Drugs used in the treatment of congestive cardiac failure and angina pectoris

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Several drug classes used in the treatment of congestive cardiac failure or angina pectoris also find use in the treatment of hypertension. These drug classes include the inhibitors of angiotensin-converting enzyme (ACE), the thiazide diuretics, inhibitors of Ca^{2+} influx and antagonists at β-adrenoceptors (*Anaesthesia and Intensive Care Medicine* **7:8:** 298). For these drug classes only detail relevant to the treatment of heart failure or angina pectoris will be provided here.

Congestive cardiac failure

The reduced cardiac output associated with chronic congestive cardiac failure results in low blood perfusion of tissues and organs, making skeletal muscle prone to fatigue. Reduced cardiac output may lower systemic arterial blood pressure, causing activation of baroreceptors, which results in an increase in sympathetic neural discharge. The rate and force of cardiac contraction are increased and regional vasoconstriction occurs, notably in the skin (peripheral cyanosis), the wall of the gastrointestinal tract and the kidney. Reduced blood perfusion of the kidney promotes the release of renin from cells of the juxtaglomerular apparatus. As a result there is increased production of angiotensin II, which induces vasoconstriction both by a direct action on vascular smooth muscle and by promoting the neural release of noradrenaline. Angiotensin II directly stimulates the reabsorption of Na^+ and HCO_3^- from the renal proximal convoluted tubule, and promotes the release of aldosterone from the adrenal cortex. Aldosterone acts on the distal convoluted tubule and the collecting ducts of the kidney to promote the reabsorption of Na^+ and the excretion of K^+ and H^+. The reabsorption of Na^+ is facilitated by the activation of aldosterone receptors on the apical membrane and rapidly activates the Na^+/H^+ exchanger. The effects of the activation of aldosterone receptors located within the cytoplasm of the renal tubular cell take longer to occur because they depend on protein synthesis, including the synthesis of Na^+/K^+-ATPase in the basolateral membrane and the synthesis of a protein that increases the number of Na^+ channels in the apical membrane. Collectively, the actions of aldosterone in the kidney lead to an expansion of the extracellular fluid volume, which, together with venoconstriction, raises the central venous pressure. This results in hepatic and pulmonary congestion and oedema of the lower limbs.

Many of the drugs (e.g. ACE inhibitors and diuretics) used in the treatment of chronic congestive heart failure are directed against the pathophysiological mechanisms (vasoconstriction; fluid retention) that compensate for the reduction in cardiac output. Other drugs (e.g. digoxin) are used to improve cardiac output by increasing the force of cardiac contraction. The principal aims of therapy are to relieve symptoms and to improve life expectancy.

Angiotensin-converting enzyme inhibitors: the ACE inhibitors are used in all grades of heart failure, usually in combination with a diuretic. By blocking the formation of angiotensin II they relax vascular smooth muscle and reduce the release of noradrenaline from sympathetic nerve terminals. As a result arteriolar dilation and venodilation occur, thus reducing cardiac afterload and preload, respectively. By blocking the formation of angiotensin II the ACE inhibitors produce a natriuresis. This results not only from reduced activity of angiotensin II in the proximal convoluted tubule but also from reduced secretion of aldosterone (see above). The ACE inhibitors reduce the symptoms of breathlessness and fatigue in patients with congestive cardiac failure, and several clinical trials have shown that these agents prolong the life of such patients.

By inhibiting aldosterone release the ACE inhibitors promote the retention of K^+. To prevent the development of hyperkalaemia, K^+ supplements or K^+-sparing diuretics should be removed from the treatment regimen before starting a patient on an ACE inhibitor. However, in severe heart failure, spironolactone (a K^+-sparing diuretic) can form a useful addition to a regimen that includes an ACE inhibitor and a loop diuretic (see below). In patients receiving a loop diuretic, the initial administration of an ACE inhibitor can evoke profound hypotension. For this reason a small, initial, test dose given under specialist supervision is advisable.

