Bumetanide

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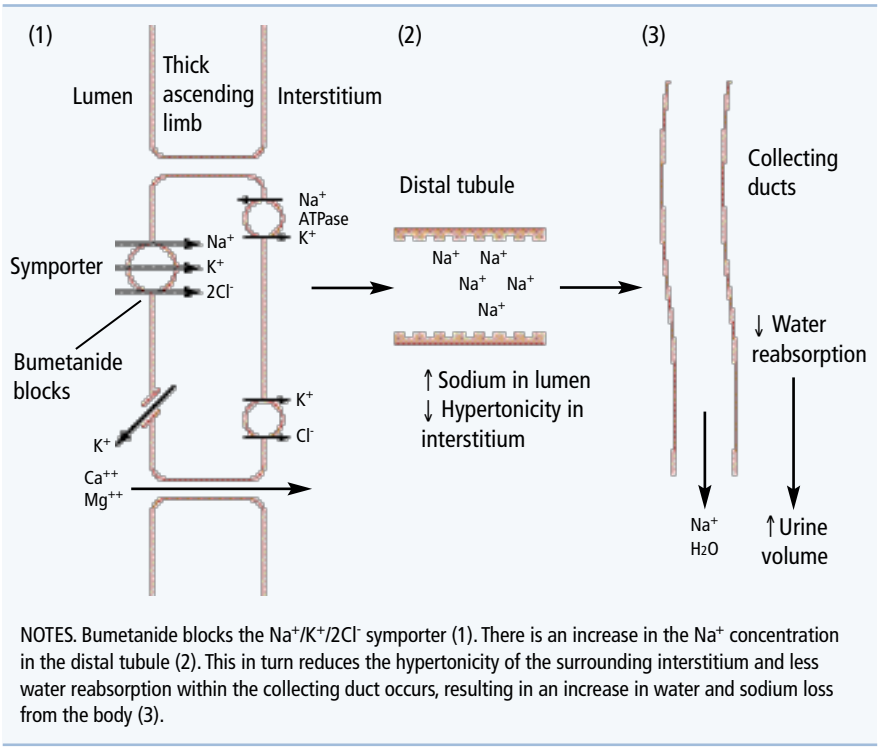

NOTES. Bumetanide blocks the $Na^+/K^+/2Cl^-$ symporter (1). There is an increase in the Na^+ concentration in the distal tubule (2). This in turn reduces the hypertonicity of the surrounding interstitium and less water reabsorption within the collecting duct occurs, resulting in an increase in water and sodium loss from the body (3).

Figure 1. The pharmacological action of bumetanide

Introduction

Bumetanide is a potent loop diuretic. It is indicated for the management of oedema due to congestive heart failure, hepatic cirrhosis and renal disease, including nephrotic syndrome. Many patients with diabetes will require treatment with a loop diuretic given the high prevalence of oedema in this patient population whether it is a consequence of cardiac or renal disease. However, unlike the other two available loop diuretics (furosemide and torasemide) it is not licensed in the UK for use in hypertension.

Pharmacology

Figure 1 outlines the pharmacological action of bumetanide. In common with furosemide it is available as an oral, intravenous or intramuscular preparation with torasemide only available orally. The pharmacokinetic profile of bumetanide is similar via all routes of administration. The onset of action is within 30 minutes, with the effect of increased urinary excretion persisting for up to six hours. The principal site of action is in the thick ascending loop of Henlé with additional secondary action at the proximal tubule. In common with the other loop diuretics, the mechanism of action is by reversible binding to the $Na^+/K^+/2Cl^-$ co-transport system (symporter). This symporter reabsorbs approximately 25% of the sodium load filtered through the kidneys. By inhibiting this pump there is a significant increase in the distal tubular concentration of sodium. This in turn reduces the hypertonicity of the surrounding interstitium and less water reabsorption within the collecting duct occurs, resulting in an increase in water and sodium loss from the body. Magnesium and calcium reabsorption in the thick ascending loop is dependent on sodium and chloride concentrations. Therefore, as sodium and chloride concentrations change, there is inhibition of magnesium and calcium absorption which can lead to hypocalcaemia and hypomagnesaemia. The overall result from bumetanide administration is an increase in urine production and an increase in renal blood flow. This has the effect that less water is

reabsorbed into the blood, resulting in a decrease in blood volume, thereby reducing blood pressure (BP) and oedema. Retention of Na^+ in the kidney following the decline in renal tubular diuretic levels can limit or prevent a negative Na^+ balance, which not only means that a BP effect is not maintained but also that in many patients with heart failure there is a need to use two or more daily doses of loop diuretic to induce and maintain a negative salt balance. In clinical practice, loop diuretics do not have a routine role in BP reduction, but there are situations where they are helpful, including the treatment of resistant hypertension and in patients with impaired renal function. Thiazide diuretics do not work at low eGFR but for loop diuretics renal impairment prolongs the effect of the drug resulting in maintained sodium and volume depletion. The subsequent rise in renin concentration allows for a synergistic effect between the loop diuretic and ACE inhibitors and/or angiotensin II receptor blockers in these patients.

