Semester I.
Seminar 9.

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Exam titles 17-18-19

17.

- Factors influencing the drug elimination
- Uptake mechanisms, substrates and inhibitors
- Drugs used in acid-peptic disease

18.

- Drug elimination: II. Excretion
- α2 sympathomimetics and the concept of “false transmitter”
- Laxatives, antidiarrheal drugs. Drugs in the treatment of chronic inflammatory bowel disease, antiobesity drugs

19.

- Factors influencing the drug effect.
  Preclinical phase of drug development (NEXT SEMINAR)
- Pharmacology of cardiac glycosides
- Drugs promoting gastrointestinal motility. Emetics and antiemetic drugs

Drug elimination II: Excretion

Pharmacokinetics

- „Effect of the body on the drug”
- Fate of the drug is divided into 4 stages designated by the acronym ‘ADME’:

- • Absorption from the site of administration
- • Distribution within the body
- • Metabolism
- • **Excretion**

Invasion

Elimination

Excretion ways

- *excretion* consists of elimination from the body of **chemically unchanged drug or its metabolites**.
- The main routes by which drugs and their metabolites leave the body are:
  - the kidneys
  - the hepatobiliary system
  - the lungs (important for volatile/gaseous anaesthetics).
- Small amounts of some drugs are also excreted in secretions such as saliva, sweat or milk.

Excretion through the kidneys

- Three fundamental processes account for renal drug excretion:
  - 1. glomerular filtration
  - 2. tubular secretion
  - 3. passive diffusion across tubular epithelium.

Excretion through the kidneys – Glomerular filtration

- Molecular weight < 20kDa ➔ pass into the glomerular filtrate

  = most drugs cross the barrier freely
  (exception: macromolecules (e.g. heparin, biological products))

- filtration is isosmotic movement
  = drug is filtrated together with water

  The concentration of free drug will be the same in the filtration as in the plasma

  it does not affect the free concentration of drug in the plasma.

- Plasma albumin (~68kDa) is almost completely impermeant

  ➔ If a drug binds to albumin, only free drug is filtered

  ➔ **If protein-bound, drug is slowly cleared by filtration**
  (= reduced clearance)

- A maximum of 20% of renal plasma flow is filtered through the glomerulus

Excretion through the kidneys – Tubular secretion

- The remainder renal plasma flow (80%), that was not filtered, passes on to the peritubular capillaries of the proximal tubule.
- ➔ tubular secretion by:
  - organic cation transporters (OCTs) ➔ transport organic bases (carrier mediated diffusion (mainly))
  - organic anion transporters (OATs) ➔ transport acidic drugs (secondary active transport (mainly))
- The carriers transport drug molecules only, without water.
  - Only free drug molecules are taken from the plasma ➔
  - the free drug concentration falls ➔
  - bound drugs dissociate from albumin into the blood-plasm ➔
  - effectively 100% of the drug, bound and free, is available to the carrier. ➔
  - **Even if protein bound, drug is rapidly cleared by tubular secretion** (=maximal clearance)

Table 9.4 Important drugs and related substances secreted into the proximal renal tubule by OAT or OCT transporters

OAT	OCT
p-Aminohippuric acid	Amiloride
Furosemide	Dopamine
Glucuronic acid conjugates	Histamine
Glycine conjugates	Mepacrine
Indometacin	Morphine
Methotrexate	Pethidine
Penicillin	Quaternary ammonium compounds
Probenecid	Quinine
Sulfate conjugates	5-Hydroxytryptamine (serotonin)
Thiazide diuretics	Triamterene
Uric acid	

Excretion through the kidneys – Passive diffusion across tubular epithelium (=reabsorption)

- **Water** is reabsorbed from tubules➔ the volume of urine = 1% of filtrated volume
- ➔ drug concentration rises in tubules
- **Lipid-soluble drugs** ➔ 99% will be passively reabsorbed due to high concentration-gradient (=passive diffusion across tubular epithelium) ➔ excreted poorly
- Polar drugs ➔ remain in the lumen ➔ excreted well

- Ionization is pH dependent AND most drugs are weak acids/bases
  - Effect of pH on diffusion (see Seminar 4)
  - Ion-trapping (see Seminar 7)

Biliary excretion and enterohepatic circulation

- Biliary excretion
  - By liver
  - Through carrier-mediated transport (OATs and OCTs)
  - Hydrophilic drug conjugates (particularly glucuronides)
  - Into the bile ➔ into the intestines
- Enterohepatic circulation:
  - Biliary excretion
    - Hydrolisation of glucuronide conjugates by bacterial beta-glucuronidase enzymes
      - Active drug in gut
    - Reabsorption from gut (to hepatic portal vein)
  - Liver
- The effect = ‘reservoir’ of recirculating drug (20% of total drug in the body) ➔ **prolongs drug action**.
- E.g.: morphine, ethinylestradiol, indomethacin, digitoxin etc.

