

Intractable Hiccups Post Stroke: Case Report and Review of the Literature

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Introduction

Intractable hiccups are uncommon but important sequelae in the aftermath of ischaemic stroke. We present the case of a 50 year old gentleman, who developed what we believe to be the first case of intractable hiccups secondary to cerebellar infarction. The hiccups were refractory to wide range of single pharmaceutical and surgical interventions and we eventually found some success with dual pharmaceutical therapy. Intractable hiccups can have a significant impact on post stroke rehabilitation and have a considerable detrimental impact on an individual's quality of life. The mechanism is poorly understood. We performed a literature review of all known cases and have postulated a revised mechanism that includes a role for the cerebellum in this phenomenon. A portal is needed for physicians to submit their experiences within intractable hiccups, so that more can be learnt about what can be a disabling condition for the sufferer.

Case Report

A 50 year old gentleman presented to our acute medical unit in September 2007 with a brief history of headache, vertigo, vomiting and mild left facial paraesthesia. On clinical examination, he had normal tone, power and reflexes in upper and lower limbs and sensation was intact in all modalities. Nystagmus was present on bilateral and vertical gaze and he complained of diplopia at resting gaze. His gait was unstable, but difficult to assess owing to his considerable diplopia and vertigo. Full blood count, renal and liver function and electrolytes including sodium, potassium and calcium were all within normal ranges. Computed tomography (CT) showed a possible area of low attenuation in the left cerebellar hemisphere, with no haemorrhage. A lumbar puncture was performed owing to the sub-acute history and the fluid appeared clear and had a predominant mononuclear cell type, with no organisms seen on microscopy. He was treated as viral meningitis and commenced on intravenous acyclovir at 10 mg/kg. 48 hours into admission he began to develop hiccups. Repeat CT 72 hours later confirmed earlier suspicions of a left cerebellar infarction in, with a further infarct in the inferior aspect of the right cerebellum. It was felt viral meningitis may have been the aetiology of these lesions. 7 days later the headache, diplopia and vertigo had begun to settle, but hiccups persisted. He was commenced on chlorpromazine 12.5 mg thrice daily (tds). Magnetic resonance imaging confirmed wedge infarction in the aforementioned areas.

Otolaryngology review revealed no precipitant for his hiccups and CT of his neck, thorax and abdomen showed no macroscopic pathology. On subsequent review his hiccups still persisted, and he was converted to haloperidol 1.5 mg tds. Endoscopy showed only mild gastritis and he was commenced on a proton pump inhibitor. Prior to this he experienced blackouts and was commenced on lamotrigine with a diagnosis of probable seizures. On further review 10 months post discharge, he was still having significant hiccups. They were occurring at an interval of approximately 72 hours and were persistent over a 2-3 day period, whereby they would disrupt sleep, ability to eat and lead to episodes of vomiting. Indeed he went on to have

several admissions for dehydration secondary to this. He was notably depressed and tearful at this meeting and felt his quality of life was very poor during hiccup bouts. Baclofen 5 mg tds was commenced and later titrated up to 10 mg tds. Over the following 12 months he was trialled on pregabalin (max dose 150 mg twice daily), Nifedipine (5 mg tds) whilst levomepromazine, dexamethasone and ondansetron were used for their anti-emetic properties.

18 months post discharged he was referred to a neurosurgeon. It was agreed that on account of the fact he had failed multiple medical therapies, had no obvious treatable causative pathology and was disabled by his symptoms, that a vagal nerve stimulator would be of worthy trial. He underwent this, with successful block of the vagal nerve, but no resolution in his hiccups. He remained on baclofen and underwent trials of piracetam (to treat a possible myoclonic disorder), oral lidocaine and phenytoin over the following six months, again with no improvement in hiccup frequency or his quality of life. Phrenic nerve block was also attempted with cervical injection of bupivacaine, but that was also unsuccessful in terminating hiccups. With baclofen at 10 mg tds, we then introduced gabapentin, titrating the dose to 1.2 mg tds. On last clinical review he had experienced a decrease in frequency of hiccups with this regime, now citing a maximum hiccup frequency of 3-4 episodes per week that last considerably less than 12 hours and on occasion being able to go for over week with any occurrence. The option of deep brain stimulation was presented to our patient, but he has declined this invasive treatment owing to the potential risks weighed up against a strong possibility of little benefit.

