



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?**

**September 2011**

### **1. Background**

A hiccup is a repeated involuntary spasmodic contraction of the diaphragm followed by a sudden closure of the glottis which checks the inflow of air and produces the characteristic sounds. Hiccups result when afferent or efferent nerves to the muscles of respiration, or the medullary centres controlling these muscles are irritated. The underlying pathophysiology of intractable hiccups remains to be elucidated, but is believed to involve organic, drug-induced, and/or psychological causes.<sup>1</sup> There are close to a hundred causes for singultus (hiccups),<sup>2</sup> the most common causes of which are gastro-intestinal.<sup>1</sup>

Hiccups are classified according to their duration:

- Acute hiccups are defined as hiccups that last up to 48 hours.<sup>2,3</sup>
- Persistent hiccups are hiccups that last for over 48 hours.<sup>2,3</sup>
- Intractable hiccups are defined as hiccups that last more than one month<sup>3</sup> or two months<sup>2</sup>. Intractable hiccups may result in severe discomfort, decreased physical strength, mental depression, and possibly death, if left untreated.<sup>1</sup>

Palliative Meds Info: Terms and Conditions

The information outlined above is intended for healthcare professionals only. The information outlined above is believed to accurately reflect the medical literature at the time of writing. Healthcare professionals must use their own judgment to determine the accuracy and relevance of the information. See [www.olh.ie](http://www.olh.ie) for full terms and conditions.

Some drugs that are used to treat hiccups can also induce hiccups.<sup>2</sup> Drug-induced causes include benzodiazepines, corticosteroids, antibiotics, opioids, and cytotoxic agents.<sup>3</sup>

## **2. The Pharmacological Treatment of Hiccups**

The pharmacological management of hiccups is based on case studies and clinical anecdote and deciding which medication to use will include consideration of potential side-effects.<sup>4</sup> 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.

### **2.1 Acute or Persistent Hiccups**

The treatment of hiccups should address the specific cause.<sup>1</sup> There are many times when the cause of hiccups cannot be identified or addressed, and in these cases general measures/treatments should be instituted.<sup>2,3</sup>

(Detailed information on the treatment options is available in section 2.2)

#### **2.1.1 Pharyngeal Stimulation**

- Nebulised 0.9% saline (2mls over 5 minutes).<sup>5</sup>

#### **2.1.2 Reduce Gastric Distension**

##### **➤ Peppermint Water**

Peppermint water facilitates belching by relaxing the lower oesophageal sphincter.<sup>5</sup> Peppermint water may have to be extemporaneously prepared for the patient. It may be difficult for patients to source in the community.

- **Antiflatulent<sup>5</sup>**, e.g. Simethicone 25mg  
(Maalox Plus<sup>®</sup> or Rennie Deflatine Chewable Tablets (both also contain

antacids))<sup>6,7</sup>

➤ **Prokinetic**

Metoclopramide 10mg tightens the lower oesophageal sphincter and hastens gastric emptying.<sup>2,5</sup>

N.B. Peppermint water and metoclopramide should not be used concurrently.<sup>5</sup>

### 2.1.3 Gastro-oesophageal reflux:

➤ **Prokinetic** e.g. metoclopramide 10mg q.d.s po.<sup>2</sup>

and/or

➤ **H<sub>2</sub>-receptor antagonist** or **Proton Pump Inhibitor (PPI)**.<sup>2</sup>

### 2.1.4 Diaphragmatic irritation or other cause:

➤ Baclofen 5-20mg three times daily orally (occasionally more).<sup>2</sup>

➤ Nifedipine 10-20mg three times daily orally (occasionally more).<sup>2</sup>

➤ Haloperidol 1.5-3mg at night orally.<sup>2</sup>

➤ Sodium valproate, aim for 15mg/kg/24h in divided doses.<sup>2</sup>

➤ Midazolam 10-60mg/24h by CSCI if all else fails.<sup>2</sup>

### 2.1.5 Central suppression of the hiccup reflex

The blockade of dopamine or the potentiating of GABA can cause central suppression of the hiccup reflex.<sup>5</sup>

*Dopamine antagonists:*

- Metoclopramide (as above).<sup>2</sup>
- Haloperidol 5-10mg PO or IV if no response.<sup>2</sup>
- Chlorpromazine 10-25mg PO or IV if no response.<sup>2</sup>

