ADVERSE DRUG REACTIONS

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OUTLINE

A. Definitions
B. Epidemiology
C. Classification
D. Risk factors and mechanisms
E. Diagnosis
F. Prevention

WHAT IS AN ADVERSE DRUG REACTION(ADR)?

- **"A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function."**

WHO,1972

DEFINITIONS

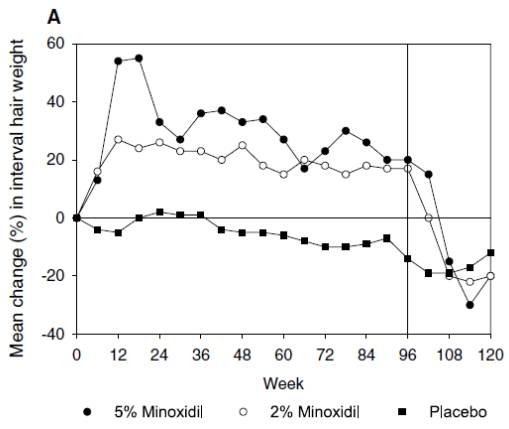
Adverse event :

- ....a harmful event that occurs in a patient during his/her drug treatment
- The harmful event may or may not have occurred due to the drug concerned

DEFINITIONS

Side effect :

- .... is any effect caused by a drug other than the intended therapeutic effect
- Can be beneficial, neutral or harmful



J Am Acad Dermatol 2002

DEFINITIONS

Toxic effect :

- .... is a harmful effect caused by a drug when it is given above the maximum therapeutic dose

BURDEN OF ADRS..

- Account for…
  - 6.5% of hospital admissions
  - 4% of the hospital bed capacity
- Fatality was 0.15%
- Projected annual cost of such admissions is £466m

BMJ 2004

CLASSIFICATION OF ADRS

- Type A - "Augmented"
  - Exaggerated pharmacological effect
  - Dose related
- Type B – "Bizarre"
  - Idiosyncratic
  - cannot be predicted from the drug's known pharmacology.

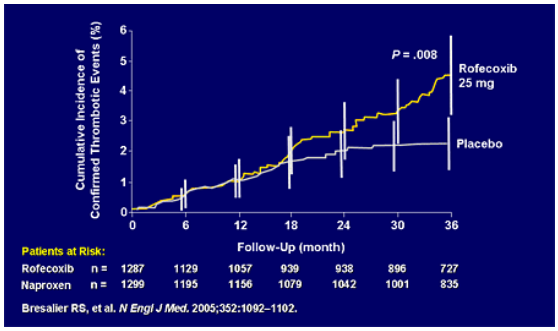
Rawlins and Thompson 1977

Table 1: Adverse Drug Reactions
A comparison of type A and type B adverse drug reactions

	TYPE A "Accentuated"	TYPE B "Bizarre"
Dose relationship	Yes	No
Frequency	Common (~75% of total)	Rarer
Mortality	Lower	Higher
Morbidity	Higher	Lower
Treatment	Stop drug/reduce dose	Stop drug

Rawlins and Thompson 1977

ROFECOXIB AND THROMBOSIS



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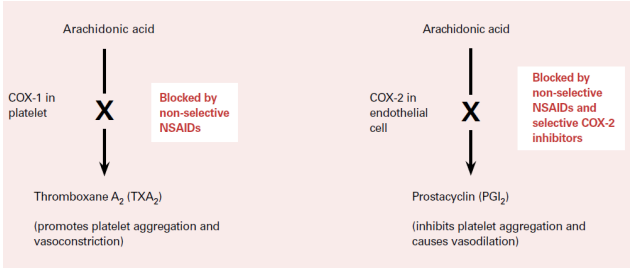

Chronic	C	• Uncommon • Related to the cumulative dose	• Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
Delayed	D	• Uncommon • Usually dose-related • Occurs or becomes apparent some time after the use of the drug	• Teratogenesis (eg, vaginal adenocarcinoma with diethylstilbestrol) • Carcinogenesis • Tardive dyskinesia
End of use	E	• Uncommon • Occurs soon after withdrawal of the drug	• Opiate withdrawal syndrome • Myocardial ischaemia (β-blocker withdrawal)
Failure	F	• Common • Dose-related • Often caused by drug interactions	• Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers

