Published online on 10 July 2012 Ann Clin Biochem, doi: 10.1258/acb.2011.011281

Review Article

Diuretics: a review

David Wile

Department of Clinical Biochemistry, University Hospital, Aintree, Longmoor Lane, Liverpool L9 7AL, UK
Corresponding author: Dr David Wile. Email: david.wile@aintree.nhs.uk

Abstract

Diuretics, in one form or another, have been around for centuries and this review sets out to chart their development and clinical use. Starting with the physiology of the kidney, it progresses to explain how diuretics actually work, via symports on the inside of the renal tubules. The different classes of diuretics are characterized, along with their mode of action. The clinical use of diuretics in conditions like congestive cardiac failure and hypertension, as well as some rarer, but clinically important, conditions is then examined. An account is given of the adverse effects of diuretics and how they come about. Common adverse effects like hypokalaemia and hyponatraemia are examined in some detail, and other electrolyte disturbances like hypomagnesaemia also gain a mention. Diuretic use in chronic kidney disease is examined and new guidelines that have been introduced are presented. A section on diuretic abuse is included as this is becoming an all too common clinical scenario, and the sometimes tragic consequences of this abuse are emphasized. Diuretics also find a role in the diagnosis of forms of renal tubular acidosis and this role is explored. Finally, a selection of some of the newer approaches to diuretic therapy are presented, often the consequence of the increasing development of molecular biology, and some of the novel compounds – which may be in drug formularies of the future – are revealed.

Ann Clin Biochem 2012: 1–13. DOI: 10.1258/acb.2011.011281

Introduction

Historical perspective

The word diuretic has a Greek stem, diu (through) *ουρειη* (to urinate),[1] and a diuretic is defined as any substance that increases urine flow and thereby water excretion.[2] Diuretics are among the most commonly used drugs and the majority act by reducing sodium chloride reabsorption at different sites in the nephron (Figure 1), thereby increasing urinary sodium, and consequently, water loss.

Paintings found in the ruins of Pompeii have depictions of grapes, ivy, olives and sweet cherry – all of these have diuretic properties described in the writing of Pliny the Elder (23–79 AD).[3] A treatise published in 1788 by Joseph Plenick (1735–1807) lists several hundred plants, of which 115 have diuretic properties, including garlic, Chinese lantern, saffron, fennel, liquorice, sassafras and dandelion (*Taraxacum officinale*).[4] The latter derives its name from the French 'dent de lion' (tooth of the lion) on account of the shape of its leaves which impart its diuretic property – probably because of that it is commonly called, in French, 'pissenlit', literally 'piss in bed'.[5,6] Its diuretic properties are thought to be due to potash (potassium carbonate, K_2CO_3).[7]

From 1919 until the 1960s, the most effective diuretics, used as the mainstay of treatment, were the mercurials, but they are no longer used because of their toxicity.[8] Other options during this period were osmotic diuretics like urea, mannitol and sucrose, acidifying salts such as ammonium chloride, xanthine derivatives and digoxin, which has a diuretic effect in addition to its inotropic effect.

In 1937, Southworth realized that patients treated with the antibiotic sulphanilamide not only breathed deeply (they developed a mild metabolic acidaemia) but also produced an alkaline urine, with increased sodium and water excretion.[9] Sulphanilamide was found to be a carbonic anhydrase inhibitor[10] and by 1949, Schwartz[11] had successfully treated congestive heart failure patients with sulphanilamide. Karl Beyer, having heard of Schwartz's clinical success, began searching for and testing a range of sulphanilamide-like agents on animals.[12]

Substitution of a carboxy group for the aromatic amino group of sulphanilamide generated carboxybenzenesulphonamide (CBS), also a carbonic anhydrase inhibitor that increased sodium and chloride excretion. Introducing a second sulphamoyl group meta- to the first was found to increase potency, and exploration of substituted disulphamoylbenzene analogues finally led to the discovery of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide (chlorothiazide), the first thiazide diuretic.[13,14] It was because the original compounds were benzothiadiazine derivatives that this class of diuretics became known as

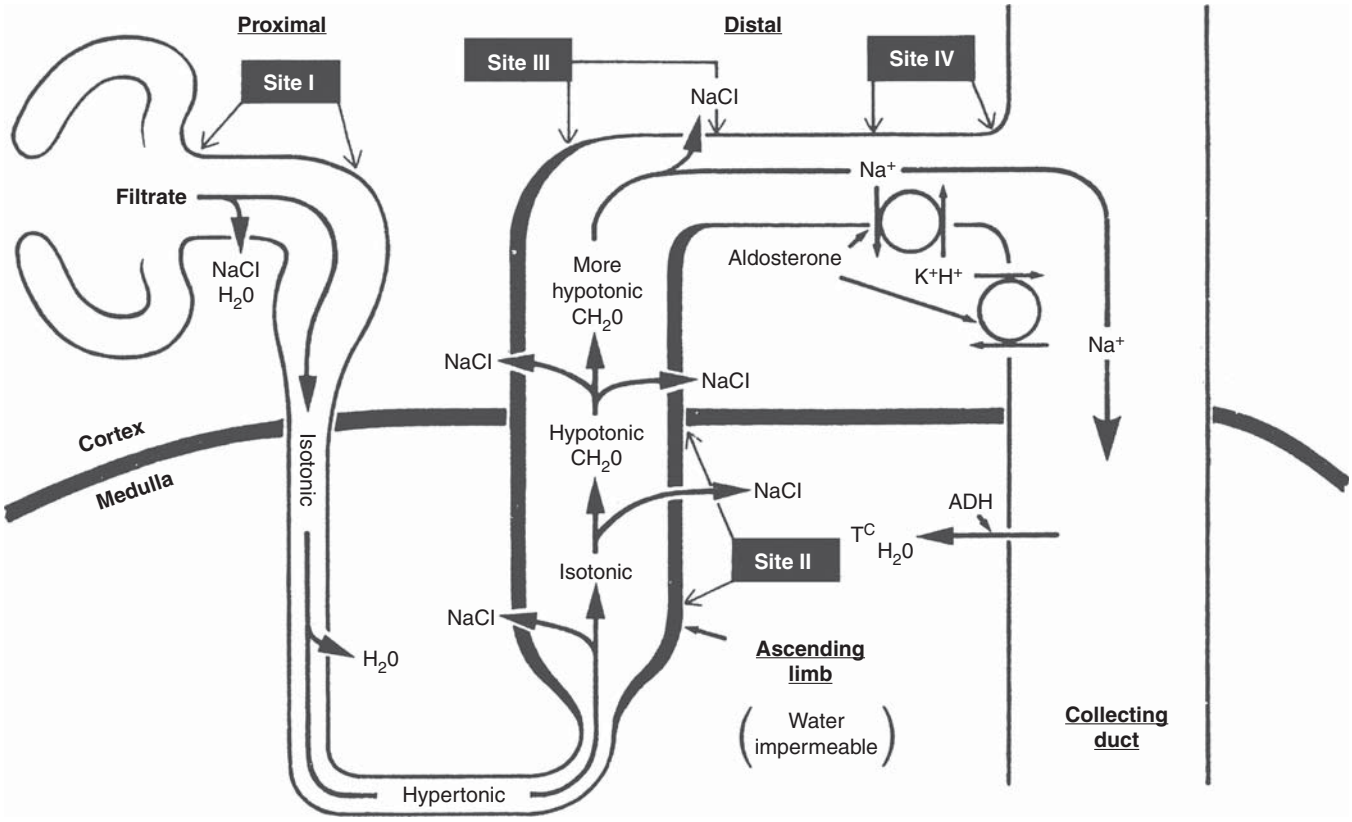


Figure 1 Diagram of the renal tubule showing principal sites of diuretic action. Reproduced from Lant[26] with kind permission from Wolters Kluwer Pharma Solutions

thiazide diuretics. Later compounds that were pharmacologically similar to thiazide diuretics but were not thiazides appeared, and acquired the name 'thiazide-like' diuretics (Figure 2), many being heterocyclic compounds like metolazone.

The British National Formulary (BNF) currently lists 15 individual diuretics available for use in the UK but the original one, chlorothiazide, is not among them, although its derivatives, hydrochlorothiazide and benzothiazide, do feature in combination preparations.[8] They are grouped into familiar categories – thiazides, loop diuretics (also known as high ceiling diuretics), potassium-sparing, osmotic and carbonic anhydrase inhibitors (Table 1). This review elaborates on each of these and some miscellaneous compounds (caffeine, alcohol and water), and finally discusses some exciting recent developments.

Role of the kidney in water homeostasis

Renal tubular reabsorption of filtered water occurs by osmosis, and, since the glomerular filtrate is essentially isosmotic, depends on sodium reabsorption to create an osmotic gradient.[15] After formation of a plasma ultrafiltrate in the glomerulus, the tubular fluid enters the proximal convoluted tubule, where specific transporters reabsorb sodium, chloride, bicarbonate, glucose and amino acids. About 60% of the water and most of the organic solutes are also reabsorbed in the proximal tubule.[16] At the boundary between the inner and outer stripes of the outer medulla, the thin descending limb of the loop of Henlé begins. The thick ascending limb of the loop of Henlé actively reabsorbs sodium and chloride from the lumen (about 35% of the filtered sodium), but unlike the proximal tubule and the descending limb, it is virtually impermeable to water.[17] Sodium chloride reabsorption in the thick ascending limb effectively dilutes the tubular fluid, so this segment is called the 'diluting segment.' The loop of Henlé therefore acts as a countercurrent multiplier producing a gradient of hyperosmolarity in the medullary interstitium. In the distal convoluted tubule, which connects with the diluting segment, around 10% of filtered sodium chloride is reabsorbed. Like the thick ascending limb, the membrane is relatively impermeable to water, so further tubular fluid dilution ensues.[18] The final arbiter of urine composition is the collecting duct, where 2–5% of sodium chloride reabsorption occurs. Importantly, this is where mineralocorticoids exert their influence, especially aldosterone. Sodium is reabsorbed in exchange for potassium under the influence of aldosterone and it is here that almost all diuretic-induced changes in potassium balance occur.

