

Akathisia and Anesthesia: Refusal of Surgery After the Administration of Metoclopramide

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Akathisia (from the Greek for "not to sit") is a distressing side effect of some medications often prescribed to patients (1,2). Akathisia usually presents with objective motor restlessness and subjective mental changes. Perioperative medications known to produce akathisia include droperidol, metoclopramide, perphenazine, prochlorperazine, naloxone, and flumazenil. Patient refusal to have surgery after the administration of droperidol has been repeatedly reported (3,4), but our literature search revealed only one case report of the cancellation of surgery after the administration of metoclopramide (5). We believe that central nervous system side effects of this severity may be rare, but less severe effects of metoclopramide and other medications may be more common than appreciated. It is possible that there is substantial underdiagnosis and misinterpretation of acute akathisia because of unfamiliarity with the condition (6). We report two cases of the cancellation of surgery by patients in our institution who displayed akathisia-like symptoms after they received an IV bolus of metoclopramide. After these episodes, we changed the way metoclopramide is given preoperatively.

Case Report 1

A 30-yr-old man, ASA physical status II, with Hodgkin's disease presented for right cervical lymph node biopsy. He had received general anesthesia for a similar neck biopsy 1 yr earlier without complication. His other medical conditions included hypertension, asthma, esophageal reflux, sleep apnea, and morbid obesity. He denied any history of psychiatric illness. His therapy included diltiazem, albuterol, and continuous positive airway pressure (CPAP) at night. Examination showed a calm and cooperative man with unremarkable airway, chest, and cardiac findings.

The patient was premedicated with sodium citrate 30 mL *per os* and metoclopramide 10 mg given IV for 1 min. On arrival in the operating room, approximately 4 min later, the patient stated that he was feeling "funny." He complained, "I have a feeling something bad is going to happen. I need to walk around!" As he said this, he removed his IV line and walked out of the operating room. The symptoms improved after approximately 2 h, and the patient went home without undergoing surgery. In the following days, he was counseled by phone that his unpleasant experience may have been a reaction to the metoclopramide.

Case Report 2

A 33-yr-old man, 74 kg, ASA physical status I, presented for surgical repair of a canalicular tear in his left eye. Clinical examination revealed a calm patient and no remarkable findings. Aspiration prophylaxis of 30 mL of Bicitra orally and 10 mg bolus of metoclopramide IV were given. Three minutes later, the patient became erratic and combative. He removed the IV cannula from his hand and left the hospital in the company of his wife, despite explanations that his feelings of discomfort were due to the medications just given. The patient was lost to further follow-up through this institution.

Discussion

Drugs that may produce akathisia are often prescribed to patients (1,2) (Table 1). Drug-induced akathisia (DIA) is often difficult to diagnose and may present in varying grades of severity. DIA is a psychoneuromotor phenomenon of an overwhelming compulsion to move and an inability to sit or stand still (2,7,8). It is usually described as having a subjective mental or psychological component and an objective, observable motor component. Subjectively, the patient may describe an unpleasant feeling of inner restlessness or tension referable most commonly to the lower limbs. A desire to get up and walk, an inability to think properly, anxiety, and a sense of impending doom and fear of death have also been reported (7). Violent and suicidal ideation has been reported as a manifestation

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Table 1. Drugs Implicated in Causing Akathisia

Neuroleptics	All neuroleptics including droperidol
Antidepressants	Tricyclics, fluoxetine, sertraline, paroxetine
Dopamine-depleting agents	α -Methyl tyrosine, reserpine, tetrabenazine
Calcium channel blockers	Diltiazem, flunarizine, cinnarizine
Antiemetics	Metoclopramide, prochlorperazine, perphenazine
Dopamine agonists	Amphetamine, methylphenidate, fenfluramine, nomifensine, amantidine, pemoline
Anticonvulsants	Carbamazepine, ethosuximide
Withdrawal akathisia	Naloxone, flumazenil , cessation of smoking

Adapted with permission from Reference 2.
The drugs often given in the perioperative period are in bold.

of akathisia by patients being treated with neuroleptics (9,10). The objective motor components include restlessness of the lower limbs in the form of rocking foot to foot, crossing and uncrossing of legs, and pacing. Less severe forms may present with mental changes without objective movement disorder, which may mimic or aggravate normal preoperative anxiety.

The neuropharmacological basis of akathisia is still incompletely understood. A disturbance in the integrated function of the locus ceruleus, basal ganglion, and the limbic system brought about by dopaminergic, noradrenergic, and/or other neurotransmitters seems to be involved (11). Disturbances in the dopaminergic modulation of the rich noradrenergic system in the spinal cord may have a role (11,12). In addition, opioid, γ -aminobutyric acid and cholinergic receptor systems are involved in modulating the dopaminergic and adrenergic systems. Interestingly, both droperidol and metoclopramide act, in part, via presynaptic dopamine antagonism (3,4). An overactive adrenergic system secondary to presynaptic dopamine receptor block in key parts of the brain and spinal cord may be an oversimplified but useful way of looking at the mechanism of DIA (11). The inner anxiety that patients occasionally feel when sedated with droperidol may perhaps be a manifestation of akathisia.

The incidence of neuroleptic-induced akathisia in psychiatric patients is often underdiagnosed (6). The reported incidence ranges from 8% to 76%, with 20%–30% being a conservative estimate (13). The incidence is much higher in oncology patients treated with large-dose antiemetic therapy.

