Drugs and the kidney

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Introduction

- Kidneys have an important role in elimination of drugs, toxins and waste products
- Factors that make the kidneys vulnerable to the effect of drugs and toxins :
  - High blood flow = 25% of cardiac output
  - High medullary concentration gradient
  - Relative medullary ischaemia
  - High metabolic activity of tubular epithelium
  - Prolonged half life of drugs
  - Interference to the prostaglandin metabolism by drugs

Renal handling of drugs

Kidneys can excrete drugs:

- in unchanged form
- as active or inactive metabolite

Three process involved in drug handling:

- Glomerular filtration
- Tubular reabsorption
- Tubular secretion

Glomerular filtration

Depends:

- plasma concentration of the drug
- molecular size
- electrical charge
- degree of protein binding
- glomerular filtration rate (GFR)

Factors that facilitate filtration:

- Small molecular size, poor protein binding and water solubility

Tubular reabsorption

- Passive process
- Occurs mainly in the proximal tubule
- Depends on:
  - concentration
  - pH
  - solubility
  - other factors

Tubular secretion

- Energy dependent active transport process in the proximal tubule
- Bidirectional pathways for secretion and reabsorption
- Depends on renal blood flow
- It has a tubular maximum

Drug induced renal damage

1. Very high blood flow rate per gram of kidney tissue, resulting in delivery of a large amount of the drug
2. Drug metabolism by tubular cells which are rich in enzymes – the parent drug or metabolites may cause tissue damage
3. Large surface area of nephrons in contact with drugs
4. Precipitation of drugs in the tubules depending on the concentration and pH
5. Concentrating capacity of nephrons, resulting in high levels of the drugs in the tubules
6. Availability of specific transport mechanism that mediate cellular uptake of drugs

Mechanism of drug induced renal damage

Prerenal mechanism

- *Hypovolaemia:* potent loop diuretic
- *Renal salt and water loss:* from hypercalcaemia induced by vitamin D therapy
- *Decreased cardiac output:* beta-blockers
- *Decreased renal blood flow:* ACEI
- *Inhibition of prostaglandin synthesis:* NSAIDS
- *Intense renal vasoconstriction:* radiographic contrast media

Renal mechanism

- *Acute tubular necrosis:* aminoglycosides, amphotericin, paracetamol
- *Acute tubulointerstitial nephritis:* penicillins, sulphonamides, NSAID, allopurinol, rifampicin
- *Chronic tubulointerstitial nephritis:* NSAID, irradiation, lead and cadmium intoxication
- *Immune complex mediated glomerulonephritis:* penicillamine, gold, mercury, heavy metals, NSAID
- *Loss of tubular and collecting ducts function:* lithium, cisplatin

Postrenal mechanism

- *Retroperitoneal fibrosis* (with urinary tract obstruction): methysegide, practolol
- *Obstruction by crystals*: acyclovir, uric acid crystal produced during chemotherapy

Use of drugs in patients with impaired renal function

- Absorption: unpredictable in uraemia due to reduced absorption, nausea and vomiting
- Metabolism: rate of drug metabolism through kidney is reduced due to decreased drug catabolism (e.g. insulin)
- Protein binding: hypoproteinemia - increased free drug concentration

Contd.

- Vol. distribution: salt/ water overload/ depletion- affects concentration of drug
- End organ sensitivity: renal response to drug may decrease in CKD eg diuretics
- Renal elimination:major of the drugs are normally excreted by kidneys. Water soluble excreted/metabolized from kidney; lipid soluble from liver metabolized

How to overcome of these problems

- Safe prescription of drugs in Renal ds
- Justify the need of drugs
- Consider renal fn status
- Think about the toxicities of drugs
- Select the safe drug
- Dose adjustment in according to severity of renal diseases
- Monitoring the drug toxicities
- Consult nephrologists

Dose titration

- Drug dose= Normal dose X Ccr/100
- Methods of dose modification:

1. Dose reduction but frequency same
2. Interval extension but same dose
3. Combination of both