

“Ping-pong gaze” secondary to monoamine oxidase inhibitor overdose

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ABSTRACT

An infrequent manifestation of monoamine oxidase inhibitor (MAOI) toxicity is “ping-pong gaze” (PPG). We describe the case of a 26-year-old female who was found unresponsive after taking 40 tablets of phenelzine. On presentation to the hospital, her eyes were moving in characteristic “ping pong” fashion. After 6 hours her gaze terminated. The following day her neurologic exam was benign and she had no long-term sequelae. While the etiology of PPG is unknown, it is most often seen with irreversible structural brain damage. However, a detailed literature review revealed that previous cases of MAOI toxicity where the patient survived have all had complete neurologic recovery.

Key words: Monoamine oxidase inhibitor toxicity, phenelzine, ping pong gaze, short-cycle periodic alternating gaze

INTRODUCTION

Monoamine oxidase inhibitor (MAOI) toxicity can have a range of presentations that more commonly include sequelae of serotonin syndrome including tachycardia, diaphoresis, hyperthermia, hypertension, coma and death.^[1] A unique aspect of this toxidrome includes catecholamine depletion leading to cardiovascular collapse.^[2] Another manifestation is short-cycle periodic alternating gaze otherwise known as ping-pong gaze (PPG), which is

defined as slow conjugate deviation of the eyes from one extreme to the other with fixed frequency and without pause. The etiology of the gaze is unknown, but is more often seen with irreversible structural brain damage and carries a grave prognosis. MAOI toxicity is unique in that this global cerebral dysfunction is transient and has been associated with complete neurologic recovery in cases where the patient survived.^[3]

CASE REPORT

We describe the case of a 26-year-old Caucasian female with a past medical history significant for anorexia, bulimia, depression, and previous suicide attempt. One week prior to

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admission, the patient experienced a spontaneous abortion at 16 weeks of gestation requiring dilation and curettage. She had been depressed since the procedure and had gone to see her primary care provider who prescribed phenelzine 15 mg daily. After being unsupervised for approximately 4 h, the patient was discovered unconscious with a partially empty medication bottle at her side with an estimated phenelzine ingestion of 40 tablets. There was no indication of any other ingestion. Initial vitals in the emergency department revealed a temperature of 101.1 F, blood pressure of 131/80 mmHg, heart rate of 116 bpm, respiratory rate of 28, and an oxygen saturation of 94% on 2 L nasal cannula. The ECG showed sinus tachycardia with a rate 125, QRS 84 ms, and QTc 409 ms. Pupils were dilated to 7 mm bilaterally, and were slowly deviating conjugately from one lateral side of the eyes to the other without pause or nystagmus with a frequency of 3–4 seconds. They did not react to light. Physical exam was also significant for diaphoresis, muscular hypertonicity, and inducible clonus. She could not respond to questions and was not protecting her airway and so was intubated and transferred to our facility on a lorazepam infusion.

On admission to our facility the patient continued to have the slowly deviating gaze. Her blood pressure was actually low when she arrived with systolic 100/68 mmHg. As the patient met systemic inflammatory response syndrome criteria as well as had recent dilation and curettage, she was started on broad spectrum antibiotics. White blood count was 15.3 k/mm³ without a left shift, both urinalysis and chest x-ray were normal. Urine drug screen was only positive for benzodiazepines; acetaminophen and salicylate levels were normal and there was no osmolar gap as well. Other laboratory values for kidney and liver function as well as electrolytes were within normal limits. All cultures returned negative. Creatine phosphokinase (CPK) was initially 3466 IU/L and peaked at 3623 IU/L. A pelvic ultrasound was negative for material or debris in the endometrial canal.