Excretion through the lungs

Reverse process of absorption through the lungs:

- Mostly excretion of gases and other volatile liquides (anasthetics)
  and alchohol (in unchanged form)
- Other examples: sulfapyridine, sulfanilamide
- Passive diffusion
- Affected by:
  - Partial pressure in the alveolar air
  - Breathing frequency
  - Pulmonary circulation
  - Solubility
    (if more soluble in water, elimination through the lungs takes more time)
  - Here volatility is more important than its polarity!

Other types of excretion

- Salivary glands (passive diffusion)
  - drugs through this way are not eliminated easily as saliva is swallowed (”salivary circulation”)
  - drug monitoring
  - E.g. caffeine, theophylline, phenytoin, metronidazole
  - E.g. bitter taste/metallic taste after ingestion (e.g. macrolide antibiotics, metronidazole)
- Sweat (passive diffusion)
  - not many drugs are excreted this way (e.g. vitamin B6, amphetamin, morphine, cocaine, ethanol) ➔ drug monitoring
- Breast Milk (passive diffusion)
  - passive diffusion of lipofil, non-ionized agents is intense!
  - Ion-trapping mechanism also exist (pH of milk is 6.8 ⇔ plasma pH is 7.4)
    - E.g. erythromycin
  - Other examples: heroin, methadon, tetracycline, diazepam

Factors influencing the drug effect

Interindividual variations

- **Variability is a serious problem; if not taken into account, it can result in:**

– lack of efficacy or - unexpected side effects.

- **<u>Types of variability may be classified as:</u>**

– pharmacokinetic

– pharmacodynamic

– idiosyncratic.

- **<u>The main causes of variability are:</u>**

– age

- pregnancy

– pathological states (e.g. kidney or liver disease)

– immunological factors

– genetic factors

– drug interactions (see next Seminar)

Age

- Variations in pharmacodynamic sensitivity:
  - Physiological factors
    - e.g. altered cardiovascular reflexes
  - Pathological factors
    - e.g. hypothermia, malnutrition, which are common in elderly
    - Multiple diseases (in elderly)
- Variations in pharmacokinetic state:
  - Elimination less efficient in newborn babies and in old people ➔ drugs may produce greater and more prolonged effects ($t_{1/2}$ is longer)
  - Excretion
    - Glomerular filtration rate (GFR) in the newborn is 20% of adults'; tubular function is also less
  - Metabolism in neonates is not developed (especially if premature)
    - hepatic microsomal oxidase, glucuronyltransferase, acetyltransferase and plasma esterases ➔ naonatal jaundice (& kern-icterus) and grey baby syndrome (see former Seminar)
    - These enzymes take 8 weeks or longer to reach the adult level of activity.

Effect of AGE on elimination $t_{1/2}$

Drug	Mean or range of half-life (h)		
	Term neonate[a]	Adult	Elderly person
Drugs that are mainly excreted unchanged in the urine			
Gentamicin	10	2	4
Lithium	120	24	48
Digoxin	200	40	80
Drugs that are mainly metabolised			
Diazepam	25–100	15–25	50–150
Phenytoin	10–30	10–30	10–30
Sulfamethoxypyridazine	140	60	100

[a] Even greater differences from mean adult values occur in premature babies.

(Data from Reidenberg 1971 Renal function and drug action. Saunders, Philadelphia; and Dollery 1991 Therapeutic drugs. Churchill Livingstone, Edinburgh.)

Rang&Dale 7th ed.

PREGNANCY

Pregnancy causes physiological changes that influence drug disposition in mother and fetus.

- Maternal plasma albumin concentration is reduced ➔ influencing drug protein binding.
- Cardiac output is increased, ➔ increased renal blood flow and GFR ➔ increased renal elimination of drugs.
- The foetus is a new distributional volume
  - Lipophilic molecules rapidly traverse the placental barrier, whereas transfer of hydrophilic drugs is slow, limiting fetal drug exposure following a single maternal dose

Variations due to diseases

Pharmacokinetic alterations in:

• Absorption:

– gastric stasis (e.g. migraine)

– malabsorption (e.g. steatorrhoea from pancreatic insufficiency)

– oedema of ileal mucosa (e.g. heart failure, nephrotic syndrome).

• Distribution:

– altered plasma protein binding (e.g. of phenytoin in chronic renal failure)

– impaired blood–brain barrier (e.g. to penicillin in meningitis).

• Metabolism:

– chronic liver disease

– hypothermia

• Excretion:

– acute and/or chronic renal failure.

