

# Dealing with cases of hiccups

In this article, **Christine Clark** gives a general overview of hiccups and the rarer condition of intractable hiccups

Although almost everyone has experienced hiccups, little is known about their cause or significance. In contrast to reflexes such as coughing and sneezing, hiccups do not appear to have a useful function. Some scientists suggest that the mechanism is a remnant of our evolution from amphibians.<sup>1</sup>

The term “hiccup” is thought to be derived from the sound of the event. The medical term is “singultus”. Episodes range from transient minor attacks to protracted bouts that can continue for days or weeks. The longest recorded bout of hiccups lasted for 60 years. Hiccups can occur at any age. Fetuses hiccup *in utero* and this has given rise to the hypothesis that the hiccup reflex circuitry might be important in the development of a suckling reflex — the sequence of movements during suckling is similar to hiccupping, with the glottis closing to prevent milk entering the lungs.

## Mechanism

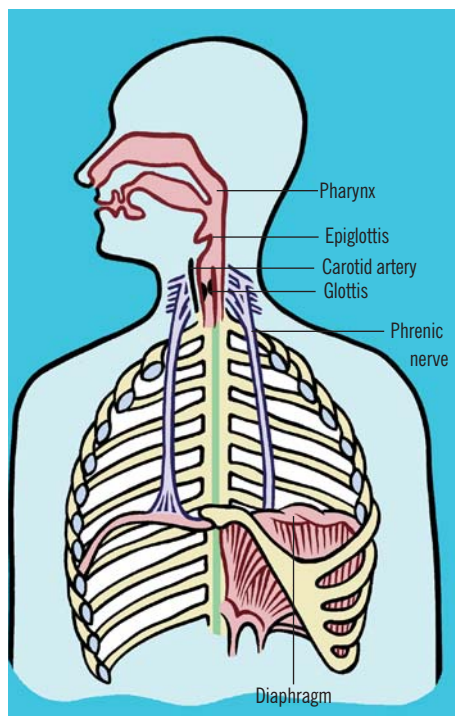
Physiologically, hiccups are forceful contractions of the inspiratory muscles produced by recurring, unpredictable contractions of the diaphragm. They involve involuntary lowering of the diaphragm and closure of the glottis and this produces the characteristic sound as breath is drawn. The glottis closes 35 milliseconds after electrical activity in the diaphragm and intercostal muscles rise, preventing further inspiration. Hiccups are associated with irritation of the phrenic nerves (see Panel 1, p648).

Observations have shown that hiccups follow a pattern in any individual. They will occur between four and 60 times per minute. The frequency remains relatively constant for that individual and is inversely related to arterial partial pressure of carbon dioxide ( $pCO_2$ ). Increasing  $pCO_2$  can reduce hiccup frequency.

**Reflex arc** A hiccup reflex arc has been described. The afferent limb of the arc (carrying impulses to the central nervous system [CNS]) is composed of the vagus and phrenic nerves and parts of the sympathetic nervous system arising from thoracic segments (T6–T12). The “hiccup centre” is located in the upper spinal cord (cervical spinal cord nerves C3–C5). The efferent limb (carrying impulses from the CNS to the target organs) of the reflex is primarily the phrenic nerve with involvement of the nerves to the glottis and accessory muscles of respiration.

## Causes of hiccups

Hiccups can occur spontaneously or can be precipitated by gastric distension. Causes of gastric distension include overeating, eating

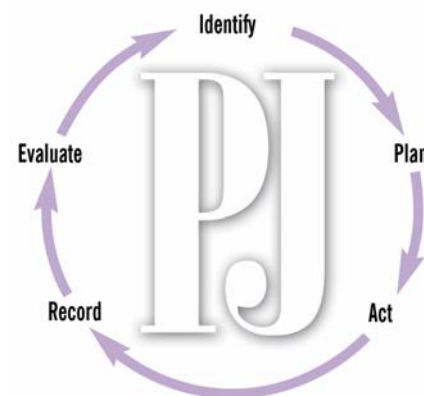


too fast, drinking carbonated drinks, aerophagia (swallowing air), a sudden change in temperature (eg, hot or cold food or drinks, a cold shower), alcohol or excess smoking. Hiccups can also be psychogenic (ie, caused by sudden excitement or emotional stress).

**Intractable hiccups** Most cases of hiccups resolve spontaneously. Episodes of long duration are described as “protracted”, “persistent”, or “chronic” if they last for more than 48 hours. Hiccups lasting for more than one month are described as “intractable”. Protracted or intractable hiccups are usually associated with an underlying disease and should be investigated. Although hiccups occur equally commonly in men and women, protracted and intractable hiccups are seen more commonly in men.

