

CARDIOVASCULAR AND RENAL PHARMACOLOGY

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Summary

This chapter discusses the groups of drugs used to treat cardiovascular and renal disease. Firstly, the diuretics (e.g. the thiazides and high ceiling diuretics) and their use in diseases such as hypertension and heart failure are discussed. Secondly, consideration is given to the anti-platelet, anticoagulant and fibrinolytic agents. The antiplatelet drugs (e.g. aspirin, clopidogrel) are used to prevent myocardial infarction and ischemic stroke, the anticoagulants (e.g. heparin, warfarin) are used to prevent the formation of thrombi, and the fibrinolytics (e.g. streptokinase) are used to break down thrombi. Systemic hypertension increases the risk of stroke and coronary artery disease with myocardial infarction and sudden death. Drugs to increase or decrease blood pressure are discussed with most of the emphasis being on drugs to decrease systemic blood pressure (e.g. inhibitors of the renin-angiotensin system, calcium channel blockers, and β -adrenoceptor blockers). The treatments of renal and pulmonary hypertension are also discussed briefly. Drug treatments for attacks of angina pectoris and for preventing angina are covered. This includes the use of nitrates in preventing and treating angina attacks. Drugs, such as the cardiac glycosides, β -adrenoceptor antagonists, ACE inhibitors, AT_1 -receptor antagonists, aldosterone receptor antagonists, which are used in the treatment of heart failure, are included. After, briefly considering the mechanisms of cardiac arrhythmias, the classes of antiarrhythmic drugs are discussed with examples of each class (lignocaine, atenolol, (+)-sotalol, calcium channel blockers, adenosine) and drugs that have multiple actions are also included (e.g. amiodarone). The drugs used in the treatment of hyperlipidemia to prevent atherosclerosis include the statins and fibrates, and these are discussed. Finally, drugs used in the treatment of renal disease are considered.

1. Diuretics

1.1. Introduction

Diuretics are agents that promote the excretion of water from the body. When the water loss is associated with sodium loss the process is known as natriuresis.

The two main therapeutic uses of diuretics are in the treatment of high blood pressure (hypertension) and in the treatment of excessive water retention (edema). In

hypertension, diuretics promote the loss of water from the body, and this leads to a decrease in blood volume, and then to a decrease in blood pressure. Edema is secondary to cardiac, hepatic or renal disorders.

The cardiac disorder most commonly associated with edema is heart failure. In heart failure, both the sympathetic nervous system and the renin-angiotensin-aldosterone systems are activated.

This leads to vasoconstriction, and a decreased glomerular filtration rate. A decreased glomerular filtration rate is associated with increased salt and water retention. This excess water retention is stored in the lungs, causing pulmonary edema, and the breathing difficulties associated with heart failure.

The hepatic disorder most commonly associated with accumulation of fluids is cirrhosis, which (in turn) is most commonly caused by alcoholism. In cirrhosis of the liver, fluid accumulates in the peritoneal cavity, and this condition is known as ascites. Ascites is associated with an overactive renin-angiotensin-aldosterone system.

In this section we discuss the endogenous diuretics and then the other diuretics (osmotic, carbonic anhydrase inhibitors, thiazide diuretics, loop (high ceiling) diuretics, K⁺-sparing diuretics and aldosterone antagonists).

The diuretics most commonly used in the treatment of hypertension are the thiazide diuretics, whereas the loop (high ceiling) diuretics are most commonly used in the treatment of edema. Some of the agents that were originally developed as diuretics for use in hypertension or edema are no longer used for this, but do have other therapeutic uses, and these are discussed.

1.2. Endogenous Diuretics

Atrial natriuretic peptide (ANP) is predominantly derived from the atria of the heart. ANP has natriuretic, diuretic and vasodilator properties. However, ANP has not been shown to be beneficial in either heart or renal failure. Brain natriuretic peptide (BNP) was originally characterized from the brain, but was later shown to be predominantly found in the ventricles of the heart.

BNP is also natriuretic, diuretic and vasodilatory. Intravenous human recombinant BNP, known as **nesiritide**, is used in the treatment of decompensated heart failure to decrease the edema associated with this condition (discussed further in Section 5).