Definitions and Aetiologies

So what are hiccups? Hiccups (hiccoughs or singultus) can be described as synchronous contraction of the diaphragm and intercostal muscles, followed by sudden closure of the glottis, the latter part being responsible for the characteristic 'hiccup' sound that is heard [1]. Intractable hiccups (IH) are generally defined as hiccups lasting for a period in excess of one month.

Many of us will have witnessed hiccups in the aftermath of strokes affecting the posterior circulation. The lateral medullary or Wallenberg's syndrome is the one most commonly described [2,3], indeed Keane's analysis found 56% of his experience with central hiccups were secondary to lateral medullary infarcts [4]. However, any ischaemic insult to the brainstem or pons [5] will place an individual

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Received October 09, 2012; Accepted October 26, 2012; Published October 28, 2012

Citation: Ferdinand P, Oke A (2012) Intractable Hiccups Post Stroke: Case Report and Review of the Literature. J Neurol Neurophysiol 3:140. doi:10.4172/2155-9562.1000140

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at risk of developing IH, and haemorrhage [4,6], haematomas [7], vertebral artery dissection [8] and aneurysms (in particular of the posterior inferior cerebellar artery) [9] are other documented vascular causes.

IH are also seen in a variety of space occupying lesions including cavernous angiomas [10-12], haemangioblastomas [13], astrocytomas [14] and tuberculomas [15]. It is of note that IH can be the initial and often only presenting complaint in many of these patients. Demyelinating pathologies such as multiple sclerosis [16,17], neuromyelitis optica [18-20] and progressive multifocal leukoencephalopathy [21] can also portray such Characteristics, and IH can also represent a neurological manifestation of a systemic disorder such as sarcoidosis [22,23] or systemic lupus erythematosus [24].

For the majority, the location of “the lesion” has been either in the brainstem, pons or cervical cord, much in keeping with the ideological hypothesis of the hiccups reflex arc. However, a few cases report lesions in other areas of the brain such as the cerebellum (our patient), basal ganglia [25], insula cortex [26], and infarcts to the corona radiata or that follow extensive middle cerebral artery infarction [27]. These reports challenge this hypothesis and require a revision of the central component of the hiccups phenomenon. There are many ‘peripheral’ causes of IH and often identification and treatment of them will result in their termination. Discussion of them is beyond the scope of this article.

Physiology

Marinella and colleagues were able to demonstrate that in their cohort of patients with advanced malignancy, the left hemi-diaphragm was the side of hiccup origin in 80% of the cases [28]. Hiccups have been documented to occur in foetal life from eight weeks gestation [29] and can continue into early neonatal life, waning rapidly from there onwards. The exact function of hiccups has never been fully understood. Its more frequent existence in utero has led many to believe it is either an evolutionary or primitive reflex. With a considerable number of ‘peripheral aetiologies’ it may well represent a very basic non-discriminant alert mechanism to thoraco-abdominal disturbance.

Currently, the hiccups reflex arc is believed to have three components. The afferent arm consists of the phrenic and vagus nerves and the T6-T12 portion of the sympathetic chain, all of which convey sensory information from the thoraco-abdominal cavity. All information from these fibres is relayed to a central “hiccup centre” in the brainstem and then the hiccup action is facilitated via efferents carried in the phrenic nerve, external intercostal muscle (T1-T11) nerves and the scalene anticus nerve supplying the scalene muscles [30]. If indeed the hiccup represents an archaic or primitive reflex and we have already proven that damage to the central nervous system can lead to hiccup production, the reflex must be under constant suppression and damage to the areas of inhibition will lead to hiccups.

