



Palliative Care Medicines
Information Service



tel: 01 4912578 Harold's Cross
palliativemedsinfo@olh.ie & Blackrock

Question: What are the treatment options for hiccups in palliative care patients?

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Summary

Various different therapies have been proposed for the treatment of hiccups. Chlorpromazine is the only licensed medicine for the treatment of intractable hiccups. However, other medicines, as outlined below, have also been found to be effective. Combination therapies consisting of cisapride, omeprazole, baclofen, +/- gabapentin, have also been proposed when symptoms are refractory to other treatments.

Background

Hiccups, or singultus, are repeated involuntary, spasmodic diaphragmatic and inspiratory intercostal muscle contractions, largely in irregular series with glottic closure mediated by sensory branches of phrenic, dorsal sympathetic, and vagus nerves.¹ There are close to a hundred causes for hiccups, with the most common being gastrointestinal in nature.¹

Hiccups are classified according to their duration:

- Acute hiccups are defined as hiccups that last up to 48 hours.^{1,2}
- Persistent hiccups are hiccups that last for over 48 hours.^{1,2}
- Intractable hiccups are defined as hiccups that last more than one month² or two months.¹

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Causes may be **natural**; pathology of the gastrointestinal tract, thoracic viscera, and central nervous system is among the most common etiologies of persistent and intractable hiccups²; **or drug induced**, and the same agents that are used to treat hiccups may also induce them.¹ Drug-induced causes include benzodiazepines, corticosteroids, antibiotics, opioids, and cytotoxic agents.²

The Pharmacological Treatment of Hiccups

Much of the approach to hiccup therapy is based upon observational studies, case reports and small series that do not directly compare treatment options.³ A 2013 systematic review found no randomized trials evaluating pharmacologic treatments and insufficient evidence to guide the pharmacological or nonpharmacological treatment of persistent or intractable hiccups.³

Nevertheless, if a specific illness is found to potentially be causing the hiccups, the choice of treatment should be directed towards treating the illness e.g. treatment with a proton pump inhibitor or an H₂ antagonist if gastroesophageal reflux disease is a likely cause.³

The information outlined below relates only to the pharmacological management of hiccups. The management of acute or persistent hiccups and the management of intractable hiccups are discussed.

Acute or Persistent Hiccups

There are many times when the cause of hiccups cannot be identified or addressed, and in these cases general measures/treatments should be instituted.¹ Medications will be discussed in greater detail in the next section.

1. Pharyngeal Stimulation

- Nebulised 0.9% saline (2mls over 5 minutes).⁴

2. Reduce Gastric Distension ± gastro-oesophageal reflux

- Peppermint Water

Peppermint water facilitates belching by relaxing the lower oesophageal sphincter.⁴ Peppermint water may have to be extemporaneously prepared for

the patient. It may be difficult for patients to source in the community.

- Antiflatulent⁴, e.g. simethicone
Maalox Plus[®] or Rennie Deflatine chewable tablets also contain antacids^{5,6}
- Prokinetic e.g. metoclopramide⁴
N.B. Peppermint water and metoclopramide should not be used concurrently because of their opposing actions.⁴
- Proton Pump Inhibitor e.g. lansoprazole⁴

3. *Muscle relaxant*

- Baclofen⁴
- Nifedipine⁴
- Midazolam⁴

4. *Central suppression of the hiccup reflex*

Dopamine antagonists:

- Metoclopramide⁴
- Haloperidol⁴
- Chlorpromazine⁴
- Methylphenidate⁴

GABA agonists:

- Baclofen⁴
- Sodium valproate⁴
- Gabapentin⁴

Intractable Hiccups

Evidence supporting drug treatment for intractable hiccups remains inconclusive. Drug therapy should be reserved for treatment of hiccups when physical manoeuvres have failed.³ If hiccups subside following treatment, drug treatment can usually be stopped the day after cessation of hiccups.³ Most drug treatments can be used for seven to ten days.³ If hiccups persist, it is reasonable to consider another pharmacologic or non-pharmacologic treatment option.³ In the absence of data comparing drug treatments, chlorpromazine is suggested as first-line drug therapy.³ Chlorpromazine has been one of

the most commonly used drugs for hiccups, has good efficacy, and is generally well-tolerated at low doses.³

A significant number of medicines have been associated with the treatment of hiccups. Only the most common medicines are discussed below.

