Drugs and the kidney

Dr.Nathasha Luke

Drugs and the kidney-objectives

Objectives

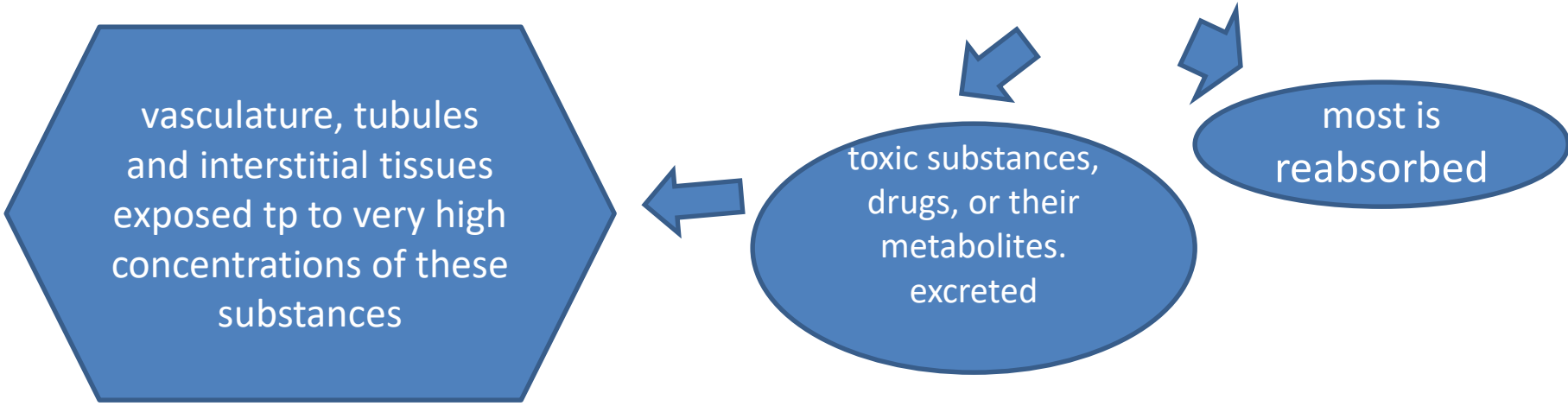
- Drugs affecting kidneys
- Prescribing in renal disease

Drugs affecting kidneys

- Why do drugs affect kidneys?
- What are the mechanisms of damage?
- What types of damage do they cause?
- How to prevent/minimize the damage?

Why are kidneys vulnerable to insult?

- Kidney ⟹ 0.5% of body weight
  ⟹ 25% of cardiac output.
- Glomerular filtration ⟹ 180 l of ultrafiltrate daily.



- The kidneys, therefore, quite commonly are subjected to adverse effects of drug therapy
- Underlying renal disease can aggravate toxicity

Drugs affecting kidneys

- Why do drugs affect kidneys?
- What are the mechanisms of damage?
- What types of damage do they cause?
- How to prevent/minimize the damage?

Mechanisms of renal damage

- Salt and water depletion/Changes in renal blood supply
- Biochemical effects

-direct

-indirect

- Immunological effects
- Renal obstruction

Salt and water depletion

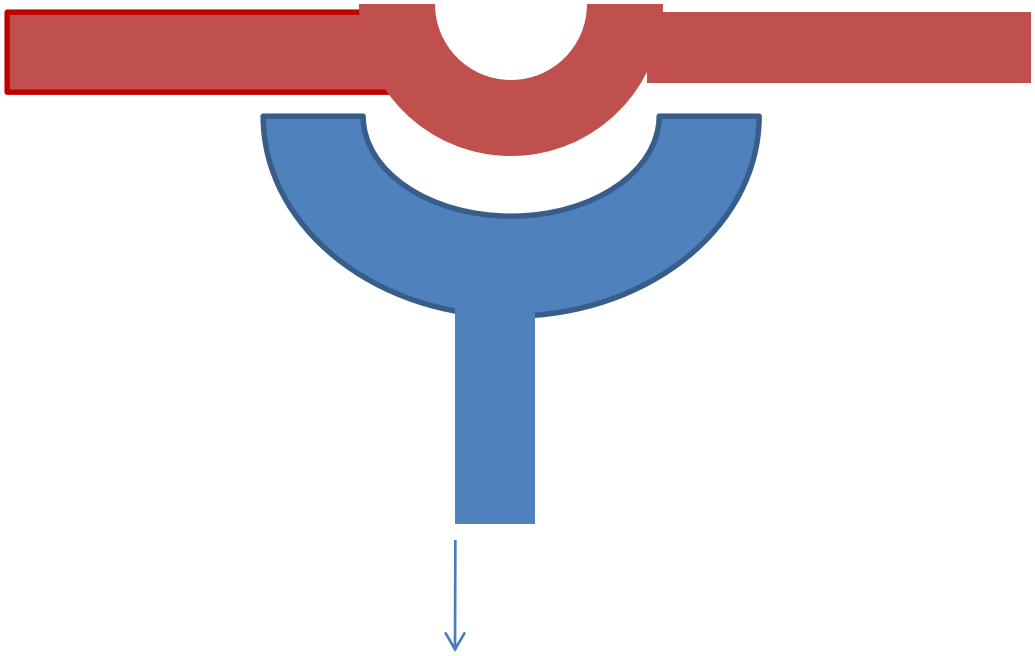
- Causes a reduction in glomerular perfusion pressure
- Patients with already compromised circulation are at a higher risk

