Therapeutic Reviews

Series Co-Editors: Andrew Wilcock, DM, FRCP, and Paul Howard, BMedSci, MRCP

Therapeutic Reviews aim to provide essential independent information for health professionals about drugs used in palliative and hospice care. Additional content is available on www.palliativedrugs.com. Country-specific books (Hospice and Palliative Care Formulary USA, and Palliative Care Formulary, British and Canadian editions) are also available and can be ordered from www.palliativedrugs.com. The series editors welcome feedback on the articles (hq@palliativedrugs.com).

Furosemide AHFS 40:28.08

Laura Carone, BMedSci, Stephen G. Oxberry, PhD, Robert Twycross, DM, FRCP, Sarah Charlesworth, BPharm (Hons), DipClinPharm, MRPharmS, Mary Mihalyo, BS, PharmD, RPh, CGP, BCPS, CDE, and Andrew Wilcock, DM, FRCP

University of Nottingham (L.C.), Nottingham, United Kingdom; Kirkwood Hospice (S.G.O.), Huddersfield, United Kingdom; Oxford University (R.T.), Oxford, United Kingdom; Mylan School of Pharmacy (M.M.), Duquesne University, Pittsburgh, Pennsylvania, USA; Nottingham University Hospitals NHS Trust (S.C.), Nottingham, United Kingdom, and University of Nottingham (A.W.), Nottingham, United Kingdom

Class: Loop diuretic.

Indications: Edema, hypertension (unresponsive to usual treatments), †malignant ascites associated with portal hypertension and hyperaldosteronism (with **spironolactone**).

Contraindications: Hepatic encephalopathy, anuric renal failure.

Pharmacology

Loop diuretics inhibit Na^+ (and hence water) resorption from the ascending limb of the loop of Henlé in the renal tubule. They also increase urinary excretion of K^+, Mg^{2+}, H^+ and Cl^-. Loop diuretics, of which furosemide is the most commonly prescribed, are used to treat fluid overload in CHF and ESRD in order to improve symptoms of breathlessness and edema.[1–4]

A diuretic-induced reduction in plasma volume can activate several neurohumoral systems, e.g. renin-aldosterone-angiotensin, resulting in impaired renal perfusion and increased Na^+ and water resorption. These changes contribute towards a reduced effect of the diuretic ('diuretic resistance') and also renal impairment. Strategies to overcome 'resistance' to furosemide include:

- a progressive increase in dose and b.i.d. administration
- switching to a loop diuretic with a higher/more consistent bio-availability
- adding a thiazide diuretic
- switching to parenteral administration.

Other loop diuretics include **bumetanide** and **torsemide** (rINN **torasemide**), with respective PO doses of 1mg and 10mg equivalent to 40mg of furosemide.[5–7] Compared with furosemide, they are more expensive, but they have a higher (≥80%) and more consistent PO bio-availability.[5,6] Thus, some patients may have a better diuresis when switched to them from furosemide.

Furosemide may be given SL (off-label). The bio-availability of Lasix® (Sanofi-Aventis) 20mg tablet by this route is at least as good as PO, if not better.[8] However, this may be formulation-dependent.

In the USA, parenteral formulations of **bumetanide** and furosemide are available (in the UK, only furosemide is available in a parenteral formulation). When switching from PO to IV because of fluid overload, a 1:1

Address correspondence to: Andrew Wilcock, DM, FRCP, Hayward House Macmillan Specialist Palliative Care Unit, Nottingham University Hospitals NHS Trust, Nottingham NG5 1PB, United Kingdom. E-mail: andrew.wilcock@nottingham.ac.uk

Accepted for publication: May 20, 2016.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2016.05.004

conversion is generally used.[9] For furosemide, based on bio-availability, this represents an increase in dose. Thus, although some use the same PO:IV conversion ratio for furosemide in patients with *controlled edema* no longer able to take drugs PO at the end of life, a conversion ratio of 2:1 may be sufficient. *Whatever the circumstance and dose used, patients receiving parenteral loop diuretics require close monitoring.*

