Drugs and the Kidney

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1 Renal Physiology and Pharmacokinetics

2 Drugs and the normal kidney

3 Drugs toxic to the kidney

4 Prescribing in kidney disease

Normal Kidney Function

- 1 Extra Cellular Fluid Volume control
- 2 Electrolyte balance
- 3 Waste product excretion
- 4 Drug and hormone elimination/metabolism
- 5 Blood pressure regulation
- 6 Regulation of haematocrit
- 7 regulation of calcium/phosphate balance (vitamin D3 metabolism)

Clinical Estimation of renal function

- **Clinical examination**

  pallor, volume status, blood pressure measurement, urinalysis
- **Blood tests**
- Routine Tests
- haemoglobin level
- electrolyte measurement (Na ,K , Ca, PO_4)
- urea
- creatinine normal range 70 to 140 µmol/l

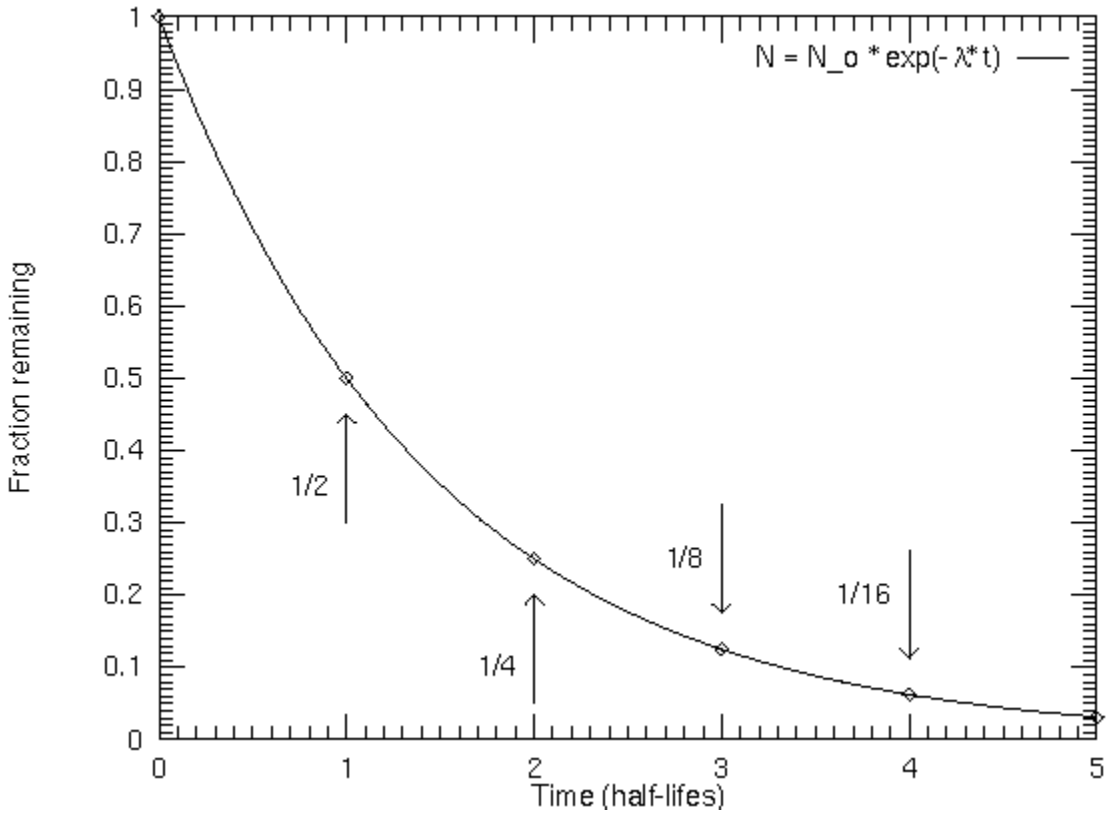
Serum Creatinine and GFR

- Muscle metabolite- concentration proportional to muscle mass
  - High: muscular young men
  - Low: conditions with muscle wasting
    - elderly
    - muscular dystrophy
    - Anorexia
    - malignancy

- "Normal" range 70 to 140 µmol/litre

Serum Creatinine and GFR

Serum creatinine



Glomerular filtration rate (GFR)

Tests of renal function cont.