Ex-diuretics

Changes in renal blood supply

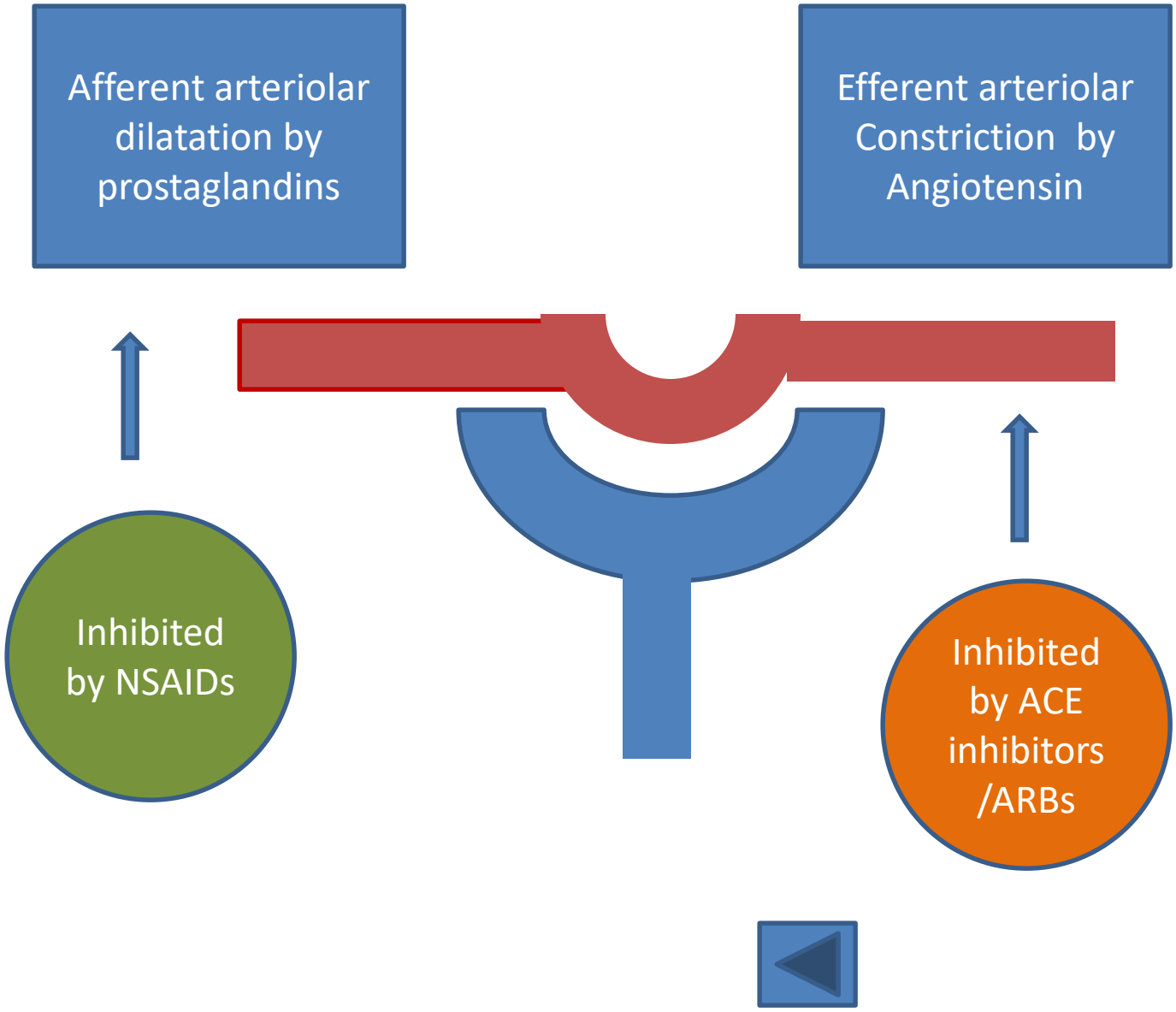
Afferent arteriolar dilatation by prostaglandins

