Toxic Piperazine Relative? Yay!
by Murple

Dose: T+ 0:00  50 mg  oral Pharms - Trazodone pill / tablet

Body weight:  0 lbs

Desyrel (trazodone) is a unique substance used in high doses (150-600mg per day) as an antidepressant and in low doses (50mg at night) as a sleep aid. It is unrelated to any other sleep or depression drugs, although its theoretical method of action is related to SSRI activity.

I decided to try it after being given a free sample by an associate, having had some intermittent insomnia off and on lately and wanting to try something which was neither an addictive drug like most GABA active sleep drugs (benzos, Ambien, Imovane, barbiturates) nor an antihistamine like Benadryl or Unisom. Erowid had nothing on trazodone, a Google search turned up mostly spam links for online pharmacies, so I mostly went by rxlist.com and textbooks in my library. All of these indicated it was a remarkably safe drug.

Well, on Christmas Eve I decided to try it. I took the smallest dose pill made, a single 50mg tablet. I began to feel a little light headed after 45 minutes, and at about 75 minutes I was feeling the need to go to bed. It was more like being whacked over the head than a buzz or naturally tired feel.

I got in bed, fell asleep quickly. I slept hard and had vivid and bizarre dreams. I suddenly awoke, expecting it had been many hours, but my clock told me it had been only 2 hours. I felt very drugged, or like I'd been hit in the head very hard. I was awake for perhaps 10 minutes and then fell back asleep. I woke up about 2 hours later after more strange dreams, and this cycle repeated for about 7 or 8 hours - 2 hours of weird and not always pleasant dreams followed by sudden wakings of 10 minutes where I'd feel very drugged in an unpleasant, impaired manner. It was a very unrestful night of 'sleep'...

When I woke up, the first thing I noticed aside from still feeling a little drugged was that my fingers and toes were numb and had the pins-and-needles feel of poor circulation. This passed within a few hours, as did the drugged feel. The other symptoms were a little more disturbing however.

First, when I went to the bathroom, I was pretty shocked to see my urine was the color of Coca-Cola, Guinness, or coffee. This soon was joined by a sharp stabbing pain in my left side just below my rib cage. This combination, of course, set off all sorts of alarms...these are classic symptoms of kidney damage/disease. I began checking and found a few references to colored urine being a known side effect of trazodone, but no mention of the other symptoms (kidney pain, numb fingers, etc). More disturbing was when I found a few references to the fact that trazodone metabolizes into the piperazine mCPP - a chemical I had a very unpleasant run-in with several years ago. This
fact shocked me, and still does...I can’t believe that something which turns to mCPP in the body
is sold as an unscheduled prescription drug!!!

I decided to wait and see if the symptoms cleared before running to the hospital, only because I
recall peeing brown for a few hours after mCPP. (Under ordinary circumstances if you ever pee
brown, call your doctor immediately!) The pain and brown urine lasted all of Christmas day. The
next day, the pain was pretty much gone, but about half my urinations were still brown. Then,
that night, the pain returned to the point where I was involuntarily arching my back and twitching
out of pain. More brown pee. I began to worry and read up on kidney problems to see what other
possibilities there were. The next day, the pain again was gone when I woke up...off and on brown
pee. That night the pain returned, milder, but still pretty agonizing. I was considering that it
could be a kidney stone, kidney infection, a physical injury of some kind, or some other kidney
problem and was making plans to visit the hospital the next day. Then, it disappeared over the
course of about an hour. No more pain. No more brown pee.

Today, there was no pain at all. Urinations all clear and yellow or clear.

I suspect that my original guess that this is related to trazodone’s metabolism into mCPP is the
correct explanation. A kidney stone would’ve passed painfully over more time. A kidney infection
or damage would’ve gotten worse without medical treatment. This just cleared up over about 3
days - a timeframe not unlike the 3-4 day flu-like hangover that I experienced after my piperazine
experiments several years back.

I’m pretty disgusted that the mCPP factor is so little documented in most medical texts on
trazodone - I only found it due to some rather keyword heavy searches on MedLine. Its mentioned
nowhere in things like rxlist, the PDR or the Nursing Drug Handbook. While colored urine is
mentioned very briefly there is nothing indicating how strongly colored it can be, and there’s not
a hint of kidney pain being a possible side effect.

I had a rather severe reaction - granted, not a typical one from what little information I could find
- and I’m pretty shocked and angry that there is almost no documentation of even the possibility
of this sort of reaction in either patient literature or professional medical reference works. This is
the kind of information that should be made public if this drug is to be on the market.

I should also add that there was a cyclic nature to the symptoms after the first day (where they
were constant). The pain was dominant in the evening, and the brown urine was dominant in the
morning and afternoon, with paler but still discolored urine in the evenings. To me this seemed
like metabolites collecting in the bladder overnight.

Also, should point out that numb fingers were something I noticed during my earlier piperazine
experiments.

Priapism only becomes an issue with doses around 300mg from all information sources I could
find. Besides, priapism will make your pecker hard for a couple days, not spew out brown pee.

