Personalised and Palliative Medicine

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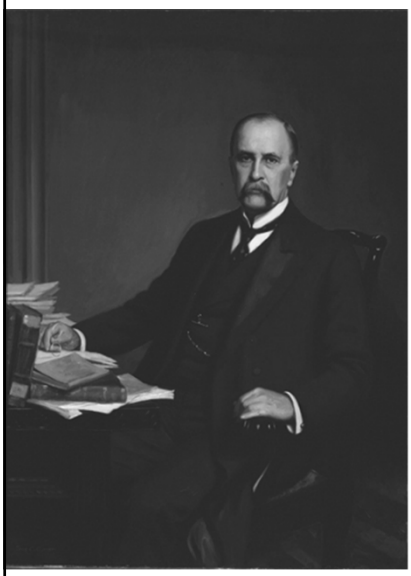
Why is this important?

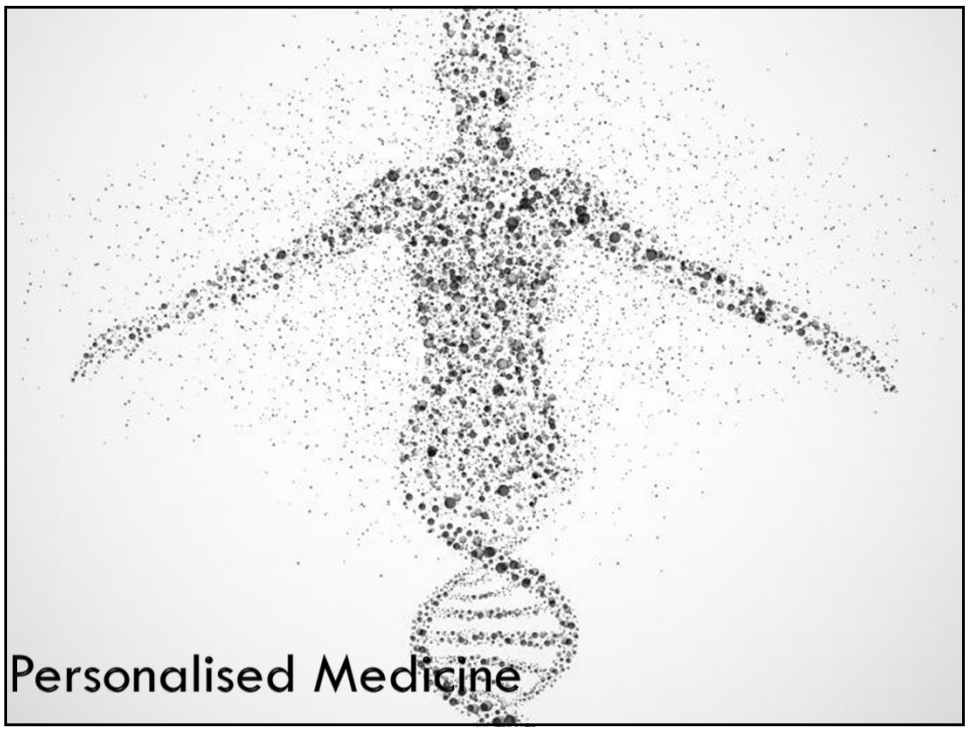
- Recent advances in understanding of metabolic pathways
- Can explain unexpected patient responses to drugs
- Part of a move to "individualised medicine"
- Can help us in everyday practice



If it were not for the great variability among individuals, medicine might as well be a science and not an art.

Sir William Osler, 1892

(Founder of Modern Medicine)



- PHARMACOKINETICS describes the rate and manner that a drug is absorbed, distributed and eliminated.
- In other words, *what the body does to the drug*

Pharmacokinetics

Pharmacodynamics

- PHARMACODYNAMICS describes the effect of the drug and how it works in terms of its interaction with a receptor or site of action.
- In other words, *what the drug does to the body*

- *PHARMACOGENETICS* is the study of how variation in an individual gene affects the response to drugs which can lead to adverse drug reactions, drug toxicity, therapeutic failure and drug interactions

Pharmacogenetics

- *PHARMACOMETABOLOMICS* involves determination of the metabolic state of an individual as affected by environmental, genetic, and gut microbiome influences
- The *metabotype* is a unique biochemical identity that results from these interactions and informs about how an individual will respond to treatment

Pharmacometabolomics

Drug Interactions

What is a drug interaction?

- A drug-drug interaction occurs when effect of one drug changed by presence of another
- Outcome can be harmful or beneficial

Drug Interactions

Importance to Palliative Medicine?