The reports above highlight that the brainstem has a well established role in the pathway of IH. However, the intrinsic mechanism underlying this is not clear. In an individual there is close interaction between the respiratory inspiratory centre (nucleus tractus solitarius as its nucleus), the more antero-lateral expiratory centre (nucleus ambiguus as its nucleus) and the apneustic centre in the lower pons which has a mutual inhibitory role on the expiratory centre. Al Deeb et al. [15] reminds us that normal respiration comprises of a continuous signal

from the nucleus tractus solitarius that then goes on to be inhibited via pneumotaxic inhibition of the apneustic centre and therefore the inspiratory centre and allow expiration to take place. In the hiccups scenario, there would appear to be an abnormal sudden discharge presumably down the vagus nerve from the nucleus ambiguus which one would presume is normally under inhibitory control and thus a hiccup is generated. Various other neural connections with areas such as the nucleus raphe magnum [31], Guillian- Mollaret triangle (inferior olive complex, dentate nucleus and red nucleus) [32] and the area postrema [20] have independently been suggested to be involved and interact with this pathway, but clearly damage to these connections leads to a switching off of an hiccup inhibitory mechanism. But does the origin of hiccup inhibition come from within the brainstem itself?

Our patient presented with solely cerebellar infarcts, implying that it may have some inhibitory control over hiccups genesis. In her paper, Bastian describes the ‘feedforward’ mechanism of movement control that the cerebellum has [33]. This is the concept that the cerebellum is involved in the predictive aspect of movement, that is, the part of an action that is pre-planned and is unchanged prior to it happening. This is in contrast to reactive movements in which changes are made on the basis of peripheral feedback mechanisms. Furthermore the cerebellum is also able to learn from previous errors and thus make predictive adjustments in the future. Earlier we described how hiccups are seen in infants from eight weeks gestation and we also know that the foetus may be hiccupping 2-5% of the time it is in utero [34]. It is possible therefore that the rapid decrease in hiccups postpartum represents the developing cerebellum’s ability to suppress the hiccup mechanism pathway via a learned response developed in utero, recognising that a hiccup has a relatively non-descript functional use in humans.

At this point we must not forget that hiccups have been reported in supratentorial infarctions, notably the basal ganglia, the insula, corona radiata and in an extensive MCA infarction. What is not clear is whether or not the input from these areas also represents an inhibitory response that is not quick enough to suppress a hiccup, or whether it is a remnant of a now unnecessary physiological function and represents the true origins of hiccup genesis. It could be that the cerebellum interacts with these connections at some point prior to them entering the brainstem.

From what we have presented we feel that the hiccups mechanism is somewhat more complex than previously thought. A possible mechanism is as follows. There are still afferents from the phrenic, vagus and sympathetic portion of T6-T12. These afferents provide information regarding thoraco-abdominal irritation and cause what we could term an ‘appropriate hiccup’. This then feeds to the brainstem. At this point the information is conveyed further to the cerebral cortex, where efferents for hiccups genesis begins and are relayed back to the brainstem. The reports we have found would suggest that the insula and basal ganglia are involved in this. The cerebellum maintains inhibition of hiccups possibly using a learned ‘feedforward’ mechanism through connections to the respiratory centres and nuclei in the medulla and also by inhibiting the descending information from the cortex. In an intact central circuit, when an afferent input is received to the cortex, it could be that the cerebellar inhibition is relaxed, allowing the generation of an ‘appropriate hiccup’ in response to a peripheral stimuli. Infarction of the brainstem may cause disruption of inhibitory connections from the cerebellum and lead to formation of hiccups. Infarction of the cerebellum may cause a loss of a learned feedforward

inhibition and lead to hiccups. It is not entirely clear how cerebral infarction may lead to hiccups, particularly with an intact cerebellum, but from the case reports highlighted above it is clear there is some supra-tentorial involvement in the hiccups pathway.