Water is reabsorbed through the action of the posterior pituitary hormone vasopressin (also known as antidiuretic hormone [ADH], although vasopressin is the preferred term) and the final urine to enter the renal pelvis is diluted or concentrated, achieved by the countercurrent mechanism that creates a concentration gradient from 50 mOsm/kg at the outer cortex to 1200 mOsm/kg at the inner medulla.[19,20]

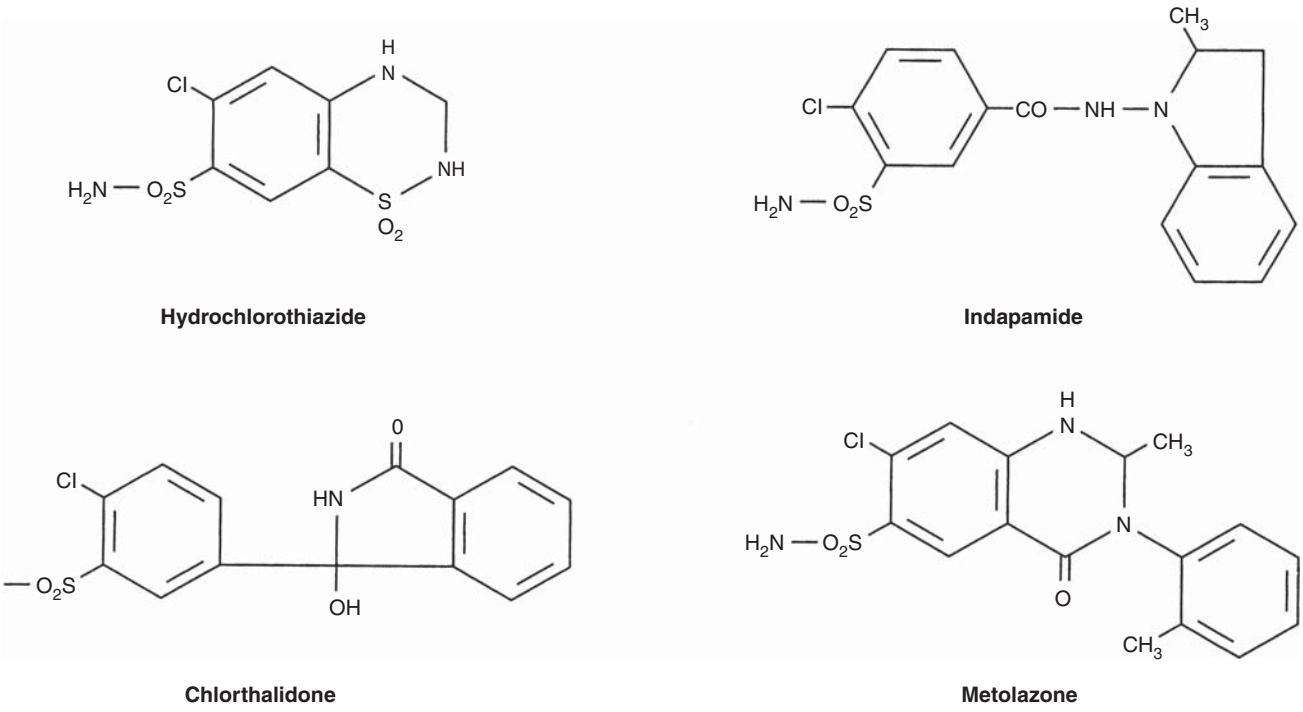


Figure 2 Structures of some 'thiazide-like' diuretics

Transporters

Absolutely germane to the understanding of diuretic action is the concept of transporters. Those that operate by having to bind more than one substance to the transport protein, then facilitating the transport of these substances, together, across the membrane are called symports (or symporters). If they transport only one substance, they are uniports,[21] and others that exchange one substance for another are the antiports. The archetypal antiport is the Na^+–K^+-ATPase, which moves three Na^+ ions out of the cell for each two K^+ ions that it moves into the cell. From the elucidation of these mechanisms, a new and functional classification of diuretics has arisen.

Table 1 Diuretics currently licensed for use in the UK

Class of diuretic	Examples
Thiazides and related diuretics	Bendroflumethiazide Chlorthalidone Cyclopenthiazide Indapamide Metolazone Xipamide
Carbonic anhydrase inhibitors	Acetazolamide
Loop diuretics	Furosemide Bumetanide Torasemide
Osmotic diuretics	Mannitol
Potassium-sparing diuretics	Amiloride Triamterine
Potassium-sparing diuretics and aldosterone antagonists	Spironolactone Eplerenone
Potassium-sparing diuretics with other diuretics	Co-amilozide Co-amilofuse Co-triamterzide

How diuretics work

Most diuretics exert their action by decreasing renal tubular sodium reabsorption, thereby reducing the luminal-cellular osmotic gradient, which limits water reabsorption and results in a diuresis. With the sole exception of spironolactone and its analogue, all the transporters that they inhibit are on the luminal surface of the tubule, so the diuretic agents have to actually 'get there' in order to block the symport or uniport transporter.[22] This means they have to be secreted into the tubular fluid and arrive at their target destination in sufficient concentration to be useful. The process involves facilitated diffusion and in the case of loop diuretics, thiazides and the carbonic anhydrase inhibitor acetazolamide, all of which are acidic, secretion into the tubular fluid, through the organic acid pathway in the proximal tubule. Amiloride and triamterene, being organic bases, enter the tubular lumen via the organic base secretory mechanism, also in the proximal tubule. Spironolactone and other aldosterone antagonists act via a cytosolic receptor and so are delivered to their target area via the blood and the basolateral membrane.

If the diuretic is very highly protein bound (>96%), then glomerular filtration is limited. Even in hypoalbuminuria, there is not enough 'free' drug at one time to get across. Other considerations apply as well and these will be

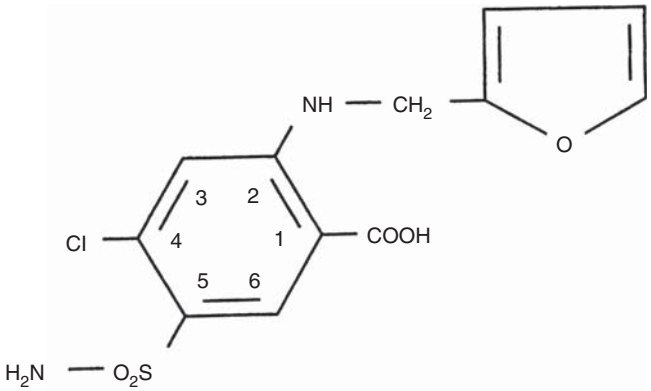
examined separately, with the diuretic or disease that influences it.

Loop diuretics

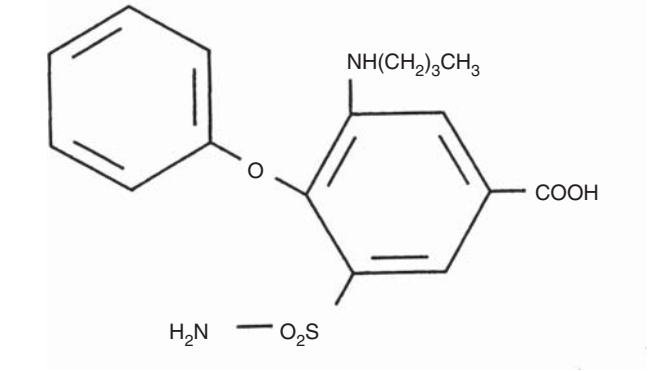
This group of diverse chemical agents (e.g. furosemide and bumetanide) have one common property – they are all inhibitors of the $Na^+K^+-2Cl^-$ symport which transfers ions from the tubular lumen into the tubular cells.[23] The symport is electroneutral and is activated when all four sites are occupied. The Na^+ that has entered the tubular cell is pumped out into the systemic circulation by the Na^+-K^+-ATPase antiport located in the basolateral membrane.[24] By its action, a very favourable electrochemical gradient for Na^+ to enter the cell from the lumen is established because the Na^+ concentration inside the cell is left low. A separate basolateral chloride channel (called CLCN) provides a basolateral exit conduit for Cl^-. The availability of luminal potassium limits activity of the $Na^+K^+-2Cl^-$ symport so potassium entering the cell is recycled by the ROMK (renal outer medullary potassium) channel, which is an ATP-dependent potassium channel in the luminal membrane that not only plays an important role in potassium recycling in the thick ascending limb, but also in potassium secretion in the cortical collecting ducts of the nephron. The depolarization of the basolateral membrane sets up a transepithelial voltage difference (10 mV or so) with the lumen positive compared with the interstitial space. Because of the asymmetrical stoichiometry (3 Na^+ per 2 K^+), this voltage repels cations (Na^+, Ca^{2+} and Mg^{2+}) towards the interstitial space and drives reabsorption of these cations via paracellular paracellin-1. This region (ascending limb of the loop of Henlé) is virtually impermeable to water because unlike the proximal tubule, it does not have water channels (aquaporins, AQPs) which grossly facilitate the movement of water. Therefore, the actions of the symport remove Na^+ and Cl^- but not water, effectively diluting the tubular fluid, to the extent that about 25–35% of filtered sodium is reabsorbed here.