Efferent arteriolar Constriction by Angiotensin



Maintains glomerular perfusion pressure

Changes in renal blood supply



Biochemical effect -direct

- Antimicrobials-aminoglycosides , amphotericin
- Radiological contrast media
- Analgesics –NSAIDs

Biochemical effect -indirect

- Cytotoxics and uricosuric drugs may cause urate to be precipitated in the tubule

- Diuretics and laxative abuse –tubule damage secondary to potassium and sodium depletion

Immunological effect

- A wide range of drugs produce a range of injuries
- Injuries include-glomerulonephritis , interstitial nephritis, SLE

Renal obstruction

- **Tubular obstruction by crystal deposition**

-Cytotoxic drugs causing tumor lysis syndrome

- **Obstructive uropathy**

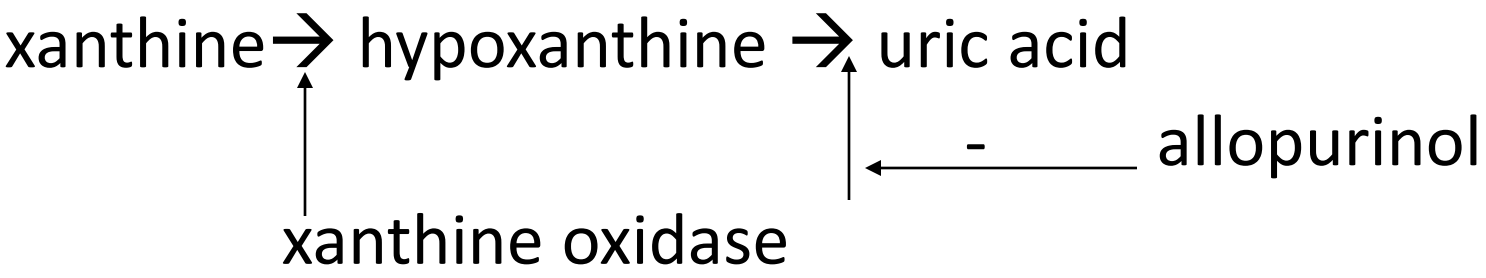
-Renal stone formation with excessive vitamin D
-Ureteric obstruction due to external compression

Methysergide, bromocriptine
→ retroperitoneal fibrosis

Crystalluria -Tumour Lysis Syndrome

- Cytotoxic drugs → large number of cells destroyed together
- This causes release of urate in large amounts which cause obstruction of tubular lumen

- To prevent : allopurinol prophylactically



Drugs affecting kidneys

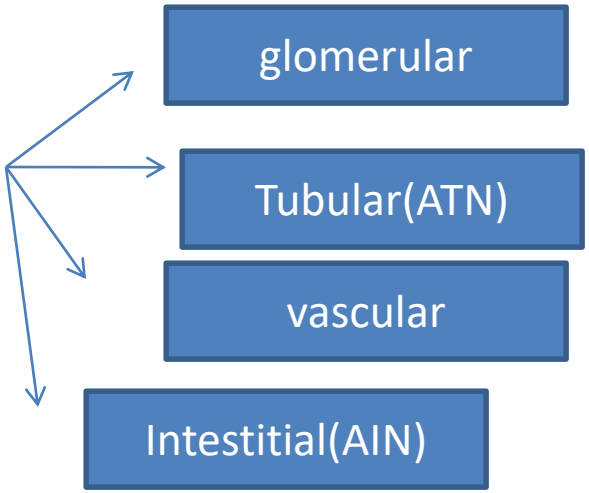
- Why do drugs affect kidneys?
- What are the mechanisms of damage?
- What types of damage do they cause?
- How to prevent/minimize the damage?