*GABA agonists:*

- Baclofen.<sup>2</sup> (as above)
- Sodium valproate 200-500mg PO.<sup>2</sup>

## **2.2 Intractable Hiccups**

Evidence supporting drug treatment for intractable hiccups remains inconclusive.<sup>1</sup> Due to the relatively rare occurrence of intractable hiccups, most of the documented cases are single case reports or retrospective case studies.<sup>1</sup> If intractable hiccups remain resistant to non-pharmacological techniques, the strongest evidence to date supports the use of chlorpromazine 25 to 50 mg administered intravenously, with a second dose within 2 to 4 hours intravenously or intramuscularly.<sup>1</sup> The patient should be monitored carefully for anticholinergic side effects, particularly sedation.<sup>1</sup> If chlorpromazine fails to control intractable hiccups, nifedipine, metoclopramide, baclofen, or sodium valproate may be considered.<sup>1</sup> A significant number of medicines have been associated with the treatment of hiccups. Only the most common medicines are discussed below.

### **2.2.1 Chlorpromazine**

**Dose:** Chlorpromazine 10-25mg PO or IV if no response.<sup>2</sup>

Chlorpromazine, a dimethylamine derivative of phenothiazine, acts centrally by dopamine antagonism in the hypothalamus.<sup>1</sup> Chlorpromazine is the only drug licensed for the treatment of hiccups.<sup>8</sup> Chlorpromazine has been considered the drug of choice for intractable hiccups. However, chlorpromazine can cause drowsiness, faintness, palpitations, and tachycardia even in a single dose.<sup>1</sup>

### 2.2.2 Metoclopramide

**Dose:** Metoclopramide 10mg four times daily orally.<sup>2</sup>

Metoclopramide may reduce the intensity of oesophageal contractions.<sup>1</sup>

Metoclopramide has been utilised for at least 20 years and is often effective for termination of hiccup, most likely through central dopaminergic blockade.<sup>2</sup>

### 2.2.3 Baclofen

**Dose:** Baclofen 5-20mg three times daily orally (occasionally more).<sup>2</sup>

Baclofen, a gamma-amino butyric acid (GABA) analogue that activates an inhibitory neurotransmitter is thought to aid in blocking the hiccup stimulus.<sup>1</sup> Baclofen should be used with extreme caution in patients with renal impairment.<sup>9</sup> It may not be well tolerated in the elderly due to the frequent occurrence of ataxia, delirium, dizziness and sedation.<sup>2</sup>

### 2.2.4 Nifedipine

**Dose:** Nifedipine 10-20mg three times daily orally (occasionally more).<sup>2</sup>

Nifedipine, a calcium channel blocker, may play a role in reversing the abnormal depolarization in the hiccup reflex arc.<sup>1</sup> 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.<sup>2</sup>

### 2.2.5 Midazolam

**Dose:** Midazolam 10-60mg/24h by CSCI.<sup>2</sup>

It has been successfully utilized in patients with terminal hiccups. Midazolam infusion may be especially useful if intractable hiccups occur in the setting of refractory terminal delirium or agitation.<sup>2</sup>

### 2.2.6 Haloperidol

**Dose:** Haloperidol 5-10mg PO or IV.<sup>2</sup>

Haloperidol, a dopamine antagonist, may be useful in patients with concurrent agitated delirium, but monitoring for extrapyramidal symptoms is important.<sup>2</sup>

### 2.2.7 Methylphenidate

The neurostimulant methylphenidate may terminate hiccups through inhibition of dopamine and the inhibition of norepinephrine uptake. Patients with concurrent depression or opioid-induced sedation may be good candidates for methylphenidate treatment of hiccups.<sup>2</sup> 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. Methylphenidate was started at 10mg once daily. It was rapidly efficient and well tolerated.<sup>10</sup>

### 2.2.8 Nefopam

It 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.<sup>2</sup>

Intravenous nefopam is unlicensed in Ireland and the UK. Therefore, it may be difficult to source. Nefopam tablets are licensed in Ireland. However, there is no information currently available to support the use of oral nefopam to treat hiccups.

