

Use of Baclofen in the Treatment of Persistent Hiccups: Report of Two Cases

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Abstract

We present two cases of persistent hiccups attributed to lateral medullary syndromes that were refractory to common pharmacological treatment. Introduction of baclofen resulted in the rapid and sustained resolution of hiccups in these patients, with no significant adverse effects noted. Our reports serve to strengthen the limited evidence base for baclofen as a pharmacological agent for treatment of hiccups, and suggest the consideration of its use as a first line treatment specifically in hiccups secondary to lateral medullary infarcts.

Keywords: Baclofen; Persistent Hiccups

Introduction

Hiccups, or singulata, are repeated involuntary, spasmodic and temporary contractions of the diaphragm accompanied by sudden closure of the glottis, producing a distinguishing "hic" sound [1]. Hiccups are commonly experienced by most people at one time or another but are usually brief and self-limiting. The physiological purpose of hiccups is uncertain [1,2]. As fetuses and premature infants hiccup often, it is suggested that hiccups are a programmed isometric inspiratory muscle exercise, which is useless after the neonatal period but may be restimulated by irritation along the reflex arc [1,3]. The neuroanatomical center for hiccups is not well-known, although the major component of central connection is presumed to be a part of the brain stem and hypothalamus [4,5,6]. The afferent pathway is made up of the sensory branches of the phrenic and vagus nerves and the dorsal sympathetic fibers, whereas the efferent pathway is formed by the motor fibers of the phrenic nerve.

Persistent hiccups (lasting > 48 hours) are uncommon, and warrant a complete medical work-up to uncover underlying pathology [2], as well as to prevent potential undesirable consequences, including psychological distress, difficulties in feeding resulting in dehydration and malnutrition, poor quality of sleep, and even potentially life-threatening complications such as aspiration pneumonia [7], resulting in increased morbidities and prolonged hospital stays [8]. The causes of persistent hiccups can be classified into central and peripheral [2,6]. Central hiccups occur with lesions between the pathway from the central nervous system to the phrenic nerve, mainly in diseases of the brain stem such as ischemic stroke, dolichoectatic basilar artery, tumors, encephalitis, multiple sclerosis, and had also been reported in patients with focal seizures [9]. Peripheral hiccups can be caused by either diseases at the phrenic nerve level involving diaphragmatic irritation, such as gastric distention, subdiaphragmatic abscess or hepatosplenomegaly, [2,6,10]; diseases causing vagal nerve stimulation such as pharyngitis, gastritis, peptic ulcer disease and pneumonia; or irritation of

the laryngopharynx and glottis from endotracheal intubation. In addition, toxic or metabolic causes that may affect nerve function, such as alcohol intoxication, uremia, electrolyte imbalances and diabetic ketoacidosis will also need to be excluded [8]. Lastly psychiatric issues including emotional upset and stress may be a diagnosis of exclusion [11].

Lateral medullary syndrome (LMS) remains an interesting clinical entity with a wide range of clinical presentations of cerebrovascular accidents [12]. The area of the brain stem involved in LMS is the posterolateral part of the medulla oblongata [6], which is the portion receiving arterial blood supply from the posterior inferior cerebellar artery (PICA) [10,13]. The usual symptoms of lateral medullary infarction (LMI) include vertigo, dizziness, nystagmus, ataxia, nausea and vomiting, dysphagia, hoarseness, hiccups, impaired sensation over half the face, impairment of pain and thermal sensation over the contralateral side of the trunk, limbs and the ipsilateral face and Horner's syndrome.

Hiccups are more frequent when the infarct is in the dorsal area of the medulla, primarily because a number of complex structures which mediate the hiccups reflex, specifically the vagus nerve, respiratory center, solitary nucleus, nucleus ambiguus, central sympathetic tract, and spinal tract of trigeminal nucleus are all located in this area. These lesions may result in a dysfunction of the vagus nerve, sympathetic nerves, and an incoordination between the glottis closure complex and inspiratory complex, thus generating persistent hiccups [8,14,15].

Case Reports

We present two patients having lateral medullary infarcts complicated with persistent hiccups, with highlights to their treatment course of events:

Case 1

A 58 year-old gentleman with past medical history of hypertension, presented with an unsteady gait of two days duration associated with constant veering towards the left side on ambulation. His presentation was accompanied by an episode of vertigo that lasted for about 30 minutes, one episode of vomiting and neck pain of same duration as unsteady gait. Neurological examination revealed right beating horizontal nystagmus, right uvula deviation, persistent unsteady gait and left ptosis. MRI brain revealed restricted diffusion in the left lateral aspect of medulla, confirming the diagnosis of an acute left lateral medullary infarct.

On the second day of his admission, the patient started complaining of persistent hiccups with the sensation of nausea. The patient was experiencing up to five to six bouts of hiccups daily, with the longest duration of hiccups lasting several minutes. The

hiccups were severe enough to interfere with our patient's sleep and his participation in rehabilitation therapy.