If one is not convinced of the cerebellum's involvement in the control of hiccups, alternative diagnosis for our patient are that the hiccup represents a form of cerebellar diaphragmatic ataxia and actually represents the inability to correctly co-ordinate diaphragmatic movement, or it may be part of a myoclonic disorder spectrum, but it is of note that he failed treatment for the latter. The fact that IH has not been described in cerebellar infarction previously may be due to previous lack of involvement of associated areas involved the pathway, the possibility that suppressive information may be stored in both cerebellar hemispheres and requires both areas to be infarcted to disrupt inhibition or that concomitant pontine/medullary infarction has occurred and masked the cerebellar involvement.

Consequences of Hiccups

So why should we care about IH? IH is associated with poor oral intake, leading on to weight loss [1] and malnutrition. Many of these patients are also likely to have varying degrees of dysphagia. Couple this with an increased likelihood of regurgitation [35] and gastro-oesophageal reflux in IH and concerns develop regarding aspiration and the subsequent development of pneumonia [3]. Individuals with a high hiccups rate will also have increased energy expenditure and thus increased energy requirements [28], an issue only further compounded by the aforementioned factors.

IH can also have an impact on the ability to hold conversation [36] and one can only imagine the additional frustration of a patient who is already either dysarthric, dysphonic or has expressive dysphasia. Generalised exhaustion and confusion can occur, often the result of the marked disturbance in sleep experienced by sufferers [37]. Kumar et al. [5] demonstrated that patients with IH had a nine day longer hospital stay than those without, highlighting clearly the difficulties in rehabilitation that this disorder brings. Unfortunately, a depressive illness can evolve during this process. There have been some reports of more extreme sequelae of intractable hiccups, most notably severe bradyarrhythmias [38] (likely owing to the increased vagal tone as a hiccup can often mimic a valsava manoeuvre) and bilateral carotid artery dissection [39].

Some have also voiced concern with regards to many of the treatments for IH having sedative side effects which may cause concerns over airway protection and aspiration during episodes of regurgitation secondary to IH and also having unwanted motor side effects (parkinsonism, dystonia and akathisia) which will further impair rehabilitation in individuals with varying degrees of motor impairment.

Treatment

Treatment of hiccups (whether IH or not), ranges from the anecdotal, pharmacological and the more invasive. Anecdotal treatments include digital rectal examination [40,41], sexual intercourse [42], smoking marijuana [43], breath holding, valsava manoeuvres and inhaling and exhaling through a paper bag [28] (as the latter will increase carbon dioxide levels which have been documented to slow hiccup rate down).

A wide range of pharmacological agents have been used for hiccups. Whilst in the UK it is chlorpromazine and haloperidol that are currently licensed for treatment, current literature suggests better outcomes with other medication, in particular gabapentin [44-48] and baclofen [49-54]. Porzio et al. [55] reported a five year experience in treating palliative patients with IH with gabapentin, reporting an improvement or at least reduction in hiccup frequency in 74.4% of patients treated with 900mg/day and a further 20.93% at 1200mg/day. Guelaud and colleagues reported significant improvement in hiccups in 28/37 patients taking baclofen (with complete resolution in 18 cases) for IH [56], and Ramirez and Graham have performed the only randomized control study to date (although it only contained 4 patients) showing that Baclofen decreased the severity but not frequency of IH [57]. Success has been seen with a number of other agents including but not limited to nefopam [58,59], lidocaine [60,61], nifedipine [62], sertraline [63], olanzapine [64], benztropine [65], carvedilol [66], amantadine [67], amitriptyline [68], midazolam [31,69] and general anaesthesia [70]. Various forms of acupuncture have no less robust evidence than any of the aforementioned potential treatments and as a barely invasive procedure and one with no side effects, is certainly an alternative to, or an option for those refractory to medical therapy [71-75].