1.3 Diuretics

The diuretics are discussed in the sequence that they act on the kidney nephron, from osmotic diuretics that act on the proximal convoluted tubule to K⁺-sparing diuretics that act on the collecting duct (Figure 1)

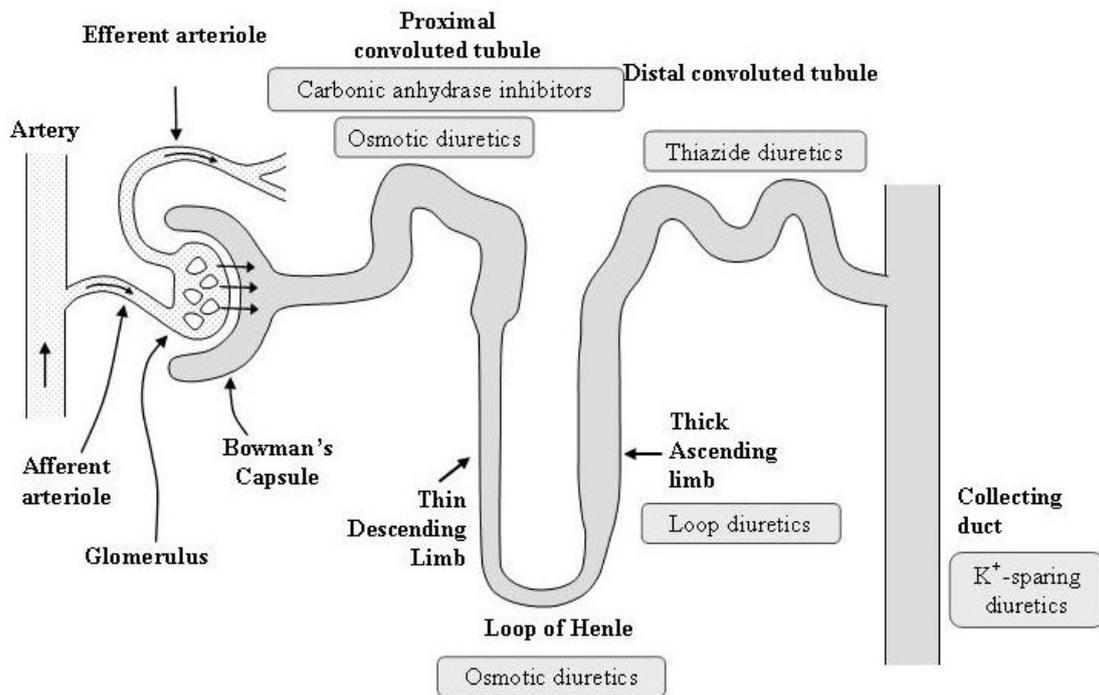


Figure 1. Nephron structure and site of diuretic action

1.3.1. Nephron Structure

The main functions of the kidney include the secretion of waste products (such as urea, uric acid and creatinine), fluid and electrolyte balance and acid-base balance. Approximately 99% of water is reabsorbed from the kidney, and therefore a slight interference with water reabsorption will cause a large increase in the volume of urine. The functional unit of the kidney is the nephron, and there are about one million nephrons in each kidney. Each nephron consists of a glomerulus (which consists of glomerular capillaries and the Bowman's capsule) and the renal tubular network, which is comprised of (in order of flow) the proximal convoluted tubule, the loop of Henle, the distal convoluted tubule and the collecting tubule and duct (Figure 1). Fluid from the glomerular capillaries is filtered into the Bowman's capsule by hydrostatic pressure, removing all proteins and protein-bound substances.

The osmotic diuretics act at the proximal convoluted tubule and the loop of Henle. The carbonic anhydrase inhibitors act on the proximal convoluted tubule, whereas the thiazide diuretics act on the distal convoluted tubule. The loop diuretics are so named because they act on the loop of Henle. The K^+ -sparing diuretics act on the collecting tubule and duct.

1.3.2. Osmotic Diuretics

To act as an osmotic diuretic, an agent has to be freely filterable at the glomerulus, undergo limited reabsorption and be pharmacologically inert. **Mannitol** is an osmotic diuretic. Mannitol is not absorbed from the gastrointestinal tract, and consequently has

to be used intravenously. Mannitol does not cross the blood-brain barrier. Mannitol has an osmotic effect when in the proximal tubule and descending limb of the loop of Henle, and this leads to retention of water (inhibition of water reabsorption) in the kidney tubule.

The osmotic effect of mannitol is useful in preventing acute renal failure. Acute renal failure is associated with some surgery, injury or poisons that reduce glomerular filtration and tubular function. Under these circumstances, the osmotic effect of mannitol maintains tubular function and survival.