- Patients, particularly older patients, may be at risk:
  - Polypharmacy
  - Co-morbidity (disease and physiological changes)
  - Reduced absorption
  - Altered distribution
  - Reduced metabolism
  - Reduced excretion
- "Start low, go slow" appropriate

Drug Interactions

- Drug interactions can be difficult to predict
- Can be identified qualitatively (usually from theory)
- No idea of quantitative impact (clinical significance)
- An interaction known to occur in one patient may not cause problems in another

Drug Interactions

- To help, important to understand principles of:
- Pharmacokinetics
- Pharmacodynamics
- Pharmacogenetics
- Pharmacometabolomics

Drug Interactions

a) Pharmacokinetic Interactions

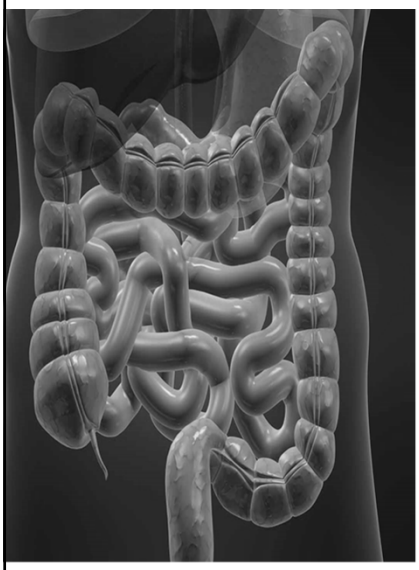
- difficult to predict
- due to alterations to drug absorption, distribution, metabolism and excretion

Drug Interactions

b) Pharmacodynamic Interactions

- easier to predict
- occur when the effects of two or more drugs are additive or antagonistic

Drug Interactions



- First pass metabolism is the loss of drug before it enters systemic circulation
- Cytochrome P450 enzymes line the gut wall and are present in hepatocytes
- Explains why some drugs inactive orally
  - e.g. fentanyl

Transport Proteins

- Transport proteins are now well recognized determinants of drug disposition and effects
- Two types:
  - influx (mediating the uptake of drugs into cells)
  - efflux (mediating the export of drugs or drug metabolites out of cells)
- TPs expressed in e.g. small intestine, liver, kidney, brain
- May have important role in drug interactions

Transport Proteins

- Efflux transporter P-glycoprotein (P-gp) is the most studied
- General function of P-gp is to:
  - Remove drugs absorbed in the intestines back into the gut lumen
  - Maintain the integrity of the blood brain barrier
  - Remove drugs from the kidneys and liver into the urine and bile respectively

Transport Proteins

- It is expressed in several tissues including intestine, kidney, liver and brain
- P-gp exhibits genetic variation and is subject to induction and inhibition interactions
- E.g loperamide
  - inhibition of P-glycoprotein at the blood brain barrier results in central opioid effects
  - Itraconazole
  - Lansoprazole

Metabolism

- Most drugs are lipophilic – readily cross cell membranes
- Many drugs are chemically altered to make more water soluble and easier to excrete or remove
- Usually results in loss of activity
  - Tramadol, codeine, tamoxifen

Metabolism

- Liver major site of metabolism but other sites include lungs, GI tract (e.g. 1st pass metabolism), brain
- One drug can affect metabolism of another by either inducing or inhibiting enzyme
- Most drug interactions occur at point of metabolism

Metabolism

Phase I

- Main pathway involves the cytochrome P450 (CYP450) system
  - CYP3A4 metabolises ≈ 50% of drugs
  - CYP2D6 metabolises ≈ 25% of drugs
  - CYP1A2, CYP2C9 and CYP2C19, CYP2E1
- Hydrolysis, oxidation and reduction
- Susceptible to drug inhibition/induction as well as genetic variation

Metabolism

Phase II

- Involves conjugation reactions
- Most compounds will have undergone Phase I metabolism
  - Morphine is metabolised by phase II only
  - Tapentadol mainly metabolised by phase II
- Main phase II reaction involves glucuronidation
- Conjugate usually inactive and less lipophilic than precursor
- More readily excreted in bile or urine

Metabolism

Phase II

- Previously thought to be resistant to drug interactions
- Also susceptible to genetic variation
- Clinical significance remains largely unknown

Pharmacokinetic Interactions

Enzyme Induction

- Can take several days or even weeks to develop
- May persist for a similar duration after discontinuation
- Drug toxicity can occur if doses are increased but not reduced once the inducer is stopped
- There are no inducers of CYP2D6

Pharmacokinetic Interactions

Enzyme Inhibition

- Most often responsible for life-threatening interactions
- Reduced drug effect where activation of a pro-drug is required
- Clinically relevant interactions can be evident within 2 days
- Substrates competing for the same isoenzyme can give rise to competitive inhibition

Enzyme Inducers[1]

