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Review on Trazodone Hydrochloride

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ABSTRACT:

Triazolopyridine derivative trazodone is unconnected to other antidepressants that are currently on the market in terms of pharmacology and chemistry. It has some hypnotic, anxiolytic, and antidepressant properties. A small number of patients with depression and pre-existing cardiovascular illness have also been successfully treated with trazolodone. With moderate success, trazodone has been used as a hypnotic for insomnia caused by psychotropic drugs or other conditions in more recent times. To validate these first findings, more clinical experience is necessary. Elderly patients treated with trazodone experienced significantly less cardiovascular and anticholinergic side effects when compared to those treated with older tricyclic antidepressants. M-chlorophenyl piperazine (Mcpp), the active metabolite of trazodone, acts as partial antagonist at several other subtypes of serotonin receptors as well as a potent 5-HT2C antagonist.

Tradazone hydrochloride, antidepressants, anxiolytic, hypnotic, M-chlorophenyl piperazine (Mcpp)

INTRODUCTION

Food and Drug Administration (FDA)-approved prescription drug trazodone is used as an antidepressant.

This medication affects your body in a number of ways. Its functions include controlling the neurotransmitter serotonin, which facilitates communication between brain cells and affects a wide range of functions including mood, hunger, behavior, sleep, and thinking

Trazodone can make you feel drowsy, exhausted, and relaxed, even at lower dosages. It accomplishes this by inhibiting brain chemicals, such as 5-HT2A, alpha1 adrenergic receptors, and H1 histamine receptors, that interact with serotonin and other neurotransmitters.

Even at lower doses, trazodone can cause you to feel relaxed, tired, and sleepy. It does this by blocking chemicals in the brain that interact with serotonin and other neurotransmitters, such as, 5-HT2A, alpha1 adrenergic receptors, and H1 histamine receptors.

Trazodone use has been linked to an elevated risk of suicidal thoughts and behaviors in young adults and pediatric patients. The development of suicidal thoughts and behaviors as well as increasing symptoms should be closely watched in individuals using this medicine. The use of trazodone in pediatric patients is not authorized.

LITERATURE REVIEW

1. Wen B, Ma L, Rodrigues AD, Zhu M: Detection of Novel Reactive Metabolites of Trazodone: Evidence for Cyp2d6-mediated Bioactivation Of M- chloro phenyl piperazine. Drug Metab Dispos. 2008 May;36(5):841-50. Doi: 10.1124/Dmd.107.019471. Epub 2008 Jan 31. [Article]
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From the article cited above the information related to the review on trazadone hydrochloride are collected and represented them as an example.

History

Trazodone was developed in Italy, in the 1960s, by Angelini Research Laboratories as a second-generation antidepressant. It was developed according to the mental pain hypothesis, which was postulated from studying patients and which proposes that major depression is associated with a decreased pain threshold.

trazodone was patented and marketed in many countries all over the world.

It was approved by the Food and Drug Administration (FDA) in 1981 and was the first nontricyclic or MAOI antidepressant approved in the Us.

Trazodone was approved for medical use in the United States in 1981. It is available as a generic medication. In 2020, it was the 21st most commonly prescribed medication in the United States, with more than 26 million prescriptions.

Chemistry

Nefazodone and etoperidone, which are also derivatives of triazolopyridine, share structural similarities with trazodone, a phenylpiperazine. Trazadone has an analog in flibanserin.

PHARMACEUTICAL INFORMATION

Drug Substance Proper name: Trazodone Hydrochloride

Chemical name: 2-{3-[4-(3-chlorophenyl)-1-piperazinyl] propyl} -1,2,4-triazolo-[4,3-a] pyridine- 3(2H)-one monohydrochloride.

Molecular formula: C19H22ClN5O HCl

Molecular mass: 408.32 g/mol

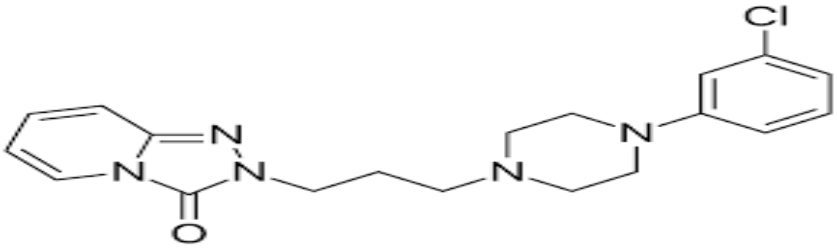
Physicochemical properties:

Description: White, odorless crystals (plates) with a bitter taste.

The melting point for trazodone free base is 96°C.

The hydrochloride salt melts with decomposition in the range 222-228°C.

Trazodone Hydrochloride is sparingly soluble in chloroform and in water. The reported pKa for trazodone in 50% ethanol is 6.14.



Pharmacology

Though the exact mechanism of action in humans is unknown, trazodone's potentiation of serotonergic activity in the central nervous system is thought to be involved. It's Also Known as a Serotonin Reuptake Inhibitor (SARI) and Serotonin 2A/2C Antagonist.

Preclinical Research Has Demonstrated That Trazodone Inhibits Serotonin Reuptake Weakly and Acts as an Antagonist at 5-HT2A and 5-HT2C Receptors.

M-chlorophenyl piperazine (Mcpp), the active metabolite of trazodone, functions as a partial antagonist at several other subtypes of serotonin receptors as well as a potent 5-HT2C antagonist.

