Dystonic–like Reaction Following Cisapride Therapy

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A 43-year-old woman with gastroesophageal reflux disease developed a dystonic–like reaction approximately 3 days after starting oral cisapride therapy. Office evaluation revealed a patient who moved her head rhythmically from side to side as she stared into space, generally unresponsive to external stimuli. She had increased tone of the sternocleidomastoid muscles bilaterally, with occasional tongue protrusion, and a slow shuffling gait. Following discontinuation of cisapride, the patient recovered completely.

Key words. Cisapride; dystonia; drug-induced dyskinesia; movement disorders; gastroesophageal reflux; drug-induced abnormalities.

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Cisapride (Propulsid) is a prokinetic agent available for the symptomatic relief of nocturnal heartburn caused by gastroesophageal reflux disease.[1] Although cisapride is structurally related to metoclopramide (Reglan), its proposed mechanism of action is different. Cisapride enhances the release of acetylcholine rather than inhibiting the dopaminergic receptors of the gastrointestinal tract or the central nervous system. It has been reported that cisapride does not have the extrapyramidal effects associated with metoclopramide.[2,3] According to the package insert, cisapride-induced extrapyramidal effects have seldom been reported, and in these rare cases, the relationship of cisapride to the event was unclear.[4] We report a case of a patient with gastroesophageal reflux disease who developed a dystonic–like reaction following cisapride administration.

Case Report

A 43-year-old woman was brought to the office by her family with the complaint that she had been "acting strangely" since the previous evening. They explained that she had begun moving very slowly, staring into space, moving her head slowly from side to side, and generally ignoring those around her. She had been only occasionally responsive during this period by way of grunts or simple interjections. Three days earlier, she had been released from the hospital after undergoing surgical drainage of bilateral axillary abscesses. At the time of her discharge from the hospital, she had been at her baseline mental status and activity level, neither of which showed any global or focal deficits.

The patient's medical problems included insulin-dependent diabetes mellitus (IDDM), hypertension, gastroesophageal reflux disease (GERD), and axillary abscesses. Her hospital discharge medications included: cefadroxil monohydrate 500 mg twice daily, metronidazole 250 mg three times daily, lisinopril 10 mg daily, insulin (Humulin 70/30) 40 units in the morning and 30 units in the evening, and cisapride 10 mg 30 minutes before meals and at bedtime. She had been taking lisinopril and insulin for more than 6 months. Oral antibiotics to treat the abscesses were started on the day of discharge. The patient had been taking metoclopramide 10 mg four times daily for the previous several months, but she was switched to cisapride on the day before discharge with the expectation that it would control her GERD more effectively.

On the second night following discharge, the patient began experiencing the aforementioned symptoms. When the symptoms continued the following morning, she was brought in for evaluation. The patient's family

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confirmed that she had taken medications only as prescribed and directed on her release from the hospital. A correct pill count supported the family's recollection of related events. The patient had consumed no alcohol or illicit drugs and had followed her usual diabetic diet. The family denied any evidence of fever, chills, vomiting, diarrhea, loss of consciousness, or witnessed seizure activity.

Physical examination showed her to be afebrile with a pulse rate of 72 beats per minute, a respiration rate of 16 to 18 breaths per minute, blood pressure of 160/90 mm Hg, and weight of 108 lb (49 kg). The patient was able to sit up, but was only vaguely aware of her surroundings. She moved her head rhythmically from side to side, walked with a slow shuffling gait, and exhibited oral facial dyskinesia manifested by occasional tongue protrusion. With hands placed palm down on her thighs, she responded to verbal stimuli only with nondirected grunts.

Her pupils were of normal size and responded equally to light and accommodation. No papilledema was noted on fundoscopic examination. Her neck showed increased tone of the sternocleidomastoid muscles bilaterally. Cardiovascular, respiratory, and abdominal examinations revealed no abnormalities. Abscess drainage sites in both axillae showed granulation tissue formation without evidence of further infection. Neurologic examination showed cranial nerves II to XII without focal deficits bilaterally. Most of this examination was obtained by observation since the patient could not participate actively. Deep tendon reflexes were 2+ bilaterally in upper and lower extremities. Toes were down-going bilaterally, and pinprick sensation was judged to be intact by the patient's withdrawal responses. Her blood glucose level was 237 mg/dL (13.2 mmol/L).

The patient's symptoms and examination were thought to be consistent with a dystonic reaction. She was given 50 mg of diphenhydramine intramuscularly. After 1 hour, her ability to respond to simple yes/no questions improved, and her answers to more complex questions were more intelligible and accurate. Involuntary head movements also decreased. An additional 25 mg of diphenhydramine was given intravenously. Within 10 minutes, she appeared to be back to her normal baseline functioning level. Verbal response was good with clear sensorium, and all abnormal movements and posturing had resolved. Questioning of the patient revealed that she did not remember being brought to the office nor did she recall events of the previous evening. She vehemently denied any alcohol or illegal drug use since discharge from the hospital.