In evaluating for possible peripheral causes for his hiccups, there were no known triggers (eg. carbonated drinks, post-meal), no symptoms suggestive of gastro-esophageal reflux disease (GERD) or respiratory tract infections (RTI), no clinical evidence of sepsis, in particular pneumonia, hepatitis or liver abscess; and electrolytes, sugars and liver function test done were all unremarkable. There was also no ictal phenomenon to suggest focal seizures as a cause. Patient was started on a trial of oral Metoclopramide 10mg TDS and Haloperidol 1g ON with no effect. He was subsequently given a range of pharmacological agents including Ondansetron 4mg TDS, Domperidone 10mg TDS and Chlorpromazine 25mg TDS to no effect. After commencing the patient on Baclofen 5mg TDS, the patient reported subjective improvements in the frequency and duration of hiccups. Further increase in his Baclofen dose to 10mg TDS resulted in complete resolution of hiccups. Baclofen therapy was continued for five days and subsequently ceased with no further recurrence of hiccups.

Case 2

A 64 year-old man with past medical history of hypertension and diabetes mellitus, presented with a one day history of sudden onset occurrence of unsteady gait, dizziness, vomiting, weakness and numbness of the right upper and lower limbs. Neurological examination revealed gait ataxia with increased swaying to the right, impairment of pain sensation over the left upper and lower limbs and mild right hemiparesis. MRI Brain revealed the presence of an acute infarct at the dorsal and lateral aspect of the right medulla, confirming the diagnosis of an acute right lateral medullary infarct.

The patient developed bouts of paroxysmal hiccups on day three after onset of presenting symptoms, potential causes were excluded, in a similar fashion as Case 1. Hiccups were initially treated with oral Metoclopramide for a total of three days and then with oral Prochlorperazine for a total of five days with no improvement. These drugs were stopped and oral Baclofen was started at 5mg at 8am and 2pm, and 10mg at 8pm. Hiccups resolved within 48 hours after the first dose was given. Baclofen was administered for a total of five days with no recurrence of symptoms on discontinuation of the drug.

Discussion

The management of hiccups involves searching for and treating the underlying cause, pharmacological and non-pharmacological methods. In hiccups associated with cerebrovascular disease, focal seizures should be considered as a cause, particularly in cases where the hiccups are paroxysmal. However, as not all underlying causes can be corrected, and non-pharmacological methods are frequently ineffective for persistent hiccups [16], symptomatic treatment with medications may be necessary [17] to avoid the negative consequences described earlier.

Pharmacological treatment of persistent hiccups is generally still unsatisfactory, as evidenced by the myriad of pharmacological agents available. The infrequent occurrence of hiccups makes it difficult to perform large, well-controlled clinical trials. Traditional choices include dopaminergic antagonists, specifically chlorpromazine and metoclopramide [18], which are purportedly acting via dopamine blockade in the hippocampus, a component of the hiccup centre. However, chlorpromazine is poorly tolerated by those with a recent brain infarction and should be avoided. Its side effect of sedation must be recognised, and long-term administration is not recommended because of possible irreversible tardive dyskinesia. Other agents with dopaminergic antagonistic properties

including metoclopramide, haloperidol and prochlorperazine have been tried with variable results.

Baclofen is a gamma-aminobutyric acid (GABA) agonist used primarily to treat spasticity and the therapeutic effects of baclofen on hiccups is due to the decrease in excitability and increase in inhibition of the hiccup reflex [16]. Baclofen is absorbed rapidly after oral administration and is eliminated via renal excretion, with a half-life of 3-4 hours. It is generally well-tolerated, with the most common side effects being sedation, insomnia and weakness [16].

Multiple studies have demonstrated the efficacy of baclofen on persistent hiccups in general. The randomised controlled trial done by Ramirez [19], for example, showed that there was a consistent and statistically significant improvement in hiccup severity with baclofen, both subjectively and by hiccup-free periods, but not the hiccup frequency. A later trial done by Guelaud [20] revealed a 40-71% complete resolution of hiccups with baclofen treatment (doses ranging from 15-75mg/day) in patients with idiopathic persistent hiccups and those with evidence of esophageal disorder but failed conventional treatment.

Specifically, for hiccups occurring post lateral medullary infarction, baclofen probably has the best evidence base, being the only drug which had undergone a number of RCTs [21]. However, all these trials are limited in statistical size, not unexpectedly however, in view of the rarity of both lateral medullary infarction and persistent hiccups.

Our case studies above, therefore, stand to strengthen this limited evidence base, professing for the consideration of baclofen as first line therapy in treatment of hiccups attributable to lateral medullary infarction. In particular, for both of our patients, baclofen was initiated after the trial of multiple, more conventional agents failed, and in turn resulted in the rapid success of hiccups treatment. This suggests that the resolution of hiccups is probably more related to the effects of baclofen rather than being attributable to spontaneous recovery. Of note, in contrast to earlier studies [19], there was complete resolution of hiccups and the discontinuation of baclofen did not lead to a return of hiccups in both our patients.

There may be some concern regarding serious neurotoxicity of baclofen arising from case reports [22,23], but these are mainly in patients with significant renal failure with resultant impairment in the clearance of baclofen. The sudden discontinuation of baclofen after long-term use can be associated with withdrawal symptoms, such as convulsions, so it is recommended that the dose be tapered down slowly when discontinuing the medication from prolonged use [24]. In both our cases, the rapid onset and maintenance of therapeutic effects did not necessitate prolonged usage of baclofen, and hence there was no requirement to tail down prior to discontinuing.

Conclusion

In conclusion, when considering pharmacological treatment for hiccups attributable to lateral medullary infarction, we strongly suggest baclofen as the first-line option in the absence of significant renal impairment, particularly if there is concomitant spasticity as an additional treatment target, based on current available evidence strengthened by our personal experiences.

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