Benztropine for the treatment of intractable hiccups: New indication for an old drug?

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Introduction

Intractable hiccups interfere with eating and sleeping, and are exhausting and distressing to patients. As a result, patients with hiccups periodically present to the emergency department (ED) to request therapy. Although many treatments have been suggested, hiccups may prove difficult to treat. This report describes a patient who presented to the ED with prolonged hiccups that were resistant to conventional treatments. He responded dramatically to one dose of benztropine, a commonly used medication with few side effects. A Medline search revealed no previous articles discussing the use of benztropine for refractory hiccups.

Case report

A 55-year-old male presented to the ED with a 12-day history of hiccups that started shortly after the ingestion of rancid yogourt. After 3 days of symptoms, he consulted his family physician, who documented a normal physical examination and prescribed chlorpromazine (50 mg orally with a second dose to be repeated later). The hiccups continued after a short period of relief, and he revisited his doctor 2 days later. At this time he was given chlorpromazine, 50 mg intramuscularly (IM), and oral pantoprazole. The hiccups stopped for 24 hours, then returned. His doctor administered chlorpromazine 50 mg IM, and prescribed ongoing pantoprazole and chlorpromazine, 25 mg tid, as needed.

During this time he was also seen twice in the ED, where intravenous (IV) chlorpromazine and lorazepam were administered, but with no lasting relief. During one ED visit, various folk remedies were employed over 2fi hours, with no effect. Complete blood count (CBC), liver function tests, amylase, blood urea nitrogen, creatinine, chest x-ray and the results of an abdominal ultrasound were all within normal limits. After 12 days of hiccups, the patient returned for his third ED visit, stating that the hiccups were so intense he was unable to eat or sleep and, at times, had difficulty breathing.

A recent upper gastrointestinal series had identified a small duodenal ulcer, and his past medical history also included an appendectomy, tonsillectomy, cholecystectomy and renal colic. Medications included triple therapy for *Helicobacter pylori*, as well as pantoprazole and chlorpromazine. He was allergic to codeine. He was a smoker but did not drink alcohol.

Vital signs, including temperature, were normal. Examination of the head, neck and chest was unremarkable, and the abdominal and cardiovascular exams were normal. Because numerous tests had already been done, no further investigation was performed during this visit.

At this time, 2 mg of benztropine was administered by IM injection. Forty minutes later the hiccups resolved completely. The patient was given a prescription for benztropine, 1 mg po tid, as needed. Follow-up telephone contact was made at 3 and 11 weeks. The hiccups never recurred, and no cause was discovered.

Discussion

The mechanism of hiccups (singultus) is complex. A stimulus follows the phrenic nerve, vagus nerve or thoracic sympathetic fibers to a central brainstem connection linking the respiratory centre, reticular formation and hypothalamus. Efferent signals then travel via the phrenic nerves to the diaphragm, the intercostal nerves to the intercostal muscles, the scalenus anticus nerve to the scalene muscles and the recurrent laryngeal nerve to the glottis.

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Simultaneous activation of these efferent nerves eliminates ventilatory effect at the moment of the hiccup.[1–3]

Hiccups may be a vestigial reflex. They occur in utero and are common in premature infants.[4,5] Kahrilas and Shi postulate that hiccups may be a programmed isometric exercise for the development of inspiratory muscles in utero.[1] Koladzik and Eilers have proposed a classification system where hiccups may be considered prolonged (greater than 2 hours), persistent (greater than 48 hours), or intractable (greater than 1 month).[2] Table 1 summarizes the potential causes of prolonged hiccups.

A plethora of anecdotal reports exist for the treatment of hiccups. Folk medicine interventions include breathing into a paper bag, gasping, swallowing sugar and drinking ice water. Other potentially useful interventions include stimulation of the posterior pharynx with a rubber catheter, massage of the palate with a cotton tip applicator, and the administration of a variety of medications: nebulized lidocaine, chlorpromazine, nifedipine, haloperidol, phenytoin, famotidine, metoclopramide, pantoprazole, baclofen, methylcellulose, valproic acid and gabapentin.[2,6–11] Some innovative patients have successfully used sexual intercourse[12] and marijuana[13] to alleviate their hiccups. Others have required surgical phrenic nerve interruption or diaphragmatic pacing.[2]

Hiccups may be a form of dystonia (disorder of muscle tonicity) involving the diaphragm, intercostal muscles and glottis. The pathophysiology of dystonia is unclear; however, it is thought to be centrally mediated by acetylcholine. Anticholinergics have been studied in patients with chronic dystonia,[14–17] and a recent article by Epstein[14] suggests that benztopine may relieve acute lumbar and cervical muscle spasm. No randomized clinical trials have assessed the use of benztropine in patients with hiccups; however, we have had anecdotal success using it to treat muscle spasm, and we believe it may be a potentially useful therapy for hiccups.

