



## Hypertensive Urgency after Administration of a Single Low Dose of Mirtazapine- A Case Report

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### Abstract

Mirtazapine is a new antidepressant that can increase noradrenergic and serotonergic neurotransmission. It is also a postsynaptic antagonist of 5-HT<sub>2</sub> and 5-HT<sub>3</sub>. In addition, it has only a weak affinity for 5-HT<sub>1</sub> receptors and has very weak muscarinic anticholinergic and histamine (H<sub>1</sub>) antagonist properties. We report a case of hypertensive urgency that ensued after a patient took a single low dose of mirtazapine.

**Keywords:** Mirtazapine, Antidepressant, Hypertensive urgency

### Introduction

Mirtazapine (MTZ) is a new antidepressant, which is a member of the tetracyclic piperazinoazepines (1). It is a prominent presynaptic  $\alpha_2$ -antagonists that can increase noradrenergic and serotonergic neurotransmission. MTZ is also a postsynaptic antagonist of 5-HT<sub>2</sub> and 5-HT<sub>3</sub>. In addition, it has only a weak affinity for 5-HT<sub>1</sub> receptors and has very weak muscarinic anticholinergic and histamine (H<sub>1</sub>) antagonist properties.

In terms of individual adverse events, most experiences were mild and transient. Frequently reported adverse events occurring during MTZ treatment were low dose related drowsiness and weight increase, which may be attributed to affinity of the antihistaminic (H<sub>1</sub>) receptor (2). Some specific considerations were hepatotoxicity, arthralgia, coagulopathy, acute Pisa syndrome (3-5). MTZ is less likely to cause hypertension or tachycardia (6).

We report this case of a man who developed hypertensive urgency after a single low dose of MTZ.

### Case report

A 73-year-old man with hypertension for 25 years takes 5mg amlodipine daily for 10 years. His recorded blood pressure was controlled to 120-130/70-80 mmHg. He was also taking aspirin 100 mg daily. He had no history of tuberculosis, HIV infection, diabetes mellitus, hyperlipidemia, or other major organ disease. He had no allergies to drugs, foods and pollens. He had no smoking or drinking appetite. He came to the emergency room complaining of severe headache and vertigo one hour after taking 7.5mg MTZ. He complained of shortness of breath, chest distress and sweating. Physical examination was significant in a pale appearance.

In the emergency center, his vital signs were blood

pressure 215/145 mmHg, heart rate 116 beats/min, respiratory rate 35 breaths/min, and tympanic temperature 36.5 °C. An electrocardiogram showed sinus rhythm with infrequent premature atrial contractions.

He was injected with 50 mg urapidil due to less obvious response to 5 mg nitroglycerin sublingual tablet taken before, with persistent low flow oxygen therapy and monitoring by electrocardiograms (ECG). Twenty min later, the blood pressure decreased to 180/105 mmHg, heart rate 96 beats/min, respiratory rate 22 breaths/min. The chest distress and shortness of breath were disappeared and, headache was alleviated. The patient had a ruddy complexion one hour later without headache, but still lacking in strength. His blood pressure returned to 145/92mmHg with heart rate decreasing to 84 beats/min.

He stayed in the emergency room overnight and felt better the next morning. The patient was instructed to use 0.4mg alprazolam every night and monitor his self-BP no more than once a day, but avoid using MTZ. His blood pressure was 132/74mmHg in a following phone interview one week later. There were no other discomforts. According to the Narajio adverse drug reaction probability scale (7), the relationship between the patient's hypertensive urgency and MTZ was probable.

## Discussion

It is suspected that the pharmacologic action and metabolism led to hypertensive urgency. MTZ is a centrally active presynaptic  $\alpha_2$ -receptor antagonist, which controls norepinephrine and serotonin release. The affinity of MTZ for central presynaptic  $\alpha_2$ -autoreceptors is about ten-fold higher than for central postsynaptic and peripheral presynaptic autoreceptors (8). MTZ enhances norepinephrine release by presynaptic  $\alpha_2$ -autoreceptor antagonism of noradrenergic neurons. This inhibits negative feedback on these neurons and facilitates the release of synaptic norepinephrine. MTZ blocks inhibitory  $\alpha_2$ -autoreceptors at two sites on the noradrenergic neurons. In the terminal region, this

blockade results in increased amounts of norepinephrine being released per nerve impulse. In the cell body region, antagonism at the  $\alpha_2$ -autoreceptors causes cell firing and accelerates transmitter synthesis. The result is increased availability of synaptic norepinephrine.

MTZ is metabolized in the liver. Major pathways of biotransformation are demethylation and hydroxylation, followed by glucuronide conjugation. MTZ lacks both auto-induction and auto-inhibition of hepatic isoenzymes (cytochrome P450). MTZ is a substrate for the P450 isoenzymes 1A2, 2D6 and 3A4 (9). Amlodipine is also metabolized in the liver mostly. Amlodipine undergoes the oxidative metabolism of dihydropyridine to a pyridine analogue by CYP3A4 (10). It shows inhibitory effects on CYP3A4 *in vitro* (11). Therefore, we proposed a competitive inhibition of active hepatic metabolism.

We reviewed two cases of MTZ-induced hypertensive urgency in the literature (12, 13). Both two patients used MZT and clonidine. Clonidine is presynaptic  $\alpha_2$ -receptors to cause a reduction in endogenous release of norepinephrine. It is suspected that these patients experienced an interaction between MZT and clonidine. Comparing this case one case has a higher dose (45mg/day); the other has the longer period (two weeks). However, all three patients have hypertension.

With numerous researches, MZT shows positive features in terms of efficacy, safety and tolerability. Although a few hypertensive events were reported, pharmacist and physicians must be aware of potential drug interactions especially in patients with cardiovascular risk. Plasma concentrations of mirtazapine would be monitored in those patients with combination therapy of antihypertensive agents.

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