Thiazide-type diuretics, e.g. **hydrochlorothiazide**, **indapamide**, **metolazone**, block distal tubule Na^+ resorption and thereby antagonize part of the renal adaptations to a loop diuretic. All thiazides are equally effective when added to a PO/IV loop diuretic, and the combination can avoid the need for parenteral administration of a loop diuretic in both CHF and ESRF.[4,10] Close monitoring of plasma electrolytes and renal function is required, particularly because of the increased risk of hypokalemia ± hypomagnesemia. Initially, when diuresis is likely to be at its greatest, daily monitoring may be necessary. An aldosterone antagonist, e.g. **spironolactone**, is sometimes also added to augment the diuresis and conserve K^+.[10]

Compared with bolus IV doses, furosemide by CIVI appears to provide a greater diuresis with a similar or better safety profile.[11] However, the data are inconsistent and insufficiently robust to specifically recommend one approach rather than the other.[3]

Furosemide is effective when given by SC injection (off-label). However, because the concentration of the injection is 10mg/mL, volume considerations may limit feasibility. Diuresis reaches a maximum at 2−3h and lasts for about 4h.[12,13] Furosemide has been successfully given SC/CSCI as a means of avoiding hospital admission, and for when oral medication becomes problematic in the last days of life.[14,15] In a report of 47 episodes of the use of furosemide CSCI in 37 patients with end-stage CHF, the majority benefited (>80%), with mild or severe site reactions seen in one quarter and one episode respectively.[14]

Nebulized furosemide has been used in a patient at home with decompensated CHF as a temporary measure when IV access could not be established. A dose of 80mg resulted in a rapid improvement in pulmonary edema and breathlessness, diuresis and a weight loss of 1kg. However, despite repeated daily doses, overall there was insufficient diuresis to prevent admission for central line insertion and IV furosemide.[16]

Ascites: when caused by a *transudate* associated with portal hypertension, e.g. from cirrhosis, extensive liver metastases, furosemide alone has little effect, even when used in total daily doses of 100−200mg PO.[17,18] Thus, furosemide in ascites is best limited to concurrent use with **spironolactone**, when the latter alone is insufficient.

Octreotide 300microgram SC b.i.d. can suppress the diuretic-induced activation of the renin-aldosterone-angiotensin system and its addition has improved renal function and Na^+ and water excretion in patients with cirrhosis and ascites receiving furosemide and **spironolactone**.[19,20]

Breathlessness: There is current interest in the use of *nebulized* furosemide for the treatment of breathlessness (see Box). However, a review of 42 trials concluded that there was insufficient evidence to currently support its routine use.[21] Further, in one study,[22] 5/7 patients reported a deterioration in their breathing after furosemide. Thus, ideally, nebulized furosemide should be used only in a clinical trial.

Box. Nebulized furosemide and breathlessness

Experimentally-induced cough and breathlessness
Allergen-induced asthma
Nebulized furosemide 20−40mg attenuates cough and breathlessness,[23−25] possibly via an effect on vagal sensory nerve endings.
The reduction in breathlessness may result from increasing sensory traffic to the brain stem from sensitized slowly adapting pulmonary stretch receptors. However, the effect:
- has not been demonstrated consistently
- shows wide interindividual variability
- is of short duration (generally <2h)
- systemic absorption can be sufficient to induce a diuresis.[26−28]

COPD
Compared with placebo in moderate−severe COPD, nebulized furosemide has reduced breathlessness ± increased exercise time during endurance testing,[29,30] but *not* incremental exercise testing.
The mechanism underlying the benefit is unclear, but improvements are seen in airway function (e.g. slow vital capacity at rest) and dynamic ventilatory mechanics (e.g. inspiratory capacity and breathing pattern).[30] Although small but significant bronchodilation was seen in one study,[29] this is unlikely to be a direct effect of nebulized furosemide.