Prolonged or severe attacks of hiccups have been associated with significant morbidity. They are exhausting and extremely distressing. Prolonged hiccups disturb eating, drinking and sleeping resulting in weight loss, malnutrition and exhaustion. Wound dehiscence and death have also been reported.

The underlying causes of persistent or intractable hiccups are a heterogeneous collection of conditions that stimulate the nerves involved in the hiccup reflex. Such stimulation can be due to a range of causes: structural



## Identify knowledge gaps

1. How are intractable hiccups defined?
2. What are the causes of hiccups?
3. What drugs (licensed and unlicensed) are used to treat intractable hiccups?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society’s areas of competence for pharmacists are listed in “Plan and record”, (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to “drug therapies in the context of overall patient and disease management” (see appendix 4 of “Plan and record”).

(eg, diaphragmatic irritation caused by pericarditis or subphrenic abscess); metabolic (eg, uraemia or hypokalaemia); toxic (eg, acute alcoholism); inflammatory (eg, appendicitis, cholecystitis, or inflammatory bowel disease); demyelinating (eg, multiple sclerosis); neoplastic (eg, central nervous system or gastro-oesophageal tumours); or infectious (eg, chest infections).

Some drugs, including benzodiazepines, methyl dopa and antibiotics, have been linked to the onset of hiccups. There are also various reports of hiccups occurring secondary to corticosteroid therapy (especially at high-doses). It has been suggested that corticosteroids allow hiccups to occur by lowering the synaptic threshold in the brainstem.

In addition, hiccups are listed as a side effect for buprenorphine, nicotine replacement therapy, ondansetron and aprepitant.

## Treatment of hiccups

Hiccups have been known since ancient times. In Plato’s ‘Symposium’, Eriximachus the physician advises Aristophanes: “. . . hold your breath, and if after you have done so for some time the hiccup is no better, then gargle with a little water, and if it still continues, tickle your nose with something and sneeze, and if you sneeze once or twice, even the most violent hiccup is sure to go.” In fact,

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## Panel 1: Glossary

**Carotid sinus** The carotid sinus is a widening of the wall of each carotid artery (two carotid arteries run up either side of the front of the neck) that contains baroreceptors.

**Glottis** The glottis is the space between the vocal cords.

**Pharynx** The pharynx is the space at the back of the mouth that leads to the digestive tract and the respiratory tract.

**Phrenic nerves** The phrenic nerves are the two major nerves that supply the diaphragm. Arising from the third, fourth and fifth cervical spinal nerves (C3, C4 and C5), they pass through the chest and each phrenic nerve supplies one side of the diaphragm, the main muscle used in breathing. The phrenic nerves, therefore, control breathing. They also provide sensory innervation for many components of the mediastinum, pleura and the upper abdomen (eg, the liver). Pain arising from structures served by the phrenic nerve is often referred to other somatic regions served by spinal nerves C3–C5. For example, the pain of angina pectoris is classically felt in the chest and down the left arm.

most hiccups will stop spontaneously and rarely require treatment.

Evidence from controlled trials for the treatment of hiccups is lacking and guidance is generally based on evidence from case studies or anecdotal reports. A variety of measures appear to be successful including physical manoeuvres, drug treatment, acupuncture, electrical stimulation and nerve blocks. Many of the measures that have passed into popular folklore do have a sound physiological basis.

**Physical manoeuvres** A number of simple physical manoeuvres that attempt to interrupt the hiccup reflex have been devised (or have been recognised over the years). Stimulation of the nasopharynx is often recommended in emergency medicine manuals. This is done by rubbing the patient's soft palate with a swab, catheter tip or finger, just short of stimulating a gag reflex. This is continued for several minutes. Other measures that achieve much the same thing include inhaling smelling salts, tasting vinegar or angostura bit-

## Panel 2: Self help methods for hiccups

- Sip iced water
- Swallow granulated sugar
- Bite on a lemon
- Hold your breath, hyperventilate or breathe into a paper bag
- Get someone to give you a sudden fright, causing you to gasp
- Pull your knees to your chest

ters, forcible traction of the tongue and drinking out of the wrong (far) side of a glass.

Vagal stimulation can be effective. The vagal nerves supply the throat, larynx, lungs and oesophagus. Probably the best-known example of vagal stimulation is the Valsalva manoeuvre. This is when a patient attempts to breathe out against a closed glottis. The patient is usually instructed to close his mouth, hold his nostrils closed and attempt to breathe out. This results in an increase in intra-thoracic pressure. Everyone knows how to perform a Valsalva manoeuvre because it is done instinctively when "bearing down" during a bowel movement. Vagal stimulation can also be achieved by carotid sinus (see Panel 1) massage but this should only be performed under medical supervision.