The bioavailability of bumetanide is 80% compared to furosemide which ranges from 40–70%. Interestingly, in patients with heart failure the rate of absorption is affected for both furosemide and bumetanide, blunting the clinical effect, but not bioavailability.[1] Heart failure patients can demonstrate resistance to both bumetanide and furosemide necessitating the use of IV doses in clinical practice. Bumetanide is 40 times more potent than furosemide (1mg bumetanide = 40mg furosemide).

The main side effect of loop diuretics is fluid and electrolyte imbalance – hyponatraemia, hypokalaemia, hypomagnesaemia and hypocalcaemia. They can also cause an increase in cholesterol, triglyceride and glucose, but these metabolic effects are less commonly seen as compared with thiazide diuretics. They can also precipitate gout. However, another side effect to consider is ototoxicity manifesting itself as tinnitus, hearing impairment, deafness and vertigo. Hearing impairment and deafness are usually, but not always, reversible. Ototoxicity occurs more commonly with rapid IV administration and care should be taken to inject slowly if the IV route is being used.

Trials of safety and efficacy: is there any benefit vs furosemide?

There are several small clinical studies that have been conducted to compare safety and efficacy of bumetanide and furosemide in patients with congestive cardiac failure. As already discussed, heart failure may reduce the absorption of bumetanide and furosemide, but one randomised clinical trial compared the safety and effectiveness of bumetanide vs furosemide over a six-month period in 42 outpatients suffering oedema due to congestive heart failure.[2] Both medications resulted in no adverse reactions during the trial. No statistically significant differences in the signs of congestive cardiac failure such as body weight, oedema and hepatomegaly were noted. Monitoring of serum sodium, potassium, chloride and uric acid revealed similar results with both drugs. BP was lowered in both groups; this was more consistent in the furosemide group but was not statistically significant. Therefore, this study showed that both drugs were safe and effective in reducing oedema from congestive heart failure with no real clinical advantage of one over the other.

Bumetanide use in diabetes

There are no major studies for the use of bumetanide in patients with diabetes. However, diabetes can result in left ventricular systolic dysfunction with pulmonary and peripheral oedema, as well as oedema secondary to nephrotic syndrome in the context of diabetic nephropathy. In both of these situations there may be the need to use a diuretic acutely or chronically, with bumetanide at least being as effective as furosemide. However, bumetanide is not licensed for use in hypertension management. Many patients with diabetes need high doses of loop diuretic to manage their BP when eGFR is low and thiazides become ineffective. Currently, the choice of loop diuretic in this setting is furosemide, although in practice bumetanide is likely to be as effective. The metabolic effects on glucose levels and lipids are less of an issue for loop diuretics than they are for thiazide diuretics, an important consideration when treating patients with diabetes. A double-blind, 24-week, cross-over, placebo-controlled study with 27 patients was undertaken to determine whether loop diuretics were more effective than placebo in reducing BP without raising serum lipid levels.[3] It further aimed to determine if bumetanide was more effective than furosemide. This study demonstrated that the loop diuretics bumetanide and furosemide were effective in reducing BP and influenced serum lipid levels significantly less than thiazide diuretics. Additionally, the study was unable to demonstrate a significant difference in BP control or serum lipid levels between bumetanide and furosemide.

Key points

- Diabetes can result in oedema secondary to heart failure and/or kidney disease requiring the use of a loop diuretic
- Bumetanide is a potent loop diuretic (40 times the potency of furosemide)
- Bumetanide has better bioavailability than furosemide but is likely to have similar clinical effects in managing oedema
- Although its effects on lipid profile and blood pressure are similar to those of furosemide it is not indicated for the treatment of hypertension

Discussion

Bumetanide can be used in the treatment of oedema in patients with diabetes. Although it may have a BP lowering effect, it is not licensed for this indication. When compared to furosemide the effect on BP, fluid overload and serum lipid levels is similar. Loop diuretics have less of an effect on lipid profile than thiazide diuretics and are better for the management of hypertension in patients with impaired kidney function. Although better oral bioavailability may provide a persuasive argument for using bumetanide over furosemide, there appears to be no good evidence for one over the other in terms of efficacy and safety.

Declaration of interests

There are no conflicts of interest declared.

References

References are available online at www.practicaldiabetes.com.

References

1. Brater DC, *et al.* Bumetanide and furosemide in heart failure. *Kidney Int* 1984;26(2):183–9.
2. Konecke LL. Clinical trial of bumetanide versus furosemide in patients with congestive heart failure. *J Clin Pharmacol* 1981;21(11–12 Pt 2):688–90.
3. van Der Heijen M, *et al.* A randomized, placebo-controlled study of loop diuretics in patients with essential hypertension: the bumetanide and furosemide on lipid profile (BUFUL) clinical study report. *J Clin Pharmacol* 1998;38(7):630–5.