If the $Na^+-K^+-2Cl^-$ symport is blocked, then about 25% of filtered sodium would not be reabsorbed, and would remain in the tubular fluid to be presented to the collecting duct, where, under the influence of aldosterone, some Na^+ would be retrieved – but at the expense of exchange for K^+, which would be lost. The other consequence of jamming this symport would be to reduce, if not abolish, the voltage difference whereby calcium and magnesium are reabsorbed. Blocking this symport would lead to a substantial natriuresis, hyponatraemia, possibly some hypokalaemia, with hypocalcaemia and hypomagnesaemia a distinct possibility.[25]

The mode of action of loop diuretics, e.g. furosemide and bumetanide (Figure 3), is to block the $Na^+-K^+-2Cl^-$ symport (site II, Figure 1), and it is thought that these agents bind the Cl^--binding site that lies within the symporter's transmembrane domain.[26] They owe their designation as loop diuretics to their site of action and they have acquired the synonym 'high ceiling' diuretics because progressive increase in dose is accompanied by an increasing diuresis (actually natriuresis because both water and solute [NaCl] are lost) – they have a high ceiling to their effect. As they block the region of the nephron that has the capacity to reabsorb the most sodium, they are the most potent and effective natriuretic compounds and so have claimed yet a third name – that of 'high efficiency' diuretics.



Furosemide



Bumetanide

Figure 3 Structures of some 'loop diuretics'

These names belie the fact that they come from cosmopolitan background chemistry. Some like furosemide are sulphonamide derivatives, one was a sulphonylurea (torasemide) and the other, no longer in common use, a phenoxyacetic acid derivative, ethacrynic acid. This fell from favour because it had particularly marked side-effects of nausea and ototoxicity, although, unlike the others, it was also uricosuric. Ototoxicity is a general feature, usually dose-dependent, of loop diuretics. A transporter with a chloride channel is present in the inner ear, almost identical to the chloride channel that is part of the $Na^+-K^+-2Cl^-$ symport, which is also blocked by the same inhibitors.

Incidentally, mutations in the gene for the $Na^+-K^+-2Cl^-$ co-transporter, called NKCC2, result in the classic form (there are variants) of a disorder named Bartter's syndrome,[27] the clinical features of which are hypokalaemia, hypercalciuria and metabolic alkalosis, similar to those seen in a patient taking a loop diuretic.

Thiazides and related diuretics

The other major group of diuretics is the thiazide group mentioned earlier and this description includes the thiazide-like diuretics (Figure 2), which are not true benzothiazides but are heterocyclic variants (e.g. metolazone) having the same pharmacological action. Their site of action is the cortical portion of the ascending loop of Henlé and the distal convoluted tubule (site III, Figure 1) where they inhibit sodium and chloride reabsorption by inhibiting the electroneutral Na^+-Cl^- symport located there. They can only act as moderate natriuretics, conspicuously less potent than loop diuretics, because even at maximal doses, they can only inhibit, at most, 3–5% of the filtered sodium present in the tubular fluid. Thiazides are believed to inhibit the Na^+-Cl^- symporter by binding competitively to the chloride binding site.[28]

The Na^+–Cl^- symporter derives its energy from the Na^+-K^+-ATPase antiport in the basolateral (blood side) membrane, which maintains a low sodium concentration, in the tubular cell so there is a favourable electrochemical gradient for Na^+ reabsorption from the lumen, similar to the situation in the $Na^+-K^+-2Cl^-$ symporter (but without the K^+ recycling). The attachment of sodium to its binding site on the Na^+-Cl^- symporter results in an affinity increase for Cl^- to its site on the symporter. Once the Na^+ and Cl^- are both bound, the symporter undergoes a conformational charge that transfers both Na^+ and Cl^- across the luminal membrane.

Although sodium entry into the cell from the tubular lumen is primarily mediated by the Na^+-Cl^- symporter, another mechanism is involved – that of the Na^+-H^+ and $Cl^--HCO_3^-$ parallel exchangers. With the parallel exchangers, the dynamics differ; intracellular water and CO_2 combine to form $H^++HCO_3^-$ ions. The H^+ and HCO_3^- ions are then secreted into the lumen in exchange for Na^+ and Cl^-, respectively. The secreted H^+ and HCO_3^- ions combine within the lumen to form water and CO_2 which can re-enter the cell and repeat the cycle to promote further NaCl reabsorption.

Some of the older thiazides (chlorothiazides but not bendroflumethiazide) can slightly impair sodium transport in the proximal tubule as well; not surprising, when one recalls their developmental history from sulphonamide agents with carbonic anhydrase inhibitor activity. This does not have a noticeable effect on diuresis, because any excess fluid leaving the proximal tubule is retrieved later, in the loop of Henlé (thin limb). Thiazides can also increase potassium and hydrogen ion exchange for sodium in the distal convoluted tubule, resulting in increased excretion of potassium and hydrogen ions. Unsurprisingly therefore, mutations in the Na^+-Cl^- symporter lead to a form of inherited hypokalaemic alkalosis called Gitelman's syndrome.

The distal convoluted tube is also the main site of an effect that is independent of sodium transport – active calcium reabsorption.[29] Thiazides, as well as inhibiting sodium reabsorption in this segment, also increase calcium reabsorption; the exact opposite of loop diuretics in their respective operational segment. This effect can be very useful in patients with recurrent nephrolithiasis arising from hypercalciuria, but a note of caution should be sounded because, while thiazides rarely, if ever, actually cause hypercalcaemia, they can unmask it due to other causes, in particular hyperparathyroidism, malignancy or sarcoidosis.[23]

Potassium-sparing diuretics

In the next nephron segment, the late distal tubule and the collecting duct, there is yet another type of sodium transport mechanism, an ion channel, which used to be called the 'amiloride-inhibitable sodium channel' and the name itself gives a clue as to the type of diuretic involved. They are now referred to as epithelial sodium channels (ENaCs)[30] and are located in the principal cells in the luminal membrane. They are aldosterone-sensitive and are inhibited directly by amiloride and triamterene, but indirectly by spironolactone and eplerenone. The four are known collectively as potassium-sparing diuretics.

The principal cells not only have ENaCs, but also ROMK and water channels (AQP2). Another type of cells, the type A intercalated cells, are the primary sites of proton (H^+) secretion into the lumen, tubular acidification being driven by a proton pump (luminal H^+-ATPase). The ion channels (ENaCs and ROMKs) exclude anions, so the transport of Na^+ or K^+ leads to a net movement of charge across the membrane.

Na^+ enters the cell down the favourable electrochemical gradient created by the basolaterally sited Na^+–K^+-ATPase antiport. The driving force for Na^+ entry is therefore considerably greater than the exit force for K^+ and the result is the generation of a lumen negative transepithelial voltage difference of some 10–50 mV. It is this voltage that provides the motive force for K^+ to enter the lumen via the ROMK channels. It is also this voltage difference across the epithelium that (partly) affects H^+ secretion into the lumen via the proton pump. Thus both K^+ and H^+ can enter the lumen.

There is therefore a crucially important relationship between the amount of sodium arriving at the collecting duct and the consequent secretion of potassium destined to leave it in the urine. Any diuretic that acts upstream from the collecting duct (loop diuretic, thiazide or carbonic anhydrase inhibitor) will cause increased (loop most, thiazide moderate, carbonic anhydrase least) delivery of sodium to the collecting duct. If it arrives with an anion that cannot be as easily reabsorbed as chloride (e.g. HCO_3^-), then the resulting lumen negative potential will be greater, and as a consequence more K^+ secretion will ensue. Add to this mechanism the increased aldosterone secretion from volume depletion activation of the renin–angiotensin–aldosterone system, and we have an explanation for virtually all the diuretic-induced potassium loss, leading to hypokalaemia and its associated metabolic alkalosis. Conversely, inhibition of sodium reabsorption in this nephron segment will inevitably result in hyperkalaemia and metabolic acidosis, the products of coexisting reductions in K^+ and H^+ excretion.[29]

Amiloride, a pyrazinoylguanidine derivative,[23] and triamterene, a pteridine (Figure 4), act at site IV (Figure 1) to decrease the number of open ENaCs. Spironolactone, a 17-spirolactone (Figure 4), is a synthetic steroid that is an aldosterone competitive antagonist. Eplerenone is an analogue of spironolactone with improved aldosterone receptor selectivity. The steroid structure of spironolactone means that it has the potential to cause gynaecomastia and hirsutism among other 'steroid' effects. The aldosterone receptor is cytosolic and is a member of a superfamily of receptors for steroid hormones, retinoids, vitamin D and thyroid hormones. Epithelial collecting duct cells contain mineralocorticoid receptors with high aldosterone affinity. Very importantly, in diuretic terms, aldosterone gets to its receptor from the blood via the basolateral membrane and binds to hormone-sensitive elements (sections of DNA). The complex reaches the nucleus and modulates production of aldosterone-induced proteins (AIPS) and these are believed to activate 'silent' ENaCs.[23]