The diuretic effect of mannitol is short-lived, making mannitol unsuitable for use in chronic conditions such as hypertension and heart failure. The diuretic effect of mannitol is lost over time as it accumulates in extracellular spaces outside of the brain, and draws water to these spaces. However, this effect of mannitol is useful in conditions where it is necessary to decrease intracranial or intraocular pressure. When intraocular pressure is high (glaucoma) for long periods, irreversible blindness may occur. Mannitol can be used to decrease intracranial pressure in head injury or with brain tumours, or to decrease intraocular pressure in glaucoma.

1.3.3. Carbonic Anhydrase Inhibitors

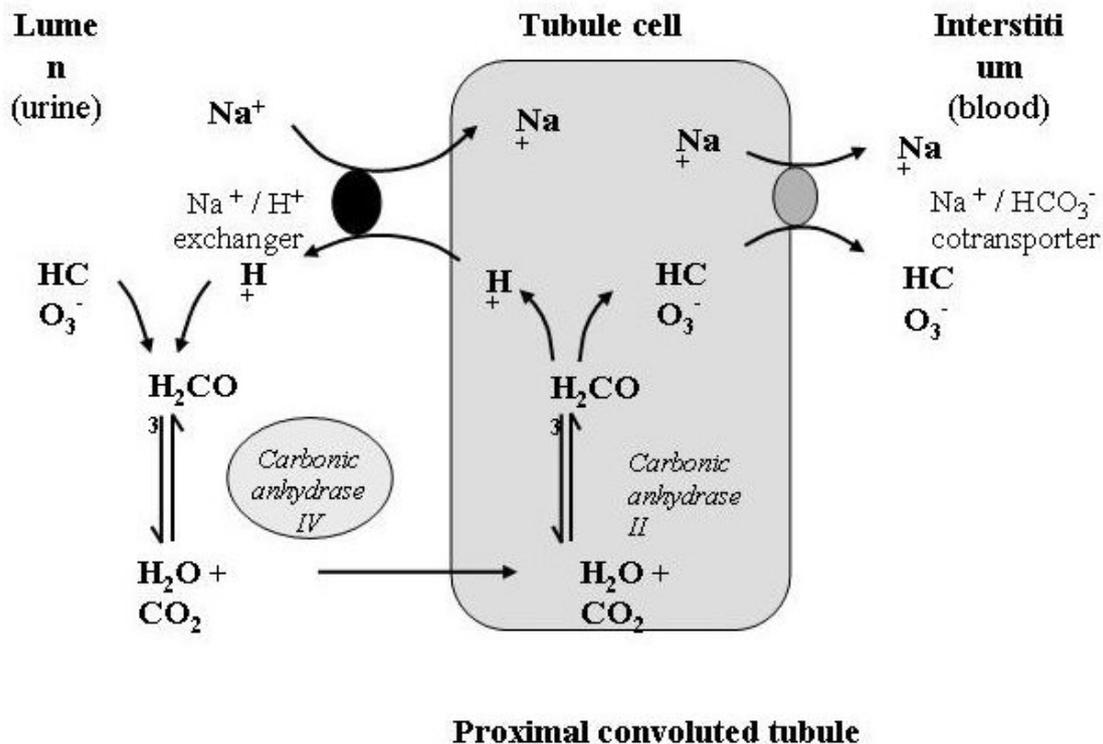


Figure 2. Carbonic anhydrase in the nephron

In the proximal tubule, carbonic anhydrase has an important role in bicarbonate reabsorption (Figure 2). There are several forms of carbonic anhydrase, and in the

kidney, carbonic anhydrase II is cytoplasmic, whereas carbonic anhydrase IV is bound to membrane of the proximal tubule. On the lumen side of the proximal convoluted tubule, there is a Na^+/H^+ exchanger involved in Na^+ reabsorption (Figure 2). On the interstitium side of the proximal tubule, there is a $\text{Na}^+/\text{HCO}_3^-$ cotransporter that is involved in the reabsorption of both Na^+ and HCO_3^- (Figure 2).

