What's new in therapeutics?

Management of hiccups in the palliative care population

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Abstract

There are close to a hundred causes for hiccups, or singultus, the most common of which are gastrointestinal. Causes may be natural or drug induced, and the same agents that are used to treat hiccups may also induce them. Hiccups can be classified by their duration, as follows: up to 48 hours, acute; longer than 48 hours, persistent; and more than two months, intractable. Treatment options for hiccups can include both pharmacologic and nonpharmacologic agents. If the cause of hiccups can be identified, it is, of course, preferable to direct the treatment at that cause. However, many times a cause cannot be identified; in this case, general measures or treatments should be instituted.

Intractable hiccups can occur in the palliative care population. When they do, it can be extremely distressing and have a significant impact on quality of life. Pharmacologic approaches are often the most rational therapies for these patients. Baclofen seems to be a promising drug for use with both palliative care and perioperative patients, and using garabentin as an add-on to baclofen may also be a reasonable option to consider.

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Introduction

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] The hiccup reflex is thought to be composed of three parts: an afferent limb (e.g., phrenic nerve, vagus nerve, sympathetic chain [T6 - T12]), a central mediator, and an efferent limb (e.g., phrenic nerve with accessory connections to the glottis and inspiratory accessory/intercostal muscles).[2] The efferent limb also includes the complex interaction between the brainstem and midbrain areas, including respiratory center, phrenic nerve nuclei, medullary reticular formation, and hypothalamus.[3] The central connection between afferent and efferent limbs seems to be a nonspecific anatomic location between the cervical spine (C3 - C5) and the brainstem.[3] The main efferent limb of the diaphragmatic spasms is mediated by motor fibers of the phrenic nerve.[1]

Each individual's hiccup rate usually is reasonably consistent for hiccup episodes, and they tend to occur with a frequency of 4 to 60 hiccups per minute.[4] Hiccups lasting up to 48 hours are referred to as a hiccup bout and are considered acute.[5] Chronic hiccups are considered either persistent or recurrent and are generally "pathologic" in nature. Hiccups lasting longer than 48 hours are referred

to as persistent hiccups, and, if hiccups last more than two months, they are considered intractable.[5]

A broad classification of the many causes of hiccups include: vagus and phrenic nerve irritation (e.g., intraoperative manipulation, esophagitis), central nervous system disorders (e.g., head trauma, multiple sclerosis, encephalitis), toxic-metabolic or drug-related disorders (e.g., uremia, alcohol intoxication, general anesthesia), and psychogenic factors (e.g., stress, anxiety).[5] Other perioperative causes include intubation, neck extension, gastric distention, and traction on viscera[5] (Table 1). Hiccups can occur in the perioperative period and be extremely distressing and debilitating to the patient. Hiccups can lead to respiratory alkalosis in tracheotomized patients due to hyperventilation.[6] Additionally, persistent hiccups may lead to fatigue, sleep disturbances, dehydration, and wound dehiscence. A wide variety of medical treatments have been used for idiopathic and intractable hiccups, including valproic acid, metoclopramide, chlorpromazine, prochloperazine, promethazine, haloperidol, carbamazepine, nifedipine, and recently baclofen.[1,7-12]

Causes of hiccups

Cymet published a retrospective analysis of all 54 patients seen in a community hospital with hiccups over a five-year period (from 1995 to 2000).[4] The majority of patients evaluated with hiccups were male (91 percent), over age 50 (range 9 months to 80 years), and had comorbid conditions (78 percent).[4]

There are probably close to a hundred causes for hiccups, with the most common being gastrointestinal in nature.[6] Gastroesophageal reflux disease (GERD) may be the most important cause.[6] Metabolic derangements may enable or contribute to hiccups as well (Table 1). Pharmacologic agents can induce hiccups. Thompson and Landry published that corticosteriods and benzodiazepines are the most frequent types of drugs associated with the development of hiccups.[13] Other agents include: chemotherapy (e.g., cis-platinum)[14] and opioids (e.g., hydrocodone).[15]

Agents that have been used to treat hiccups, such as antidopaminergic drugs (e.g., perphenazine) and midazolam, can also induce hiccups,[16] and agents that have been known to induce/facilitate hiccups (e.g., anticholinergic drugs) have also seemed to be able to treat hiccups (e.g., atropine).[17]