Thiazide diuretics: In patients with good renal function (creatinine clearance 30 ml/min or greater), the thiazides reduce oedema associated with mild congestive cardiac failure. In patients with poor renal function a loop diuretic is preferred. In some patients with severe congestive cardiac failure oedema may persist despite the use of high-dose loop diuretics. In this circumstance the addition of a thiazide has a synergistic effect. However, combinations of loop diuretics and thiazides may produce metabolic disturbances (e.g. hypokalaemia) and patients receiving these diuretic combinations should be carefully monitored.

Loop (high-ceiling) diuretics: Loop (or high-ceiling) diuretics are used to control oedema associated with congestive cardiac failure particularly when renal function is poor. These agents include furosemide (frusemide), bumetanide and torasemide. The loop diuretics are well absorbed from the gastrointestinal tract. They bind strongly to plasma proteins, and, therefore, do not appear in the glomerular filtrate to any extent. They mainly enter the renal tubular lumen by the process of active secretion in the proximal convoluted tubule. At the luminal membrane of cells of the thick segment of the loop of Henle ascending limb, these agents bind

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to the Cl^- site of the $Na^+/K^+/2Cl^-$ co-transporter and thereby inhibit the reabsorption of Na^+ and Cl^-.

The reabsorption of solutes from the ascending limb of the loop of Henle is an important factor for increasing the tonicity of the interstitial fluid in the renal medulla. The loop diuretics inhibit this process. Nascent urine that is relatively rich in Na^+ and Cl^- passes onwards down the renal tubule. The increased delivery of Na^+ to the renal collecting ducts stimulates the Na^+/K^+ exchange mechanism producing increased K^+ secretion. H^+ secretion is also promoted. The reduced solute concentration in the interstitial fluid of the renal medulla, together with the increased solute concentration in nascent urine, leads to reduced reabsorption of water from the collecting ducts. The net effect is a profuse diuresis in which the urine is rich in Na^+ and K^+.

In addition to their activity on the renal tubule, the loop diuretics have venodilator activity. The mechanism by which these agents cause venodilatation is poorly understood, but may involve either a direct action on the vascular smooth muscle cells or the release of a mediator substance from the kidney. Whatever the underlying mechanism is, the venodilatation precedes the diuretic action. These actions contribute to a lowering of central venous pressure and therefore reduce the signs and symptoms of fluid overload in patients with congestive cardiac failure.

Unwanted effects of the loop diuretics include hypokalaemia, metabolic acidosis, Ca^{2+} and Mg^{2+} depletion and precipitation of gout (caused by competition for the secretion of uric acid in the proximal convoluted tubule). The hypokalaemia induced by loop diuretics also increases the toxicity of digoxin (see below).

Spironolactone is a prodrug that is metabolized both in the wall of the gut and in the liver to form the active principle, canrenone. Canrenone is an antagonist at aldosterone receptors, and hence prevents the Na^+- and water-retaining effects (see above) of aldosterone. In patients prescribed an ACE inhibitor and a loop diuretic for severe heart failure, the addition of the spironolactone to the treatment regimen has been shown to reduce symptoms and mortality. In patients prescribed an ACE inhibitor, reduced production of angiotensin II leads to a fall in plasma aldosterone concentration. However, the plasma aldosterone concentration eventually returns towards the control value despite the continued use of the ACE inhibitor. This phenomenon is known as 'aldosterone escape' and reflects the fact that angiotensin II is not the only regulator of aldosterone release. By blocking aldosterone receptors, spironolactone tends to negate the effects of the 'aldosterone escape' process. By removing the renal effects of aldosterone, spironolactone promotes the loss of Na^+ and water. For the same reason it promotes the retention of K^+ and hence counteracts the K^+-depleting effect of the loop diuretics. Unwanted effects of spironolactone include hyponatraemia, hyperkalaemia, hepatotoxicity, gynaecomastia and menstrual irregularities.

