stopping medication prescribed by medical colleagues but the safety and wellbeing of the patient is what is paramount here.

All Type B and many Type A ADRs should be reported to the Medicines & Healthcare Products Regulatory Agency (MHRA) via the Yellow card found in the back of the BNF or online and as detailed above.

Some drugs are more likely to cause ADRs than others. These drug groups include:

Drug	Type A Reaction	Type B
Antibiotics	Severe diarrhoea	Anaphylaxis
Clozapine	Kinetic disorders	Agranulocytosis
NSAIDs	Gastric ulceration	Thrombotic events
Lithium	Kidney changes	Arrhythmia
Carbamazepine	Anaemia	Stevens-Johnsons Syndrome

Minimising ADRs

There is much a prescriber can do to minimize or prevent ADRs:

- drugs should only be prescribed for a good indication, particularly during pregnancy
- a check should be made on all current and previous medication including any previous reactions to medicines or perceived or actually allergy

- any non-drug allergies should be identified including food allergies/sensitivities or topical allergies (e.g. sticking plasters)
- age should always be taken into consideration (e.g. the elderly or a young child)
- check for any hepatic and/or renal disease
- clear instructions should be provided regarding medication to the patient including possible side-effects to help them identify ADRs
- familiar drugs should be prescribed where possible, as side-effects are better known

Anaphylaxis

Anaphylaxis is an *acute multi-system severe type I hypersensitivity allergic reaction*. Anaphylaxis is associated with systemic vasodilation that results in low blood pressure. It is also associated with severe bronchoconstriction to the point where the individual finds in increasingly difficult to breathe. Many patients experience swelling and oedema and skin reactions and some have vomiting and diarrhoea. Many go on to have seizures or loss of consciousness if untreated. Symptoms develop quickly over a few minutes. Anaphylaxis can occur in response to any allergen. Common triggers include insect bites or stings, foods, medications and latex. The most common medicines to trigger anaphylaxis are antibiotics, aspirin, ibuprofen and other analgesics.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out, for a drug class from your area of practice what side effects or adverse effects may be classified in the allergy or anaphylaxis category.

References & Further Reading

Barber and Robertson (2015) Essentials of Pharmacology for Nurses 3rd Edition McGraw Hill London

BNF Online https://www.bnf.org/products/bnf-online/

Electronic Medicines Compendium https://www.medicines.org.uk/emc/

Rang, H.P., Ritter. J.M., Flower. R.J. and Henderson, G. (2015) Rang and Dales Pharmacology 8th ed. Churchill Livingstone. London.