Acetazolamide is a carbonic anhydrase inhibitor that was originally developed as a diuretic. The diuretic effect of acetazolamide is short-lived, making it unsuitable for use in chronic conditions such as hypertension or heart failure. When carbonic anhydrase is inhibited, the Na^+/H^+ exchanger and the $\text{Na}^+/\text{HCO}_3^-$ cotransporter are inhibited indirectly, and there is an increased concentration of Na^+ and HCO_3^- remaining in the lumen. Water reabsorption passively follows ionic reabsorption in the proximal convoluted tubule and in the descending limb of the loop of Henle, and therefore when the reabsorption of ions is inhibited, water reabsorption is also inhibited. Thus, short-term acetazolamide is a diuretic, and the diuresis is associated with the loss of bicarbonate. Unfortunately, this loss of bicarbonate leads to a metabolic acidosis, which in turn inhibits the action of carbonic anhydrase inhibitors. Thus, the action of acetazolamide is short-lived, and it is rarely used as a diuretic.

Carbonic anhydrase is also found in the eye, where inhibiting carbonic anhydrase is associated with a decrease in the rate of aqueous humor formation, and a decrease in intraocular pressure. Oral acetazolamide is used in the treatment of glaucoma. Recently, topically acting carbonic anhydrase inhibitors, such as **dorzolamide**, have been developed as anti-glaucoma agents.

1.3.4. Loop Diuretics

The loop (high ceiling) diuretics, which include **furosemide**, **bumetanide** and **ethacrynic acid**, act on the thick ascending limb of the loop of Henle to inhibit the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter (Figure 3). This has two consequences. Firstly, the concentrations of Na^+ , K^+ and Cl^- in the distal tubule are increased, and this inhibits the water reabsorption from the distal tubule to give a diuretic effect. Secondly, there is an indirect effect on the passive reabsorption of water in the descending limb of the loop of Henle. Much of the water reabsorption from the kidney occurs in the descending limb by passive diffusion, and the amount of diffusion depends on the ionic levels of the surrounding interstitium. When the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter is inhibited, there is a decrease in ionic levels in the interstitium. This decreased hypertonicity of the interstitium leads to a decrease in the passive water reabsorption from the descending limb of the loop of Henle. The loop diuretics are the most potent of the diuretics, and this is why they are sometimes referred to as the 'high ceiling' diuretics.

Furosemide (also known as frusemide) is the most common loop diuretic used in therapeutics. Furosemide is readily absorbed from the gastrointestinal tract, and when used orally produces a diuretic effect within 30 minutes. When a faster diuresis is required, it is administered intravenously, and there is diuresis within 2 to 10 minutes. Furosemide is actively secreted into the proximal tubule, and passes along the nephron to the ascending limb of the loop of Henle, where it inhibits the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter. Furosemide is active for 4-8 hours before excretion in the urine.

Furosemide can be used in severe hypertension, but is more commonly used in edematous states such as acute pulmonary edema, the edema associated with heart failure, and ascites associated with hepatic cirrhosis. Furosemide has been used in renal failure, but recent evidence suggests that it has no clinical benefit in the prevention or treatment of acute renal failure.