### 2.2.9 Carvedilol

**Dose:** Carvedilol 6.25 mg 4 times daily PO.<sup>11</sup>

Carvedilol suppressed a 2-year bout of hiccups in a patient with tardive dyskinesia. Although the mechanism is unclear, antagonism of the sympathetic component of the afferent hiccup arc may be responsible. It is unclear if beta-adrenergic antagonists

as a class, are useful for treating hiccups, as data is insufficient.<sup>2</sup> Stueber et al 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).<sup>11</sup>

### **2.2.10 Gabapentin**

**Dose:** Gabapentin 300 mg three times daily orally. Titrate according to response.<sup>12</sup> Gabapentin produces blockade of neural calcium channels and increases release of GABA, which may modulate diaphragmatic excitability. 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.<sup>2</sup> 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.<sup>12</sup> They described complete resolution of hiccups, in 31 (83.8%) of 37 in-hospital patients and 4 (66.7%) of 6 patients observed at home. Four (10.8%) of the 37 in-hospital patients and 2 (33.3%) of the 6 patients observed at home experienced a reduction of hiccups. Using the In 2 patients (5.4%), a worsening of hiccups was registered. 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%).<sup>12</sup>

### **2.2.11 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.<sup>2</sup> 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.<sup>2</sup>

### **2.2.12 Olanzapine**

**Dose:** Olanzapine 2.5mg once daily PO.

Alderfer and Arciniegas outlined a case report of a 20 year male patient with a brain injury.<sup>13</sup> They treated intractable hiccups with olanzapine.<sup>13</sup> They found that a maintenance dose of olanzapine 2.5mg once daily provided remission of his intractable hiccups.<sup>13</sup> (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.<sup>13</sup> 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.<sup>13</sup> They proposed that olanzapine, by antagonizing these postsynaptic serotonergic receptors, may decrease phrenic motoneuron excitability and thereby reduce hiccups.<sup>13</sup> 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.<sup>13</sup>

### **2.2.13 Cisapride**

**Dose:** Cisapride 10mg three times daily orally,

Cisapride is a 5-hydroxytryptamine<sub>4</sub> agonist used to facilitate stomach emptying.<sup>14</sup> It has an effect similar to that of metoclopramide.<sup>14</sup> Cisapride is an unlicensed product and may be difficult to source.

## **2.3 Combination Therapy for Intractable Hiccups**

### **2.3.1 Cisapride, omeprazole and baclofen (COB).<sup>2</sup>**

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.<sup>14</sup> They concluded that COB is an effective empiric therapy in some patients with intractable hiccups.<sup>14</sup>

### **2.3.2 Cisapride, omeprazole, baclofen and gabapentin (COBG).<sup>2</sup>**

Another study by Petroianu et al recommended that in cases where the results are not entirely satisfactory, the addition of gabapentin should be considered.<sup>15</sup>

### **3. 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, 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.

### **References**

- 1) Hiccups – etiology and treatment. Drugdex<sup>®</sup> Consults. Micromedex 2.0. Available from <http://hslibrary.ucdenver.edu/>. Accessed September 2011.
- 2) Smith HS, Busracamwongs A. Management of hiccups in the palliative care population. *Am J Hosp Palliat Care*. 2003 Mar-Apr;20(2):149-54.
- 3) Marinella M. Diagnosis and management of hiccups in the patient with advanced cancer. *J Support Oncol*. 2009;7:122-127,130.
- 4) Watson M, Lucas C, Hoy A, Back I, Armstrong P. Hiccups Palliative Adults Network Guidelines. 3<sup>rd</sup> Edt 2011. Pg 99.
- 5) Twycross R, Wilcock A. Symptom Management in Advanced Cancer. 3<sup>rd</sup> Edt. Radcliffe Medical Press. 2008.
- 6) Antacid preparations containing simeticone. British National Formulary 62. [bnf.org](http://bnf.org). September 2011.

- 7) Summary of Product Characteristics Rennie Deflatine Chewable Tablets.  
Accessed on the 28/09/2011. Available from [www.medicines.ie](http://www.medicines.ie).
- 8) Summary of Product Characteristics Chlorpromazine Elixir BP 25mg/5ml Oral Solution. Accessed on the 28/09/2011. Last updated September 2010. Available from [www.imb.ie](http://www.imb.ie).
- 9) Summary of Product Characteristics Lioresal tablets 10mg (Baclofen). Accessed on the 28/09/2011. Available from [www.medicines.ie](http://www.medicines.ie).
- 10) 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.
- 11) Stueber D, Swartz CM. Carvedilol suppresses intractable hiccups. *J Am Board Fam Med*. 2006 Jul-Aug;19(4):418-21.
- 12) Porzio G, Aielli F, Verna L, Aloisi P, Galletti B, Ficorella C. Gabapentin in the treatment of hiccups in patients with advanced cancer: a 5-year experience. *Clin Neuropharmacol*. 2010 Jul;33(4):179-80.
- 13) 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.
- 14) 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.
- 15) 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.