

BRIEF REPORTS

Carvedilol Suppresses Intractable Hiccups

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Carvedilol (6.25 mg, 4 times daily) relieved 2 years of constant hiccupping, marked tardive dyskinesia, compulsive self-induced vomiting, and feelings of hopelessness and low mood in a 59-year-old African-American man. He previously failed trials of ranitidine, chlorpromazine, promethazine, tegaserod, ondansetron, metoclopramide, pantoprazole, pyloric injections of botulinum toxin A, and a vagal nerve stimulator. At a 5-month follow-up, improvement was maintained; there had been several instances of rapid relapse on carvedilol discontinuation. (J Am Board Fam Med 2006;19:418–21.)

This report describes a case of persistent and intractable postoperative hiccups of 2 years duration that responded to carvedilol after nonresponse to typical therapies. The chronic singultus was one of several concurrent pathologic conditions, including self-induced vomiting, tardive dyskinesia secondary to metoclopramide use, and depressed mood.

Although major causes of hiccups are associated with gastrointestinal ailments, persistent hiccups can be induced by tumors, chemotherapy, diabetes, uremia, or brain disease. The hiccup reflex arc, as generally accepted and clearly described by Hansen and Rosenberg,¹ has 3 main neuronal components: afferent, central, and efferent. Afferent pathways derive from somatic sensory input ascending to the brain, primarily from the gastrointestinal tract. The central component usually refers to chemoreceptor function located in the peri-aqueductal gray subthalamic nuclei. Besides the hiccup reflex arc, hiccupping can be caused by a hyperdopaminergic state² or other pathology.³ The efferent pathway involves aberrant vagal nerve stimuli associated with dyssynchrony of the diaphragm. Remedies target individual points along this arc and include mechanical and pharmacologic interventions.

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Conflict of interest: CMS lectures on tardive dyskinesia and tardive psychosis and the use of carvedilol and holds a use patent on carvedilol for the treatment of tardive dyskinesia.

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Case Reports

The patient was a 59-year-old African-American man, admitted to the hospital for nausea, frequent coffee ground hematemesis, and associated anemia, besides unrelenting hiccups. Hiccups began episodically 10 years prior. These episodes were initially relieved by self-induced vomiting and attributed to diabetic gastroparesis. The patient underwent several upper endoscopic examinations, which revealed gastric erosions, a 3-cm hiatal hernia, and a small Schatzki ring in the lower esophagus. Esophageal manometry and gastric peristalsis were within normal limits. He underwent Nissen fundoplication as expected definitive therapy for the esophageal changes, but postoperatively he developed unremitting hiccups, nausea, vomiting, and a feeling of epigastric fullness.

These continued unrelieved by trials of ranitidine (150 mg orally, twice daily), chlorpromazine (25 mg, 4 times daily), tegaserod (6 mg orally, twice daily), and promethazine, ondansetron, and pantoprazole in various doses. He occasionally obtained partial improvement from intravenous metoclopramide. No evidence of obstruction or paralytic ileus was found on radiograph films or computed tomography scans of the abdomen. He failed trials of pyloric botulinum toxin A injections and a vagal nerve stimulator (Cyberonics, Inc., Houston, TX).

The hiccups interfered with his ability to eat. Weight loss of 60 pounds over 24 months was documented. A gastro-jejunostomy tube was placed 1 year after the Nissen fundoplication, and he began overnight tube feedings. He complained of a constant compelling need to vomit. He retched several times hourly. He experienced Mallory-Weiss tears and numerous bouts of hematemesis

attributed to self-induced vomiting. He was repeatedly hospitalized for bleeding and anemia. The patient, his family, and the primary care physicians stated that the hiccupping and weight loss would probably lead to his death soon. Our psychiatric consultation was requested because of a suspected obsessive-compulsive quality to the self-induced vomiting.

He had longstanding insulin-dependent diabetes mellitus complicated by gastroparesis, gastroesophageal reflux disease, and Barrett's esophagus, a history of colonic polyps, and peripheral vascular disease. Additional cardiovascular problems included coronary artery disease with previous deep venous thrombosis, hypertension, and dyslipidemia. He had chronic obstructive pulmonary disease. He survived a subarachnoid hemorrhage with residual right upper and lower extremity weakness and mild noticeable psychomotor slowing; the left anterior cerebral artery was clipped. Past surgeries included vagal nerve simulator implantation 2 years prior, Nissen fundoplication 4 years prior, left anterior cerebral aneurysm clipping 7 years prior, placement of a Greenfield filter 7 years prior, femoral popliteal bypasses 10 and 11 years prior, and coronary artery bypass graft 18 years prior.

Current medications were glyburide, lisinopril, insulin, metoprolol sustained release, amlodipine, potassium, pantoprazole, aspirin, metoclopramide, and gabapentin. He had no allergies, and there were no familial gastrointestinal illnesses. He was on disability and lived with his wife. He had quit smoking 8 years prior and denied use of alcohol and illicit substances.

Review of systems revealed pervasive feelings of anergy, weakness, and demoralization tied to his medical problems. The patient denied other depression and anxiety symptoms and there were no fevers, chills, night sweats, dyspnea, palpitations, cough, headaches, seizures, blackouts, or urinary problems.

On examination blood pressure was 196/100, pulse 96, and respiratory rate 20. He was alert, recumbent, in observable mild distress, and fully oriented. He repetitively and tensely complained of anger and frustration from repeated hospitalizations, home confinement, and ruination of the quality of his life from hiccups and vomiting. Recent and remote memory were intact. His speech was interrupted every 5 seconds by hiccupping. He spoke softly and mumbled frequently. His replies

were typically 2 to 3 words. He avoided eye contact and frequently showed restless movements, fidgeting, and shifting. He showed continuous chewing movements, frequent tongue protrusion, and lip licking; he was unaware of these. He claimed a virtually constant urge to vomit and he clutched an emesis basin.

