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BACLOFEN IN THE TREATMENT OF PERSISTENT HICCUP: A CASE SERIES

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Abstract

Background—Persistent hiccup is a worrying symptom both for patients, because of reduced quality of life, and for physicians, because of frustration for unsuccessful treatments.

Aim—To test baclofen administration for the treatment of persistent hiccup.

Methods—We report a series of seven patients affected by persistent hiccup successfully treated with baclofen.

Results—Hiccup stopped in all patients after a single administration of the drug.

Conclusions—Baclofen is a GABA_B receptor agonist. It is conceivable that the reduction of dopamine release by GABA_B receptor stimulation is able to interrupt hiccup's reflex arc.

Keywords

baclofen; hiccup

Introduction

Hiccup is an involuntary contraction of inspiratory muscles, generating a sudden inspiration, followed by glottis closure, producing the onomatopoeic sound “hic”.¹ The occurrence of hiccup is widespread, although neuronal origins and physiological significance are still debated.² Several factors may cause hiccup:^{1,3} sparkling beverages, air deglutition, gastric distension, changes in food temperature, spices, alcohol, tobacco, central nervous system (CNS) diseases, metabolic disorders, fever, pneumonia, lung tumor, pericardial/pleural effusion, myocardial infarction, gastroesophageal reflux disease (GERD), acute hepatitis, gastric tumors, peritonitis, surgery, chemotherapy, benzodiazepines, corticosteroids, barbiturics, morphine. Hiccup may also be idiopathic.

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Conflict of interest: none

Hiccup's reflex arc is poorly understood. The afferent limb is represented by phrenic, vagus and sympathetic nerves. Central chemoreceptors (peri-aqueductal gray-matter and sub-thalamic nuclei) process the signal. Efferent branch is located in motor fibers of phrenic nerves to diaphragm and accessory nerves to the intercostal muscles. Dopamine and gamma-aminobutyric-acid (GABA) are the main neurotransmitters involved.^{1,2}

“Transient” hiccup lasts less than 48 hours, while “persistent” or “chronic” lasts 48h or more, or it occurs with recurrent attacks.³ Several anecdotal treatments are described, including pulling-out the tongue, pushing-up the uvula with a cold spoon, swallowing granular sugar, tasting a lemon, smelling ammonia or salt, breathing in a bag, frightening the patient, etc. Pharmacological treatments include chlorpromazine, metoclopramide, nifedipine, carbamazepine and marijuana.¹ The GABA_B receptor agonist baclofen can affect both neuronal transmission of the reflex arc and lower esophageal sphincter tone; preliminary data indicate that baclofen may be effective in stopping hiccup.⁴

We report a series of seven patients affected by persistent hiccup successfully treated with baclofen. Hiccup resolved 0.5–3 hrs after the first baclofen administration in all patients.

After receiving information on the characteristics, dosing and possible side effects of the drug, all patients signed informed consent before baclofen administration.

CASE 1: a 23-years-old male presented with hiccup for 5 consecutive days. After first two days, the patient went to the Emergency Room (ER) where chlorpromazine was prescribed. The patient experienced sedation, but hiccup persisted, even during sleep hours. After 3 days, the patient was seen in our Internal Medicine outpatient unit. Physical exam and medical history were negative, other than history of smoking (10 cigarettes/day for 4 years). Routine blood test, electrocardiography (ECG) and chest X-ray were normal. Chlorpromazine was discontinued and a single dose of baclofen 10 mg was prescribed, which resulted in the remission of hiccup without recrudescence. Further administrations were not needed.

CASE 2: a 73-years-old woman developed hiccup four days after hip replacement. Hiccup started after the awake from anesthesiology, and three days after was still present. Hiccup was not responding to metoclopramide nor to chlorpromazine. Patient suffered from hypertension, treated with ramipril and hydrochlorothiazide. Blood tests, ECG and chest X-ray were normal. Baclofen 10 mg was administered with hiccup remission and without recrudescence. Further administrations were not needed.