- Carbamazepine
- Phenytoin
- Phenobarbital
- Rifampicin

- Dexamethasone (high dose)
- Enzalutamide
- Smoking (CYP1A2)

1. Summary of Product Characteristics. Available at: http://www.mhra.gov.uk/spc-pil/ (accessed 25th October 2015)

Enzyme Inhibitors[1,2]

- Abiraterone (CYP2D6)
- Amiodarone (CYP2C9/CYP2D6/CYP3A4)
- Clarithromycin (CYP3A4)
- Duloxetine (CYP2D6)
- Fluoxetine (CYP2D6)
- Levomepromazine (CYP2D6)
- Paroxetine (CYP2D6)

1. Summary of Product Characteristics. Available at: http://www.mhra.gov.uk/spc-pil/ (accessed 26th April 2015)
2. MHRA. MHRA UK Public Assessment Report: Tamoxifen: reduced effectiveness when used with CYP2D6 inhibitors. [Online]. 2011. Available at: http://www.mhra.gov.uk/home/groups/s-par/documents/websiteresources/con129101.pdf (accessed 26th April 2015)

Clinical Significance

- Difficult to predict - many drugs not metabolised by one specific pathway
  - tramadol: CYP2D6 and CYP3A4
  - oxycodone: CYP2D6 and CYP3A4
  - methadone: CYP1A2, CYP2B6, CYP2D6, CYP3A4
- Studies of potential DDIs usually only evaluate 2 drugs
- Application of results to patients with co-morbidity and polypharmacy is difficult
- Genetic variation will influence significance

Implications for Pain Management

- The activity of CYP2D6 is particularly relevant for:
  - Codeine
  - Tramadol
- The activity of CYP3A4 is particularly relevant for:
  - Fentanyl
  - Oxycodone
    - Inhibition forces metabolism through CYP2D6 – oxymorphone produced

Implications for Pain Management

Effect of inhibition of [CYP2D6] and [CYP3A4] on the pharmacokinetics of i.v. oxycodone

Grönlund et al., Clin Drug Investig 2011; 31(3):143-53

- DDIs arising from CYP2D6 inhibition alone - minor clinical importance
- Clinically significant interactions may occur if both CYP2D6 and CYP3A4 pathways are inhibited

Implications for Pain Management

Cytochrome P450-Mediated Changes in Oxycodone PK/PD and their Clinical Implications

Söderberg Löfdal KC et al., Drugs 2013; 73(6):533-43

- CYP2D6 inhibition does not influence oxycodone analgesic efficacy
- CYP3A4 activity, but not CYP2D6, is important for analgesic effect of oxycodone

Pharmacogenetics

- Differences in DNA sequences give rise to polymorphism
- In most cases, a polymorphism is of little clinical consequence
- Polymorphism in a critical region can lead to altered protein synthesis, leading to abnormal drug response
- May impact on adverse effects, effectiveness, drug interactions

Pharmacogenetics

- Genetic variability can affect an individual's response to drug treatment by influencing pharmacokinetic and pharmacodynamic processes, e.g.
  - cytochrome P450 isoenzymes
  - drug receptors
  - transport proteins

Pharmacogenetics

- Several polymorphisms that affect drug metabolism have been identified
- Functional changes as a result of a polymorphism can have profound effects:
  - Adverse drug reaction
  - Toxicity
  - Lack of effect
  - Drug interaction

Pharmacogenetics

- Isoenzymes CYP2D6, CYP2C9 and CYP2C19 display high levels of polymorphism
- These have been shown to affect the response of individuals to many drugs

- Codeine - metabolised by CYP2D6 to morphine.
- PMs derive no analgesia from codeine
- Drugs that inhibit CYP2D6 will mimic PM
- UMs are at risk of life-threatening adverse drug reactions as codeine is metabolised at a very high rate.

Clinical Significance?

Pharmacogenetics of analgesic drugs

Cregg et al., Br J Pain. 2013;7(4):189-208

"Pain experience and analgesic response are complex traits, and as such are likely to be influenced by a host of gene–gene and gene–environment interactions."

"Environmental and patient variables……. contribute to the ultimate endpoint of analgesic response."

The Future

- Pharmacometabolomics
- The brain possesses unique P450s that metabolize drugs
- May alter the pharmacodynamics of drugs through novel biotransformation pathways
- More information about transport protein drug interactions

Final Words…..

- Metabolism of substrates is competitive - drug inhibition can be additive
- Many drug interactions can develop insidiously
- If a patient's condition deteriorates, or result of drug therapy unanticipated, suspect a DDI
- Potential DDIs far outnumber actual DDIs
- Many DDIs may not warrant medication adjustment
- One size (dose) does not fit all!