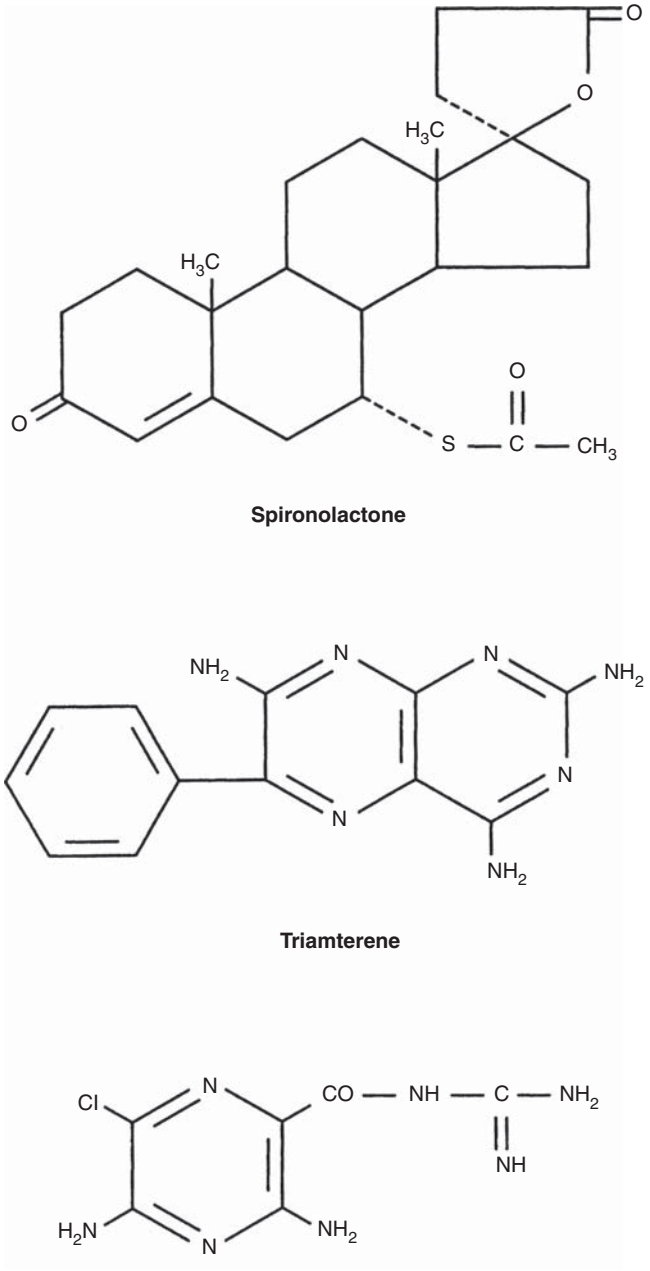


Figure 4 Structures of some diuretics acting at the distal tubule

The effect of spironolactone on aldosterone classifies it as an aldosterone antagonist. The potassium-sparing diuretics are very weak natriuretics indeed, capable of a maximum excretion of 1–2% of filtered sodium.[29] Their main use is in combination with a loop or thiazide diuretic to minimize potassium loss, although the aldosterone antagonists have some special uses in other clinical settings.

Although not generally regarded as diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists promote renal excretion of sodium and water by blocking the effects of angiotensin II in the kidney and by reducing aldosterone secretion.

ENaCs are comprised of three subunits encoded by three different genes.[30] The α subunit transports Na^+, while the β and γ subunits enhance Na^+ transport by the α subunit. Mutations in the β subunit (and less commonly the γ subunit) cause them to 'activate' and become functional, leading to sodium retention and hypertension in an autosomal dominant disorder, Liddle's syndrome.[31]

Carbonic anhydrase inhibitors

The use of the bacteriostatic agents, sulphonamides, led to the realization that they caused an alkaline diuresis with hyperchloraemic metabolic acidaemia. Vast numbers of sulphonamides were synthesized and tested for their inhibition of carbonic anhydrase and now only one survives in clinical use – acetazolamide.

The discovery of carbonic anhydrase in the kidney was made in 1941 by Davenport and Wilhelmi, and it is now known to be a zinc metalloenzyme found in large amounts in the luminal and basolateral membranes of the proximal tubule, either fixed to the membrane by a glycophosphatidylinositol anchor (similar to bone alkaline phosphatase) as the type IV enzyme or free in the cytoplasm as the type II enzyme.[32] The reaction between water and CO_2 is a slow process, but under the influence of carbonic anhydrase, it is speeded up several thousand-fold.

By non-competitively inhibiting carbonic anhydrase ($H_2O + CO_2 \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$) in the proximal tubule (site I in Figure 1), acetazolamide decreases the availability of H^+ for the $Na^+ - H^+$ exchanger so that not only the Na^+ reabsorption is reduced, but there is impaired neutralization of luminal HCO_3^- and increased Cl^- reabsorption resulting in an alkaline diuresis and the development of a hyperchloraemic (normal anion gap) acidaemia.[33] The diuresis produced is minimal, partly because tubular fluid leaving the proximal tubule gets reclaimed further down the nephron, and partly because the developing metabolic acidaemia self-curtails the diuretic action. Acetazolamide can be given orally or intravenous and its effect lasts about 12 h, since tolerance is induced by respiratory compensation for the metabolic acidaemia.

Acetazolamide finds a use in the management of glaucoma by reducing intraocular pressure because aqueous humour is bicarbonate-rich (carbonic anhydrase in the ciliary processes) and acetazolamide inhibits its production. It can alkalinize urine, which aids removal of weak acids like uric acid and cystine, and most importantly can be used to treat oedematous patients with metabolic alkalosis, the urinary excretion of bicarbonate tending to restore acid–base balance. It has also been used to treat familial periodic paralysis and to enhance ventilation in case of altitude sickness. In familial periodic paralysis, there is a sudden drop in serum potassium due to its exchange with sodium in cells, an effect countered by the rise in H^+ in serum generated by acetazolamide, allowing sodium ions to exchange for H^+ rather than potassium ions. Side-effects are few: bone marrow suppression, allergic reactions (rashes) and interstitial nephritis are the main ones.[34]

Osmotic diuretics

Urea, isosorbide, glycerin and mannitol all have been used in the past.[35] Mannitol is the only one that remains in current clinical use and appears in the BNF as a 10% or 20% solution for intravenous use. Mannitol is a polyalcohol which is filtered by the glomerulus and not reabsorbed by the nephron. It therefore increases the tubular fluid osmolality, which decreases water reabsorption.[36] All osmotic diuretics, including mannitol, exert their effect at nephron sites which have AQP water channels. Mannitol acts at the proximal tubule and thin descending limb of the loop of Henlé, both sites of AQP1 channels.

Intravenous administration causes water to move from the intracellular to the extracellular compartment, which raises plasma and consequently tubular fluid osmolality.[36] The lower gradient in osmolality between the tubular cells and lumen impairs water reabsorption, resulting in water diuresis and hypernatraemia.[37] Unlike any of the other diuretics, mannitol produces a water diuresis rather than a natriuresis; water being lost over and above sodium and potassium. In patients with renal failure though, mannitol may be retained and substantially increase the plasma osmolality when water will leave cells, drawn by the osmotic gradient created and cause a dilutional hyponatraemia; the physician needs to be aware of this and treat the hyperosmolality and not the hyponatraemia.[38]

One of the most common uses of mannitol is its short-term use to decrease brain bulk and cerebrospinal fluid production as a means of lowering intracranial pressure.[39] Following crush injuries, or after cardiac and major vascular surgery, it can be used in an effort to minimize the acute decrease in glomerular filtration rate (GFR) that accompanies acute tubular necrosis predisposing to acute renal failure.

Miscellaneous diuretics

Both ethanol and water can be counted as diuretics, using the broad definition given earlier. The main function of the posterior pituitary hormone vasopressin (ADH) is water conservation, so if vasopressin is inhibited, or its secretion inhibited, then a diuresis results. Both ethanol and water are inhibitors of vasopressin secretion and so act as diuretics. Vasopressin acts on either a V_1 or a V_2 receptor, with action on the latter resulting in rapid activation of the $Na^+-K^+-2Cl^-$ symporter in the thick ascending limb of the loop of Henlé, along with rapid insertion of prefabricated AQP2 water channels into the apical membrane of the principal cells of the collecting duct.

Both theophylline and caffeine are methylxanthines, caffeine being 1,3,7-trimethylxanthine. They cause an increase in GFR by smooth muscle relaxation in the afferent arteriolar bed of the glomerulus, and probably a direct effect inhibiting salt reabsorption in the proximal tubule.[40]

Clinical uses of diuretics

Which diuretic, for which patient and why

Diuretics are used in conditions where there is oedema and those which are non-oedematous. A detailed description of the pathogenesis of oedema is not appropriate here, but an overview to be commended is that of Morrison.[41] Oedema occurs in heart failure, renal failure, the nephrotic syndrome and with ascites in hepatic cirrhosis. The non-oedematous states include hypertension, nephrolithiasis, hypercalcaemia and diabetes insipidus. The choice of diuretic for each one depends on the combination of factors in the patient (a patient with heart failure may also have chronic kidney disease), the efficacy, the speed of onset of action, the metabolism and side-effects of the agent considered.

One cannot rely on chemical grouping as a guide (as one can with oral hypoglycaemic agents), as reference to Figures 2 and 3 helps illustrate. There are three groups of sulphonamide-containing diuretics – with totally dissimilar renal pharmacologies. There is the carbonic anhydrase inhibitor, acetazolamide, the benzothiadiazines and the sulphamoyl benzoates. The prototype of these is furosemide (discovered in 1964), being chemically 4-chloro-*N*-furfuryl-5-sulphamoyl anthranilic acid. Referring to Figure 3, one sees the 4-chloro-5-sulphamoyl substitution of the benzene ring in furosemide as reflecting a thiazide, but the presence of the monocyclic system with a furfuryl substitution at position 2 confers the 'high ceiling' activity of a loop diuretic, not a thiazide.