Interruption of normal respiratory function is a well-known approach (eg, holding your breath, which also increases carbon dioxide pressure) and counter-irritation of the diaphragm (eg, by leaning forward to compress the chest) can also be effective. Methods suggested by Prodigy guidance on hiccups<sup>2</sup> are listed in Panel 2 and pharmacists can recommend these. However, prolonged or intractable hiccups should be referred for investigation, which would probably include checking serum electrolytes and blood glucose and performing a full blood count. If an organic cause is found for persistent or intractable hiccups, treatment should be directed at the underlying disorder.

**Drug therapy** Drug therapy is indicated for persistent or intractable hiccups. It is directed at blocking impulses in the hiccup reflex arc, by creating counter-stimulating impulses, or affecting the cause. Chlorpromazine and haloperidol are licensed for the treatment of hiccups. Chlorpromazine should be given in a dose of 25mg three times a day. If hiccups are not relieved, the dose may be increased by one 25mg tablet each day, to a maximum of eight tablets in 24 hours. It is not known which of chlorpromazine's many actions is responsible for its beneficial effect in hiccups. Haloperidol should be given in a dose of 1.5mg three times a day. If hiccups are not relieved, the dose may be increased by one 1.5mg tablet each day up to a maximum of six tablets in 24 hours. If one does not work, the other is tried. It is worth noting, however, that although haloperidol is less sedative than chlorpromazine it is more likely to produce extrapyramidal effects.

Metoclopramide, in a dose of 10 mg every eight hours, can be particularly useful for treating hiccups associated with gastric stasis. Although not licensed for this indication, it is commonly used in palliative care for this purpose.

Numerous other drugs including baclofen, nifedipine, carbamazepine, amitriptyline, phenytoin, sodium valproate and lidocaine have been recommended for the treatment of hiccups but none of these is licensed for this purpose. Numerous case reports are available, illustrating the use of these drugs in hiccups.

The World Health Organization has made recommendations for drug treatment of intractable hiccups in cases of terminal illness.<sup>3</sup>

**Alternative therapies** Acupuncture and hypnotherapy might be effective in some cases and electrical stimulation or surgical or chemical disruption of the phrenic nerve may be considered for hiccups that fail to respond to drug treatment and that cause significant discomfort.

**1977 protocol** Despite the paucity of evidence for intractable hiccup treatments, a treatment protocol was suggested by Williamson and Macintyre in 1977.<sup>4</sup> This proposes several treatment steps, starting with correcting any metabolic abnormalities and administering granulated sugar and ending with phrenic nerve crush.

## References

1. Randerson J. Tadpoles take the blame for human hiccups. Available at [www.newscientist.com](http://www.newscientist.com) (accessed 30 September 2004).
2. Prodigy guidance on hiccups 2002. Available at: [www.prodigy.nhs.uk](http://www.prodigy.nhs.uk) (accessed 30 September 2004).
3. World Health Organization. Hiccup In: Symptom relief in terminal illness. Geneva: WHO; 1998.
4. Williamson BWA, Macintyre IMC. management of intractable hiccup BMJ 1977;2:501–3.

## Resources

- Wilkes G. Hiccups. eMedicine Available at: [www.emedicine.com](http://www.emedicine.com) (accessed 30 September 2004).

## Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Visit the Prodigy website and read the information available on drugs used to treat hiccups (see reference 2).
2. Discuss the treatment of intractable hiccups with a palliative care pharmacist.
3. Search medical journals for case reports of hiccups. For example:
  - "Benzotropine for the treatment of intractable hiccups: New indication for an old drug? (2002)" [www.caep.ca/004.cjemjcmu/004-00.cjem/vol-4.2002/v43-205.htm](http://www.caep.ca/004.cjemjcmu/004-00.cjem/vol-4.2002/v43-205.htm)
  - "Cervical phrenic nerve block for intractable hiccups in cancer patients (2002)" <http://jncicancerspectrum.oupjournals.org/cgi/content/full/jnci;94/15/1175>
  - "The steroid-responsive hiccup reflex arc: competitive binding to the corticosteroid receptor? (2003)" [http://www.nel.edu/24\\_34/NEL243403C01\\_Dickerman.htm](http://www.nel.edu/24_34/NEL243403C01_Dickerman.htm)

## Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?