CASE 3: a 67-years-old man developed hiccup three days after radical prostatectomy. Hiccup started a few hours after surgery. Two days after hiccup was still present and not responding to chlorpromazine. Patient had a history of hypertension and prostate cancer, and was assuming enalapril, cyproterone acetate, and terazosin. Blood tests and ECG were normal. Chest X-ray was normal and chest CT-scan did not show mediastinal abnormalities. Baclofen 10 mg was administered with remission of hiccup and without recrudescence. Further administrations were not needed.

CASE 4: a 55-years-old man went to the ER with hiccup, nausea and blood-traced vomit for 3 consecutive days. He reported chronic nimesulide use because of osteoarthritis. Blood tests showed clinically significant elevation of liver tests (transaminases, gamma-glutamyl-transferase, alkaline phosphatase and bilirubin). An esophagogastroduodenoscopy was performed indicating the presence of haemorrhagic gastritis. Patient was admitted to our Internal Medicine inpatient unit with diagnoses of acute cholestatic hepatitis and haemorrhagic gastritis, probably due to nimesulide induced toxicity. Treatment included bed rest, intravenous glucose administration, proton pump inhibitors and metoclopramide. The patient, however, continued to complain of persistent hiccup that was making rest impossible. Baclofen 10 mg t.i.d. was started with remission of hiccup after the first dose. Baclofen was discontinued two days later with hiccups recidivism after 12 hours from the last administration. Thus the treatment was restarted, with remission of hiccup after the first dose. The patient was discharged with the indication to assume baclofen until liver enzymes normalization, and to continue follow-up as outpatient. After two weeks, liver enzymes returned normal and baclofen was discontinued with no hiccup recidivism.

CASE 5: a 77-year-old man went to the ER because of abdominal pain occurred after physical activity. The patient had a recent history of cardioembolic ictus and was assuming warfarin for two months. At the ER, a large abdominal wall hematoma was diagnosed and the patient was admitted to our inpatient clinic. At admission, the International Normalized Ratio (INR) was 7.9. Because of the increasing size of hematoma, with respect to ER evaluation, and severe pain, surgical evacuation was performed after INR normalization, and abdominal wall drainage was left. Few hours after the surgical procedure, the patient developed intractable hiccup refractory to chlorpromazine and metoclopramide. After 48 hours, baclofen 10 mg t.i.d. was started with remission of hiccup after the first dose, and it was continued for 5 days, until the removal of abdominal wall drainage, with no recrudescence of hiccup.

CASE 6: a 47-years-old man who received liver transplantation for liver cirrhosis, was admitted to our inpatient unit for fever, liver enzymes elevation, jaundice and abdominal pain. Patient was on immunosuppressive therapy with methylprednisolone and tacrolimus. Abdominal CT scan showed two liver abscesses. Broad-spectrum antibiotic treatment was started together with radiological percutaneous liver abscesses drainage. Two drainage tubes were placed. A few hours after the procedure, patient developed hiccup, which persisted even during sleep despite metoclopramide. After 24h, baclofen administration 10 mg t.i.d. was started with hiccup suppression. Three days later, because of accidental misplacement, drainage was replaced. After 48h baclofen was discontinued with no recrudescence.

CASE 7: a 79-years-old man came to our observation because of intractable hiccup for 15 days and dysphagia. He was affected by advanced lung carcinoma with mediastinal lymphadenopathies, and brain metastases. Because of poor performance status, palliative treatment with dexamethasone in adjunction to phenobarbital was prescribed. Hiccup developed after three days of dexamethasone therapy. Routine blood tests and ECG were normal. Chest X-ray confirmed multiple metastases. Baclofen 10 mg t.i.d. was prescribed with remission of hiccup after the first administration. Baclofen administration was

continued because of the impossibility to stop dexamethasone, with no recrudescence of hiccup.