The introduction of a phenoxy group at position 4 with a butylamino substitution at position 3 produced bumetanide, an agent that is on a weight basis 40 times more potent than furosemide, with absorption approaching 100% (80–100%). On average, the amount of furosemide absorbed is 50%, but this ranges from 10% to 100%, making it difficult to predict in an individual patient how much furosemide will be absorbed. About 50% of a dose of furosemide is excreted, unchanged, in the urine, the other 50% being conjugated to glucuronic acid in the kidney. Thus, in patients with renal insufficiency, the half-life of furosemide is lengthened by a decrease in urinary excretion and also in renal conjugation.

Bumetanide and torasemide are mostly hepatically metabolized (50% and 80%, respectively), so in renal

insufficiency their half-lives are little altered. Conversely, in liver disease, the half-lives of both drugs will be prolonged and more drugs will be available to the tubular fluid, thereby increasing potency.

The kaliuretic potency of bumetanide is 20 times greater than that of furosemide on a weight basis and so is claimed to be more 'potassium-sparing'. There is also some evidence that it is likely to impair glucose tolerance and lead to retention of urate.

It should now become clear that not all diuretics within a classification category are necessarily very similar and that the differences relate to their varied chemistry.

Diuretics are commonly used to treat hypertension, but their effectiveness does not always relate to their diuretic effect. For example, thiazides work in hypertension[42] by lowering peripheral vascular resistance over time,[43] and because of this, they tend to be the preferred choice in this condition. Those patients with mild congestive heart failure, associated with mild oedema, are also suitable candidates for thiazides, but most will require a loop diuretic, although the rate of absorption of loop diuretics is slower in patients with severe heart failure. The maximum response will not occur for four hours or more after the dose.[44]

Use of diuretics is not devoid of risks, with many side-effects being well recognized; however, some are less well known. Bendroflumethiazide is known to cause calcium retention, so care should be exercised when bendroflumethiazide is co-prescribed with either vitamin D or calcium supplements, and it is generally recommended that the dose of calcium or vitamin D supplement is reduced by 50%.

Inhibition of distal sodium reabsorption may lead to some compensatory increase in proximal tubular reabsorption. This is of relevance in patients receiving lithium therapy since lithium shares the same reabsoptive pathway as sodium in this region of the nephron. Hence, distally acting diuretics (such as thiazides and spironolactone) stimulate proximal tubular reabsorption of lithium and the risk of toxicity.[45] Furosemide does not seem to be associated with such enhanced reabsorption. Similarly, furosemide can be used in the treatment of hypercalcaemia as it increases urinary calcium excretion, whereas thiazides cause urinary calcium retention and can therefore cause hypercalcaemia.

In the years since diuretics have been used to treat hypertension, it has been recognized that lower doses than originally used can be effective at providing good blood pressure control, with consequently fewer side-effects.[46] For example, bendroflumethiazide is used at a dose of 2.5 mg/d, the previously used 5 mg dose affording no better blood pressure control and contributing to reduced glucose tolerance and hyperlipidaemia, especially hypertriglyceridaemia. It has long been acknowledged that thiazides could worsen diabetes in established diabetic patients, but their role in provoking glucose intolerance in previously glucose-tolerant patients remained controversial until, in 1982, Murphy *et al.*[47] published their findings in the *Lancet*, demonstrating that stopping the thiazide (after 14 years of treatment) improved glucose tolerance.

Hypertension is conventionally thought of as being systemic hypertension, but diuretics, particularly the carbonic anhydrase inhibitor acetazolamide, are used to treat an uncommon form – that of idiopathic intracranial hypertension.[48] This is often a chronic condition characterized by symptoms and signs of intracranial hypertension (where the cerebrospinal fluid is normal and no cause is identified by imaging), but where vision can be lost from papilloedema; depression and difficult to treat headaches are common. It is said to occur in around 20 per 100,000 obese women and the rational for using acetazolamide is thought to be the reduction of the formation of cerebrospinal fluid.[49] A randomized placebo-controlled study to address the role of acetazolamide is currently being undertaken in the USA.[48] Carbonic anhydrase is found not only in the proximal tubule but also the central nervous system, and common adverse effects are hyperchloraemic metabolic acidosis (with a normal anion gap) and nephrolithiasis, probably because the metabolic acidosis produces a low urine citrate and so the calcium is in a less soluble form. Acetazolamide also finds a use in periodic paralysis; the acetazolamide-generated rise in serum hydrogen ion concentration offers an alternative cation to potassium with which sodium can exchange.[50] The BNF lists the diuretics currently available in the UK along with their licensed indications, contraindications and side-effects, as well as their recommended doses. These are shown in Table 1.

Indipamide, xipamide and metolazone are structurally related to furosemide, although they are thiazide diuretics by class, and consequently their actions differ from those of the other thiazide diuretics.

Indapamide, for example, in very low doses has little diuretic effect and is a weak diuretic, but reduces vascular tone and lowers blood pressure effectively.[51] It has a marked influence on the serum concentrations of potassium, glucose, lipoproteins and, significantly, urate.

Xipamide[52] is chemically related to salicylic acid, and although it has a powerful diuretic action similar to that of furosemide, its onset of action (about 1 h) and duration of action (often in excess of 12 h) are more akin to hydrochlorthiazide, which is a medium-acting thiazide. Its long duration of action can prove troublesome for elderly recipients, and serum potassium concentrations as low as 2.2 mmol/L have been encountered with its long-term use. Regular serum potassium measurements are therefore needed.

Metolazone belongs to the chemical class of quinazoline sulphonamides and can initiate diuresis within an hour of oral administration.[53] In patients with renal impairment, it can generate an effective diuresis, and has been used in combination with furosemide when 'furosemide resistance' has been encountered. The BNF therefore includes a statement 'also profound diuresis on concomitant administration with furosemide (monitor patient carefully)'.[8]

Torasemide differs from furosemide in that it is approximately twice as potent and has a somewhat longer duration of action, which facilitates once daily dose. This effectively does away with the paradoxical antidiuresis that is now and again encountered with furosemide. Additionally, its effect on potassium and calcium excretion is less marked.[54]

The BNF also includes an unusual (and unlicensed) application for acetazolamide – that of prophylaxis against mountain sickness (although it does stress that it is not a

substitute for acclimatization).[8] High altitude mountain sickness occurs over 3000 m, and is more likely if the ascent has been too rapid. The cause of the symptoms is hypoxia. The normal response to decreasing levels of oxygen tension is hyperventilation, but this is inhibited as alkalosis develops. The acetazolamide-induced metabolic acidosis increases respiratory drive, which helps to maintain the arterial oxygen saturation. This is particularly relevant at night; the time when (undesirable) attacks of apnoea have occurred. In particular, unpleasant (and hazardous) symptoms not only include lassitude and nausea, but also cerebral and pulmonary oedema.[50]

Fluid retention resulting in peripheral oedema and dyspnoea are cardinal features of the progressive stages of congestive cardiac failure, often referred to as chronic heart failure. Diuretics find their major role in the management of this condition. Peripheral (ankle) oedema is not always associated with chronic heart failure as it occurs in nephrotic syndrome (discussed later).

The term heart failure embraces two separate but associated conditions, namely heart failure with preserved ejection fraction and heart failure due to left ventricular systolic dysfunction. It is crucial to distinguish heart failure with low ejection fraction from that with preserved ejection fraction because most high-quality evidence on treatment is for patients with low ejection fraction.[55] Heart failure affects around 900,000 people in the UK, and is likely to become even more common as prognosis continues to improve for ischaemic heart disease (the major cause of heart failure) and an ever-increasing ageing population.[55] Heart failure symptoms are classified according to the New York Heart Association Classification (NYHA).

Fluid retention may be present in patients who have dyspnoea, an increase in weight of more than 2 kg from baseline in less than three days, raised jugular venous pressure, hepatomegaly, crepitations on chest auscultation or signs of peripheral oedema.

In 2003, the National Institute for Health and Clinical Excellence (NICE) produced guidelines for the diagnosis and management of heart failure, and other studies have suggested that diuretics should be considered for patients with heart failure who have dyspnoea or ankle or pulmonary oedema. They should be given at the same time, or before ACE inhibitors, and both should precede the start of β-blockers.[56] Although there is no obvious evidence that they positively influence mortality, diuretics are used on an individual basis to reduce fluid retention.[56] Over-treatment can lead to dehydration as well as renal dysfunction, particularly with loop diuretics.

Bumetanide, furosemide and torasemide (all loop diuretics) are all used and if pulmonary or ankle oedema persists, then the addition of a thiazide, metolazone or potassium-sparing diuretic-like spironolactone can be extremely useful. The different diuretic classes, acting as they do on different parts of the nephron, are thought to have an additive effect.[56] It is important to monitor electrolytes, especially at the outset of treatment. Elderly patients can find some side-effects (e.g. frequent micturition) distressing and as long as their symptoms remain stable (and on ACE inhibitors and β-blockers), then consideration can be given to lowering the dose of loop diuretic, changing solely to a thiazide, or even stopping diuretics altogether. In patients with heart failure associated with a low ejection fraction classified as having NYHA class III or IV, an aldosterone antagonist like spironolactone can be life-saving.[57] Hyperkalaemia should be looked for, especially when starting the drug, and this is more likely if the patient is also on an ACE inhibitor. Doses of spironolactone more than 25 mg/d should be used judiciously.