A toxicology consult recommended switching to midazolam infusion to treat her rigidity and avoid the long-term effects of continuous lorazepam infusion. She was titrated up to 6 mg/h over a period of 6 h following admission. After a total of 8 h of benzodiazepine therapy (including the 2 h of lorazepam infusion she received during transfer), the patient spontaneously terminated her gaze and was withdrawing to pain and moving purposefully. The patient was also treated with multiple fluid boluses due to her elevated CPK; her blood pressures remained above a mean arterial pressure of 65 mmHg although her systolic BP did stay in the low 100s. Her vitals remained stable and the following day the patient had significantly improved and was extubated on the midazolam infusion. This was eventually titrated off in favor of oral diazepam as the patient had residual hypertonicity in her lower extremities.

DISCUSSION

MAOIs presently approved in the United States include phenelzine, isocarboxazid, tranylcypromine, and selegeline.^[4] We also include a case of PPG involving moclobemide, which is not available in the United States but available in other countries such as India, the United Kingdom, and Australia.^[5] Phenelzine is a non-selective irreversible MAOI and has been presently approved for major depressive disorder, especially atypical depression, treatment-resistant major depressive disorder, and bipolar depression. It is known to irreversibly inhibit MAO for the life of the enzyme, and so the physiologic effects can last up to 1–2 weeks known as the “wash-out period.”^[4] Phenelzine has been shown to stimulate the release of norepinephrine from sympathetic nerve endings. However, following the initial release there is resultant decreased amount available for discharge from presynaptic vesicles. This biphasic reaction has been demonstrated clinically with an early stimulatory phase followed later by central nervous system depression and cardiovascular collapse.^[2–6]

The treatment for MAOI overdose begins with the usual measures, including the administration of activated charcoal if the patient presents within 1 h of ingestion and has no contraindications. It is recommended that MAOI overdose be monitored in the intensive care unit for a full 24 h due to the previously mentioned delayed toxicity. Treatment strategies are largely supportive and include airway maintenance and ventilatory support, antipyretic agents and cooling blankets for fever, benzodiazepines for mild to moderate CNS excitation and muscular irritability, phenytoin usage if seizures develop, and paralyzing agents if neuromuscular hyperactivity or seizures impair ventilation. Severe hypertension can be treated with a rapid short-acting parenteral agent like phentolamine or sodium nitroprusside. Beta blockers are tend to be avoided because of the potential for unopposed alpha adrenergic stimulation. Hypotension unresponsive to volume expansion should be treated with vasopressors, with norepinephrine the preferred agent to an indirect pressor like dopamine as it does not require the release of intracellular amines.^[2,7] There is currently no strong evidence for diuresis or dialysis reducing the toxicity of MAOIs and so these are not routinely recommended.^[2]

Short-cycle periodic alternating gaze, or PPG, was first described in 1967. It had initially been described in patients with large bihemispheric infarctions and carried a grave prognosis. However, when it occurred secondary to a toxic or metabolic encephalopathy, patient’s eye movements spontaneously recovered.^[7] A proposed mechanism for PPG has been disconnection of the cerebrum from the horizontal gaze centers in the brainstem, leading to disinhibition of the inherent rhythms in the oculovestibular system reserved for sleep states.^[8]

To date, there have been six previous cases of PPG associated with MAOI toxicity [Table 1]. The first case was reported in 1989. The patient was a 55 year old male who had taken a total of 500 mg of tranylcypromine in a suicide attempt. He was described as exhibiting PPG in a cycle lasting 3–4 seconds. Pupillary responses were normal. The movements continued for 12 h followed by nystagmus for 36 h and then all abnormal eye movements spontaneously terminated. The patient was hemodynamically stable and managed supportively. It is not stated if benzodiazepines were given.^[9]

The next two cases of were reported together in 1995. The first patient was a 28-year-old female who had taken a combination of phenelzine, amantadine, and bethanechol in a suicide attempt. Her PPG alternated every 3 to 4 seconds and pupils were dilated at 4 mm. The patient's clinical course was complicated by rhabdomyolysis secondary to severe muscular rigidity. The gaze terminated after 24 h following treatment that included benzodiazepines and paralytics. The next case was a 37-year-old female found down next to empty bottles of isocarboxazid, alprazolam, and trazodone. On presentation her PPG was found to be completing a cycle every 2 to 3 seconds and pupils were dilated at 9 mm. Her clinical course was complicated by hypotension, as well as rhabdomyolysis, acute renal failure, and thrombocytopenia. She was managed with vasopressors, benzodiazepines, and paralytics. Both patients had complete neurologic recovery.^[3]