24h Urine sample-Creatinine clearance

- chromium EDTA Clearance
- gold standard Inulin clearance

Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Elimination
  - filtration
  - secretion

Nephrotoxic Drugs

- Dose dependant toxicity
  - NSAIDs including COX 2
  - Aminoglycosides
  - Radio opaque contrast materials
- Idiosyncratic Renal Damage
  - NSAIDs
  - Penicillins
  - Gold, penicillamine

NSAIDs (Non-steroidal anti inflammatory drugs)

- Commonly used
  - Interfere with prostaglandin production, disrupt regulation of renal medullary blood flow and salt water balance
- Chronic renal impairment
  - Habitual use
  - Exacerbated by other drugs (anti-hypertensives, ACE inhibitors)
  - Typical radiological features when advanced

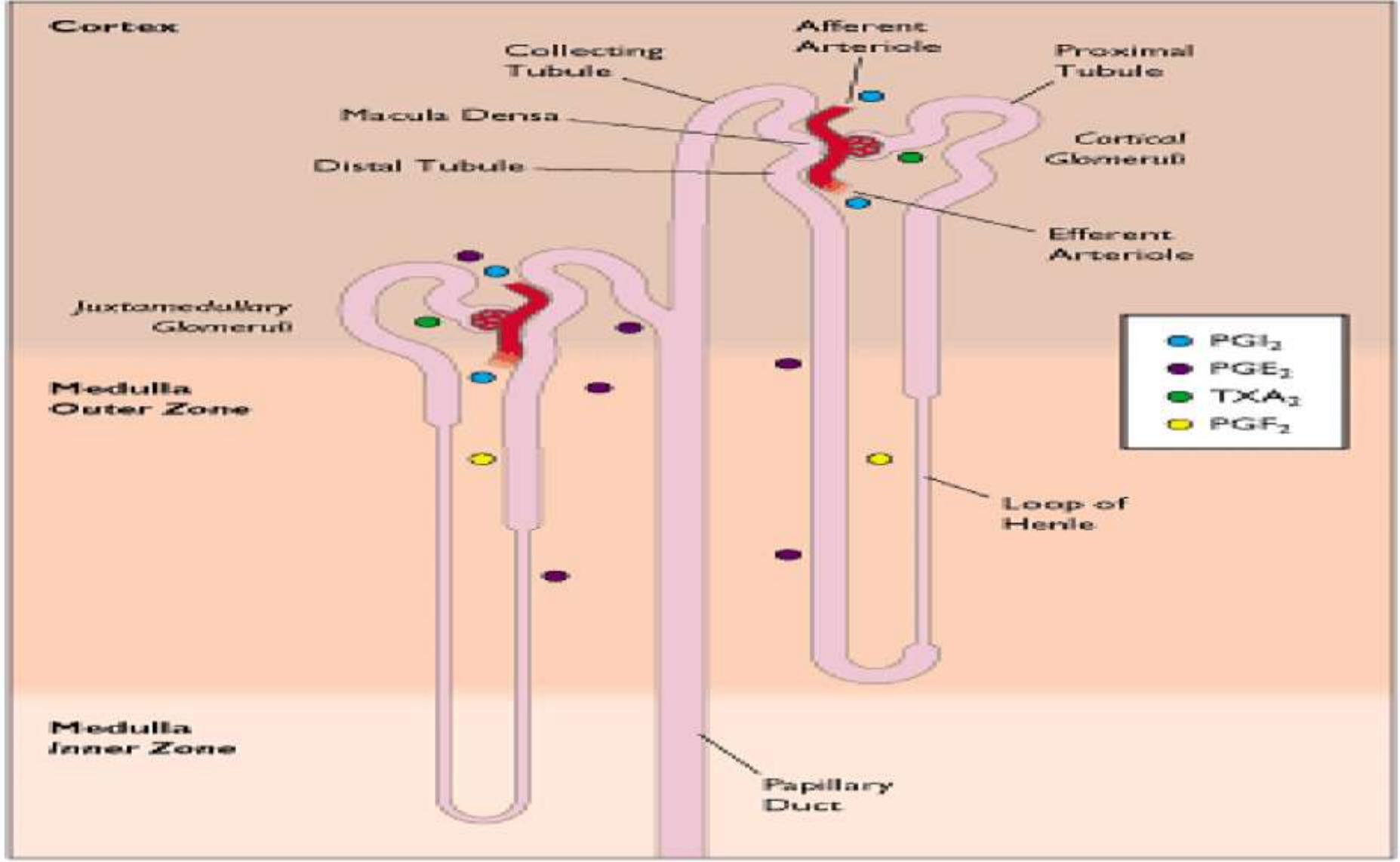


Illustration: Seward Hung

Figure 3. Anatomic locations of renal prostaglandin (PG) biosynthesis imply modulatory roles in renal function. Identification of PGI_2 in cortical glomeruli and arterioles suggests, for example, a role in renal hemodynamics, while identification of PGE_2 in medullary interstitial cells, the loop of Henle, and the medullary portion of the collecting duct suggests a role in salt and water balance. In general, renal prostaglandins such as PGI_2, PGE_2, thromboxane A_2 (TXA_2), and PGF_2 appear to modulate the actions of systemic and local hormones, perhaps most crucially as a counterregulatory system when the kidney is faced with pathologic states threatening its function.

Aminoglycosides

- **Highly effective antimicrobials**
  - Particularly useful in gram -ve sepsis
  - bactericidal
- **BUT**
  - Nephrotoxic
  - Ototoxic
  - Narrow therapeutic range

Prescribing Aminoglycosides

- **Once daily regimen now recommended in patients with normal kidneys**

  High peak concentration enhances efficacy

  – long post dose effect

  – Single daily dose less nephrotoxic

- **Dose depends on size and renal function**

Intravenous contrast

- **Used commonly**
  - CT scanning, IV urography, Angiography
  - Unsafe in patients with pre-existing renal impairment
  - **Risk increased in diabetic nephropathy, heart failure & dehydration**
  - Can precipitate end-stage renal failure
  - Cumulative effect on repeated administration
- **Risk reduced by using Acetylcysteine ?**

Prescribing in Kidney Disease

- Patients with renal impairment
- Patients on Dialysis
- Patients with renal transplants

Principles

- Establish type of kidney disease
  - Most patients with kidney failure will already be taking a number of drugs