The patient returned home, continuing her original medications, with the exception of cisapride. She finished her course of antibiotics without incident, and the abscesses healed completely. At 1-, 2-, and 3-month follow-up, she displayed no further dystonic symptoms.

Discussion

Cisapride is a synthetic, piperidinyl benzamide prokinetic drug chemically related to metoclopramide.[1,5] It was approved in July 1993 for the symptomatic relief of nocturnal heartburn caused by gastroesophageal reflux disease.[1] Cisapride was developed as a "targeted" prokinetic agent with a unique mechanism of action.[5] It is thought that cisapride increases gastric motility by enhancing the release of acetylcholine from the myenteric plexus.[1,2] In contrast to metoclopramide, cisapride is believed to stimulate gastrointestinal motility *without* producing dopaminergic inhibition of either the gastrointestinal tract or central nervous system.[2] Cisapride is believed not to penetrate the central nervous system (CNS), and thus is thought to have fewer neurologic adverse effects than metoclopramide.[2] Controlled studies have demonstrated that the CNS adverse effect profile for cisapride is more favorable than that of metoclopramide.[6,7] Movement disorders induced by metoclopramide are discussed extensively elsewhere.[8]

Adverse effects reported with cisapride include headache, nausea, diarrhea, and rhinitis.[1] The package insert states "in U.S. and international trials and in foreign marketing experience, there have been rare reports of [seizures and] extrapyramidal effects. The relationship of cisapride to the event was not clear in these cases."[4] Similarly, other sources state abnormal movements have rarely been reported during cisapride therapy, although a causal relationship has not been established.[5,9] Tremor has also been reported to occur in 1% or less of patients.[4]

An acute dystonic reaction is defined as sustained muscular spasm producing twisting, squeezing, and pulling movements within minutes or hours of drug exposure.[8] Drug-induced parkinsonism is similar to Parkinson's disease, except that it tends to be more symmetrical and is associated with a more rapid and postural tremor.[8] Tardive dystonia is characterized by sustained slow or rapid twisting movements of the face, neck, trunk, or limbs, and may occur following days of therapy.[8] This patient's presentation would appear to encompass characteristics of these effects, as well as a slowed ability to respond (ie, characteristics of bradykinesia or an akinetic mute).

The patient in this case developed a dystonic–like reaction, which resolved when cisapride was discontinued and diphenhydramine was administered. It was concluded that the reaction was induced by cisapride because of the temporal relationship to cisapride administration

and the reversal of the reaction on office administration of diphenhydramine. When cisapride was discontinued, the patient recovered completely. A possible explanation for this effect may be that cisapride inhibits dopaminergic receptors involved in motor function.

Confusion as a side effect has rarely been reported with the concomitant use of lisinopril and cefadroxil.[10] This patient improved despite the continued use of these medications; therefore, a causal relationship is unlikely. Metoclopramide-induced tardive dyskinesia, which is usually seen following discontinuation of the drug and manifested by orobuccolingual dyskinetic movements,[11] was also considered. This possibility seemed unlikely based on the patient's marked improvement with diphenhydramine administration.

Summary

In theory, cisapride is less likely to cause movement disorders than metoclopramide; however, this case demonstrates the possibility of such reactions. As experience with cisapride increases, more information about the nature and incidence of movement disorders associated with this medication may become available. The possibility of such an adverse effect should be considered in the evaluation of patients who present with a movement disorder while being treated with cisapride.

References

1. Anon. Cisapride for nocturnal heartburn. Med Let 1994; 36:11–3.
2. Brown CK, Khaderia U. Use of metoclopramide, domperidone, and cisapride in the management of diabetic gastroparesis. Clin Pharm 1990; 9:357–65.
3. Cisapride drug interactions. Facts and comparisons drug newsletter 1993; 12:89.
4. Cisapride package insert. Titusville, NJ: Janssen Pharmaceutica, October 1993.
5. Baronne JS, Jessen LM, Colazzi JL, et al. Cisapride: a gastrointestinal prokinetic drug. Ann Pharmacother 1994; 28:488–500.
6. Arabehety JT, Leitao OR, Fassler S, et al. Cisapride and metoclopramide in the treatment of gastroesophageal reflux disease. Clin Ther 1988; 10:421–8.
7. Manousos ON, Mandidis A, Michailidis D. Treatment of reflux symptoms in esophagitis patients: comparative trial of cisapride and metoclopramide. Curr Ther Res 1987; 42:807–14.
8. Miller LG, Jankovic J. Metoclopramide-induced movement disorders. Clinical findings with a review of the literature. Arch Intern Med 1989; 149:2486–92.
9. McCallum RW. Cisapride: a new class of prokinetic agent. Am J Gastroenterol 1991; 86:135–49.
10. Olin BR, ed. Facts and comparisons drug information update monthly. St. Louis, Mo: Facts and Comparisons, Inc, 1994: 165f,336D.
11. Mcvoy GK, ed. AHFS drug information 94. Metoclopramide. Bethesda, Md: American Society of Hospital Pharmacists, 1994:1934.