Another case was in 2001 in a 56-year-old female found unresponsive after taking a combination of tranylcypromine, thioridazine, and clomipramine. She demonstrated PPG and her gaze deviation lasted 3 to 4 seconds with pupils dilated at 4 mm. Clinical course was complicated by rhabdomyolysis, but renal function remained intact and the patient had complete

neurologic recovery after receiving supportive care. It is not stated if benzodiazepines were used for this patient.^[10] Finally, the most recent case in 2005 describes a 35-year-old female with intentional overdose of moclobemide and paroxetine. She was noted to be demonstrating PPG with pupillary dilation although time of gaze cycling and depth of pupillary dilation were not documented. She was intubated for respiratory failure and developed severe muscular rigidity unresponsive to paralytics, benzodiazepine infusion, cyproheptadine and dantrolene. She experienced cardiopulmonary arrest after 20 h and died most likely from metabolic acidosis secondary to severe serotonin syndrome.^[11]

Our case was similar to most of them as the PPG spontaneously remitted and the patient had complete neurologic recovery and received supportive care which included benzodiazepines. However, a link between the pathophysiology of PPG and benzodiazepines has not been established. Like most of the previous cases our patient had rhabdomyolysis but no evidence of renal injury. Our patient was also hypotensive like one of the previous cases but responded to IV fluids. This may have been secondary to catecholamine depletion from MAOI toxicity or else due to midazolam infusion.

CONCLUSION

Our case illustrates several important manifestations of MAOI toxicity that are unique from serotonin syndrome. Each of the previous cases of PPG were associated with ingestion of a MAOI, and the association appears unique to this drug class. A detailed literature search could not find other drug classes solely associated with PPG without concurrent ingestion of a MAOI. While PPG may portend a grave prognosis for those with structural brain damage, when it is secondary to

Table 1: Reports of ping-pong gaze associated with MAOI toxicity

	Age (years)/ gender	Medication (s)	Duration of gaze	Description of gaze	MAOI toxicity complications	Neurologic recovery
Watkins and Ellis (1989)	55/male	Tranylcypromine	12 h	Gaze cycled every 3-4 seconds	None	Yes
Erich <i>et al.</i> (1995)	28/female	Phenelzine, amantadine, bethanechol	24 h	4 mm dilated; gaze cycled every 3-4 seconds	(1) Rhabdomyolysis	Yes
Erich <i>et al.</i> (1995)	37/female	Isocarboxazid, alprazolam, trazodone	24 h	9 mm dilated; gaze cycled every 2-3 seconds	(1) Hypotension requiring vasopressors (2) Rhabdomyolysis (3) Thrombocytopenia (4) Acute renal failure	Yes
Prueter <i>et al.</i> (2001)	56/female	Tranylcypromine, thioridazine, clomipramine	24-48 h	4 mm dilated; gaze cycled every 3-4 seconds	(1) Rhabdomyolysis	Yes
Sener <i>et al.</i> (2005)	34/female	Moclobemide, paroxetine	20 h until patient died	Not documented	(1) Rhabdomyolysis (2) Severe metabolic acidosis (3) Cardiopulmonary arrest/death	Unknown; patient died from severe serotonin syndrome
Attaway <i>et al.</i> (2014)	26/female	Phenelzine	10 h	7 mm dilated; gaze cycled every 3-4 seconds	(1) Rhabdomyolysis	Yes

MAOI=Monoamine oxidase inhibitor

MAOIs all previous cases where the patient survived had full neurologic recovery.

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Conflicts of interest

There are no conflicts of interest.

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