  - Interactions are common
  - Care needed to avoid drug toxicity
- Patients with renal impairment and renal failure
  - Antihypertensives
  - Phosphate binders

Dosing in renal impairment

- Loading dose does not change (usually)
- Maintenance dose or dosing interval does

T ½ often prolonged

- Reduce dose OR
- Increase dosing interval

- Some drugs have active metabolites that are themselves excreted renally
  - Warfarin, diazepam

Amphotericin

- Class
  - Anti fungal agent for topical and systemic use
- Mode of action
  - Lipid soluble drug. Binds steroid alcohols (ergosterol) in the fungal cell membrane causing leakage of cellular content and death. Effective against candida species
  - Fungistatic or fungicidal depending on the concentration
  - Broad spectrum (candida, cryptosporidium)

Amphotericin

- Indications
  - iv administration for systemic invasive fungal infections
  - Oral for GI mycosis
- Side effects
  - Local/systemic effects with infusion (fever)
  - Chronic kidney dysfunction
    - » Decline in GFR with prolonged use
    - » Tubular dysfunction (membrane permeability)
    - » Hypokalaemia, renal tubular acidosis (bicarb wasting type 1/distal), diabetes insipidus, hypomagnesaemia
    - » Pre hydration/saline loading may avoid problems

Toxicity can be reduced substantially by liposomal packing of Amphotericin

Lithium toxicity

- Lithium carbonate - Rx for bipolar affective disorder
- Toxicity closely related to serum levels
- Symptoms
  - CVS arrhythmias (especially junctional dysrrythmias)
  - CNS tremor – confusion - coma
- Treatment
  - Supportive - Haemodialysis and colonic irrigation for severe levels
  - Inadvertent intoxication from interaction with ACEI & loop/thiazide diuretic
  - Carbamezepine and other anti epileptics increase neurotoxicity

Digoxin toxicity

- Incidence
  - High levels demonstrated in 10% and toxicity reported in 4% of a series of 4000 digoxin samples
- Kinetics
  - large volume of distribution (reservoir is skeletal muscle)
  - about 30% of stores excreted in urine/day

Treatment of digoxin toxicity

- Supportive
  - Correction of electrolyte imbalances
  - Atropine for bradycardia avoid cardio stimulants because arrythmogenic
- Limitation of absorption
  - Charcoal effective within 8 hours (or cholestyramine)
- Specific measures
  - DIGIBIND Fab digoxin specific antibodies. Binds plasma digoxin and complex eliminated by kidneys (used when OD is high/near arrest)
- Enhanced elimination
  - Dialysis is ineffective. Charcoal/cholestyramine interrupt enterohepatic cycling.