Bagheri et al. reported on drug-induced hiccups in France, reviewing the French pharmacologic vigilance database.[18] Between 1985 and 1997, 53 cases of drug-induced hiccups were reported to the French pharmacovigilance network.[18] Of the total cases reported, 23 percent were related to corticosteroids, 15 percent to "psychiatric medications" (mainly dopaminergic anti-Parkinson's), 12 percent to antibiotics (e.g., beta-lactams, macrolides, fluoroquinolones), 7 percent to cardiovascular (e.g., digoxin), 6 percent to analgesics (e.g., opioids), and 6 percent to nonsteriodal anti-inflammatory drugs.[18] Rechallenge was positive in seven cases, with two cases considered "serious" according to the World Health Organization definition.[18]

Progesterone-induced hiccups may be due to the glucocorticoid-like effects of progesterone.[19] Anabolic steroid-induced hiccups have occurred in an elite power lifter within 12 hours of increasing his dose.[19] It has been proposed that progesterone, anabolic steroids, and corticosteriods may lower the threshold for synaptic transmission in the mid brain and directly stimulate the hiccup reflex arc (predominantly afferent limb or efferent limb components).[19]

Nonpharmacologic causes of hiccups are also numerous and will not be enumerated, but they include any subdiaphragmatic, hepatic, or other processes (e.g., tumor, infection, inflammation) that irritate the diaphragm and/or nerves to the respiratory muscles involved in the hiccup reflex arc.

Other more unusual causes of hiccups include: thoracic epidural injection,[20] obstructing ureteric calculus,[21] acute myocardial infarction,[22] pacemaker malfunction,[23] and the ingestion of star fruit (Averrhoa carambola) in uremic patients (which can also lead to death).[24] Perry and Stevenson reported an unusual case of persistent hiccups associated with cavitating pulmonary tuberculosis.[25]

Additionally, hiccups can result from structural or functional disorders of the medulla or various other supraspinal neural elements.[26] Newsom Davis conducted studies using electrophysiological techniques and concluded that hiccups are mediated by supraspinal mechanisms distinct from those generating rhythmic breathing.[27] The major site of interaction of the hiccup discharge with other descending drives to the respiratory motor neurons seems to be at the spinal level.[28] Etiologies of neurogenic hiccups include: after posteroventral pallidotomy,[28] multiple sclerosis,[29] medulla oblongata cavernoma,[30] basilar artery aneurysm,[31] and cerebellar hemangioblastoma.[32] Cymet reported that all of the patients who had hiccups for 48 hours or more (52 percent of all patients in the study) had an underlying disease or pathology to which the hiccups could be attributed.[4] (Souadjian and Cain studied 220 patients with singultus and also found that persistence of hiccups pointed to an organic cause.[5]) Laboratory values seemed to add little in deciding which therapies would be most efficacious.[4] Eighty-nine percent of patients received some type of active treatment.[4] The most common medication was

Table 1. Causes of hiccups		
CNS/PNS	**Head and neck**	**Thorax**
Trauma Infection Vascular Tumors (brain stem) Multiple sclerosis Irritation of phrenic/vagus nerves V-P shunts	Foreign body Goiter Aneurysm Pharyngitis/laryngitis Tumor/cysts Membrane stimulation	Trauma Pneumonia Pleuritis Pericarditis Aneurysm Esophagitis Achalasia Esophageal stricture/injury Esophageal obstruction Hiatal hernia Diaphragmatic eventration Tumor Lymphadenopathy
Abdomen	**Metabolin/infectious**	**Drugs**
Ulcers Abscess Gastritis Gastric distention Cholecystitis Pancreatitis GERD Neoplasm Bowel obstruction	Hypokalemia Uremia Hypocalcaemia Influenza Herpes zoster Malaria Tuberculosis Alcohol Diabetes mellitus Hypocarbia (hyperventilation)	IV Methylprednisolone Dexamethasone Barbiturates Chlodiazepoxide Methyldopa
Psychogenic	**Surgical**	**Idiopathic**
Stress/excitement Conversion/grief reaction Anorexia nervosa Schizophrenia Malingering	Anesthesia Gastric distention Neck extension	
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thorazine used in 54 percent of patients, with compazine used in 15 percent of patients. No treatments showed any statistically significant effects.[4] Aside from obvious detraction from quality of life and significant discomfort, severe intractable persistent hiccups may affect conversation, concentration, or oral intake and can lead to disruption of sleep onset[33] and even atrioventricular asystole.[34]

