DRUG INTERACTIONS

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OUTLINE

A. Definition

B. Epidemiology

C. Classification
   i. Pharmacokinetic DIs
   ii. Pharmacodynamic DIs

D. Recognition

E. Prevention

DRUG- DRUG INTERACTIONS

- ......alteration of the effects of one drug by another co-administered drug
- Can be,
  - Beneficial by enhancing the efficacy of one drug by the other
  - Harmful by reducing the efficacy of one drug by the other and by causing adverse effects

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BURDEN OF DRUG INTERACTIONS..

- With an ageing population, an increasing number of new drugs and more polypharmacy,potential for DIs increase exponentially

- In a large prospective study of 18,820 patients, 6.5% of hospital admissions were related to an adverse drug interaction, of which one in six was due to a drug-drug interaction

- Many theoretical drug interactions are not clinically relevant as they do not result in a clinically significant adverse outcome

BMJ 2004

CLASSIFICATION

1. **Pharmacokinetic DIs**
   - Absorption
   - Distribution
   - Metabolism
   - Excretion
2. **Pharmacodynamic DIs**
   - At receptor / effector site
   - Effects on physiological processes

PHARMACOKINETIC DIs

During Absorption:

a. Complex with drugs and reduce the extent of absorption

   e.g. aluminium, calcium, and magnesium antacids -↓ quinolone, tetracyclines and iron absorption

   cholestyramine - ↓ absorption of warfarin, levothyroxine, digoxin

a. Change the gastric emptying rate and alter absorption

   e.g. Metoclopramide - ↑absorption rate of paracetamol

   opiates- ↓ absorption of paracetamol

PHARMACOKINETIC DIs

During Distribution:
- Drugs extensively bound to plasma proteins can be displaced from its binding site by another with greater binding affinity, increasing the amount of (unbound) drug available to cause an effect
  > e.g. diazepam displaces phenytoin from plasma proteins

- The effects of protein displacement are of **no clinical significance** as the metabolism of the affected drug usually increases in parallel with the increased concentration of unbound drug

P-GLYCOPROTEIN (PgP) MEDIATED DRUG INTERACTIONS

- PgPs are plasma membrane glycoproteins acting as an energy-dependent efflux pumps for a wide variety of compounds from ions to peptides

- Acting as an absorption barrier and excreting drugs into the intestinal lumen, can cause reduced effective absorption

- Also prevent transport of medicines into cells in the vascular compartment and into deeper compartments such as the brain

P-GLYCOPROTEIN (PgP) MEDIATED DRUG INTERACTIONS
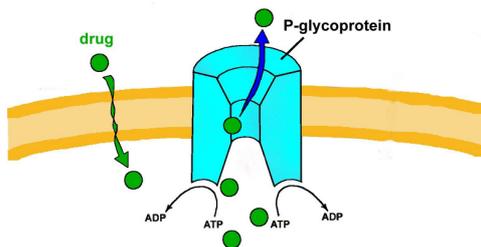
P-GLYCOPROTEIN (PgP) MEDIATED DRUG INTERACTIONS

- Inhibition of the transporting function of PgP can cause clinically significant drug interactions by causing accumulation of drugs in tissues

  e.g. increase of plasma digoxin concentration and the increased risk of CNS toxicity when digoxin is co-administered with quinidine

P-GLYCOPROTEIN (PgP) MEDIATED DRUG INTERACTIONS

- P-gp induction accelerate efflux transport and reduce the bioavailability of drugs

  e.g. Inefficacy of digoxin after coadministration of carbamazepine

P-GLYCOPROTEIN (PgP) MEDIATED DRUG INTERACTIONS

Inducers	
Anticonvulsants	Carbamazepine (oxcarbazepine less so), phenytoin, phenobarbital, primidone
Tuberculostatics	Rifampicin
Antiretroviral	Efavirenz
St. John's wort extract	Hyperforin
Inhibitors	
Antimycotics	Itraconazole, ketoconazole
Calcium channel blockers	Diltiazem; felodipine; nicardipine; nifedipine; verapamil especially
Macrolide antibiotics	Erythromycin, clarithromycin, not azithromycin
HIV protease inhibitors	Indinavir; nelfinavir; ritonavir especially; saquinavir
Immunosuppressants	Ciclosporin
Antiarrhythmic drugs	Amiodarone, quinidine, propafenone

PHARMACOKINETIC DIs

During Metabolism:
- Liver is the major site of drug metabolism, and the major group of drug metabolising enzymes is the cytochrome P-450 system (CYPs)

- The relative non-specificity of CYPs, leads to interactions between drugs that use this route of metabolism

PHARMACOKINETIC DIs

During Metabolism:
- The interactions involving CYPs cause,
  a) Induction of the metabolism of one drug by another
  b) Inhibition of the metabolism of one drug by other drugs
  c) Mutual induction and inhibition

