Therapeutic Reviews

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Furosemide AHFS 40:28.08

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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

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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.

When given alongside initial 'standard' treatment for an exacerbation of COPD, nebulized furosemide results in additional improvement in breathlessness and various respiratory parameters.[31] However, it does not have an established role in this setting.

Cancer

In patients with cancer, nebulized furosemide has been used to relieve severe breathlessness.[32,33] However, RCTs have failed to show benefit.[22,34]

Pharmacokinetic data are summarized in the Table.

Table
Pharmacokinetic details[8,35,36]

Drug	*Bumetanide*	*Furosemide*	*Torsemide*
Bio-availability PO (%)	80–95%	60–70%[a]	~80%
Onset of action (min)	30–60 PO ≤2 IV	30–60 PO 30 SC 2–5 IV	≤60 PO
Tmax (h)	0.5–2 PO	1.5 PO/SL	≤1 PO
Plasma halflife (h)	1–2	0.5–2 (healthy) 1–6 (CHF) 10 (ESRD)	3.5
Duration of action (h)	4–6 PO 2 IV	4–6 PO 4 SC 2 IV	≤8 PO

[a]varies widely due to erratic absorption and can be as low as 10%.

Cautions

Severe electrolyte disturbances (correct before treatment and monitor during use); elderly (lower doses); renal impairment (monitor during use); hepatic impairment; diabetes, hypoproteinemia.

Some patients receive long-term diuretic therapy for hypertension or non-heart failure ankle edema. This often becomes inappropriate as physical deterioration progresses, and may lead to postural hypotension and prerenal failure. In such circumstances the dose of furosemide should be reduced and possibly discontinued altogether. However, the withdrawal of diuretics requires careful monitoring to prevent the subsequent insidious onset of CHF.[37]

Drug interactions

Serious drug interactions: furosemide-induced electrolyte disturbances, particularly hypokalamia, can increase the risk of:

- cardiac arrhythmia and death with drugs known to prolong the QT interval, e.g. **citalopram, methadone**
- **digoxin** toxicity
- **lithium** toxicity (possibly).[38]

Plasma electrolytes, drug concentrations, and the patient's clinical condition should be monitored closely.

Concurrent use of furosemide with **risperidone** is associated with an increased risk of death in elderly patients with dementia. The reason is unclear, but the manufacturer advises avoiding this combination unless the benefits clearly outweigh the risks.

Furosemide can *decrease* **vancomycin** levels by up to 50%.

Aliskiren, **phenytoin** (up to 50% reduction), **indomethacin** and possibly other NSAIDs can reduce the diuretic effect of furosemide; a larger dose of furosemide may be required.

Additive pharmacodynamic interactions with furosemide increase the risk of:

- hypokalemia with other K^+ depleting drugs, e.g. corticosteroids, β_2 agonists, and **theophylline**
- hyponatremia with other Na^+ depleting drugs, e.g. **carbamazepine**
- hypotension with other drugs that lower blood pressure, e.g. ACE inhibitors, angiotensin II receptor antagonists, TCAs
- nephrotoxicity with other renally toxic drugs, e.g. NSAIDs, aminoglycosides
- ototoxicity, e.g. aminoglycosides, **vancomycin.**

Cholestyramine, **colestipol** and **sucralfate** decrease absorption of furosemide; give furosemide 2–3h before these drugs.

Undesirable effects

Transient pain at the site of SC injection.[36]

Frequency not stated: dyspepsia, thirst, dizziness, dehydration, drowsiness, weakness, muscle cramps.

Rare: tinnitus and deafness (generally after rapid injection; may be permanent).

Biochemical disturbances: hyperglycemia, hyperuricemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, metabolic alkalosis.

Dose and use

Ascites

Use only as a supplement to **spironolactone**:

- start with 40mg PO each morning
- increase in steps of 40mg each morning every 3–5 days
- maximum dose 160mg each morning.

Symptomatic relief of fluid overload in CHF and ESRD

- start with 40mg PO each morning
- if necessary, increase the dose progressively in 40mg increments
- usual maximum daily dose 160mg, generally given as 80mg each morning and noon
- in patients admitted to hospital with decompensated CHF, much higher doses are sometimes used, e.g. ≤600mg/24h.[7]

Once the excess fluid has been cleared, attempts can be made to reduce the furosemide to the lowest effective maintenance dose. Excessive diuresis is generally indicated by worsening renal function. Conversely, weight gain is an early indicator of fluid overload. Some patients are taught to adjust their diuretic dose according to changes in body weight.