1. *Chlorpromazine* 10-25mg PO or IV if no response (maintenance 25-50mg TDS)⁴

Chlorpromazine, a dimethylamine derivative of phenothiazine, acts centrally by dopamine antagonism in the hypothalamus.¹ Chlorpromazine is the only drug licensed for the treatment of hiccups.⁷ However, it may not be optimal for all patients due to adverse effects such as hypotension, urinary retention, glaucoma, or delirium.²

2. *Metoclopramide* 10mg (maintenance 10mg TDS-QDS)⁴

Metoclopramide tightens the lower oesophageal sphincter and hastens gastric emptying.⁴ Metoclopramide may reduce the intensity of oesophageal contractions.¹ Metoclopramide has been utilised for at least 20 years and is often effective for termination of hiccup, most likely through central dopaminergic blockade.²

3. *Baclofen* 5mg PO (maintenance 5-20mg TDS, occasionally more)⁴

Baclofen, a gamma-amino butyric acid (GABA) analogue that activates an inhibitory neurotransmitter is thought to aid in blocking the hiccup stimulus.¹ Lower doses should be selected in patients with renal impairment.⁸ It may not be well tolerated in the elderly due to the frequent occurrence of ataxia, delirium, dizziness and sedation.² Baclofen has been shown to successfully treat persistent and intractable hiccups in several cases.⁹

4. *Nifedipine* 10mg PO (maintenance 10-20mg TDS, occasionally more)⁴

Nifedipine, a calcium channel blocker, may play a role in reversing the abnormal depolarization in the hiccup reflex arc.¹ It has been reported to terminate persistent hiccups but has a propensity for inducing hypotension, which may be especially severe in volume contracted patients or those receiving opioids.² For intractable hiccup doses ≤160mg/24 hours PO have been used with concurrent fludrocortisone 0.5-1mg PO to overcome associated orthostatic hypotension.¹⁰

5. *Midazolam* 10-60mg/24h by CSCI if patient in the last days of life⁴

Midazolam infusion may be especially useful if intractable hiccups occur in the setting of refractory terminal delirium or agitation.²

6. *Haloperidol* 5-10mg PO or IV if no response (maintenance 1.5-3mg at night PO)⁴

Haloperidol acts centrally by dopamine antagonism in the hypothalamus.¹ It may be useful in patients with concurrent agitated delirium, but monitoring for extrapyramidal symptoms is important.²

7. *Methylphenidate* 5mg PO (maintenance 5-10mg BD)⁴

The neurostimulant methylphenidate may terminate hiccups through inhibition of dopamine and the inhibition of norepinephrine uptake.² Patients with concurrent depression or opioid-induced sedation may be good candidates for methylphenidate treatment of hiccups.² Maréchal et al report a case study of a 56-year-old man with metastatic small-cell lung cancer, a persistent hiccup was refractory to classic treatments.¹¹ Methylphenidate was started at 10mg once daily.¹¹ It was rapidly efficient and well tolerated.¹¹

8. *Sodium Valproate* 200-500mg PO (maintenance 15mg/kg/24hr in divided doses)⁴

Sodium valproate enhances GABA transmission centrally and is thought to aid in blocking the hiccup stimulus.¹

9. *Gabapentin* 300 mg three times daily orally & titrate according to response¹³ or