INDUCTION OF METABOLISM

- Drug interactions due to enzyme induction require new enzyme formation, ∴ takes 1-2 weeks for the maximum effect
- Similarly, the effect of enzyme induction can take a week or more to disappear when the inducer is withdrawn
- Usually result in decreased drug action
- Rarely toxicity may occur if the production of toxic metabolites is increased

e.g. phenobarbital increases the demethylation of pethidine to norpethidine

INDUCTION OF METABOLISM

Some clinically important drugs that induce oxidative metabolism

Barbiturates
Carbamazepine
Oxcarbazepine
Phenytoin
Primidone
Rifampicin
Rifabutin
St John's Wort
Ethanol (CYP2E1)
Cigarette smoke (CYP1A2)

INHIBITION OF METABOLISM

- Lead directly to toxic concentrations of some drugs
- Most occur relatively early after taking the combination of drugs
- The effects of inhibition are usually short-lived once the inhibitor is withdrawn
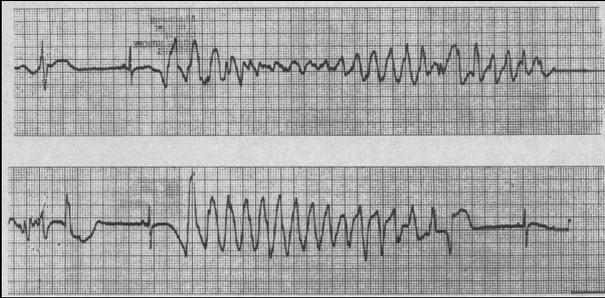
INHIBITION OF METABOLISM

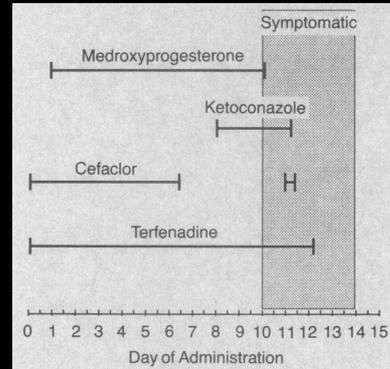**Some clinically important inhibitors of drug metabolism**

Amiodarone
Cimetidine
Some macrolides

Some 4-quinolones
Some antifungals
Some HIV agents
Metronidazole
Some selective serotonin re-uptake inhibitors (SSRIs)

TERFENADINE & KETOCONAZOLE

TERFENADINE & KETOCONAZOLE

MUTUAL INDUCTION AND INHIBITION OF METABOLISM

- In many cases inhibition is of the competitive type, two simultaneously administered drugs may inhibit the metabolism of each other
- Mutual induction of the CYP3A4 isoenzyme by anti-epileptics necessitates drugsdose adjustments

e.g. Co-prescripion of *phenytoin & carbamazepine*

PHARMACOKINETIC DIs

During Excretion:
- Tubular secretion is the process in renal excretion that lead to clinically important drug interactions

  e.g. Probenecid and salicylates can reduce the elimination of methotrexate via tubular secretion

PHARMACODYNAMIC DIs

- Occur when one drug alters the response of the body to another by interaction at the receptor site, or by acting at a different site to enhance or diminish the other drug's effects

  e.g. life-threatening hyperkalemia with ACE inhibitors and potassium sparing diuretics

GASTROINTESTINAL BLEEDING WITH SSRIs AND NSAIDs
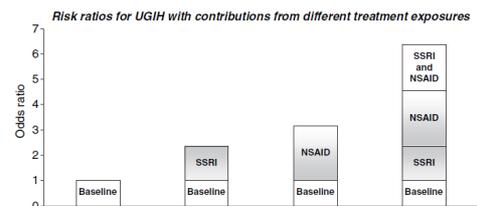
Alimentary Pharmacology & Therapeutics 2008

PHARMACODYNAMIC DIs

- Additive DIs : The effects of Two interacting drugs add up

- Synergistic DIs: an interaction where the result of Two interacting drugs is more than additive

  e.g. Relative risk(RR) of peptic ulcer with NSAIDs – 4
       RR of peptic ulcer with corticosteroids –1.1
       RR of peptic ulcer with both NSAIDs and corticosteroids –15

RECOGNITION OF DRUG INTERACTIONS

- Because of the growing number of recorded drug interactions, it is impossible for even experienced prescribers to remember all the important DIs

- Computerized drug interaction systems
  http://reference.medscape.com/drug-interactionchecker

  http://secure.medicalletter.org/adi

RECOGNITION OF DRUG INTERACTIONS

British National Formulary
BNF 61
March 2011

Appendices and indices
Appendix 1: **Interactions**   **800**

AVOIDANCE OF DRUG INTERACTIONS

- Most serious adverse interactions occur with drugs which have a low therapeutic index

- ∴ The decision to use these agents should be considered carefully and if prescribed the patient monitored closely

- Whenever possible, if there is a choice should choose the drug with the highest therapeutic ratio

AVOIDANCE OF DRUG INTERACTIONS

- The fewer people prescribing for a single patient, the lower the risk that an interaction will occur

- Interactions may not be immediately obvious when combinations are first prescribed, ∴ patients should be encouraged to alert doctors about symptoms that occur when new drugs are introduced