Pharmacodynamic alterations in:

• Receptors (e.g. myasthenia gravis, familial hypercholesterolaemia).

• Signal transduction (e.g. pseudohypoparathyroidism, familial precocious puberty).

• Unknown mechanisms (e.g. increased sensitivity to pethidine in hypothyroidism).

IDIOSYNCRATIC REACTIONS

- **DEF.: An idiosyncratic reaction is a qualitatively abnormal, and usually harmful, drug effect that occurs in a small proportion of individuals**

- Immunological mechanisms underlie many idiosyncratic reactions. Propensity to these is genetically determined

For example,

- chloramphenicol causes aplastic anaemia in approximately 1 in 50000 patients
- Malignant hyperthermia is a metabolic reaction to drugs including **suxamethonium and various** *inhalational anaesthetics and antipsychotic drugs*

Genetic variations (+ethnicity)

Genetic variation is an important source of pharmacokinetic variability.

- There are several clear examples where genetic variation influences drug response, including:

– fast/slow acetylators (**hydralazine, procainamide, isoniazid)**

– plasma cholinesterase variants (**suxamethonium)**

– hydroxylase polymorphism (**debrisoquine).**

- In future, profiling an individual's DNA (e.g. for combinations of single nucleotide polymorphisms) could provide a way to anticipate drug responsiveness

Pharmacogenetics/genomics

- Pharmaco**gene**tics: study of individual gene-drug interactions, usually one or two genes that have dominant effect on a drug response (SIMPLE relationship)

- Pharmaco**genom**ics: study of genomic influence on drug response, often using high-throughput data (sequencing, SNP chip, expression, proteomics - COMPLEX interactions)

Metabolization and genetics

1. slow (poor) metabolizers (PM) → many side effect / toxicity
2. intermediate metabolizers (IM) → some side effects
3. rapid (extensive) metabolizers (RM) → normal response
4. ultra-rapid metabolizers (UM) → high risk to interactions

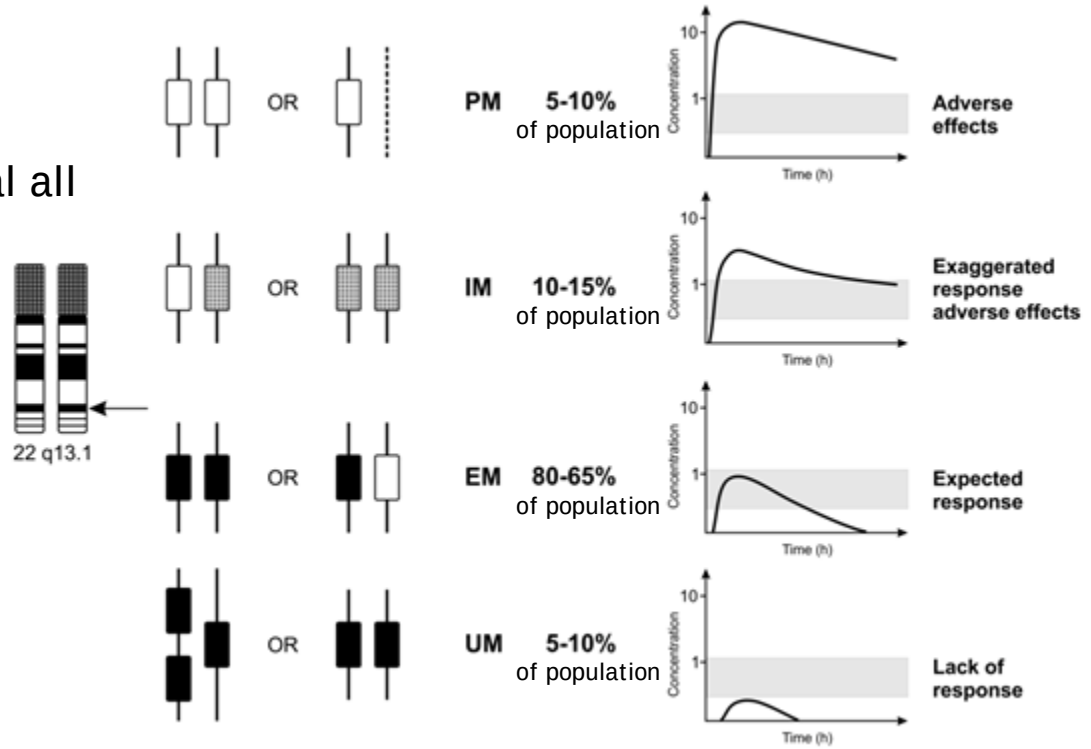
CYP2D6 phenotypes of Caucasian population:

