COMMENT & CRITIQUE

Are we done with trazodone? The potential for damage by m-CPP – a metabolite of trazodone

To the Editor:

Trazodone has been in use for over two decades now. It was one of the first non-tricyclic, non-monoamine oxidase inhibitor antidepressants, initially marketed as a safe and effective antidepressant in mid-1980s. On introduction to the market then, data showed that trazodone was equivalently potent to tricyclics, but in day-to-day use, trazodone was never widely used to treat depression. Why trazodone never found wide use as an antidepressant has never been explained, and most clinicians found it ineffective at doses patients could tolerate. However, as of spring of 2007, trazodone is quite commonly used for sleep induction or maintenance and rarely for antidepression treatment. This article will argue that trazodone's continued general use for sleep induction and maintenance is probably ill advised because of trazodone's metabolite m-chlorophenylpiperazine (m-CPP).

m-CPP introduction

m-CPP is the primary catabolic product of trazodone, found in varying amounts in people treated with trazodone for insomnia or depression (1, 2, 3). Often m-CPP levels can be high (3). Higher m-CPP levels are seen with concomitant fluoxetine use (2), are a lot higher in smokers, and increase with duration of trazodone use. It is hepatic p450 3A4 that is primarily responsible for m-CPP generation from trazodone (1). Half-life of m-CPP is between 2 and 6 h (3). Wide interindividual variation in m-CPP half-life and plasma concentrations are seen but unexplained. The short half-life is thought to account for patients frequently not consciously experiencing some of the m-CPP ill effects outlined below because they are asleep when m-CPP peak effects occur.

m-CPP has complex signaling effects on various serotonin-2 (5-HT2) receptor subtypes. m-CPP is both a partial agonist and a partial antagonist on all 5-HT2 receptors but when tested *in vitro* in cells transfected to express human 5-HT2 receptors, 5-HT2C agonism is prominent. Partial agonism at 5-HT2A is usually found to be significantly weaker than its 5-HT2A antagonism. Relative rank order of 5-HT2 partial agonism is found to be 5-HT2C $\gg$ 5-HT2B $>$ 5-HT2A (4).

m-CPP is also generated from another trazodone-related antidepressant, nefazodone, *in vivo* during clinical use in depression treatment. The cautions advocated in this commentary should be applied to nefazodone use as well for this reason. m-CPP itself is removed, further catabolized, by P450 2D6; therefore, potent inhibitors of P450 2D6 would be expected to increase m-CPP levels during nefazadone or trazodone treatment. Poor metabolizers at P450 2D6, about 8% of the European and USA population, would be expected to be more susceptible to the ill effects of trazodone as would patients with concomitant use of bupropion, fluoxetine, paroxetine and others, which are potent 2D6 inhibitors. The street drug of abuse 3-4-methylenedioxymethamphetamine (MDMA or 'Ecstasy') is a particularly potent, and irreversible, inhibitor of 2D6. Trazodone use in patients with recent use of MDMA would be particularly worrisome.

Specific m-CPP adverse effects

m-CPP slowed reaction times in normal male volunteers and increased cortisol and prolactin levels (5, 6, 7). Cognitive slowing (5) and brief postinfusion elevated blood pressure (6) were noted, although long-term treatment with trazodone does not seem to elevate daytime blood pressure.

m-CPP is experienced by conscious humans without psychiatric history as extremely unpleasant, anxiogenic and dysphoric (5, 7). Evidence indicates that at least in rats, m-CPP's anxiogenic effects are mediated by 5-HT2C agonism (8). Experimental studies on humans and laboratory animals often use m-CPP to generate anxiety.

Evidence indicates that m-CPP increases platelet activation and is potentially thrombogenic (9). m-CPP increased *in vitro* synthesis of inflammatory mediators tumor necrosis factor-alpha and interleukin-6 (10). m-CPP is a potent trigger for migraine attacks in both known migraineurs and in normals without history of migraine or headaches (11). Intravenous administration of m-CPP to guinea pigs resulted in dose-proportional dural protein extravazation, probably mediated by its 5-HT2B agonism (12).

Although not common, clinical use of trazodone occasionally results in provocation of serious daytime anxiety. Unusually high daytime m-CPP levels have not been measured in such patients, but it is the suspected culprit.

Chronic overexpression and stimulation of 5-HT2B receptors in the heart of experimental animals leads to cardiac hypertrophy and heart failure (13), and functional 5-HT2B receptors on cardiac fibroblasts are required for the generation of isoproterenol-induced hypertrophic cardiomyopathy (14). It thereby becomes a potential generator of or contributor to hypertrophic cardiomyopathy.

