Letter to the Editor

Prolonged Hypotension Due to Deliberate Trazodone Overdose in the Presence of Fluoxetine

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A 37-year-old woman was admitted with normal consciousness 2 hours after the deliberate ingestion of 2000 mg trazodone. She was currently treated by trazodone and fluoxetine, but also occasionally took furosemide. In the intensive care unit (ICU), she rapidly developed hypotension (70/40 mm Hg) with a relative bradycardia (57/min). The initial EKG revealed a prolonged QTc interval at 542 msec. Hypotension persisted despite colloids infusion. Hypokaliemia and hypomagnesemia were also present. A first episode of "torsade de pointe" was successfully treated 4 hours after admission by electric cardiac counter-shock and magnesium administration. A new episode occurred 4 hours later even though ionic disturbances had been corrected. The patient remained markedly hypotensive for a period of 6 days despite the infusion of significant doses of epinephrine and dopamine (Figure 1). The QTc interval normalized after the same delay and the patient was discharged from the ICU. The initial trazodone serum concentration was 5.4 mcg/ml. The calculated elimination half life was 17.8 hours for trazodone and 22.2 hours for its metabolite, m-chlorophenylpiperazine (m-CPP). Initial fluoxetine level was 5.3 μg/ml, above the therapeutic range, and nor-fluoxetine was 0.3 mcg/ml.

Significant cardiac arrhythmias including “torsade de pointe” have been reported following trazodone overdose. A prolonged QT interval was present in all the patients with ventricular arrhythmias. Prolonged hypotension is a less common feature and could be related to trazodone itself or to one of its metabolites. Blood pressure and heart rate may be substantially increased or decreased by the activation of distinct brain serotonin receptors through a positive or negative modulation of the autonomic nervous system tonus (1). The 5-HT2 receptor family seems involved in cardiovascular regulation. Trazodone is a powerful 5-HT2A receptor antagonist, without effect on peripheral norepinephrine recapture. In contrast, it blocks α1 central adrenoreceptors. As for m-CPP, it is a powerful post-synaptic serotonin receptor agonist and animal data have shown increased dopamine, epinephrine and norepinephrine plasma concentrations after intravenous infusion of m-CPP in the rat (2). m-CPP preferentially stimulates 5-HT2c receptors. In rat experiments, it has been shown that the intraventricular administration of m-CPP evoked a significant hypertensive response in non-stressed rats that seems to be specifically due to the selective activation of brain 5-HT2c receptors (1). In contrast, stress-induced hypertensive response in animals treated with m-CPP or saline was not statistically different. However, the selective blockade of central 5-HT2c receptors prior to m-CPP administration may blunt the rise in blood pressure by restraint stress (1). In the present observation, several mechanisms could explain the occurrence of a sustained hypotension. A pharmacokinetic interaction between trazodone and fluoxetine was likely. After 2 to 4 weeks of a combined treatment with fluoxetine and trazodone, an increase of both trazodone and m-CPP blood concentrations has been described (3). Trazodone is metabolized via CYP2A1 and CYP2D6. It seems that CYP3A4 is the major isof orm responsible for the production of m-CPP, while CYP2D6 may be involved more in the metabolism of m-CPP than of trazodone (4). Fluoxetine
and its metabolite nor-fluoxetine are both CYP2D6 and CYP3A4 inhibitors, leading to increased trazodone and m-CPP blood concentrations with prolonged half-life. A pharmacodynamic interaction may also be discussed as fluoxetine has been found a competitive and reversible antagonist of 5-HT$_{2C}$ receptors (5).

In summary, sustained hypotension could be due to prolonged blockade of $\alpha_1$ central adrenoreceptors by trazodone itself, but also to a less effective 5-HT$_{2C}$ receptors stimulation by m-CPP in the presence of fluoxetine.

REFERENCES

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Figure 1  Trazodone and m-chlorophenylpiperazine (m-CCP) Toxicokinetic Data in Relationship with Cardiac Changes. Dopamine Was Administered by Continuous Infusion until Systolic Blood Pressure Could Be Maintained at 100 mm Hg.