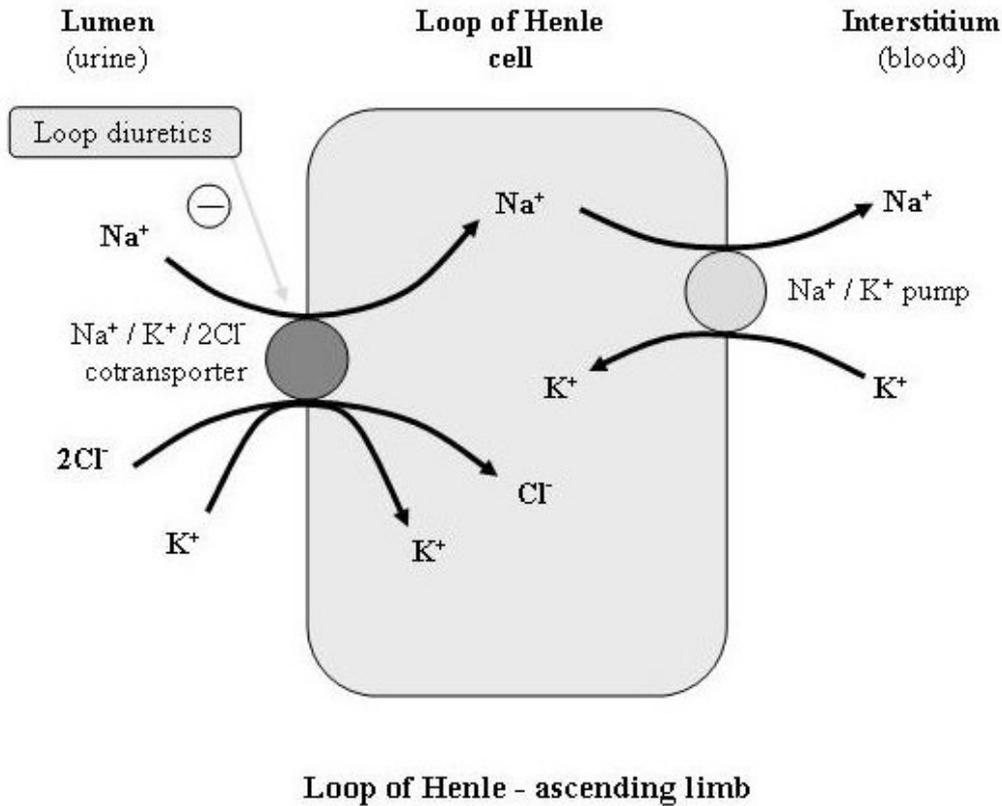


Figure 3. Mechanism of action of loop diuretics

Adverse effects are common with the loop diuretics. They can cause excessive K^+ loss by increasing the volume of luminal fluid and Na^+ in the distal tubule, which in turn promotes the secretion of K^+ into the luminal fluid. Hypokalemia can precipitate cardiac arrhythmias, and may be avoided by the use of K^+ supplements, by eating high K^+ -containing foods such as bananas, and by combining the loop diuretic with a K^+ -sparing diuretic (discussed in the next section). The loop diuretics can also cause hyponatremia and hypotension, due to excessive Na^+ and water excretion. Hypomagnesemia may also occur, and this can precipitate cardiac arrhythmias that can be prevented with magnesium supplements.

Furosemide and uric acid are secreted into the proximal tubule by the same mechanism, and consequently, furosemide can inhibit uric acid secretion and excretion. The accumulation of uric acid may precipitate attacks of gout, especially in those people with a history of gout. Furosemide can also cause ototoxicity, resulting in hearing loss, which is reversible upon cessation of the drug treatment.

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Biographical Sketches

Sheila A Doggrell PhD DSc obtained her degrees from Southampton University in England. The DSc was for excellence in experimental cardiovascular pharmacology research. Sheila has published over a 100 research papers in peer reviewed journals. Much of this research was performed when Sheila was an

academic at the University of Auckland, New Zealand. Sheila used animal models of hypertension and heart failure in her research, and investigated the effects of novel drugs. Sheila has recently moved from preclinical to clinical research, and now studies ways to improve adherence to medicines.

Sheila has worked as a biomedical writer, and is the main author of over 200 articles covering all aspects of pharmacology. These articles are pharmacotherapy reviews, monographs on novel drugs, key paper evaluations, continuing education articles, conference reports, or magazine/newspaper articles.

At the University of Auckland, Sheila taught pharmacology to medical and biomedical students for 20 years. Since then, Sheila has taught pharmacology to medical, allied health students (dentistry, physiotherapy, pharmacy, nursing, midwifery, paramedic) and biomedical science students at universities in Australia (University of Queensland, Charles Darwin University, Monash University, RMIT University) and New Zealand (Auckland University of Technology). Through her biomedical writing, Sheila developed a major interest in clinical trials, and has prepared and taught a Unit on clinical trials at RMIT University. Presently, Sheila is teaching pharmacology to large numbers of allied health students at the Queensland University of Technology.

Julianne Reid completed her PhD in pharmacology at the University of Queensland in Australia, and has held a number of research fellowships at the University of West Virginia in the US, Astra Cardiovascular Research Laboratories in Gothenburg, Sweden and the University of Melbourne. She is currently Professor of Pharmacology at RMIT University in Melbourne, and holds the position of Associate Pro-Vice Chancellor Learning and Teaching in the College of Science, Engineering and Health.

In 2001, Julianne set up a new undergraduate degree program in Pharmaceutical Sciences at RMIT, which is a unique program in Australia focusing specifically on careers in the pharmaceutical industry; the degree includes a one-year industry work placement, and has developed strong links between education and the pharmaceutical industry.

Julianne has been very actively involved with the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, which is the major forum for pharmacology research in Australasia, and has organized a number of national and international symposia and conferences in both education and research. She has been an invited member of the International Union of Pharmacology membership committee and has served as a member of the National Committee in Pharmacology.

Her research interests lie mainly in the area of vascular complications in diabetes mellitus, with particular focus on the role of endothelium-derived factors such as nitric oxide, endothelium-derived hyperpolarizing factor (EDHF) and the endothelins.