Annals of Clinical Psychiatry, 19[3]:201–202, 2007

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230701464924

informa
healthcare

Letter to the Editor

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

XAVIER WITTEBOLE, MD and PHILIPPE HANTSON, MD, PHD

Department of Intensive Care, Cliniques St-Luc, Université catholique de Louvain Brussels, Belgium

PIERRE WALLEMACQ, PHD

Laboratory of Toxicology, Cliniques St-Luc, Université catholique de Louvain Brussels, Belgium

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 countershock 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-HT_2 receptor family seems involved in cardiovascular regulation. Trazodone is a powerful 5-HT_{2A} receptor antagonist, without effect on peripheral norepinephrine recapture. In contrast, it blocks $\alpha 1$ central adrenoreceptors. As for m-CPP, it is a powerful postsynaptic 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-HT_{2C} 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-HT_{2C} receptors (1). In contrast, stress-induced hypertensive response in animals treated with mCPP or saline was not statistically different. However, the selective blockade of central 5-HT_{2C} 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 isoform responsible for the production of m-CPP, while CYP2D6 may be involved more in the metabolism of m-CPP than of trazodone (4). Fluoxetine

Address correspondence to P. Hantson, Département des soins intensifs, Cliniques Universitaires St-Luc, Avenue Hippocrate, 10, 1200 Bruxelles, Belgique. E-mail: hantson@rean.ucl.ac.be

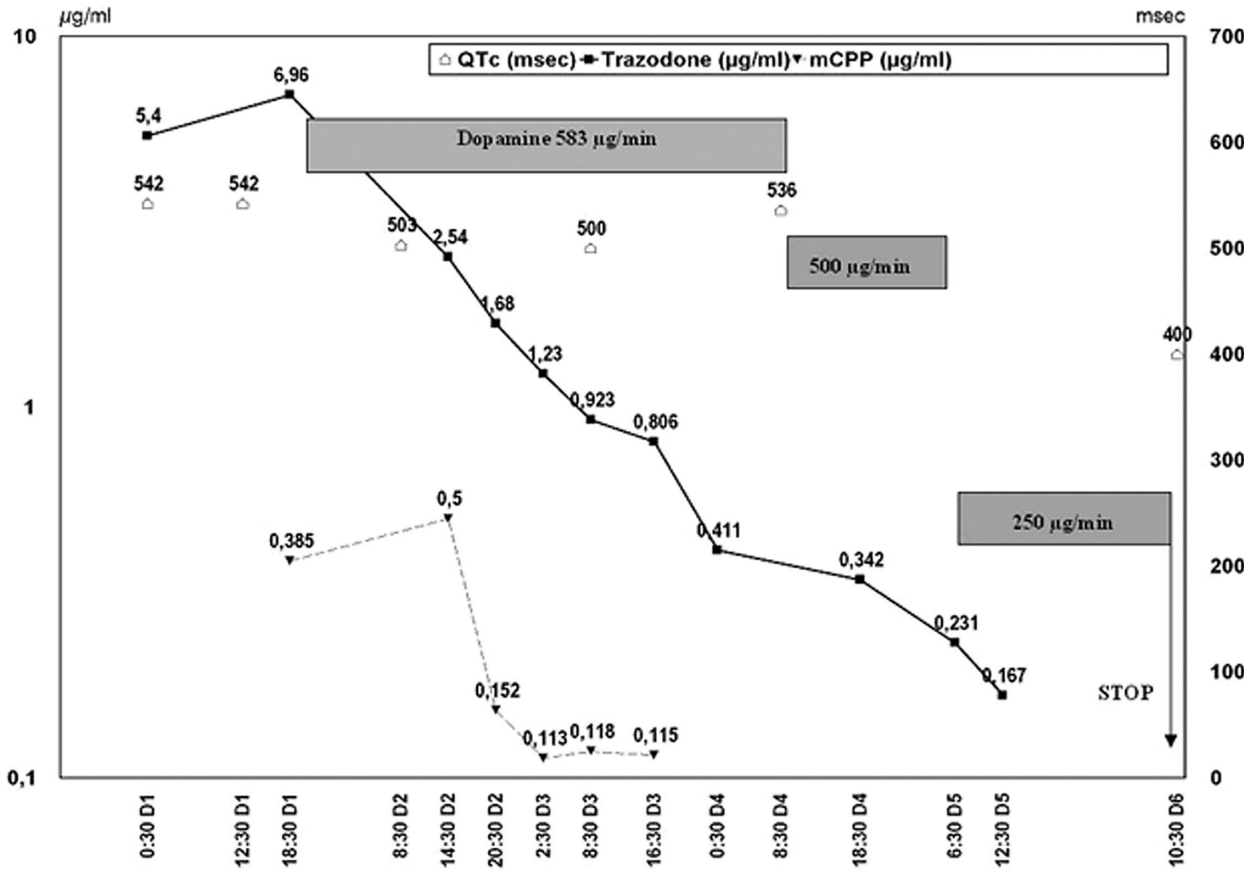

Figure 1 Trazodone and m-chlorophenylpiperazine (m-CCP) Toxicokinetic Data in Relationship with Cardiac Changes. Dopamine Was Administered by Continuous Infusion until Systolic Blood Pressure Could Be Maintained at 100 mm Hg.

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 α1 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

1. Ferreira HS, Oliveira E, Faustino TN, De Castro e Silva C, Fregoneze JB: Effect of the activation of central 5-HT_{2C} receptors by the 5-HT_{2C} agonist mCPP on blood pressure and heart rate in rats. *Brain Res* 2005; 1040:64–72
2. Bagdy G, Szemeredi K, Hill JL, Murphy DL: The serotonin agonist, m-chlorophenylpiperazine, markedly increases levels of plasma catecholamines in the conscious rat. *Neuropharmacology* 1988; 27:975–980
3. Maes M, Westenberg H, Vandoolaeghe E, Demedts P, Wauters A, Neels H, Meltzer HY: Effects of trazodone and fluoxetine in the treatment of major depression: Therapeutic pharmacokinetic and pharmacodynamic interactions through formation of meta-chlorophenylpiperazine. *J Clin Psychopharmacol* 1997; 17:358–364
4. Rotzinger S, Fang J, Baker GB: Trazodone is metabolized to m-chlorophenylpiperazine by CYP3A4 from human sources. *Drug Metab Dispos* 1998; 26:572–575
5. Ni YG, Miladi R: Blockage of 5HT_{2C} serotonin receptors by fluoxetine (Prozac). *Proc Natl Acad Sci USA* 1997; 94:2036–2040