For those who have exhausted medical and homeopathic therapies, hope of IH termination lies in more invasive therapies, namely phrenic [1,76], vagal or glossopharyngeal nerve [77] blockade, occasionally with a combination of phrenic and vagal nerve block [78] or even stimulation [79]. This is often achieved under the guidance of ultrasound or CT imaging and some have advocated the use of nerve stimulator in confirming correct location of target nerve block [80].

The wide range of therapies (and their known modes of action) in which cure or improvement has been reported only further emphasises how poorly understood the hiccups mechanism is and probably explains the failure of many of the treatments trialled in our patient.

Conclusion

IH have been shown to occur in all types of brain infarctions. They are important as they can delay the initial rehabilitation process and considerably disturb an individual's quality of life. It is a condition that is very poorly understood and as a result has an extensive list of potential therapeutic options. We recommend gabapentin or baclofen as first line treatment, but stress the importance of thorough investigation to rule out a 'peripheral' and potentially reversible cause. We describe the first case of sole cerebellar infarction as a cause of IH and we have proposed potential neurological mechanisms that underpin it. What is now required is a database where people can submit their experiences with IH post stroke or central lesions, so that more can be learned about what remains a mysterious phenomenon.

References

1. Kuusniemi K, Pyylampi V (2011) Phrenic nerve block with ultrasound-guidance for treatment of hiccups: a case report. *J Med Case Rep* 5: 493.
2. Mandalà M, Rufa A, Cerase A, Bracco S, Galluzzi P, et al. (2010) Lateral medullary ischemia presenting with persistent hiccups and vertigo. *Int J Neurosci* 120: 226-230.
3. Park MH, Kim BJ, Koh SB, Park MK, Park KW, et al. (2005) Lesional location of lateral medullary infarction presenting hiccups (singultus). *J Neurol Neurosurg Psychiatry* 76: 95-98.
4. Keane JR (2010) Hiccups due to central nervous system disease: analysis of 71 inpatients. *Can J Neurol Sci* 37: 870-872.