White = Null allele =
mutations that lead to non-functioning protein product or no protein product al all

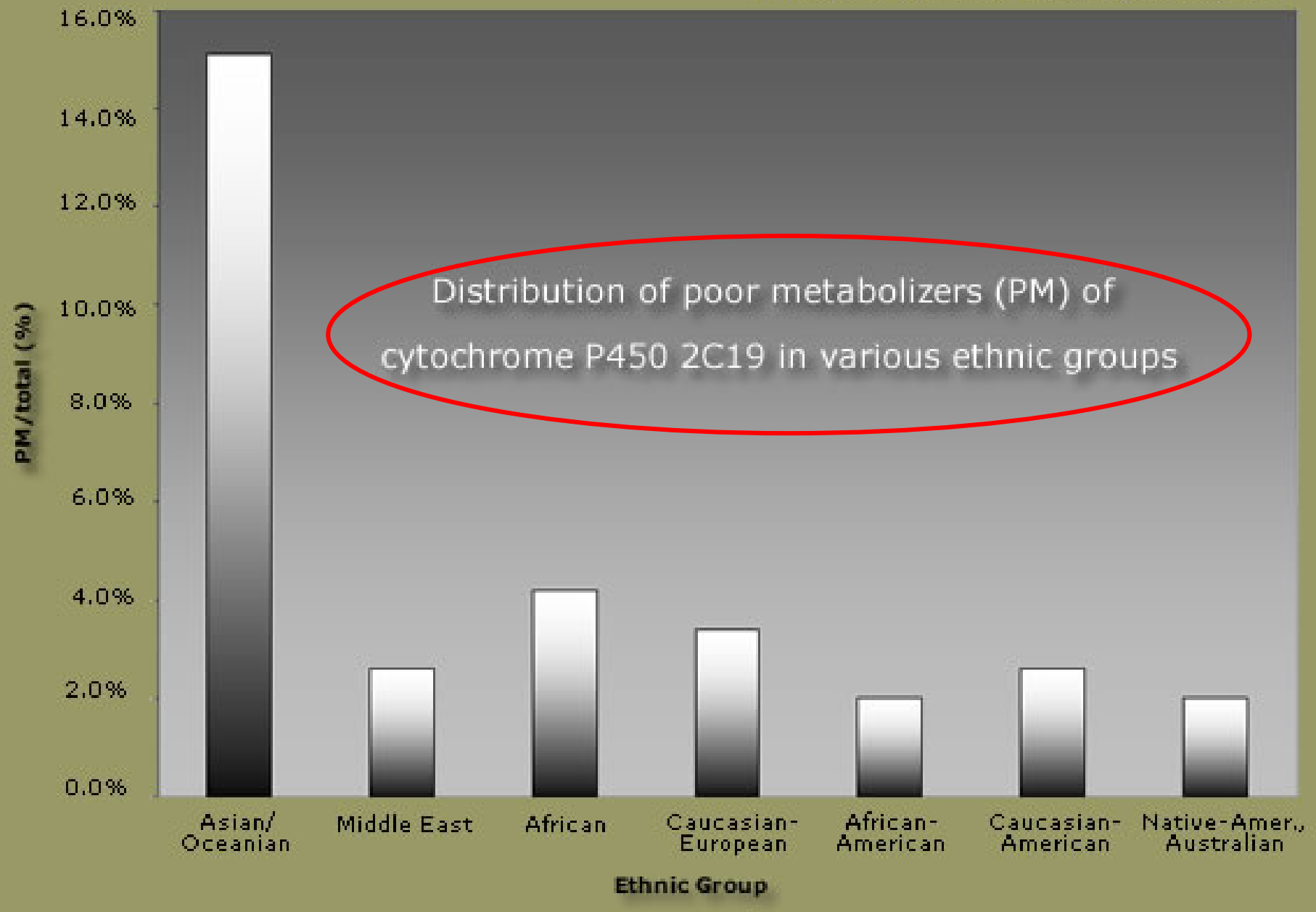
Gray = Decreased enzyme activity

Black = Wild type allele = normal

Duplication (or multiplication) ➔



Another example, not just in Causcasian population



The future - Personalized medicine

- In the near future, it will be possible to tailor the treatment to the individual patient on the basis of the patient's genotype

Use of GeneChip technique: CYP-Assay (applied pharmacogenomics)

- A matrix on a chip (high density miniaturized array of oligonucleotides) that **can identify the CYP phenotype of a patient**.
- By the year 2000 enabled rapid detection of 18 known mutations of CYP2D6 and CYP2C19.
- In 2005 cost estimated was about $950 - costs will come down…
- Something like this is likely to become a part of initial patient screening in the near(?) future.