Expecting carvedilol to mitigate the tardive dyskinesia and tardive vomiting, and to perhaps diminish the hiccupping, it was started at 3.125 mg, 4 times daily. Metoprolol and metoclopramide were discontinued. By the next day, the patient claimed improvement. Hiccupping had decreased to 6 to 8 times per minute. Observable restlessness and vomiting were less. The carvedilol dose was doubled, and the next day, hiccupping was 1 to 2 times per minute, lip licking and chewing movements were 50% improved, vomiting had stopped, he ate soft food regularly, and his outlook and mood were upbeat. His speech was dysarthric but louder and longer. He maintained eye contact. He was discharged on carvedilol 6.25 mg, 4 times daily.

At a 5-month follow-up, hiccups were absent, and no lip licking, tongue protrusions, or chewing movements were evident. The patient admitted to an instance of discontinuing carvedilol but hiccupping, vomiting, dyskinesia, and low mood resumed after 2 days. This was observed in person by a psychiatrist colleague. The primary care physician resumed the dose at 6.25 mg, 4 times daily, and the hiccupping again stopped. He complained of a residual urge to vomit, and he induced vomiting several times daily; these were not connected to meals. His outlook remained good, and he enjoyed small meals regularly with his family.

Discussion

Few treatments reliably suppress the hiccup drive and some can even cause them as a rebound effect.^{4,5} In a syndicated column, Paul Donohue, MD, identified usual therapies as chlorpromazine, metoclopramide, baclofen, and omeprazole.⁶ Chlorpromazine and metoclopramide are potent dopamine antagonists with the potential to cause tardive disorders of movement and thought⁷ particularly in frail individuals or those >55 years old.⁸ Tardive vomiting, tardive obsessive-compulsive disorder, and tardive major depression can also develop.^{4,7} Our patient showed marked tardive dyskinesia, presumably from the metoclopramide and

chlorpromazine he had taken for 2 years.⁹ Carvedilol was initiated under the expectation that the current dyskinesia, vomiting, hiccupping, and depressed mood were all primarily tardive phenomena and accordingly should all respond.

Carvedilol rapidly mitigated manifestations of tardive dyskinesia in its typical forms of choreic and athetotic movements of the tongue and lips in clinical practice.¹⁰ It also ameliorated tardive akathisia (agitation) and dystonia and was expected to relieve other tardive symptoms such as vomiting, compulsions, and depression.¹⁰ After 3 doses, carvedilol (3.125 mg, twice daily) entirely suppressed frequent involuntary prominent tongue protrusion in a 37-year-old woman with a chronic haloperidol treatment. Carvedilol (6.25 mg, 3 times daily) ameliorated tongue protrusion, lip pouting and puckering, and agitation in a 47-year-old woman with longstanding neuroleptic use. A 53-year-old man with dystonia of the neck requiring tube feeding attributed to haloperidol (and possibly exacerbated by lithium) achieved 70% improvement after 3 doses of carvedilol (6.25 mg, twice daily). Patients rapidly relapsed to pretreatment severity with carvedilol discontinuation. Tolerance to carvedilol was not seen, and its continuation provided continuing benefit. In one patient, a short course of carvedilol seemed to provide continuing benefit.¹⁰

Coadministration of carvedilol attenuated orofacial dyskinesia in rats given 21 days of dopamine blockers haloperidol or chlorpromazine.¹¹ This was hypothesized as related to antioxidant effects. This study did not distinguish acute extrapyramidal (Parkinsonian) effects from tardive dyskinesia or how rapidly carvedilol effects wore off. In human patients the rapid onset of carvedilol benefits and fast decay after its discontinuation point away from an antioxidant mechanism because antioxidant-mediated clinical changes develop slowly.

Multiplicity of disease in the present case complicated the clinical presentation, but the rapid simultaneous relief of hiccupping, vomiting, low mood, and abnormal involuntary movements with carvedilol administration and its subsequent rapid re-emergence with carvedilol discontinuation points toward a common tardive pathophysiology. Although the initial hiccupping antedated dopamine-blocking drugs, the current hiccupping is apparently tardive type, in view of its association with tardive dyskinesia and dopamine-blocking drugs. Because dopamine-blocking drugs can acutely di-

minish hiccupping, their chronic rebound effects—which are opposite and presumably hyperdopaminergic—should include singultus.

Carvedilol has several clinical pharmacologic effects, including nonspecific β blockade, α -1 blockade, and calcium channel inhibition, as well as antioxidant activity.^{10–12} As a sympatholytic, carvedilol should diminish somatic tension anxiety as other lipophilic β blockers do.^{4,5,13} This should diminish manifestations of sympathetic nervous system irritation, such as compulsions and low mood, but this does not seem sufficient to explain all the benefits of carvedilol in the present case.

Conclusion

Because of the rapid responses and recurrences corresponding to carvedilol administration and discontinuation, it is clear that carvedilol effectively suppressed hiccupping, vomiting, dyskinesia, and depressive symptoms in this patient. It is not clear which pharmacological effects of carvedilol contribute to these actions. Similarly, it is not apparent if tardive hiccupping is the only kind of hiccupping that carvedilol diminishes. Carvedilol should be safer than metoclopramide or chlorpromazine, especially in long-term use and in patients over age 55. Mitigation of singultus, as in our patient, seems to require long-term carvedilol continuation.

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