Treatment of hiccups

Treatment of hiccups should be directed at a specific cause if one can be identified. Removing offending agents and correcting etiologies/imbalances that may facilitate hiccups should constitute initial therapeutic efforts. Targeted therapy (if the cause of the hiccups is known) is the most rational. Hiccups secondary to GERD have resolved after treatment with proton pump inhibitors (e.g., lansoprazole).[35] Hiccups in a continuous ambulatory peritoneal dialysis (CAPD) patient treated with "standard" solution improved with the use of a neutral pH dialysis solution.[36]

However, there are many times when the cause of the hiccups cannot be identified or addressed, and in these cases general measures/treatments should be instituted.

Pharmacologic treatment of hiccups

Treatments for idiopathic chronic hiccups (ICH) have included pharmacologic and nonpharmacologic approaches. Baclofen, a gamma-amino butyric acid (GABA) analogue that activates an inhibitory neurotransmitter, as well as valproic acid that enhances GABA transmission centrally, are thought to aid in blocking the hiccup stimulus. Chlorpromazine, a dimethylamine derivative of phenothiazine, and haloperidol act centrally by dopamine antagonism in the hypothalamus. Metoclopramide may reduce the intensity of esophageal contractions. Nifedipine, a calcium channel blocker, may play a role in reversing the abnormal depolarization in the hiccup reflex arc. Sertraline may also be beneficial.[37] Sertraline may act via effects on peripheral $5HT_4$ receptors in the gastrointestinal tract (reducing abnormal esophageal, gastric, or diaphragmatic mobility) or via effects on $5HT_{1A}$ receptors and/or $5HT_2$ receptors by modulation of the autonomic nervous system, resulting in inhibition of the hiccup reflex arc.[37] Baclofen has also been used to treat chronic hiccups in: hiccups induced by ultraflex esophageal endoprosthesis,[38] hiccups induced by brainstem lesions,[39] palliative care patients,[40] and hemodialysis patients.[41] Patients with renal insufficiency (patients undergoing CAPD/ hemodialysis) need to be extremely cautious with baclofen therapy as baclofen is renally eliminated. Even "low-dose" baclofen therapy in patients undergoing CAPD produced severe respiratory depression.[42] Additionally, other agents/ techniques potentially beneficial for ICH include nefopam[43] (not currently available in the US), intravenous lidocaine,[44] amitriptyline,[45] amantadine,[46] short-term anesthesia,[47,48] and perhaps anecdotal stories of quinidine, stimulants of the central nervous system, ranitidine, dopamine agonists, clonazepam, and other anticonvulsants (e.g., phenytoin).

For intractable hiccups refractory to monotherapy, rational polypharmacy seems a reasonable approach. Cisapride, omeprazole, and baclofen (COB) have been used for combination hiccup therapy, and gabapentin as "add-on therapy" seems to have been occasionally successful: cisapride, omeprazole, and gabapentin (COG) and cisapride, omeprazole, baclofen, and gabapentin (COBG).[49]

Baclofen has been shown by several authors in and outside the United States to be dramatically effective in abating or alleviating hiccups. In 1992, Cabane et al.[9] reported some cases of chronic hiccups unsuccessfully treated with multiple medications even after possible pathologic causes had been cured but that eventually responded well to baclofen. In the same year, Ramirez and Graham[50] improved hiccup severity significantly in four patients by using baclofen. In 1995, Guelaud et al.[51] presented 28 of 37 cases in their study, with either a complete resolution or a considerable decrease of hiccups after initiation of baclofen. Johnson and Kriel[52] presented a case with severe chronic hiccups post-Gastrostomy and Nissen fundoplication whose symptoms ceased within weeks of initiation of baclofen. Perez del Molino et al.[53] reported seven cases with persistent hiccups unresponsive to usual therapies but all seven completely resolved with baclofen. In 1997, Petroianu et al.[54] reported a successful treatment or substantial relief of hiccups with COB in 60 percent of their patients. Nickerson et al.[10] presented a case of persistent hiccups after a lateral medullary cerebrovascular accident that were refractory to multiple interventions including therapy with promethazine, prochloperazine, and chlopromazine but that abated within 48 hours after starting baclofen. In 1998, Petroianu et al.[55] again reported the successful treatment of hiccups with the combined COB in the majority of their patients (cured in 38 percent and alleviated in 24 percent of the patients). In the same study, the authors substituted gabapentin for baclofen in the patients who failed to respond to COB. Hiccuping ceased in one and improved in two of 10 subjects. Shortly after that, Kumar and Dromerick[11] reported another successful control of hiccups with baclofen. In the past five years, at the Albany Medical Center Hospital, 10 "palliative" patients with advanced illnesses developed severe hiccups in the perioperative period after having genitourinary, cardiothoracic, or abdominal surgery. After failing multiple other medical treatment options, the hiccups either completely disappeared or were substantially improved by baclofen in all the patients within 4 to 48 hours. In three patients, the baclofen was stopped and the hiccups came back but again went away upon restarting baclofen.