5-HT2A receptor levels are high in human coronary arteries, ventricles and epicardium (15), and 5-HT2 agonism contributes to serotonin-mediated coronary artery constriction in a canine model

(16), although m-CPP is more of an antagonist than agonist at 5-HT2A, even partial agonism can become clinically significant.

Concluding remarks

This monumental list of serious and potentially harmful effects is a strong-enough argument for lowering the current common use of trazodone for sleep induction and maintenance. If careful statistical trazodone study shows trazodone use to be associated with any of the feared consequences of mCPP generation briefly outlined in this note, removing trazodone from the market might be best. The potential as outlined above for m-CPP-mediated harm is so broad and occurs in so many different physiologic domains and is of such potential seriousness that I advocate not subjecting patients to threats of m-CPP until such postmarketing surveillance can assure that the fears are unfounded. Potential risks of trazodone outweigh potential benefits. We now have many safer alternatives for sleep induction and maintenance. An even wider range of safer and more effective alternatives are available for treating depression. Nefazadone, a trazodone-like antidepressant largely fallen into disuse now because of problems with daytime sedation and rare but serious liver dysfunction, also gives rise to significant m-CPP levels, and its use too should be limited until careful research and review of the concerns raised in this article can be dismissed.

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References

1. Rotzinger S, Fang J, Baker GB. Trazodone is metabolized to m-chlorophenylpiperazine by CYP3A4 from human sources. Drug Metab Dispos 1998;**26**:572–575.
2. Maes M, Westenberg H, Vandoolaeghe E et al. 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.
3. Feuchtl A, Bagli M, Stephan R et al. Pharmacokinetics of m-chlorophenylpiperazine after intravenous and oral administration in healthy male volunteers: implication for the pharmacodynamic profile. Pharmacopsychiatry 2004;**37**:180–188.
4. Porter RH, Benwell KR, Lamb H et al. Functional characterization of agonists at recombinant human 5-HT2A, 5-HT2B and 5-HT2C receptors in CHO-K1 cells. Br J Pharmacol 1999;**128**:13–20.
5. Sabbe B, Hulstijn W, Maes M, Pier M, Scharpe S, Zitman F. Psychomotor slowing, neuroendocrine responses, and behavioral changes after oral administration of meta-chlorophenylpiperazine in normal volunteers. Psychiatry Res 2001;**105**: 151–163.
6. Ghaziuddin N, Welch K, Greden J. Central serotonergic effects of m-chlorophenylpiperazine (mCPP) among normal control adolescents. Neuropsychopharmacology 2003;**28**:133–139.
7. Silverstone PH, Rue JE, Franklin M et al. The effects of administration of mCPP on psychological, cognitive, cardiovascular, hormonal and MHPG measurements in human volunteers. Int Clin Psychopharmacol 1994;**9**: 173–178.
8. Walker EA, Kohut SJ, Hass RW, Brown EK Jr, Prabandham A, Lefever T. Selective and nonselective serotonin antagonists block the aversive stimulus properties of MK212 and m-chlorophenylpiperazine (mCPP) in mice. Neuropharmacology 2005;**49**:1210–1219.
9. Frampton AE, Andrews JC, Parfitt A, Jagroop IA, Mikhailidis DP, Henry JA. Does meta-chlorophenylpiperazine (mCPP) activate human platelets? Platelets 2006;**17**:30–36.
10. Kubera M, Maes M, Kenis G, Kim YK, Lason W. Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor alpha and interleukin-6. Psychiatry Res 2005;**134**:251–258.
11. Leone M, Attanasio A, Croci D et al. The serotonergic agent m-chlorophenylpiperazine induces migraine attacks: a controlled study. Neurology 2000;**55**:136–139.
12. Johnson KW, Nelson DL, Dieckman DK et al. Neurogenic dural protein extravasation induced by meta-chlorophenylpiperazine (mCPP) involves nitric oxide and 5-HT2B receptor activation. Cephalalgia 2003;**23**:117–123.
13. Nebigil CG, Maroteaux L. Functional consequence of serotonin/5-HT2B receptor signaling in heart: role of mitochondria in transition between hypertrophy and heart failure? Circulation 2003;**108**:902–908.
14. Jaffre F, Callebert J, Sarre A et al. Involvement of the serotonin 5-HT2B receptor in cardiac hypertrophy linked to sympathetic stimulation: control of interleukin-6, interleukin-1beta, and tumor necrosis factor-alpha cytokine production by ventricular fibroblasts. Circulation 2004;**110**:969–974.
15. Nilsson T, Longmore J, Shaw D et al. Characterisation of 5-HT receptors in human coronary arteries by molecular and pharmacological techniques. Eur J Pharmacol 1999;**372**:49–56.
16. Lamping KG. Response of native and stimulated collateral vessels to serotonin. Am J Physiol 1997;**272**: H2409–H2415.