Benztropine is a synthetic anticholinergic agent with some antihistaminic properties. It crosses the blood–brain barrier and has central therapeutic effects in Parkinson's disease and acute dystonic reactions. It is stocked in most EDs and is also easily available from psychiatric wards. It is inexpensive and simple to administer, either orally or by injection. Side effects of a single dose are generally limited to mild anticholinergic symptoms: dry mouth, nausea, vomiting, constipation, urinary retention or tachycardia. It is contraindicated in glaucoma.

Table 1. Conditions associated with hiccups[2,6]

Toxins	Alcohol, tobacco, barbiturates
Metabolic derangements	Hypocalcemia, uremia, hyponatremia
Gastric stimuli	Distension or sudden changes in gastric temperature
Central nervous system pathology	Stroke, temporal arteritis, AV malformation, encephalitis, meningitis, multiple sclerosis, neoplasm, head trauma
Thoracic conditions	Misplaced pacemaker wire, pericarditis, mediastinal or lung masses
Psychiatric	

Conclusions

Intractable hiccups may be a form of dystonic reaction akin to muscle spasm. This report describes a case of intractable hiccups that resolved immediately after treatment with benztropine. Benztropine may be an effective agent for the treatment of intractable hiccups.

Competing interests: None declared.

Key words: hiccups, therapy; benztropine, singultus, hiccoughs, dystonia, anticholinergic

References

1. Kahrilas PJ, Shi G. Why do we hiccup? Gut 1997;41:712-3.
2. Kolodzik PW, Eilers MA. Hiccups (singultus): review and approach to management. Ann Emerg Med 1991;20:565-73.
3. Peleg R, Shvartzman P. Hiccup. J Fam Prac 1996;42:424.
4. Brouillette R, Thach BT, Abu-Osba YK, Wilson SL Hiccups in infants: characteristics and effects on ventilation. J Pediatr 1980;96:219-25.
5. Swann I. Intrauterine hiccup. Br Med J 1978;2:1497-8.
6. Friedman NL. Hiccups: a treatment review. Pharmacotherapy 1996;16:986-95.
7. Gordon N. Halting hiccups. J Fam Prac 1995;40:512.
8. Macdonald J. Intractable hiccups. BMJ 1999;319:976.
9. Marien K, Havlak D. Baclofen with famotidine for intractable hiccups. Eur Respir J 1997;10:2188.
10. Neeno T, Rosenow EC. Intractable hiccups. Consider nebulized lidocaine. Chest 1996;110:1129-30.
11. Viera AJ, Sullivan SA. Remedies for prolonged hiccups. Am Fam Physician 2001;63:1684-6.
12. Peleg R, Peleg A. Case report: sexual intercourse as potential treamtent for intractable hiccups. Can Fam Physician 2000;46:1631-2.
13. Gilson I, Busalacchi M. Marijuana for intractable hiccups. Lancet 1998;351:267.
14. Epstein NL. Benztropine for acute muscle spasm in the emergency department. CMAJ 2001;164:203-4.
15. Fahn S. High dosage anticholinergic therapy in dystonia. Neurology 1983;33:1255-61.
16. Lal S, Hoyte K, Kiely ME, Sourkes TL, Baxter DW, Missala K, et al. Neuropharmacological investigation and treatment of spasmodic torticollis. In: LJ Poirier, TL Sourkes and PJ Bedard, editors. Advances in neurology, vol 24. New York: Raven Press; 1979.
17. Lang AE, Sheehy MP, Marsden CD. Actue anticholinergic action in focal dystonia. Vol. 37, Advances in neurology series. In: Fahn S, DB Calne, Shoulson I, editors. Experimental therapeutics of movement disorders. New York: Raven Press; 1983.

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