

Diagnosis and management of adverse drug reactions

David Coulter

NZ Intensive Medicines
Monitoring Programme

Adverse drug reactions 1 (ADRs)

Definition

- An ADR is '*a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man*'.

Adverse drug reactions 2 (ADRs)

Side effect

A side effect is 'any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug'.

- eg constipation with codeine phosphate

Adverse drug reactions 3 (ADRs)

Adverse event (experience)

- An AE is *'any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment'*.

The monitoring problem

How do we know if a health event is a reaction to a medicine?

Headache

Fever

Vomiting

Rash

The process of diagnosis 1

Consider all drugs / medicines

- OTC
- contraceptives
- herbal / traditional
- abused drugs / alcohol
- long term treatment

Check

The process of diagnosis 2

- Was the event present before the patient began the medicine?
- Did the event occur within a plausible time period of starting the medicine?
 - headache a few hours after - *Yes*
 - liver failure on the first day - *No*

The process of diagnosis 3

- Allergic type - *previous exposure*
- Foetal abnormality - *stage of pregnancy*
- Consider withdrawal reactions
- Neoplasms - *several years*
- Background frequency
 - agranulocytosis
 - exfoliative dermatitis

The process of diagnosis 4

Is an event pharmacologically plausible?

- Is it a side effect (class A reaction) of -
 - the drug(s) in question
 - the class?
- Is it a known allergic (class B) reaction
 - the drug(s)
 - the class?

The process of diagnosis 5

- Trial withdrawal
 - is the time to recovery consistent with the action of the drug?
- Rechallenge
 - same pattern?
 - No effect?

The process of diagnosis 6

Investigations

- Blood patterns compared with baseline
- Allergy testing
- Skin biopsy
- Blood levels

The process of diagnosis 7

- Is there the possibility of an *interaction*?
- Remember
 - OTCs
 - contraceptives
 - herbals / traditional
 - drugs of abuse / alcohol
 - long term medicines

The process of diagnosis 8

Interaction?

- OK on first drug
- Problems when a second drug is commenced
- Is it the 2nd drug or is it an interaction?
 - had the 2nd drug before?
 - OK when 1st drug withdrawn?
 - knowledge of metabolism

The process of diagnosis 9

Interactions and hepatic metabolism

- Cytochrome P450 enzyme system
 - eg CYP2D6 or CYP2C19
 - inhibition -*increased blood levels*
 - induction -*decreased blood levels*
(therapeutic effect decreased)

The process of diagnosis 10

Interactions and hepatic metabolism

- Mefloquine metabolised by CYP3A4
 - artemesinin, diazepam, diltiazem, erythromycin, fluoxetine, nifedipine, quinine
- Artemesinin -CYP2B6 & CYP3A4

The process of diagnosis 10

Which drug?

- Timing of drug and reaction
- Difficult when more than one drug is introduced at the same time
- Pharmacology
- Withdrawal
- Rechallenge

Management of ADRs 1

Decisions are made by considering

- Seriousness / severity of ADR
- Seriousness of disease
- Benefit / harm assessment

Management of ADRs 2

If the reaction is serious

- Withdraw suspected (all?) drugs
- Treat urgently

Management of ADRs 3

If the disease is serious

- Consider the effect of not having treatment
- Continue treatment and treat symptoms of reaction if necessary
- Consider an alternative drug
- Stop unnecessary drugs

Management of ADRs 4

If the reaction is mild

- Continue treatment if necessary
- Stop unnecessary drugs
- Consider dose reduction
- Reassure and do nothing
- Symptomatic treatment if warranted

Management of ADRs 5