5. Kumar A, Dromerick AW (1998) Intractable hiccups during stroke rehabilitation. *Arch Phys Med Rehabil* 79: 697-699.
6. Kumral E, Acarer A (1998) Primary medullary haemorrhage with intractable hiccup. *J Neurol* 245: 620-622.
7. Schuchmann JA, Browne BA (2007) Persistent hiccups during rehabilitation hospitalization: three case reports and review of the literature. *Am J Phys Med Rehabil* 86: 1013-1018.
8. Meher S, Churasia P, Tandon M, Singh D (2012) Vertebral artery dissection and intractable hiccups: an uncommon presentation. *Neurol India* 60: 108-109.
9. Gambhir S, Singh A, Mairindratna B, Jaeger M, Darwish B, et al. (2010) Giant PICA aneurysm presenting as intractable hiccups. *J Clin Neurosci* 17: 945-946.
10. Arami MA (2010) A case of brainstem cavernous angioma presenting with persistent hiccups. *Acta Med Iran* 48: 277-278.
11. Mattana M, Mattana PR, Roxo MR (2010) Intractable hiccup induced by cavernous angioma in the medulla oblongata: case report. *J Neurol Neurosurg Psychiatry* 81: 353-354.
12. Musumeci A, Cristofori L, Bricolo A (2000) Persistent hiccup as presenting symptom in medulla oblongata cavernoma: a case report and review of the literature. *Clin Neurol Neurosurg* 102: 13-17.
13. Nagayama T, Kaji M, Hirano H, Niuro M, Kuratsu J (2004) Intractable hiccups as a presenting symptom of cerebellar hemangioblastoma. Case report. *J Neurosurg* 100: 1107-1110.
14. Redondo-Cerezo E, Viñuelas-Chicano M, Pérez-Vigara G, Gómez-Ruiz CJ, Sánchez-Manjavacas N, et al. (2008) A patient with persistent hiccups and gastro-oesophageal reflux disease. *Gut* 57: 763, 771.
15. al Deeb SM, Sharif H, al Moutaery K, Biary N (1991) Intractable hiccup induced by brainstem lesion. *J Neurol Sci* 103: 144-150.
16. Witoonpanich R, Pirommai B, Tunlayadechanont S (2004) Hiccups and multiple sclerosis. *J Med Assoc Thai* 87: 1168-1171.
17. de Seze J, Zephir H, Hautecoeur P, Mackowiak A, Cabaret M, et al. (2006) Pathologic laughing and intractable hiccups can occur early in multiple sclerosis. *Neurology* 67: 1684-1686.
18. Takahashi T, Miyazawa I, Misu T, Takano R, Nakashima I, et al. (2008) Intractable hiccup and nausea in neuromyelitis optica with anti-aquaporin-4 antibody: a herald of acute exacerbations. *J Neurol Neurosurg Psychiatry* 79: 1075-1078.
19. Riphagen J, Modderman P, Verrips A (2010) Hiccups, nausea, and vomiting: water channels under attack! *Lancet* 375: 954.
20. Misu T, Fujihara K, Nakashima I, Sato S, Itoyama Y (2005) Intractable hiccup and nausea with periaqueductal lesions in neuromyelitis optica. *Neurology* 65: 1479-1482.
21. Hernández JL, Fernández-Miera MF, Sampedro I, Sanroma P (1999) Nimodipine treatment for intractable hiccups. *Am J Med* 106: 600.
22. Kondo T, Tanigaki T, Suzuki H, Tamaya S, Ohta Y, et al. (1989) Long-standing hiccup in a patient with sarcoidosis. *Jpn J Med* 28: 212-215.
23. Connolly JP, Craig TJ, Sanchez RM, Sageman WS, Osborn RE (1991) Intractable hiccups as a presentation of central nervous system sarcoidosis. *West J Med* 155: 78-79.
24. Sugimoto T, Takeda N, Yamakawa I, Kawai H, Tanaka Y, et al. (2008) Intractable hiccup associated with aseptic meningitis in a patient with systemic lupus erythematosus. *Lupus* 17: 152-153.
25. Schulz-Stübner S, Kehl F (2011) Treatment of persistent hiccups with transcutaneous phrenic and vagal nerve stimulation. *Intensive Care Med* 37: 1048-1049.
26. Longatti P, Basaldella L, Moro M, Ciccarino P, Franzini A (2010) Refractory central supratentorial hiccup partially relieved with vagus nerve stimulation. *J Neurol Neurosurg Psychiatry* 81: 821-822.
27. Chang CC, Chang ST, Lin JC, Li TY, Chiang SL, et al. (2006) Resolution of intractable hiccups after near-infrared irradiation of relevant acupoints. *Am J Med Sci* 332: 93-96.