Burst: e.g. 400mg TDS for 3 days, then 400mg once daily for 3 days, then stop⁴

Gabapentin produces blockade of neural calcium channels and increases release of GABA, which may modulate diaphragmatic excitability.² The role of gabapentin as front-line treatment for persistent and intractable hiccups in the palliative care and hospice settings is yet to be determined.² Porzio et al evaluated the safety and efficacy of gabapentin in the treatment of severe chronic hiccups in patients with advanced cancer. They carried out a retrospective chart review.¹² They described complete resolution of hiccups, in 83.8% (31/37) of in-hospital patients and 66.7% (4/6) of patients observed at home. 10.8% (4/37) of in-hospital patients and 33.3% (2/6) of patients observed at home experienced a reduction of hiccups. Responses were observed in 32 patients (74.4%)

with gabapentin at a dosage of 900 mg per day and in 9 patients (20.93%) at 1200 mg per day. Using the Epworth Sleepiness Scale, grade 2 sleepiness was observed in 2 patients (4.65%), and grade 1 sleepiness was observed in 10 patients (23.25%).¹² Gabapentin is well tolerated and may be used as a second line to chlorpromazine when adverse effects are not tolerated.¹³

10. Nefopam

Nefopam is a non-opioid analgesic structurally related to antiparkinsonian and antihistaminic medications, intravenous nefopam has been reported to abruptly terminate hiccups in three patients with refractory hiccups, one of whom had acute leukaemia.²

11. Carvedilol

Carvedilol suppressed a 2-year bout of hiccups in a patient with tardive dyskinesia.² Although the mechanism is unclear, antagonism of the sympathetic component of the afferent hiccup arc may be responsible.² It is unclear if beta-adrenergic antagonists as a class, are useful for treating hiccups, as data is insufficient.² Stueber & Swartz reported a case study of constant hiccupping, marked tardive dyskinesia, compulsive self-induced vomiting, and feelings of hopelessness and low mood in a 59-year-old African-American man that was relieved by carvedilol (6.25 mg, 4 times daily).¹⁴

12. Lidocaine

Bolus intravenous infusion of the sodium channel–blocking anaesthetic lidocaine has terminated hiccups in postoperative patients, but the risk for cardiovascular and neurologic toxicities should be considered in the frail patient with advanced malignancy.² Nebulised lidocaine may be effective via a local anaesthetic effect upon irritant sensory afferents and has a much greater safety profile than the intravenous route.² Kaneishi and Kawabata outline a case report where lidocaine CSCI was effective in relieving persistent hiccups unresponsive to haloperidol.¹⁵ Lidocaine 480mg/day was administered to the patient with cardiac monitoring twice daily. No local or systemic adverse effects were reported.¹⁵ (Case report is available on request).

13. Olanzapine

Alderfer and Arciniegas outlined a case report of a 20 year male patient with a brain injury was treated with olanzapine for intractable hiccups.¹⁶ They found that a maintenance dose of olanzapine 2.5mg once daily provided remission of his intractable hiccups.¹⁶ (Case report is available on request). The pharmacology of olanzapine is complex and among its major effects is antagonism of multiple types of postsynaptic serotonergic receptors.¹⁶ The most consistently demonstrated effect of serotonin on the reflex arcs involved in the generation of hiccups is at the level of the spinal cord, where serotonergic input augments phrenic motoneuronal activity.¹⁶ They proposed that olanzapine, by antagonizing these postsynaptic serotonergic receptors, may decrease phrenic motoneuron excitability and thereby reduce hiccups.¹⁶ They concluded that further investigation of the therapeutic mechanisms and potential role of atypical antipsychotics, and in particular the activity of atypical antipsychotics at serotonergic receptors, in the treatment of intractable hiccup is needed.¹⁶

14. Cisapride

Cisapride is a 5-hydroxytryptamine₄ agonist used to facilitate stomach emptying.¹⁷ It has an effect similar to that of metoclopramide.¹⁷ Cisapride has been used at a dose of 10mg three times daily orally.⁷ Cisapride is an unlicensed product and may be difficult to source.