Anyway, today was entirely symptom free again. I’m now as close to 100% convinced that this was
a trazodone reaction as I can be without repeating the experiment...which won’t be happening
Anyway, since it was so hard for me to find these references, here's some of the things I found on the trazodone/mCPP connection...

http://www.neurosci.pharm.utoledo.edu/PHCL3720/Lecture13.htm

**Quote:** Trazodone (Desyrel) and Nefazodone (Serzone): Trazodone and nefazodone selectively inhibit neuronal 5-HT reuptake. Trazodone also possesses 5-HT2 receptor-blocking activity, but this probably doesn’t contribute to its long-term effects. m-Chlorophenylpiperazine (mCPP) confounds the story further, since it is a metabolite of trazodone which is a potent 5-HT2 agonist. . . . Disposition: The trazodone half-life is 6-11 h, while the half-life for nefazodone is 2-4 hr. mCPP has a half-life of 4-8 hr. Hydroxylated metabolites of trazodone and nefazodone exhibit some activity, and roughly 1% of the compounds is excreted in urine unchanged.

http://www.mhsanctuary.com/borderline/BPDr/220.HTM

**Quote:** Q. I am writing about my daughter. I would like to know if Trazodone can cause more extreme temper tantrums, outbursts, or uncontrollable rages? She has been taking it for about 4 months now, and for a while, she was calming down. She only takes it at bedtime (125mg.) for sleep. She has always had a hard time falling asleep. We are kind of at our wits end with her behavior. She also takes Ritalin and Lamictal for her seizure disorder. We took her off of Paxil. Can you offer any suggestions for us? She has just been so out of control lately, talking back, ranting, tantrums, and she is violent.

A. With so little data, I am not sure what to tell you. There is a theory that in some folks, the breakdown product of Trazodone, mCPP, can cause increased anxiety and/or agitation. You may want to try her on Serzone as it is less likely to cause seizures, and is claming without being sedating. I would get her up to 400 to 600 mg at bedtime, as it usually does not work below 400 mg and most folks require 500 mg, including kids.

http://www.dr-bob.org/babble/20020222/msgs/95274.html

**Quote:** . . . It has an active metabolite (m-chlorophenylpiperazine, or mCPP) that is a direct serotonergic agonist. The net effect on serotonin receptors is that of a mixed agonist/antagonist. Unfortunately, the significance of this complex combination of effects on the serotonergic system is unknown. . . . I’ve heard of some people having nightmares or ‘bad trip’ experiences on trazodone. Something to watch out for. (The metabolite mCPP can trigger panic attacks in susceptible individuals, and this might be responsible for these ‘bad trip’-like events. mCPP tends to accumulate because it has a longer half-life than trazodone itself does.)

Piperazine-Derived Designer Drug 1-(3-Chlorophenyl)piperazine (mCPP): GC–MS Studies on its Metabolism and its Toxicological Detection in Rat Urine Including Analytical Differentiation from its Precursor Drugs Trazodone and Nefazodone

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Journal of Analytical Toxicology, ISSN 0146-4760, Volume 27, Number 8, November/December,
Abstract:

Quote: Studies on the metabolism and the toxicological analysis of the piperazine-derived designer drug 1-(3-chlorophenyl)piperazine (mCPP) in rat urine using gas chromatography–mass spectrometry (GC–MS) are described. mCPP was extensively metabolized, mainly by hydroxylation of the aromatic ring and by degradation of the piperazine moiety to the following metabolites: two hydroxy-mCPP isomers, N-(3-chlorophenyl)ethylenediamine, 3-chloroaniline, and two hydroxy-3-chloroaniline isomers. The hydroxy-mCPP metabolites were partially excreted as the corresponding glucuronides and/or sulfates, and the aniline derivatives were partially acetylated to N-acetyl-hydroxy-3-chloroaniline isomers and N-acetyl-3-chloroaniline. Our systematic toxicological analysis (STA) procedure using full-scan GC–MS after acid hydrolysis, liquid–liquid extraction, and microwave-assisted acetylation allowed the detection of mCPP and its previously mentioned metabolites in rat urine after single administration of a dose calculated from the doses commonly taken by drug users. The hydroxy-mCPP metabolites should be used as target analytes being the major metabolites of mCPP. Assuming similar metabolism, our STA procedure should be suitable for detection of an intake of mCPP in human urine. Furthermore, possibilities for differentiating an intake of mCPP from that of its precursor drugs trazodone or nefazodone, two common antidepressants, are described. Within the context of these studies, N-(3-chlorophenyl)ethylenediamine was identified as a new metabolite of these two antidepressants.

In vitro metabolism of trazodone by CYP3A: inhibition by ketoconazole and human immunodeficiency viral protease inhibitors

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Abstract:

Quote: Background: Pharmacologic treatment of emotional disorders in HIV-infected patients can be more easily optimized by understanding of potential interactions of psychotropic drugs with medications used to treat HIV infection and its sequelae.

Methods: Biotransformation of the antidepressant trazodone to its principal metabolite, meta-chlorophenylpiperazine (mCPP), was studied in vitro using human liver microsomes and heterologously expressed individual human cytochromes. Interactions of trazodone with the azole antifungal agent, ketoconazole, and with human immunodeficiency virus protease inhibitors (HIVPIs) were studied in the same system.

Results: Formation of mCPP from trazodone in liver microsomes had a mean ( SE) Km value of 163 ( 21) mol/L. Ketoconazole, a relatively specific CYP3A inhibitor, impaired mCPP formation consistent with a competitive mechanism, having an inhibition constant (Ki) of 0.12 ( 0.01) mol/L. Among heterologously expressed human cytochromes, only CYP3A4 mediated formation of mCPP from trazodone; the Km was 180 mol/L, consistent with the value in microsomes. The HIVPI
ritonavir was a potent inhibitor of mCPP formation in liver microsomes (Ki = 0.14 ± 0.04 mol/L). The HIVPI indinavir was also a strong inhibitor, whereas saquinavir and nelfinavir were weaker inhibitors.

Conclusions: CYP3A-mediated clearance of trazodone is inhibited by ketoconazole, ritonavir and indinavir, and indicates the likelihood of pharmacokinetic interactions in vivo.