Digoxin (a cardiac glycoside) binds to the extracellular surface of the α-subunit of cell membrane Na^+/K^+-ATPase (Figure 1) and inhibits this transporter. Na^+/K^+-ATPase utilizes the energy derived from the hydrolysis of ATP to transport two K^+ ions into the cardiac muscle cell, whilst extruding three Na^+ ions. The enzyme is thus electrogenic and helps to generate the transmembrane potential of the cell. The activity of Na^+/K^+-ATPase is intimately linked to that of the Na^+/Ca^{2+} antiporter. Na^+ ions extruded by the activity of Na^+/K^+-ATPase are transported back into the cell by the Na^+/Ca^{2+} antiporter. During this process Ca^{2+} is extruded into the extracellular fluid. By regulating the cytosolic concentration of Ca^{2+}, the Na^+/Ca^{2+} antiporter helps to control the content of the intracellular Ca^{2+} store (Figure 1).

Digoxin-induced inhibition of Na^+/K^+-ATPase results in cellular depolarization, increased cytosolic Na^+ and, hence, inhibition

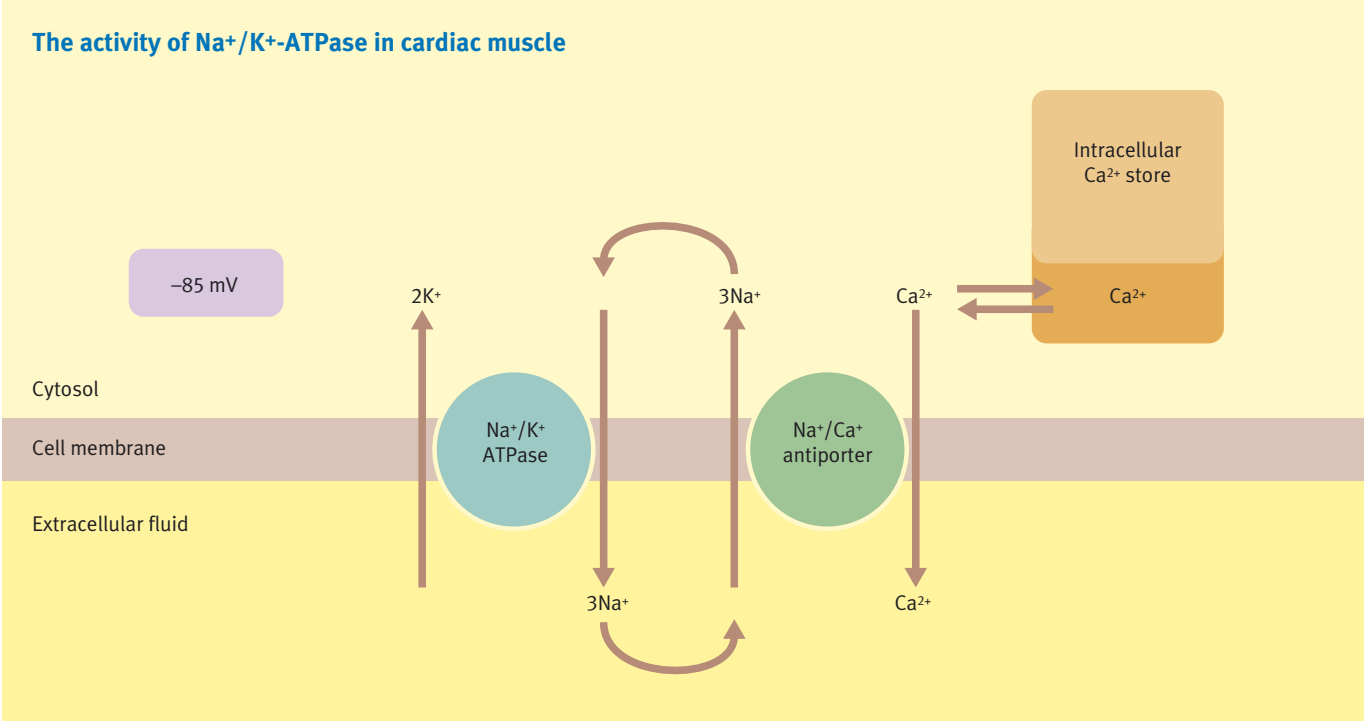

Figure 1