28. Marinella MA (2009) Diagnosis and management of hiccups in the patient with advanced cancer. *J Support Oncol* 7: 122-127, 130.
29. Launois S, Bizec JL, Whitelaw WA, Cabane J, Derenne JP (1993) Hiccup in adults: an overview. *Eur Respir J* 6: 563-575.
30. Kahrilas PJ, Shi G (1997) Why do we hiccup? *Gut* 41: 712-713.
31. Moro C, Sironi P, Berardi E, Beretta G, Labianca R (2005) Midazolam for long-term treatment of intractable hiccup. *J Pain Symptom Manage* 29: 221-223.
32. Pechlivanis I, Seiz M, Barth M, Schmieder K (2010) A healthy man with intractable hiccups. *J Clin Neurosci* 17: 781-783.
33. Bastian AJ (2006) Learning to predict the future: the cerebellum adapts feedforward movement control. *Curr Opin Neurobiol* 16: 645-649.
34. Kolodzik PW, Eilers MA (1991) Hiccups (singultus): review and approach to management. *Ann Emerg Med* 20: 565-573.
35. Lierz P, Felleiter P (2002). Anesthesia as therapy for hiccups. *Anesth Analg* 95: 494-495.
36. Woelk CJ (2011) Managing hiccups. *Can Fam Physician* 57: 672-675, e198-201.
37. Sanchack KE (2004) Hiccups: when the diaphragm attacks. *J Palliat Med* 7: 870-873.
38. Suh WM, Krishnan SC (2009) Violent hiccups: an infrequent cause of bradyarrhythmias. *West J Emerg Med* 10: 176-177.
39. Badawi RA, Birns J, Ramsey DJ, Kalra L (2004) Hiccups and bilateral carotid artery dissection. *J R Soc Med* 97: 331-332.
40. Odeh M, Bassan H, Oliven A (1990) Termination of intractable hiccups with digital rectal massage. *J Intern Med* 227: 145-146.
41. Fesmire FM (1988) Termination of intractable hiccups with digital rectal massage. *Ann Emerg Med* 17: 872.
42. Peleg R, Peleg A (2000) Case report: sexual intercourse as potential treatment for intractable hiccups. *Can Fam Physician* 46: 1631-1632.
43. Gilson I, Busalacchi M (1998) Marijuana for intractable hiccups. *Lancet* 351: 267.
44. Jatzko A, Stegmeier-Petroianu A, Petroianu GA (2007) Alpha-2-delta ligands for singultus (hiccup) treatment: three case reports. *J Pain Symptom Manage* 33: 756-760.
45. Vandemergel X, Mbeufet M, Renneboog B (2006) Intractable hiccups successfully treated with pregabalin. *Eur J Intern Med* 17: 522.
46. Hernández JL, Pajarón M, García-Regata O, Jiménez V, González-Macías J, et al. (2004) Gabapentin for intractable hiccup. *Am J Med* 117: 279-281.
47. Alonso-Navarro H, Rubio L, Jiménez-Jiménez FJ (2007) Refractory hiccup: successful treatment with gabapentin. *Clin Neuropharmacol* 30: 186-187.
48. Tegeler ML, Baumrucker SJ (2008) Gabapentin for intractable hiccups in palliative care. *Am J Hosp Palliat Care* 25: 52-54.
49. Mariën K, Havlak D (1997) Baclofen with famotidine for intractable hiccups. *Eur Respir J* 10: 2188.
50. Grant JA, Steiner EM, Johnson RH (1991) Treatment of persistent hiccups. *J Neurol Neurosurg Psychiatry* 54: 468.
51. Marino RA (1998) Baclofen therapy for intractable hiccups in pancreatic carcinoma. *Am J Gastroenterol* 93: 2000.
52. Boz C, Velioglu S, Bulbul I, Ozmenoglu M (2001) Baclofen is effective in intractable hiccups induced by brainstem lesions. *Neurol Sci* 22: 409.
53. Oneschuk D (1999) The use of baclofen for treatment of chronic hiccups. *J Pain Symptom Manage* 18: 4-5.
54. Walker P, Watanabe S, Bruera E (1998). *J Pain Symptom Manage*. 16:125-132.
55. Porzio G, Aielli F, Verna L, Aloisi P, Galletti B, et al. (2010) Gabapentin in the treatment of hiccups in patients with advanced cancer: a 5-year experience. *Clin Neuropharmacol* 33: 179-180.
56. Guelaud C, Similowski T, Bizec JL, Cabane J, Whitelaw WA, et al. (1995) Baclofen therapy for chronic hiccup. *Eur Respir J* 8: 235-237.
57. Ramirez FC, Graham DY (1992) Treatment of intractable hiccup with baclofen:

