Torasemide

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Introduction
Cardiovascular disease, including atherosclerotic vascular disease and heart failure, are common causes of morbidity and mortality in patients with diabetes mellitus. Loop diuretics are one of the cornerstones of the management of symptomatic heart failure and fluid overload states, but unlike the aldosterone antagonists spironolactone and eplerenone loop diuretics do not convey a survival benefit to patients with chronic heart failure. Furosemide is the most commonly prescribed loop diuretic in routine clinical practice. Torasemide (or torsemide) is another loop diuretic with a longer half-life and higher bioavailability, which is licensed for the management of oedema and hypertension.

Pharmacology
Torasemide (torsemide) is a pyridine-sulphonylurea type loop diuretic. In common with sulphonylureas, torasemide contains a sulphonyl moiety connected to a urea group. It does not exert an antihyperglycaemic effect, but is contraindicated in patients who are allergic to sulphonylureas.

Similar to other loop diuretics, such as furosemide and bumetanide, its mode of action is to inhibit sodium-potassium-chloride cotransporters (NKCCs). Blockade of the NKCC2 isoform of this cotransporter, which is located on the apical surface of the cells of the thick ascending loop of Henle, results in reduced reabsorption of sodium, chloride and potassium with increased natriuresis, diminished reabsorption and increased urinary output. NKCC2 is also expressed on the apical membrane of cells of the macula densa, and when this is inhibited by loop diuretics this stimulates renin secretion resulting in the generation of angiotensin II. (Figure 1.)

Loop diuretics also act on the NKCC1 isoform of the sodium-potassium-chloride cotransporter in the Vesta recta and proximal tubular epithelial cell. (Figure 1.)

NOTES. Torasemide is absorbed via the organic anion transporters into the proximal tubular cells. It is then carried through the multidrug resistance associated protein-4 (among other transporters) into the renal tubules. At the loop of Henle it exerts its action on the chloride receptor of the sodium-potassium-chloride cotransporter to cause the blockade of reabsorption of these electrolytes and therefore increasing diuresis, natriuresis and kalliuresis.
vascular smooth muscle, which may explain why loop diuretics cause vasodilatation. It also affects the afferent arteriole and the extraglomerular mesangium, which also contributes to the secretion of renin. The NKCC1 isoform is expressed widely throughout the human body including the ear, possibly accounting for the ototoxicity experienced with use of these medications.

Torasemide has higher oral bioavailability (>90%) than furosemide and a longer half-life (6 hours vs 2.7 hours) which is prolonged further in the context of chronic kidney disease. A prolonged-release preparation of torasemide has been developed which extends its diuretic effect to a period of 10–12 hours.

Loop diuretics have steep dose-response curves and are effective when present in concentrations above the ‘natriuretic threshold’. The effective therapeutic concentration of loop diuretic is higher in those with acute decompensated heart failure. The pharmacodynamics of torasemide are not adversely affected by cardiac failure to the same degree as furosemide.

Torasemide should be prescribed cautiously alongside other agents that may cause renal impairment, hypotension, hypokalaemia or ototoxicity. Monitoring of renal function and electrolytes is recommended. There have been no significant pharmacodynamic or pharmacokinetic interactions detected between torasemide and empagliflozin. Empagliflozin alone for five days increased urinary glucose excretion but did not seem to have a relevant impact on urine volume or electrolytes. When empagliflozin was co-administered with torasemide, urinary glucose excretion remained increased, and the renin-angiotensin system was activated. There are no reported interactions between torasemide and metformin, sulphonylureas, thiazolidinediones, DPP-4 inhibitors or GLP-1 receptor agonists.

Trials of safety and efficacy
Early trials of torasemide demonstrated its safety and efficacy as a natriuretic-diuretic therapy for the management of cardiac failure and other fluid over-loaded states, while being relatively potassium sparing as compared with furosemide. It has also been shown to be more effective than furosemide at managing hypertension in patients without chronic kidney disease.

A systematic review in 2012 of torasemide and furosemide for the treatment of heart failure identified only two trials and indicated the need for more research. Of the two trials included it was found that there was a significant reduction in re-admissions for cardiac failure and other cardiovascular causes, along with a numerical but not statistically significant reduction in mortality in torasemide-treated patients. Another older open-label post marketing surveillance study (the TORIC study) comparing furosemide and torasemide in patients with cardiac failure also demonstrated a significant reduction in symptoms, measured by NYHA status, and in mortality in the torasemide-treated group.

Post-hoc analyses of trials conducted on patients admitted with acute heart failure and discharged on either furosemide or torasemide have also been performed. As an example the ASCEND-HF trial examined the effects of nesiritide in heart failure. A recent post-hoc analysis examined patients discharged on either torasemide or furosemide and suggested a tendency for a reduction in mortality in torasemide-treated patients, but this did not reach statistical significance. Torasemide-treated patients tended to have more comorbidities and clinically more severe heart failure, indicating a selection bias in the choice of loop diuretic.

Specific evidence for use in diabetes
There is little specific evidence for the use of torasemide in patients with diabetes mellitus and cardiac failure. The TORIC study did not document how many patients had concurrent diabetes mellitus. In the post-hoc analysis of the ASCEND-HF trial, 43% (n=1808) of patients had diabetes mellitus. Patients who were torasemide-treated were statistically more likely to have diabetes mellitus among other comorbidities.

Discussion
Torasemide is a loop diuretic which is used less commonly than furosemide in the treatment of cardiac failure and hypertension. It has favourable pharmacokinetic characteristics and its bioavailability when administered via the oral route is high, and it is affected less than furosemide by the pathophysiological conditions that occur in acute cardiac failure. It may also cause less kalliuresis and hypokalaemia.

There are some data to support the use of torasemide over furosemide as it may reduce re-admissions to hospital with heart failure, and mortality. This potential survival benefit remains to be proven in a double-blind placebo controlled trial. The TRANSFORM-HF study (torasemide comparison with furosemide for the management of heart failure), which is not yet recruiting, will be a large-scale, pragmatic randomised, open-label study comparing torasemide with furosemide as treatment for patients hospitalised for heart failure. It aims to enrol 6000 subjects. Even if this study is positive, there will be concerns in interpreting the results because of the open-label design.

Declaration of interests
There are no conflicts of interest declared.

References

Key points
- Torasemide is a loop diuretic that is occasionally used for the treatment of heart failure
- Torasemide is contraindicated in patients who are allergic to sulphonylureas, but does not interact with commonly prescribed antihyperglycaemic medications, including empagliflozin
- Observational and post-hoc data suggest that there may be some benefit compared to furosemide in reducing heart failure hospitalisation and mortality, but there is a need for a well-conducted, blinded, randomised controlled trial