Addition of a thiazide diuretic

Seek specialist advice: When there is an inadequate response to an optimally titrated dose of furosemide PO/IV, benefit may be obtained from the addition of a thiazide diuretic (see Pharmacology). Typical starting doses are **hydrochlorothiazide** (25mg), **indapamide** (2.5mg) and **metolazone** (2.5mg) PO given each morning or less frequently (see below); other thiazide diuretics can also be used.[10]

Close monitoring of plasma electrolytes, renal function, and clinical response (e.g. blood pressure, body weight, diuresis) is generally required. Particularly for outpatients, or with ongoing use, alternate day or even less frequent dosing is preferable, e.g. 1–2 times weekly.[7]

In ESRD, prolonged benefit has been obtained from short courses, e.g. **metolazone** 2.5–5 mg once daily for 2–5 days.[4]

Parenteral administration

This may be necessary when the response to PO diuretics is inadequate in a patient with fluid overload, or when a patient is no longer able to take PO diuretics, e.g. at the end of life.

Patients with fluid overload

When switching from furosemide PO to IV a 1:1 conversion is generally used. Although data are mixed, the largest study to date suggests bolus IV and CIVI administration result in similar changes in patient's symptoms and renal function, and guidelines recommend either.[3,9] However, many centres only switch to CIVI when the maximum dose of bolus IV is insufficient, e.g.:

- start with *bolus IV:* 40–80mg b.i.d. (morning and noon); dilute with 0.9% saline to a suitable volume, e.g. 20mL, and give at a maximum rate of 4mg/min (2.5mg/min in severe renal impairment)
- if insufficient, switch to *CIVI:* 200–250mg/24h; dilute in a convenient volume of 0.9% saline
- generally, the fluid overload takes 3–5 days to clear; a switch back to the patient's usual PO maintenance dose of furosemide is then attempted.

Some palliative care services have used CSCI furosemide as a way of managing decompensated CHF in the hospice or community setting:[15]

- start with the same dose CSCI as the patient's current PO total daily dose
- weigh the patient daily
- after 48h, if the daily weight loss is not ≥1kg/day, consider obtaining cardiologist/heart failure nurse specialist advice; options include:
  - ➢ increasing the furosemide dose by 50%
  - ➢ adding a thiazide diuretic PO (see above)
  - ➢ adding or increasing the dose of an aldosterone antagonist, e.g. PO **spironolactone**
- because furosemide injection is 10mg/mL, practical daily dose limits for a CME Medical T34 syringe driver for CSCI are 200mg and 300mg for a 30mL and 50mL syringe respectively
- if CSCI furosemide fails to provide the necessary weight loss, admission to hospital/hospice for IV furosemide may be unavoidable.

Patients unable to take PO furosemide

For patients with CHF in the last days of life, unless anuric or clinically hypovolemic, a loop diuretic should generally be continued for symptom management. Once unable to take furosemide PO:

- *if fluid overloaded*, switch to IV bolus or CSCI furosemide using a PO to IV conversion of 1:1 (this represents an increase in dose; see Pharmacology)
- if *not* fluid overloaded, although some use a 1:1 conversion, using half the PO dose IV may suffice.

Alternatively, in a patient without fluid overload, some clinicians will monitor the situation *daily* and only commence parenteral furosemide if fluid overload develops. *This approach requires the whole team to have the necessary expertise to monitor for symptoms and signs of pulmonary edema.*

Incompatibility: Furosemide injection is alkaline and there is a high risk of *incompatibility* when mixed with acidic drugs. Because of this and the lack of compatibility data, *furosemide should not be mixed in the same syringe with any other drugs.*[39]

If further dilution is required, 0.9% saline is recommended; do *not* mix or dilute with glucose solutions or other acidic fluids.

Supply

Furosemide (generic)
Tablets 20mg, 40mg, 80mg 28 days @ 40mg each morning = $5.
Oral solution (sugar-free) 40mg/5mL, 10mg/mL, 28 days @ 40mg each morning = $18.50; *some formulations may contain alcohol.*
Injection 10mg/mL, 2mL amp =$2.86, 4mL amp = $3.77, 10mL amp = $4.25.

Bumetanide (generic)
Tablets 0.5mg, 1mg, 2mg, 28 days @ 1mg each morning = $25.
Injection 250microgram/ml, 4 ml = $2.52, 10 ml amp = $2.96.

Torsemide (generic)
Tablets 5mg, 10mg, 20mg, 100mg, 28 days @ 10mg each morning = $20.

Abbreviations/Key

†	Off-label use
ACE	Angiotensin-converting enzyme
b.i.d.	bis in die, twice daily
CHF	Congestive heart failure
CIVI	Continuous intravenous infusion
COPD	Chronic obstructive pulmonary disease
CSCI	Continuous subcutaneous infusion
ESRD	End-stage renal disease
IV	Intravenous
NSAID	Nonsteroidal anti-inflammatory drug
PO	Per os, by mouth
RCT	Randomized controlled trial
rINN	Recommended International Non-proprietary Name
SC	Subcutaneous
SL	Sublingual
TCA	Tricyclic antidepressant
Tmax	Time to peak plasma concentration

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