

## An Unusual Reaction to Preoperative Metoclopramide

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Metoclopramide is a drug which promotes gastric emptying. It has been shown to be effective in decreasing the risk of pulmonary aspiration when used preoperatively in combination with other agents.<sup>1-3</sup> Its use as a prophylactic preoperative antiemetic has also been recommended.<sup>1,4</sup> Side effects associated with low-dose metoclopramide administration are rare, and have only been reported in conjunction with the use of other psychotropic drugs. We report a case in which a healthy woman developed symptoms of severe dysphoria, agitation, and akathisia following preoperative metoclopramide administration.

## CASE REPORT

A 21-yr-old ASA Class 1 woman with a history of abdominal pain and a suspected ectopic pregnancy presented for outpatient laparoscopy. Preoperative evaluation revealed no previous history of medical or psychiatric illness and no history of psychotropic drug use. Premedication consisted of metoclopramide 10 mg and glycopyrrolate 0.2 mg administered iv. Approximately 10 min after administration of the premedication, the patient became agitated, verbally abusive, and refused to proceed with the surgery. Attempts by her gynecologist to calm her were unsuccessful. The surgery was canceled, and the patient was discharged in the care of her fiancé about 25-30 min after receiving her premedication. Although visibly upset and agitated, the patient agreed to stop in the hospital snack bar prior to leaving the hospital. Once there, she abruptly left her fiancé and began screaming and running through the hospital. She managed to elude her pursuers for a brief period of time, and was finally found doing jumping jacks outside the hospital emergency room. She was returned to the outpatient surgery department in an extremely agitated state. The attending anesthesiologist was called to see the patient, who was now under physical restraint. When questioned, the patient said that she felt drugged and dizzy and that her legs felt extremely restless. She stated that she felt as though she were "crawling out of her skin," and that she was having repeated thoughts which were telling her to move her legs and run, while, simultaneously, she realized that these thoughts were inappropriate. Treatment of the patient's agitated state consisted of benzotropine 2 mg im. Within 5 min, a marked decrease in the degree of agitation was seen, although, by 15 min, her symptoms, most notably the restlessness in her legs, had not completely resolved, and another 2 mg of benzotropine iv was administered. Five minutes follow-

ing this second injection, the patient's symptoms had cleared completely. The only side effects noted by the patient following benzotropine injection were blurred vision and a dry mouth.

Following resolution of her symptoms, the patient, who was now calm and rational, agreed to be readmitted to the hospital for observation. The following day, having received no premedication, she was taken to the operating room, where a diagnostic laparoscopy was performed without incident with iv thiopental and fentanyl and inhalation of isoflurane and nitrous oxide.

## DISCUSSION

Metoclopramide is a benzamide derivative with a wide variety of physiologic effects. As a gastrokinetic agent, it speeds the transit of food through the stomach and increases lower esophageal sphincter tone. The mechanism of this effect is incompletely understood, but is probably related to dopaminergic receptor blockade and enhanced release of acetylcholine by gastric intramural cholinergic neurons.<sup>5</sup> Metoclopramide is also an effective antiemetic, and is widely used in high doses (40-80 mg/day) to relieve nausea in patients receiving chemotherapy with cisplatin. The ability of metoclopramide to relieve or prevent emesis is presumably related to blockade of dopaminergic (D2) receptors, which are present in high density in the chemoreceptor trigger zone of the area postrema.<sup>6</sup> In low doses, metoclopramide is an effective prophylactic preoperative antiemetic<sup>1,4</sup> and, because it does not cause postoperative sedation, its use may be advantageous in an outpatient surgery setting.

Side effects following metoclopramide administration have been reported in 10-20% of patients. Drowsiness and lassitude are the most frequently reported symptoms. However, feelings of anxiety, agitation, and motor restlessness may occur, particularly with high doses and following intravenous administration. These symptoms are usually mild and transient, disappearing when the drug is discontinued. Extrapyramidal side effects are uncommon, occurring in less than 1% of patients, and Parkinsonian symptoms of tremor, rigidity, and akinesia are rarely seen, except with excessively high doses or in patients with decreased renal function. The onset of symptoms in most patients appears to be dose dependent, and they are uncommon with doses less than 40 mg/day.<sup>5</sup> However, small doses of metoclopramide administered in combination with phenothiazines or related drugs have been implicated in the development of a variety of side effects. Barnes *et al.*<sup>7</sup>

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reported the development of acute akathisia, a syndrome of subjective and motor restlessness associated with dopamine antagonists, in three of 14 patients who received 10 mg of metoclopramide and 20 mg of droperidol preoperatively. The affected patients spontaneously complained of feeling unable to keep their legs still, and all experienced a strong desire to "get up and walk around." Weddington *et al.*<sup>8</sup> reported a case in which a patient with intractable hiccups received chlorpromazine 50 mg followed by metoclopramide 10 mg four times a day. After several days of metoclopramide, the patient reported increasing anxiety, racing thoughts, crying spells, insomnia, and a sense of impending doom. His memory and orientation remained intact, but he sensed that he was "going crazy" and reported that his symptoms were most severe approximately 30 min after he ingested metoclopramide. In this case, discontinuation of the metoclopramide resulted in rapid reversal of symptoms. Fouilladieu *et al.*<sup>9</sup> reported a case in which a patient who had received 10 mg of metoclopramide and 100 mg of hydroxyzine preoperatively developed rigidity, generalized tremor, hypertension, and opisthotonos. His symptoms were treated with thiopental and halothane general anesthesia. No recurrence of symptoms was seen following recovery from anesthesia.

In addition to dopaminergic receptor blockade, metoclopramide increases the release of acetylcholine in the central nervous system. Benztropine, a centrally acting anticholinergic which is recommended in the treatment of phenothiazine-induced extrapyramidal disorders, presumably restores the relative balance between dopaminergic and cholinergic activity within the CNS. The fact that our patient's symptoms were promptly relieved after benztropine administration suggests a possible mechanism for metoclopramide-induced behavioral changes.

The symptoms exhibited by our patient bear many similarities to those cases just described. However, our case differs in that our patient received no other centrally active drugs preoperatively except metoclopramide. Glycopyrrolate, an anticholinergic drug with a quarternary charged nitrogen atom, does not cross the blood-brain barrier, and, thus, could not be responsible for the symptoms we observed. Our patient denied any history of psychotropic drug use, which rules out concomitant drug use as a cause of her symptoms. Previous

reports indicate that small doses of metoclopramide rarely cause significant side effects unless administered with other centrally active dopaminergic blockers. Our experience suggests that, in certain individuals, metoclopramide alone has the potential to cause bizarre behavioral changes, and that this fact should be kept in mind when metoclopramide is used preoperatively. Since encountering this patient, we have seen two other patients who have spontaneously complained of mild akathisia and anxiety following preoperative metoclopramide. While it is possible that our patient's reaction may represent an incidental hysterical reaction to a stressful situation, we feel that is unlikely given the similar, but milder, symptoms described by our other patients.

Since the frequency of side effects following small doses of metoclopramide is currently unknown, we feel that an objective double-blind preoperative study should be undertaken to definitely establish the likelihood of encountering the symptoms we observed following preoperative metoclopramide.

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