The NICE guidance for heart failure has been updated since 2003, and a summary appeared in the *British Medical Journal* in August 2010.[55] In it, as a new recommendation, an aldosterone antagonist (licensed for heart failure) is recommended if the patient has had a myocardial infarction within the past month. The new guidelines recommend the measurement of serum brain natriuretic peptides (BNP), suggesting that levels of BNP below 29 pmol/L or N-terminal proBNP below 47 pmol/L make a diagnosis of heart failure unlikely in an untreated patient. They point out, significantly, that treatment with diuretics including aldosterone antagonists may reduce serum natriuretic peptides, as indeed can obesity. In humans, atrial natriuretic peptide (ANP) acts as a diuretic and is cleared by neutral endopeptidase (NEP) in the kidney and elsewhere, as is BNP. Administration of ANP and BNP to patients with congestive cardiac failure produced a beneficial response including diuresis, improved haemodynamic parameters and suppression of the renin–angiotensin–aldosterone system.[58] As a result, candoxatril, a neuroendopeptidase inhibitor, was developed but was associated with raised endothelin concentration, the most potent vasoconstrictor peptide (NEP is not specific for natriuretic peptides) and subsequently withdrawn. The concept of 'nature's own diuretic' remains an area of research interest.[59]

Not surprisingly, in the 21st century, there are examples of molecular genetics starting to impact on the arena of diuretics. A recombinant form of BNP having the same 32 amino acid residue sequence as the endogenous peptide is now available. Called nesiritide, it is used intravenously in acute decompensated heart failure and has a mean terminal elimination half-life of 18 min. Interestingly, it can reduce serum endothelin concentration (which may be elevated in heart failure) from baseline.[60]

Other conditions in which diuretics are significantly involved in management are nephrotic syndrome, cirrhosis and, somewhat controversially, acute kidney injury. First in nephrotic syndrome, almost by definition, there exists a low serum albumin concentration, which encourages diffusion of the diuretic into the extracellular space, as they are usually bound to albumin. This means that less diuretic enters the renal tubule where it exerts its pharmacological effect (see earlier). To make matters worse, the high concentration of albumin in the tubule then binds free drug that has been secreted, rendering it inactive. Diuretic response, therefore in patients with nephrotic syndrome is suboptimal by about 50%.[22] If the hypoalbuminaemia is very marked (below 20 g/L), then infusions of albumin along with furosemide can lead to an increase in sodium excretion, having partly overcome what is a form of 'diuretic resistance'.

Many cirrhotic patients develop oedema, which is mediated through the secondary hyperaldosteronism that develops. The result is sodium and water retention, leading to oedema.[56] To combat this, the only useful diuretic is the aldosterone antagonist, spironolactone, which is more effective than loop diuretics partly not only because of its antagonism to the raised aldosterone, but also because it is far less likely to engender hypokalaemia which may precipitate hepatic encephalopathy.[61] Spironolactone is not as aggressive a diuretic as furosemide, which in cirrhosis patients is quite helpful since a massive diuresis can easily upset intravascular volume status. If spironolactone alone is not effective, then a thiazide can be added. However, for reasons that are not entirely clear, responses to loop diuretics in cirrhosis are often attenuated.[62] Lastly, as described in the physiology section of this review, spironolactone possesses one other special, and useful, property. It does not have to enter the tubular fluid in order to exert its action, as it gains tubular cell entry from the plasma by crossing the basolateral membrane before competing with aldosterone for its cytosolic receptor.

The Acute Kidney Injury Network (AKIN) is an interdisciplinary and international consensus panel, which has classified acute kidney injury (AKI) according to the RIFLE criteria (risk, injury, failure, loss and end stage kidney disease) based on changes in baseline serum creatinine or urine output. Logically, one might think of using diuretics to maintain or even increase urine flow. The concept of flushing away debris such as denuded epithelium with the avoidance of tubular obstruction and glomerular filtrate back leak is appealing. However, a systemic review of the literature undertaken by Karajala *et al*.[63] concluded that diuretics do not work in AKI. The review expounds some putative explanations centering around reduction in GFR and loop diuretic-induced renin release, including a decrease in renal perfusion pressure. The upshot is that mannitol can cause more harm, and induce nephropathy, and even nesiritide did not improve renal function in patients with decompensated heart failure and mild chronic renal insufficiency. However, it is acknowledged that nesiritide may be effective in the prevention of AKI when applied in lower doses for a prolonged time in patients with mild to moderate renal insufficiency.[63] In conclusion 'diuretics have been shown to be ineffective in the prevention of AKI or for improving outcome once AKI occurs: at best, diuretics can help decrease symptoms of pulmonary oedema secondary to volume overload'.[63] AKI that occurs perioperatively is associated with potentially serious consequences, and current advice on the use of diuretics is that in fluid-overloaded patients, loop diuretics may have a limited role. The decision to deploy them should be undertaken in consultation with a nephrologist because they will not prevent AKI and are, in high doses, associated with a risk of death and impaired renal function that does not recover, as well as possibly causing tinnitus.[64] The non-recovery may relate to more severe renal impairment with consequent resistance to the effects of the loop diuretics since they have to gain entry to the tubular fluid in order to reach their respective symports and deliver their pharmacological benefits.

The situation is considerably different when considering chronic kidney disease (CKD). Patients with CKD will frequently need a diuretic as part of the management of their other co-morbidities, hypertension and heart failure. Although a proportion of patients with CKD derive clear benefit from a combination of ACE inhibitors and spironolactone, potentially fatal hyperkalaemia often develops. In advanced CKD, such a combination mandates use with extreme caution.[65] Amiloride and triamterene also pose a hyperkalaemic risk and are to be avoided completely in advanced CKD.[66]

Acetazolamide requires a dose reduction in CKD stages 2 and 3, and should be avoided altogether in CKD stages 4 and 5 because of the high risk of acidosis and its poor efficacy in advanced CKD.[67] Thiazides take longer to clear in CKD and are not very effective in advanced CKD (they need to penetrate the nephron lumen) and, as with loop diuretics which also display reduced clearance,[68] doses need to be increased. Decreased fractional delivery of drug to the lumen results in resistance especially to loop diuretics.[69] There is an additional risk of ototoxicity with loop diuretics in CKD due to the higher doses needed and the reduced clearance. The risk of ototoxicity is likely to be worse if the patient is also in receipt of an aminoglycoside group antibiotic.[70]

Biochemical disturbances due to diuretics

The use of diuretics is not without its metabolic hazards as has been alluded to throughout the preceding sections. Table 2 lists the common metabolic complications of diuretic use.

Hyponatraemia is common, made worse by patients who drink copious volumes of water as a result of being on the diuretic in the first place. Distinguishing hyponatraemia in patients without oedema from those with oedema is an important clinical distinction. In those with heart failure, nephrotic syndrome and cirrhosis, salt and water intake should be restricted as they are more likely to have expansion of their extracellular fluid volume. The mechanism was described earlier.

Although the potassium-sparing diuretics can cause hyperkalaemia, this is more likely if used in conjunction with an ACE inhibitor or angiotensin II receptor antagonist. The same can apply to the concomitant use of potassium supplements and non-steroidal anti-inflammatory drugs (NSAIDs). These latter two are particularly important,

Table 2 Metabolic complications of diuretics

Hyponatraemia (especially with thiazides)
Hypokalaemia
Hyperkalaemia
Volume depletion
Metabolic alkalosis
Hypomagnesaemia
Hyperuricaemia
Increased urea and creatinine
Hyperkalaemia and metabolic acidosis with potassium-sparing diuretics

since they can be purchased 'over the counter' (e.g. 'Lo-Salt' and ibuprofen) and unless physicians specifically enquire, then they may be unaware that the patient is taking them. Hypokalaemia occurs with both thiazide and loop diuretics and the physician needs to be aware that additional factors can, sometimes suddenly, worsen a mild hypokalaemia and cause the patient to develop symptoms which may include cardiac dysrhythmia. Such conditions include diarrhoea, vomiting and a small bowel fistula. Drugs include corticosteroids, amphotericin and theophylline in particular, which, if used together with diuretics, can exacerbate hypokalaemia.[50] Both thiazide and loop diuretics can cause urinary magnesium loss, and if both are used together, such loss can be substantial.[22] If diuretics are used too enthusiastically, a fall in intravascular volume occurs which produces orthostatic hypotension, which can be a particular problem in elderly patients taking thiazides. Thiazides can be associated with hypochloraemic metabolic alkalosis (as well as hyponatraemia, hypokalaemia and hypomagnesaemia). They worsen NSAID-induced nephrotoxicity and the hypokalaemia can precipitate digoxin toxicity. Being sulphonamide-related drugs, allergic reactions come as no surprise and they potentiate non-depolarizing, neuromuscular-blocking agents (a fact of which anaesthetists need to be aware of).[71] Thiazides have another property: they can cause hyperuricaemia and may lead to the clinical onset of gout. Around 50% of patients on long-term thiazides develop hyperuricaemia, but only 2% develop clinical gout.[72] Two mechanisms probably operate. First, uric acid and diuretics are organic acids and likely compete with one another for the transport mechanisms that deliver them from the blood into the tubular fluid.[50] Second, diuretic-induced depletion of the extracellular fluid volume can lead to reduced glomerular filtration and increased absorption of most solutes, including urate, in the proximal tubule.[73] Loop diuretics also potentiate the effects of non-depolarizing neuromuscular blocking agents as well as aminoglycosides and cephalosporin antibiotics, in addition to the common electrolyte disturbances which they share with thiazides.[71] Further information on adverse effects can readily be found in large clinical pharmacology textbooks.[74]

Patients with porphyria present a special circumstance and advice on 'unsafe' drugs including diuretics is available, and regularly updated, on a number of websites.[75]

Diuretic abuse

Sadly, individuals can take it upon themselves to take diuretics inappropriately, in situations where no real clinical indication exists.[55] Usually associated with an eating disorder (anorexia nervosa or bulimia), the hypokalaemia which can develop may prove fatal.