Drug induced renal disease

- Acute renal failure
- Chronic kidney disease
- Nephrotic syndrome/nephritic syndrome/proteinuria
- Renal tubular dysfunction

Drug induced renal disease-Acute renal failure

- Pre renal
- Intrinsic renal
- Post renal



Drug induced renal disease-Acute renal failure

	Mechanism of injury	examples
Prerenal	Decreased perfusion	Diuretics, NSAIDs, ACE Inhibitor
Intrinsic Renal		
Acute tubular necrosis	Seen with drugs secreted by tubules. tubular Toxicity may be 1.effect of the drug per se or 2.the physiological consequence as in rhabdomyolysis	Aminoglycosides,Radiocontrast media, NSAIDs Statins(cause rhabdomyolysis)
Acute interstitial nephritis	Immune mediated Fever, rash and arthralgia Eosinophiluria seen	Penicillin, NSAIDs
vascular	TTP (anaemia/thrombocytopenia/renal and CNS dysfunction)	Cyclosporin

Drug induced renal disease-Acute renal failure

	Mechanism of injury	examples
Intrinsic Renal		
Tubule obstruction	Crystal deposition within the tubular lumen	Cytotoxic drugs causing tumor lysis syndrome

Drug induced renal disease

- Acute renal failure
- Chronic renal failure
- Nephrotic syndrome/nephritic syndrome
- Renal tubular dysfunction

Chronic kidney disease

- **Tubulointerstitial nephritis**

- Lithium

-NSAIDs

- **Obstructive uropathy**

-Ureteric obstruction due to renal stones-excess vitamin D

-Ureteric obstruction due to external compression

Methysergide, bromocriptine,
→ retroperitoneal fibrosis

Drug induced renal disease

- Acute renal failure
- Chronic renal failure
- Nephrotic syndrome/nephritic syndrome
- Renal tubular dysfunction

Nephritic/Nephrotic syndrome

- Glomerulonephritis

Membranous
- Captopril
- Gold salts
- Penicillamine

Minimal-change
- NSAIDs

Drug induced renal disease

- Acute renal failure
- Chronic renal failure
- Nephrotic syndrome/nephritic syndrome
- Renal tubular dysfunction

Renal tubular dysfunction

- **Nephrogenic diabetes insipidus**

-Failure of concentration of urine

Lithium

- **Renal tubular acidosis**

-Failure of acidification of urine

Acetazolamide /Tetracycline

Lithium/NSAIDs

- Some drugs can cause damage in more than one mechanisms

Ex- ACE inhibitors/Lithium/NSAIDS

Task

- In which ways do the drugs given below cause renal damage?

NSAIDs

Li

ACE inhibitors

- What is meant by the term ‘analgesic nephropathy’?

Risk factors for nephrotoxicity

- **Patient-related factors**

- Age
- Pre-existent renal disease
-Comorbidities (diabetes mellitus,multiple myeloma)
- Dehydraration and volume depletion
- Sepsis, shock

- **drug-related factors**

-Inherent nephrotoxic potential
-Dose
- Duration, frequency
- Repeated exposure

- **drug interactions**

-Combination of nephrotoxic drugs ex-diuretics and aminoglycosides

Drugs affecting kidneys

- Why do drugs affect kidneys?
- What are the mechanisms of damage?
- What types of damage do they cause?
- How to prevent/minimize the damage?

How to prevent?

- Awareness of possible effects & appropriate usage
- Renal function monitoring eg. ACEI, gentamycin
- Adequate hydration
- Therapeutic drug monitoring eg. Gentamycin
- Avoid combining nephrotoxic drugs eg.diuretics and aminoglycosides
- Specific measures
  N-acetylcysteine : to prevent contrast nephropathy
  Allopurinol : to prevent tumour lysis syndrome

Prescribing in renal disease

Why is prescribing in renal disease a problem?

Drugs may

- exacerbate renal disease

- accumulate due to impaired elimination ----increased adverse effects

- be ineffective

Ex-urinary antiseptics (nitrofurantoin)

- have unpredictable absorption ex-due to vomiting

Drugs known to exacerbate renal disease

- Drugs causing hyperkalaemia

  Spironolactone, ACEI, ARB, K^+ salts

- Drugs causing fluid retention

  NSAIDs, steroid

- Drugs causing acidosis

  Metformin : lactic acidosis

Impaired elimination

- Drugs that are potentially toxic and largely eliminated by the kidney ⟶ prolonged half life
  ⟶ cause significant adverse effects

Eg-	normal half life	half life in renal impairment
gentamicin	2.5h	>50h
digoxin	36h	90h

Impaired elimination

- Activity of certain drugs are terminated by metabolism

t1/2 unchanged in renal impairment

However if such drugs produce pharmacologically active metabolites which are eliminated by the kidney » they accumulate in Renal failure » increased adverse effects. ex-warfarin,pethidine ,diazepam

Prescribing in renal disease

- Use reduced dose with close monitoring
- Reduction of dosing frequency
- Alternative drug

Dose reduction

- Loading dose not affected Why?
- Maintenance dose should be reduced