Pharmacologically, baclofen selectively activates $GABA_B$ receptors pre- and postsynaptically and may modulate G-protein, thereby decreasing calcium conductance and decreasing excitatory amino acid release.[56] Baclofen may also inhibit the release of L-glutamate and substance P.[56] Postsynaptic $GABA_B$ receptors are coupled to potassium channels and therefore can mediate a slow inhibitory postsynaptic potential.[56] Baclofen appears to inhibit C-fiber afferents more effectively than A-delta afferent glutamatergic transmission in the substantia gelatinosa of the spinal cord.[56] In 1998, Oshima et al.[57] found that a hiccup-like reflex could be elicited by electrical stimulation to an area in the medullary reticular formation of cats and was suppressed after an injection of baclofen into the area.[57] This study indicates that this area in the medulla has $GABA_B$ receptors.[57] The authors also hypothesized that the nucleus raphe magnus was most likely to be the source of the GABAergic inhibitory

inputs to the hiccup reflex arc.[57] The glottis closes to prevent inspiration 35 msec after electrical activity rises above the baseline in the diaphragm and respiratory muscles.[58]

Nonpharmacologic treatment of hiccups

Nonpharmacologic treatment approaches have included: physical treatments (initiating the valsalva maneuver or counterirritation of the vagus nerve)[59] and the use of breathing pacemakers.[60]

Once attempts at removing underlying causes have been carried out, anecdotal physical maneuvers may be tried, such as breath holding, irritation of the nasopharynx, long and slow sips of water, compression of the nose while swallowing, prolonged pressure on the diaphragm, manipulation, and hypnosis.[4] Pharyngeal stimulation tends to inhibit hiccups; however, the effect may be only temporary.[61] The use of acupuncture,[62,63] Japanese electroacustim,[64] cervical epidural block,[65] cervical phrenic nerve block,[66] and even an anecdotal case report of sexual intercourse[67] have all been advanced as potential treatments for intractable hiccups. There is also an anecdoctal report of two cases of intractable hiccups that did not respond to the "usual treatments" but were eliminated with methylcellulose (three sachets of methyl cellulose in 300 ml of warm water), the rationale being that gastric distention may effectively eliminate the hiccup stimulus.[68] (It would be interesting if inhibitors of motility worked by a similar mechanism.) Surgical approaches to treatment of hiccups (e.g., phrenic nerve ablation) should be reserved as a last resort for only the most severe and intractable cases, since they carry a risk of pulmonary compromise.[69]

Conclusion

In conclusion, intractable hiccups can occur in the palliative care population and can be extremely distressing, often significantly detracting from quality of life. When possible, etiologies should be sought and targeted therapies instituted. Intractable hiccups are often found to be idiopathic, and pharmacologic approaches are often the most rational therapies for palliative care patients with intractable idiopathic hiccups.

Baclofen seems to be a promising drug of choice for idiopathic hiccups occurring not only in medical/palliative care inpatients and outpatients, but in the perioperative period as well. Gabapentin in addition to baclofen has not been used in the treatment of perioperative hiccups but may be a reasonable option to pursue for perioperative patients with hiccups refractory to baclofen alone.

A well-designed large multicenter double-blind placebo controlled prospective study is needed but would be difficult to carry out due to a low incidence of perioperative hiccups, as well as a relatively low incidence of hiccups in the general medical/palliative care population.

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