- results of a double-blind randomized, controlled, cross-over study. *Am J Gastroenterol* 87: 1789-1791.
58. Bilotta F, Pietropaoli P, Rosa G (2001) Nefopam for refractory postoperative hiccups. *Anesth Analg* 93: 1358-1360.
59. Bilotta F, Rosa G (2000) Nefopam for severe hiccups. *N Engl J Med* 343: 1973-1974.
60. Boulouffe C, Vanpee D (2007) Severe hiccups and intravenous lidocaine. *Acta Clin Belg* 62: 123-125.
61. Dunst MN, Margolin K, Horak D (1993) Lidocaine for severe hiccups. *N Engl J Med* 329: 890-891.
62. Lipps DC, Jabbari B, Mitchell MH, Daigh JD Jr (1990) Nifedipine for intractable hiccups. *Neurology* 40: 531-532.
63. Vaidya V (2000) Sertraline in the treatment of hiccups. *Psychosomatics* 41: 353-355.
64. Alderfer BS, Arciniegas DB (2006) Treatment of intractable hiccups with olanzapine following recent severe traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 18: 551-552.
65. Cunningham VL (2002) Benztropine for the treatment of intractable hiccups: New indication for an old drug? *CJEM* 4: 205-206.
66. Stueber D, Swartz CM (2006) Carvedilol suppresses intractable hiccups. *J Am Board Fam Med* 19: 418-421.
67. Askenasy JJ, Boiangiu M, Davidovitch S (1988) Persistent hiccup cured by amantadine. *N Engl J Med* 318: 711.
68. Parvin R, Milo R, Klein C, Arlazoroff A (1988) Amitriptyline for intractable hiccup. *Am J Gastroenterol* 83: 1007-1008.
69. Wilcock A, Twycross R (1996) Midazolam for intractable hiccup. *J Pain Symptom Manage* 12: 59-61.
70. Lierz P, Felleiter P (2002) Anesthesia as therapy for persistent hiccups. *Anesth Analg* 95: 494-495, table of contents.
71. Kou S (2005) An analysis on the therapeutic effects of auriculo-acupuncture in 38 obstinate hiccup cases of different races. *J Tradit Chin Med* 25: 7-9.
72. Hong L, Zhao Y, Zhang X, Zhou X, Ding J, et al. (2008) Reversal effect of electroacupuncture on the symptom of intractable hiccups in hepatitis B virus carriers. *J Pain Symptom Manage* 35: 335-336.
73. Lin YC (2006) Acupuncture for persistent hiccups in a heart and lung transplant recipient. *J Heart Lung Transplant* 25: 126-127.
74. Ge AX, Ryan ME, Giaccone G, Hughes MS, Pavletic SZ (2010) Acupuncture treatment for persistent hiccups in patients with cancer. *J Altern Complement Med* 16: 811-816.
75. Hongliang X, Xuemei C, Shizhao H, Chaofeng L (2006) Acupuncture and cupping for treatment of hiccup in cases of cerebrovascular accident. *J Tradit Chin Med* 26: 175-176.
76. Calvo E, Fernández-La Torre F, Brugarolas A (2002) Cervical phrenic nerve block for intractable hiccups in cancer patients. *J Natl Cancer Inst* 94: 1175-1176.
77. Gallacher BP, Martin L (1997) Treatment of refractory hiccups with glossopharyngeal nerve block. *Anesth Analg* 84: 229.
78. Strate T, Langwieler TE, Mann O, Knoefel WT, Izbicki JR (2002) Intractable hiccup: an odd complication after laparoscopic fundoplication for gastroesophageal reflux disease. *Surg Endosc* 16: 1109.
79. Schulz-Stübner S, Kehl F (2011) Treatment of persistent hiccups with transcutaneous phrenic and vagal nerve stimulation. *Intensive Care Med* 37: 1048-1049.
80. Okuda Y, Kitajima T, Asai T (1998) Use of a nerve stimulator for phrenic nerve block in treatment of hiccups. *Anesthesiology* 88: 525-527.