Discussion

Here we describe seven cases of persistent hiccup successfully treated with low doses of baclofen. Baclofen treatment had no significant side effects and tolerability was fair (table 1). The onset of baclofen's effect was rapid: hiccup stopped in all patients here described after a single administration of the drug. However cases 4, 5, 6 and 7 needed t.i.d. baclofen administration; after the removal of the cause, baclofen was discontinued with no recrudescence. Baclofen is a GABA_B receptor agonist approved as a medication to control spasticity.⁹ GABA_B receptor stimulation reduces dopamine release in the CNS, and this could interrupt hiccup's reflex arc. Moreover, GABA_B receptors of the motor nucleus of the vagal nerve and nucleus tract solitarius play a central role in transient lower oesophageal sphincter relaxations.¹⁰

While transient hiccup (lasting <48h) is a usually benign self-limiting condition, persistent hiccup (lasting >48h) represents a worrying symptom for patients, mostly complaining of a reduction of quality of life, impossibility to eat or even to sleep; moreover, persistent hiccup induces in the patients the fear of being affected by a serious disease. Furthermore, the identification of an etiological cause for persistent hiccup may be difficult as well as is the treatment. The differential diagnosis represents a challenge for physicians since it should consider a wide spectrum of possible causes. Duration, frequency and persistence of hiccup during sleeping should be evaluated. Comorbidities and medications need to be considered. A complete physical examination may reveal possible causes of hiccup. ECG and chest X-ray should always be performed to support clinical hypotheses and to proceed with differential diagnosis.¹¹ Moreover physicians may decide case-by-case to perform additional exams.

Since the diagnostic process could take time (several days), the treatment of such disabling condition is mandatory. Currently approved treatments for hiccup (e.g. chlorpromazine, metoclopramide) show limited efficacy and a high rate of side-effects (dizziness and sedation). Consistent with previous literature³ and with the present case series, baclofen could represent a promising drug for the treatment of persistent hiccup of any origin.

The present case series has some limitations: first the small sample size and the lack of placebo-control; however, intractable hiccup is a relatively rare disease, and the described cases are consecutive. Moreover in some of the presented cases, it is not possible to tease a part baclofen's real effect vs. removal of the triggering cause; however baclofen suppressed hiccup in all treated patients. Randomized controlled trials are needed to fully investigate the efficacy of baclofen in the treatment of hiccup.

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Founding source: none

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What's already known about this topic?

- Chronic hiccup represents a worrying symptom both for patients, because of the reduction of quality of life, and for physicians, because of the variety of underlying conditions.
- Currently approved treatments show low efficacy and high rate of side effects

What does this article add?

- Baclofen is an effective drug for the treatment of chronic hiccup of any origin

Socio-demographic and clinical characteristics of the 7 patients affected by persistent hiccup successfully treated by baclofen

Table 1

(GERD: gastro-esophageal reflux disease; M: male; F: female)

	Patient's gender, age	Underlying disease	Probable cause of hiccup	Duration of hiccup	Response to baclofen	Total used dose	Side effects
1	M, 23	none	idiopathic	5 days	after 1 st dose	10 mg	none
2	F, 73	hypertension	postoperative, anaesthetic-induced	3 days	after 1 st dose	10 mg	none
3	M, 67	prostate cancer, hypertension	postoperative ⁵ , anaesthetic-induced ⁶	2 days	after 1 st dose	10 mg	none
4	M, 55	acute cholestatic hepatitis, haemorrhagic gastritis	GERD ⁷ , acute hepatitis	3 days	after 1 st dose	520 mg	none
5	M, 77	abdominal wall hematoma	irritation of abdominal-wall sensitive fibers	2 days	after 1 st dose	150 mg	none
6	M, 47	liver abscesses	irritation of diaphragmatic sensitive fibers	1 day	after 1 st dose	60 mg	none
7	M, 79	advanced lung carcinoma, mediastinal and brain metastases	dexamethasone-induced ⁸	15 days	after 1 st dose	210 mg	none