Diuretic abuse is also encountered in sport and diuretics have been included on The World Anti-Doping Agency's (WADA) list of prohibited substances.[76] The use of diuretics is banned both in and out of competition and diuretics are routinely screened for by antidoping laboratories.[76]

Diuretics in diagnosis

Diuretics are most often regarded as therapeutic agents, but furosemide has found a particular role in the diagnosis of distal renal tubular acidosis (RTA), also known as type I RTA.[77] The furosemide-fludrocortisone test offers an alternative to the ammonium chloride urinary acidification test and is quicker to perform, as well as being a more palatable approach to test urinary acidification. One of the inherent problems with the ammonium chloride loading test is that it very often causes vomiting such that the test has to be abandoned. In the report by Walsh *et al.*,[77] none of the subjects experienced adverse effects and the simultaneous administration of furosemide and the mineralocorticoid fludrocortisone was well tolerated. The authors reasoned that the furosemide increases distal tubule sodium delivery and the consequent enhancement of distal sodium absorption increases the lumen-negative transepithelial voltage, thereby indirectly stimulating proton secretion. The fludrocortisone given simultaneously enhances both principal cell sodium reabsorption and, because it increases the activity of the H^+-ATPase, α-intercalated cell hydrogen ion secretion.[78] The combination, they proposed, should provide sufficient and consistent stimulus to elucidate an acidification defect in type I RTA, without recourse to the use of ammonium chloride which causes a systemic acid load to be excreted.[77]

Future developments

A new class of diuretics has recently been discovered and provides an exciting challenge for medical science. They are called AQP modulators, and are likely to be commercially exploited since a patent application for the first in its class, AqB013, has recently been submitted.[79] Physiologists had long pondered the existence of 'gates' that could allow rapid reabsorption of water by renal tubular cells. Diffusion will only permit a mere trickle of water across what is effectively a hydrophobic barrier – the lipid bilayer of the cell membrane first proposed in 1935 as the Danielli–Davson model.[80]

With the characterization in the early 1990s of water channels called AQPs[81] came the explanation of how water can pass through a membrane at around the rate of three billion water molecules per second per AQP channel.[82] Several members of the AQP family also allow glycerol and urea permeability. AQP1 predominates in the proximal tubule and descending thin limb of the loop of Henlé, while AQP2 is present in the principal cells of the collecting duct, where, in response to vasopressin, it shuttles between intracellular vesicles and the apical membrane.[83] Increased activity of AQP2 is a contributory factor in the pathophysiology of cirrhosis, heart failure and nephrotic syndrome (all conditions where diuretics form part of the treatment/management strategy). Mutations in the AQP2 gene cause nephrogenic diabetes insipidus.[83] Mouse knockout models have been developed to explore the possibilities of modulating AQP function and expression. Verkmann's review concludes that mouse phenotype data suggest that modulators of AQP expression/function may have wide-ranging clinical

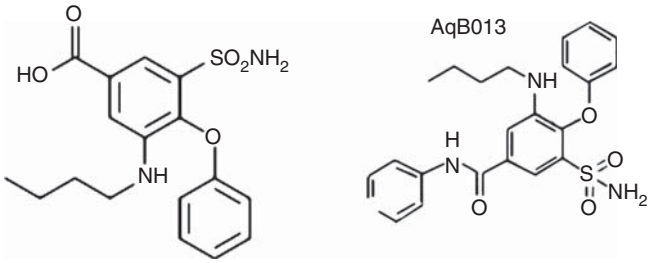


Figure 5 Structure of bumetanide and its analogue AqB013

applications such as diuretics and in the treatment of cerebral oedema, epilepsy, glaucoma, obesity and cancer.[84]

Following his discovery of 1988, Dr Peter Agre was awarded the Nobel Prize for chemistry in 2003, some 15 years later. Eleven AQP channels are recognized (AQP0–AQP10), not all being present in man. Following work on oocytes expressing AQP1 and AQP4, one of the 45 synthesized bumetanide derivatives has been found to inhibit AQP1 and AQP4 water permeability. It is the 4-aminopyridine carboxamide analogue of bumetanide designated AqB013[85] (Figure 5). It is thought to achieve its blocking action by occluding the AQP water pore at the cytoplasmic side, and the internal pore occluding binding site has been identified.[85] AQP1 channels are found in the choroid plexus involved in cerebrospinal fluid secretion in the mammalian brain, and most significantly, AQP4 channel expression has been identified in astroglial cells at the blood–brain barrier interface,[86] and AQP1 in the kidney.[87] Following a brain injury or stroke, the cerebral oedema that often subsequently develops can be life-threatening and is a major fact in determining survival. Currently, treatment options for extensive cerebral oedema are limited. The location of AQP4 at brain perivascular glial end-feet lends itself to therapeutic intervention.[85] This work is, however, at an early stage.

DECLARATIONS

Competing interests: None.
Funding: None.
Ethical approval: Not applicable.
Guarantor: DW
Contributorship: DW wrote the manuscript.
Acknowledgements: The author would like to acknowledge and thank Dr Daniel Turnock and Dr Sally Hanton for their invaluable assistance in the preparation of the manuscript.

REFERENCES

1 Hoad TF. *The Concise Oxford Dictionary of English Etymology*. Oxford: Oxford University Press, 1986
2 Macpherson G, ed. *Black's Medical Dictionary*. 40th edn. London: A&C Black, 2002
3 Melillo L. Diuretic plants in the paintings of Pompeii. *Am J Nephrol* 1994;**14**:423–5
4 Aliotta G, Capasso G, Pollio A, Strumia S, de Santo NG. Joseph Jacob Plenck (1735–1807). *Am J Nephrol* 1994;**14**:377–82
5 Funk W. *Word Origins and Their Romantic Stories*. Oxford: Oxford University Press, 1950
6 Calvet L-J. *Histoires des Mots: Etymologies Europeennes*. Paris: Editions Payot, 1993
7 Barnes J, Anderson LA, Phillipson JD. *Herbal Medicines*. London: Pharmaceutical Press, 2002
8 Joint Formulary Committee. British National Formulary. London: Pharmaceutical Press, 2010
9 Hober R. Effect of some sulfonamides on renal secretion. *Proc Soc Exp Biol Med* 1942;**49**:87–90
10 Mann T, Keilin D. Sulphanilamide as a specific inhibitor of carbonic anhydrase. *Nature* 1940;**146**:164–5
11 Schwartz WB. The effect of sulfanilamide on salt and water excretion in congestive heart failure. *N Engl J Med* 1949;**240**:173–7
12 Moyer JH. Historical aspects of the development of chlorothiazide. In: Lyght CE, ed. *A Decade with Diuril (Chlorothiazide)*. West Point, PA: Merck Sharp & Dohme, 1968
13 Beyer KH. Chlorothiazide. *Br J Clin Pharmacol* 1982;**13**:15–24
14 Lyght CE, ed. Merck Manual. 9th edn. New Jersey: Merck & Co, 1957
15 Edemir B, Pavenstadt H, Schlatter E, Weide T. Mechanisms of cell polarity and aquaporin sorting in the nephron. *Pflugers Arch* 2011;**46**:607–21
16 Maddox DA, Gennari FJ. The early proximal tubule: a high-capacity delivery-responsive reabsorptive site. *Am J Physiol* 1987;**252**:F573–84
17 Chou CL, Nielsen S, Knepper MA. Structural-functional correlation in chinchilla long loop of Henlé thin limbs: a novel papillary subsegment. *Am J Physiol* 1993;**265**:F863–74
18 Ganong WF. *Review of Medical Physiology*. 21st edn. New York: McGraw-Hill Professional, 2003: 720
19 Barrett KE, Barman SM, Boitano S, Brooks H. *Ganong's Review of Medical Physiology*. 23rd edn. New York: McGraw Hill Medical, 2009
20 Kellick KA. Diuretics. *AACN Clin Issues Crit Care Nurs* 1992;**3**:472–82
21 Ganong WF. *Review of Medical Physiology*. 21st edn. New York: McGraw-Hill Professional, 2003: 32
22 Brater DC. Diuretic therapy. *N Engl J Med* 1998;**339**:387–95
23 Jackson EK. *Diuretics*. In: Hardman JG, Limbird LE, Gilman AG, eds. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 10th edn. New York: McGraw-Hill, 2001: 757
24 Katz AI. Distribution and function of classes of ATPases along the nephron. *Kidney Int* 1986;**29**:21–31
25 Bronner F. Renal calcium transport: mechanisms and regulation – an overview. *Am J Physiol* 1989;**257**:F707–11
26 Lant A. Diuretics. Clinical pharmacology and therapeutic use (Part I). Drugs 1985;**29**:57–87
27 Simon DB, Karet FE, Hamdan JM, DiPietro A, Sanjad SA, Lifton RP. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat Genet* 1996;**13**:183–8
28 Beaumont K, Vaughn DA, Fanestil DD. Thiazide diuretic drug receptors in rat kidney: identification with [3H]metolazone. *Proc Natl Acad Sci USA* 1988;**85**:2311–4
29 Hropot M, Fowler N, Karlmark B, Giebisch G. Tubular action of diuretics: distal effects on electrolyte transport and acidification. *Kidney Int* 1985;**28**:477–89
30 Canessa CM, Schild L, Buell G, *et al.* Amiloride-sensitive epithelial Na^+ channel is made of three homologous subunits. *Nature* 1994;**367**:463–7
31 Ismailov II, Shlyonsky VG, Serpersu EH, *et al.* Peptide inhibition of ENaC. *Biochemistry* 1999;**38**:354–63
32 Maren TH. Current status of membrane-bound carbonic anhydrase. *Ann N Y Acad Sci* 1980;**341**:246–58
33 Leaf A, Schwartz WB, Relman AS. Oral administration of a potent carbonic anhydrase inhibitor (diamox). I. Changes in electrolyte and acid-base balance. *N Engl J Med* 1954;**250**:759–64
34 Preisig PA, Toto RD, Alpern RJ. Carbonic anhydrase inhibitors. *Ren Physiol* 1987;**10**:136–59
35 Kauker ML, Lassiter WE, Gottschalk CW. Micropuncture study of effects of urea infusion in tubular reabsorption in the rat. *Am J Physiol* 1970;**219**:45–50
36 Seely JF, Dirks JH. Micropuncture study of hypertonic mannitol diuresis in the proximal and distal tubule of the dog kidney. *J Clin Invest* 1969;**48**:2330–40
37 Gipstein RM, Boyle JD. Hypernatremia complicating prolonged mannitol diuresis. *N Engl J Med* 1965;**272**:1116–7

