

Anti-emetics and drug-induced parkinsonism in a gyn-onc patient

📌 One woman's difficult course offers a reminder: Recognize DIP early and remove the offending agent.

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The anti-emetics prochlorperazine (Compazine) and metoclopramide (Reglan) are commonly used in obstetric and gynecologic care. Extrapyramidal reactions are rare side effects of these drugs, and have been described with metoclopramide since 1978. Such reactions vary—from acute dystonic reaction, akathisia, and tardive dyskinesia all the way up to full-blown parkinsonism.

Drug-induced parkinsonism (DIP) can be difficult to diagnose; it is often missed by clinicians (even by neurologists).¹ This is regrettable, because DIP is usually reversible once the offending agent is withdrawn.

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In this brief report, we discuss the case of a gynecologic oncology patient who developed DIP after receiving anti-emetics to alleviate side effects of chemoradiation.

CASE | Late postop complaints

A 43-year-old G0 gyn-onc patient came to the emergency department of our hospital several weeks after radical abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node dissection for Stage IB1 squamous cell carcinoma of the cervix. Her primary complaints in the ED were “throbbing” in the thighs bilaterally and leg pain.

The woman's postop course had otherwise been uncomplicated. Because she had one pelvic lymph node positive for disease, however, she had received:

- a total dose of 240 mg/m² of external-beam pelvic radiation
- concurrent weekly doses of 40 mg/m² of cisplatin.

Before this ED visit, chemoradiation was complicated by persistent nausea that, eventually, responded to a combination of metoclopramide and prochlorperazine.

Deep-vein thrombosis was ruled out in the ED. No diagnosis or treatment was offered. **1 week later.** The patient returned, complaining of generalized weakness. The ED workup this time, comprising laboratory testing and computed tomography of the abdomen and pelvis, was negative. She was given a diagnosis of “cisplatin neurotoxicity.” No treatment was provided.

IN THIS ARTICLE

Distinguishing primary and secondary parkinsonism
page 1b

Why the risk of DIP rises with age
page 1c

CASE Continued
Off in the wrong direction?

Cisplatin neurotoxicity has a variety of presentations, including peripheral neuropathy, gait disturbance, autonomic neuropathy, seizures, and Lhermitte's sign (inducible tingling or a sensation like electrical shock in the arms and legs, upon flexion of the neck). Peripheral neuropathy, most common, begins in the hands or feet and ascends proximally.

Neurotoxicity following cisplatin is usually observed after a total dosage of 300 mg/m²; symptoms are irreversible in 30% to 50% of patients.²

Our patient had received a total cisplatin dosage of just 240 mg/m², however, and never exhibited classic signs of cisplatin neurotoxicity. Was the ED diagnosis off the mark?

10 days later. Now, approximately one month after chemoradiation, the patient visited our outpatient facility, complaining that her original symptoms ("throbbing" leg pain, restlessness in the extremities, generalized weakness) had become worse and that she had developed a generalized tremor. She had also become severely de-conditioned and required assistance with activities of daily living.

On physical exam, the patient displayed a bilateral upper-extremity resting tremor that was exacerbated by intentional movement. She drooled, and had dysarthria, a shuffling gait, and cogwheel rigidity.

Medications included metoclopramide, three times daily; prochlorperazine, every 6 hours; omeprazole; and dexamethasone.

The medical history and family history were negative for neurodegenerative disease.

A neurology consult was requested. The neurologist diagnosed drug-induced parkinsonism (DIP) secondary to metoclopramide and prochlorperazine.

What is this drug effect?

Parkinsonism encompasses a spectrum of disease. It is characterized by resting tremor, bradykinesia, rigidity, and postural instability. Secondary parkinsonism, such as DIP, has an identifiable cause and can, potentially, be reversed.

Distinguishing primary and secondary parkinsonism can be a challenge. In DIP, rigidity and bradykinesia typically dominate; DIP also:

- tends to be more common with increasing age
- occurs more often in women (2:1 prevalence)
- has a bimodal age distribution
- is characterized by a symmetric resting tremor that affects primarily the upper extremities.³

Any medication that decreases dopaminergic activity in the nigrostriatal pathway can cause parkinsonism. These include a number of medications commonly administered to OB and gynecology patients:

- disulfiram
- some calcium channel blockers
- methyl dopa
- meperidine
- some selective serotonin reuptake inhibitors
- antiepileptics
- estrogen and oral contraceptives (although estrogen can have an anti-dopaminergic effect).⁴

DIP is reported most often after neuroleptic therapy and after exposure to certain anti-emetics, such as the metoclopramide and prochlorperazine given to this patient, that block dopamine receptors.

Whether the manifestations of DIP are reversible depends on the dosage and duration of exposure to the medication. Subtle side effects, such as masked facies and difficulty swallowing, may occur within minutes, or hours, after the patient is exposed to the drug.

Most symptoms of DIP are misdiagnosed

In a series of patients reported by Miller and colleagues,⁵ 131 who had a drug-induced movement disorder continued on the offending medication for, on average, 6 months after onset of symptoms. In a study by Esper and co-workers of DIP patients at movement disorder clinics, average time to correct diagnosis after symptoms were reported was 1.8 years.¹



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Our patient exhibited symptoms for 1 month before the correct diagnosis was made, at her third visit for those symptoms.

CASE Resolved

The patient was hospitalized and the antiemetics discontinued upon the neurologist's diagnosis. Diphenhydramine and benztropine were started to counteract extrapyramidal symptoms.

Within 24 hours, neurologic symptoms improved strikingly.

At discharge, the patient was able to walk without assistance and had normal facial expressions. The tremor had ceased.

At 6-week follow-up, neurologic symptoms had not returned.

With hindsight...

Our patient's complaints encompassed the full range of extrapyramidal side effects—akathisia (leg restlessness), trouble swallowing and drooling (acute dystonic reaction), tremor, cogwheel rigidity, and dysarthria (parkinsonism).

Of new cases of parkinsonism among a series of 95 patients seen at a geriatric clinic, 51% were given a diagnosis of DIP.⁶ In a large, prospective study by Bateman and colleagues in northern Great Britain, the incidence of **metoclopramide-induced dystonia** was 1 in 213; akathisia, 1 in 320; and DIP, 1 in 512.⁷ The incidence of **prochlorperazine-induced dystonia** was 1 in 702, akathisia 1 in 937, and parkinsonism 1 in 312. Most retrospective cases of metoclopramide-induced parkinsonism occur in the elderly (older than 60 years).^{5,8,9}

Parkinsonism develops when the striatal dopamine levels fall below 80% of expect-

ed (normal) values. This may explain why certain populations in whom the dopamine level is already low, such as the elderly, may be more susceptible to DIP.⁹

It is difficult to discern which antiemetic was responsible for our patient's symptoms; both may be guilty. In the timeline of the case, symptoms manifested when prochlorperazine was started and appeared to have been compounded by addition of metoclopramide. The literature shows that both medications can produce extrapyramidal reactions and parkinsonism.

Symptoms of DIP usually resolve within weeks or months in most patients. In fact, problems that persist beyond 6 months after the medication is withdrawn should raise suspicion of primary Parkinson's disease or a permanent sequela, such as tardive dyskinesia.^{3,5}

In short, failure to diagnose and treat DIP prolongs the patient's suffering, which could be relieved by doing something as simple as stopping the agents in question. 📌

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