The purposes of preoperative medications are to reduce stress, alleviate anxiety, and reduce perioperative risks. It is disturbing that these very medications may be causing extremely unpleasant mental changes. A high incidence of varying grades of akathisia in the perioperative period may be hidden by anesthesia, sedation, patient reluctance to complain, and/or the anesthesiologist's unfamiliarity with the condition. Mild forms of akathisia may masquerade as situational anxiety. On the other hand, previously unknown or undiagnosed psychiatric or behavioral disorders may manifest during the highly stressful

perioperative period, confusing the diagnosis of akathisia. In the perioperative period, increased apprehension and restlessness ranged from 27% (14) to 45% (15) when droperidol was given as a premedication. This is in contrast to an incidence of similar symptoms of 0%–2% in control groups receiving placebo (3,15,18,21). Reports include restlessness, agitation, or extrapyramidal effects with doses as small as 0.625 mg (16). When Innovar (a mixture of fentanyl and droperidol) was popular as a premedicant, a significant number of patients refused surgery after receiving the drug (3,4). Descriptions in many of these case reports are consistent with DIA. A patient who was a psychiatrist and an expert on drug-induced movement disorders had personal experience of akathisia induced by droperidol during surgery under epidural anesthesia (17). Delayed restlessness caused by droperidol has also been reported after general anesthesia in ambulatory surgical patients (18).

Metoclopramide has been linked to akathisia in many reports (5,19,23,24). In a study of the effect of metoclopramide on prolactin and aldosterone, the incidence of akathisia was 25% after receiving 10 mg of metoclopramide IV (19). In another study of nonsurgical patients, metoclopramide in a dose of 10 mg orally qid produced symptoms attributable to akathisia in 10% of subjects (20). In all cases, the signs and symptoms included motor restlessness, a desire to get up and walk around, racing thoughts, anxiety, and/or a sense of impending doom.

In the perioperative setting, Dundee et al. (21) and Dundee and Clarke (22) reported 12% and 26% incidence of restlessness after an IM injection of 10 and 20 mg of metoclopramide, respectively. Of 14 patients, 3 developed restlessness during eye surgery when a combination of droperidol and metoclopramide was given as premedication (23). For IV 10-mg bolus doses of metoclopramide, the incidence of restlessness seems to be 20%–25% (19,24).

The speed of administration seems to be an important factor in determining the incidence of akathisia induced by metoclopramide (24,25). Patients who received metoclopramide via oral or IM routes had a lower incidence of akathisia compared with reports of

incidents with IV administered metoclopramide. Metoclopramide-induced akathisia was reduced from 18.5% to 0% when 10 mg was diluted and given slowly over 10 min. Interestingly, both patients in our report received a rapid IV administration (≤ 1 min) of metoclopramide. Anxiety or restlessness was reduced when a sedative medication was coadministered (23).

Prevention of akathisia also includes identifying patients at risk of developing DIA and properly determining the risks and benefits of using metoclopramide. There seems to be a bimodally increased incidence with respect to age (<30 or >60 yr) (28,29). Patients with acquired immunodeficiency syndrome, renal disease, and oncologic diagnosis, and women, have all shown an increased susceptibility to extrapyramidal reactions (30).

Patients with a history of DIA and those taking centrally acting medications chronically may also be at higher risk (28,29). Theoretical alternatives to metoclopramide for the indication of reducing gastric volumes include cisapride or domperidone. Cisapride acts by facilitating the release of acetylcholine from the myenteric plexus and has no central side effects. Domperidone is a peripheral dopamine antagonist that does not readily cross the blood-brain barrier. However, we are not aware of studies analyzing these drugs for use in the perioperative period.

After diagnosing an episode of DIA, prompt treatment includes discontinuation of the offending drug and initiation of treatment to reduce unpleasant symptoms. Benzodiazepines, β -blockers, α_2 -agonists, opiates, and anticholinergics have all been used to treat akathisia (2,5,16). Anticholinergic drugs seem to be more successful in relieving all symptoms of akathisia, whereas benzodiazepines tend to relieve the subjective components best. Centrally acting anticholinergics presumably restore the relative balance between dopaminergic and cholinergic activity. Diphenhydramine has also been used effectively (16).

We believe that drugs commonly administered in the perioperative period have the potential of inducing akathisia. Less severe forms may go unrecognized or may be misdiagnosed as anxiety. The more severe forms may result in refusal of surgery, as in our case reports, and in unpredictable, violent behavior (10,26) or suicidal ideation (9,27), all of which may have serious consequences. Avoidance of akathisia-inducing medications, awareness of the condition of DIA, injecting metoclopramide slowly, and administration of adjuvant opioid or sedative medications are important in reducing akathisia symptoms. In our practice, we now administer metoclopramide as a "piggy back" drip (10 mg/100 mL isotonic sodium chloride solution) or administer divided bolus doses up to the total dose over no less than 3 min. In addition, we give preoperative anxiolytics before metoclopramide unless contraindicated by comorbid conditions. If akathisia does occur, prompt recognition and

treatment with anticholinergics or benzodiazepines are necessary. On resolution of symptoms, the patient should be counseled that the experience may have been drug-induced.

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