38 Oster JR, Singer I. Hyponatremia, hyposmolality, and hypotonicity: tables and fables. *Arch Intern Med* 1999;**159**:333–6
39 Fishman RA. Brain edema. *N Engl J Med* 1975;**293**:706–11
40 Navar LG. *Renal hemodynamic effects of diuretics*. In: Seldin DW, Giebisch G, eds. *Diuretic Agents: Clinical Physiology and Pharmacology*. Massachusetts Academic Press, 1997:159
41 Morrison RT. Edema and principles of diuretic use. *Med Clin North Am* 1997;**81**:689–704
42 Musini VM, Wright JM, Bassett K, Jauca CD. Blood pressure lowering efficacy of loop diuretics for primary hypertension. *Cochrane Database Syst Rev* 2009;(4):CD003825
43 van Brummelen P, Man in 't Veld AJ, Schalekamp MA. Hemodynamic changes during long-term thiazide treatment of essential hypertension in responders and nonresponders. *Clin Pharmacol Ther* 1980;**27**:328–36
44 Vasko MR, Cartwright DB, Knochel JP, Nixon JV, Brater DC. Furosemide absorption altered in decompensated congestive heart failure. *Ann Intern Med* 1985;**102**:314–8
45 Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 1995;**29**:172–91
46 Kaplan NM. Diuretics as a basis of antihypertensive therapy. An overview. *Drugs* 2000;59(suppl. 2):21–5; discussion 39–40
47 Murphy MB, Lewis PJ, Kohner E, Schumer B, Dollery CT. Glucose intolerance in hypertensive patients treated with diuretics; a fourteen-year follow-up. *Lancet* 1982;**2**:1293–5
48 Digre KB. Idiopathic intracranial hypertension. *BMJ* 2010;**341**:c2836
49 Tomsak RL, Niffengger AS, Remler BF. Treatment of pseudotumour cerebri with diamox (acetazolamide). *J Clin Neuroopthalmol* 1988;**8**:93–8
50 Bennett PN, Brown MJ. *Clinical Pharmacology*. 9th edn. London: Churchill Livingstone, 2003
51 Chaffman M, Heel RC, Brogden RN, Speight TM, Avery GS. Indapamide. A review of its pharmacodynamic properties and therapeutic efficacy in hypertension. *Drugs* 1984;**28**:189–235
52 Prichard BN, Brogden RN. Xipamide. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985;**30**:313–32
53 Brater DC. Resistance to loop diuretics. Why it happens and what to do about it. *Drugs* 1985;**30**:427–43
54 Friedel HA, Buckley MM. Torasemide. A review of its pharmacological properties and therapeutic potential. *Drugs* 1991;**41**:81–103
55 Al-Mohammad A, Mant J, Laramee P, Swain S. Diagnosis and management of adults with chronic heart failure: summary of updated NICE guidance. *BMJ* 2010;**341**:c4130
56 Arroll B, Doughty R, Andersen V. Investigation and management of congestive heart failure. *BMJ* 2010;**341**:c3657
57 Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J* 2009;**30**:469–77
58 McDowell G, Nicholls DP. The endopeptidase inhibitor, candoxatril, and its therapeutic potential in the treatment of chronic cardiac failure in man. *Expert Opin Investig Drugs* 1999;**8**:79–84
59 McDowell G, Nicholls DP. The therapetic potential of candoxatril, a neutral endopeptidase inhibitor, in humans. *Cardiovasc Drug Rev* 2000;**18**:259–70
60 Keating GM, Goa KL. Nesiritide: a review of its use in acute decompensated heart failure. *Drugs* 2003;**63**:47–70
61 Perez-Ayuso RM, Arroyo V, Planas R, *et al.* Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Relationship between the diuretic response and the activity of the renin-aldosterone system. *Gastroenterology* 1983;**84**:961–8
62 Fuller R, Hoppel C, Ingalls ST. Furosemide kinetics in patients with hepatic cirrhosis with ascites. *Clin Pharmacol Ther* 1981;**30**:461–7
63 Karajala V, Mansour W, Kellum JA. Diuretics in acute kidney injury. *Minerva Anestesiol* 2009;**75**:251–7
64 Borthwick E, Ferguson A. Perioperative acute kidney injury: risk factors, recognition, management, and outcomes. *BMJ* 2010;**341**:c3365
65 Schepkens H, Vanholder R, Billiouw JM, Lameire N. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med* 2001;**110**:438–41
66 George CF. Amiloride handling in renal failure. *Br J Clin Pharmacol* 1980;**9**:94–5
67 Chapron DJ, Gomolin IH, Sweeney KR. Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989;**29**:348–53
68 Allison ME, Shilliday I. Loop diuretic therapy in acute and chronic renal failure. *J Cardiovasc Pharmacol* 1993;**22**(suppl. 3):S59–70
69 Kramer BK, Schwab A, Braun N, Strutz F, Muller GA, Risler T. Pharmacokinetics of torasemide and its metabolites in end-stage renal disease. *Eur J Clin Pharmacol* 1994;**47**:157–9
70 Humes HD. Insights into ototoxicity. Analogies to nephrotoxicity. *Ann N Y Acad Sci* 1999;**884**:15–8
71 O'Brien J. Diuretics. *Bull Roy Coll Anaesth* 2001;**8**:366–9
72 Beevers DG, Hamilton M, Harpur JE. The long-term treatment of hypertension with thiazide diuretics. *Postgrad Med J* 1971;**47**:639–43
73 Steele TH, Oppenheimer S. Factors affecting urate excretion following diuretic administration in man. *Am J Med* 1969;**47**:564–74
74 Hardman JG, Limbird LE, Goodman Gilman A, eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. New York: McGraw-Hill, 2001
75 EpNet. *European Porphyria Initiative* [updated 2008]. See http://www.porphyria-europe.com/ (last checked 30 November 2011)
76 Cadwallader AB, de la Torre X, Tieri A, Botre F. The abuse of diuretics as performance-enhancing drugs and masking agents in sport doping: pharmacology, toxicology and analysis. *Br J Pharmacol* 2010;**161**:1–16
77 Walsh SB, Shirley DG, Wrong OM, Unwin RJ. Urinary acidification assessed by simultaneous furosemide and fludrocortisone treatment: an alternative to ammonium chloride. *Kidney Int* 2007;**71**:1310–6
78 Schwartz GJ. Diagnosis of distal renal tubular acidosis: use of furosemide plus fludrocortisone versus ammonium chloride. *Nat Clin Pract Nephrol* 2007;**3**:590–1
79 Flynn GA, Yool AJ, Migliati ER, Ritter LS. *Aquaporin Modulators and Methods of Using Them for the Treatment of Edema and Fluid Imbalance*. Alexandria, VA, 2010, US Patent No. 7906555 B2
80 Becker WM, Kleinsmith LJ, Hardin J, eds. *The World of the Cell*. 6th edn. San Francisco: Pearson Benjamin Cummings, 2006
81 Agre P, Preston GM, Smith BL, *et al.* Aquaporin CHIP: the archetypal molecular water channel. *Am J Physiol* 1993;**265**:F463–76
82 Gade W, Robinson B. A brief survey of aquaporins and their implications for renal physiology. *Clin Lab Sci* 2006;**19**:70–9
83 Laski ME, Pressley TA. Aquaporin mediated water flux as a target for diuretic development. *Semin Nephrol* 1999;**19**:533–50
84 Verkman AS. Novel roles of aquaporins revealed by phenotype analysis of knockout mice. *Rev Physiol Biochem Pharmacol* 2005;**155**:31–55
85 Migliati E, Meurice N, DuBois P, *et al.* Inhibition of aquaporin-1 and aquaporin-4 water permeability by a derivative of the loop diuretic bumetanide acting at an internal pore-occluding binding site. *Mol Pharmacol* 2009;**76**:105–12
86 Yool AJ. Aquaporins: multiple roles in the central nervous system. *Neuroscientist* 2007;**13**:470–85
87 Yool AJ, Brokl OH, Pannabecker TL, Dantzler WH, Stamer WD. Tetraethylammonium block of water flux in aquaporin-1 channels expressed in kidney thin limbs of Henlés loop and a kidney-derived cell line. *BMC Physiol* 2002;**2**:4

(Accepted 28 December 2011)