RISK FACTORS – TYPE-A ADRs

A. Pharmacodynamic - low therapeutic index
B. Pharmaceutical
   - Changes in formulation leading to increased bioavailability
C. Pharmacokinetic
   - Renal failure
   - Liver failure
   - Drug-drug interactions
D. Pharmacogenetics – genetic polymorphism

MECHANISMS OF TYPE B ADRs

- Pharmaceutical variation
  - Excipients in drug formulations and contamination with toxic substances in the manufacturing process can lead to idiosyncratic adverse drug reactions
- Receptor abnormality
  - e.g.malignant hyperthermia with general anaesthetics

MALIGNANT HYPERTHERMIA

- Due to a rare dominantly inherited mutation of the Ca^{2+} release channel of the sarcoplasmic reticulum (the *ryanodine receptor)*
- The ryanodine receptor becomes more sensitive to lower concentrations of stimulators of Ca^{2+} channel opening
- rapid increase in intracellular calcium levels in response to inhalational anesthetics or to succinylcholine
- sustained muscle contraction, elevated temperature, increased muscle metabolism

MECHANISMS OF TYPE B ADRs

- Abnormal biological system unmasked by a drug
  e.g. primaquine induced haemolysis in glucose 6-phosphate dehydrogenase deficiency
- Abnormalities in drug metabolism
  e.g. isoniazid induced peripheral neuropathy in slow acetylators
- Immunological
  e.g. penicillin induced anaphylaxis

BIOACTIVATION VS. BIOINACTIVATION

- Bioactivation - formation of chemically reactive metabolites during phase I metabolism
- Bioinactivation - detoxification mechanisms of bioactive metabolites
- In susceptible individuals the balance between bioactivation and bioinactivation is disturbed, allowing the toxic metabolites to escape detoxification

BIOACTIVATION VS. BIOINACTIVATION

- Factors that disturb this favourable balance include genetic factors or host factors such as age, enzyme induction, and disease
- An inadequately detoxified chemically reactive

Metabolite cause toxicity,

a. directly by binding covalently to various cellular macromolecules
b. indirectly via an immune reaction

IMMUNOLOGICAL MECHANISMS

- Explained by the hapten hypothesis
- Small molecules such as drugs are not immunogenic on their own
- Drugs can mount an immune response when they become covalently bound to macromolecules such as proteins and form haptens

DIAGNOSIS OF AN ADR

- Difficult to distinguish an adverse drug reaction from disease – the great masquerader
- When an adverse event occurs during or after drug treatment it could be
  1) Due to the drug
  2) Due to the disease for which the drug was taken
  3) Due to an unrelated cause

DIAGNOSIS OF AN ADR

Factors that help diagnose ADRs:

1) Timing
   Timing of the onset of the symptoms relative to the commencement of drug therapy
2) Pattern recognition
   Can explain by known pharmacology or fit the allergy pattern of one of the suspected medicines

DIAGNOSIS OF AN ADR

Factors that help diagnose ADRs:

3) Alternative explanation
   Inability to explain by concomitant disease or other drugs or chemicals
4) De-challenge
   Disappearance of the symptom/sign after stopping the suspected medicine

DIAGNOSIS OF AN ADR

Factors that help diagnose ADRs:

5) Re-challenge
   Reappearance of the symptom/sign after restarting the suspected medicine
   Unethical except when no other alternative available

PREVENTION OF ADRs

- Bespoke prescribing (Type A)

  Tailoring initial drug doses to the individual patient and subsequently titrating the dose to avoid toxicity

  e.g. I. Monitoring warfarin therapy with INR
  II. Adjusting drug doses in renal impairment

$$\text{Creatinine Clearance} = \frac{(140 - \text{age (years)}) \times \text{Body-weight (kg)}}{0.82 \times \text{plasma creatinine } (\mu\text{mol/l})}$$

PREVENTION OF ADRs

- Therapeutic Drug Monitoring (Type A)

  To be applicable, the drug should have a concentration related therapeutic effect

  e.g. ciclosporin, digoxin, gentamicin, lithium, phenytoin, and theophylline

PREVENTION OF ADRs

- Documentation of history of drug allergy (Type B)
- Monitoring the patient using simple laboratory tests (Type B)

  e.g. Routine white cell counts to detect clozapine induced agranulocytosis

PREVENTION OF ADRs

- Pharmacogenetics (Type A and B)

  e.g. Testing for HLA-B*1502 allele in South-east Asians to prevent carbamazepine-induced Stevens-Johnson syndrome