Combination Therapy for Intractable Hiccups

For intractable hiccups refractory to monotherapy, rational polypharmacy seems a reasonable approach.¹

1. Cisapride, omeprazole and baclofen (COB)¹

Oral treatment with cisapride 10mg three times daily, omeprazole 20mg once daily and baclofen 15mg three times daily was studied by Petroianu et al in patients with intractable hiccups.¹⁷ They concluded that COB is an effective empiric therapy in some patients with intractable hiccups.¹⁷

2. Cisapride, omeprazole, baclofen and gabapentin (COBG)¹

Another study by Petroianu et al recommended that in cases where the results are not entirely satisfactory, the addition of gabapentin should be considered.¹⁸

References

- 1) Smith HS and Busracamwongs A. Management of hiccups in the palliative care

- population. *American Journal of Hospice & Palliative Care*. 2003 Mar-Apr; 20(2):149-54.
- 2) Marinella M. Diagnosis and management of hiccups in the patient with advanced cancer. *The Journal of Supportive Oncology*. 2009; 7:122-127,130.
 - 3) Lembo AJ. Overview of Hiccups. Up to Date. Available from www.uptodate.com. Accessed on the 09/03/2017.
 - 4) Twycross R and Wilcock A. *Symptom Management in Advanced Cancer*. 4th Edition. Radcliffe Medical Press. 2009. Page 174-182
 - 5) Summary of Product Characteristics Maalox Plus Chewable Tablets. Available from www.hpra.ie. Accessed on the 09/03/2017.
 - 6) Summary of Product Characteristics Rennie Deflatine Chewable Tablets. Available from www.hpra.ie. Accessed on the 09/03/2017.
 - 7) Summary of Product Characteristics Clonactil 50mg film coated tablets. Available from www.hpra.ie. Accessed on the 09/03/2017.
 - 8) Summary of Product Characteristics Lioresal tablets 10mg. Available from www.hpra.ie. Accessed on the 09/03/2017.
 - 9) Rizzo C, Vitale C et al. Management of intractable hiccups: An illustrative case and review. *American Journal of Hospice & Palliative Medicine* 2014, Vol. 31(2) 220-224.
 - 10) Monograph Nifedipine. *Palliative Care Formulary*. Available from www.palliativedrugs.com. Accessed on the 09/03/2017.
 - 11) Maréchal R, Berghmans T, Sculier P. Successful treatment of intractable hiccup with methylphenidate in a lung cancer patient. *Support Care Cancer*. 2003 Feb; 11(2):126-8. Epub 2002 Dec 7.
 - 12) Porzio G, Aielli F, Verna L, Aloisi P, Galletti B, e. Gabapentin in the treatment of hiccups in patients with advanced cancer: a 5-year experience. *Clinical Neuropharmacology*. 2010 Jul; 33(4):179-80.
 - 13) Thompsom DF and Brooks KG. Gabapentin therapy of hiccups. *The Annals of Pharmacotherapy*. 2013 Vol. 47, 897-902.
 - 14) Stueber D, Swartz CM. Carvedilol suppresses intractable hiccups. *The Journal of the American Board of Family Medicine*. 2006 Jul-Aug; 19(4):418-21.
 - 15) Kaneishi K and Kawabata M. Continuous subcutaneous infusion of lidocaine for persistent hiccup in advanced cancer. *Palliative Medicine*. 2012 27(3) 284–285

- 16) Alderfer BS. et al. Treatment of intractable hiccups with olanzapine following recent severe traumatic brain injury. J Neuropsychiatry Clin Neurosci 2006; 18:4, 551-552.
- 17) Petroianu G, Hein G, Petroianu A, Bergler W, Rüfer R. Idiopathic chronic hiccup: combination therapy with cisapride, omeprazole, and baclofen. Clin Ther. 1997 Sep-Oct;19(5):1031-8.
- 18) Petroianu G, Hein G, Stegmeier-Petroianu A, Bergler W, Rüfer R. Gabapentin "add-on therapy" for idiopathic chronic hiccup (ICH). J Clin Gastroenterol. 2000 Apr;30(3):321-4.