Trazodone is a strong antagonist of α1-adrenergic receptors that exhibits very low activity against α2-adrenergic receptors. Its primary mechanism of action at adrenergic receptors is the antagonism of α1-adrenergic receptor subtypes.

Many Other Neurotransmitter Receptors, Ion Channels, and Transporters AWeakly Affected by Trazodon

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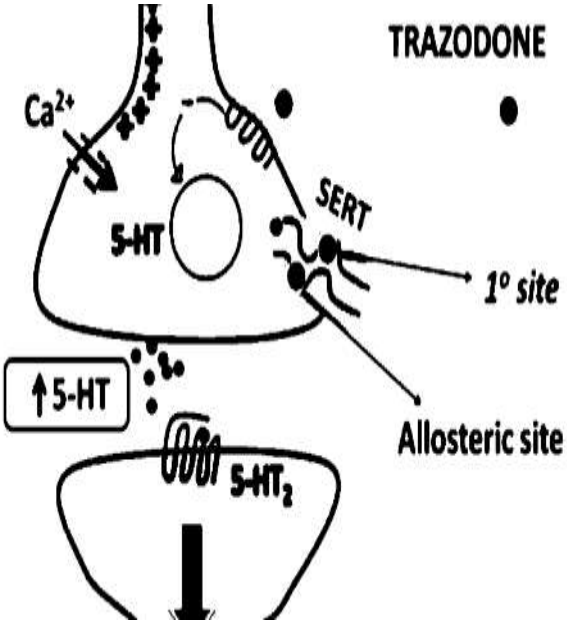


Pharmacodynamics

Trazodone functions as a weak histamine H1 receptor antagonist, a weak serotonin reuptake inhibitor, an antagonist of adrenergic receptors, and a mixed agonist and antagonist of several serotonin receptors..

To be more precise, it functions as an antagonist of the α1- and α2-adrenergic receptors, a partial agonist of the 5-HT1A receptor, and an antagonist of the 5-HT2A and 5-HT2B regions.

In addition, it binds to the 5-HT2C receptor less strongly than the 5-HT2A receptor. Trazadone may, however, function as a full agonist, partial agonist, or antagonist of the 5-HT2C receptor; this is uncertain.[10] Trazodone, like buspirone and tandospirone, is a partial agonist of the 5-HT1A receptor. To be more precise, it functions as an antagonist of the α1- and α2-adrenergic receptors, a partial agonist of the 5-HT1A receptor, and an antagonist of the 5-HT2A and 5-HT2B regions.one but with comparatively greater intrinsic activity

At the human histamine H1 receptor, trazodone has been shown to exhibit a variety of weak affinities (Ki), including 220 nm, 350 nm, 500 nm, and 1,100 nm..

Meta-chlorophenyl piperazine (mCPP), a small active metabolite of trazodone, may have some role in the pharmacological characteristics of the drug. mCPP is an agonist of different serotonin receptors, unlike trazodone.[101] Compared to trazodone, it has a lower affinity for α1-adrenergic receptors, but a higher affinity for α2-adrenergic receptors and a weaker affinity for H1 receptors..

Like fenfluramine and MDMA, mCPP is a serotonin-releasing agent in addition to its direct interactions with serotonin receptors. However, mCPP does not seem to promote long-term serotonin depletion, in contrast to these serotonin releasing drugs (a feature hypothesized to be connected to serotonergic neurotoxicity).

Trazodone's 5-HT_{2A} receptor antagonism and weak serotonin reuptake inhibition form the basis of its common label as an antidepressant of the serotonin antagonist and reuptake inhibitor (SARI) type.

Pharmacokinetics

Absorption: Trazodone hydrochloride is well absorbed after oral administration with peak plasma levels obtained within one-half to two hours after ingestion.

Distribution: Trazodone is 89-95% protein bound in vitro at concentrations attained with therapeutic doses.

Metabolism: There is a lack of characterization for the metabolic pathways involved in metabolism. Regardless, there's a chance that the cytochrome P450 enzymes CYP3A4, CYP2D6, and CYP1A2 are all implicated, albeit in different ways. It is well known that the liver extensively metabolizes trazodone by N-oxidation, N-dealkylation, and hydroxylation. A number of metabolites have been identified for trazodone, including a metabolite formed by hydroxylation of dihydrodiol, a metabolite hydroxylated at the para position of the meta-chlorophenyl ring (via CYP2D6), a metabolite formed by N-oxidation of the piperazinyl nitrogen, and metabolites formed by N-dealkylation of the piperazinyl nitrogen mediated by CYP3A4), and oxotriazolepyridinepropionic acid (TPA) and mCPP.

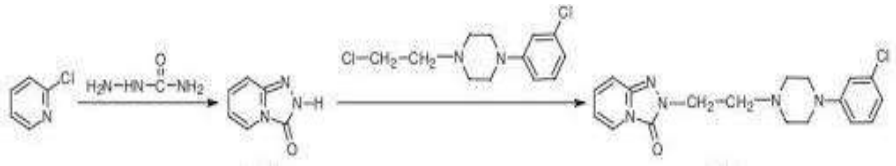
The CYP1A2, CYP2D6, and CYP3A4 genotypes do not appear to be able to predict trazodone or mCPP concentrations. In any event, there are significant interindividual differences in trazodone metabolism. Furthermore, mCPP is eliminated more slowly and is present in larger amounts in poor metabolizers of dextromethorphan, a CYP2D6 substrate, than in extensive metabolizers. Trazadone's effects, such as its antagonistic effect on serotonin, may slightly outweigh those of mCPP.

Elimination:

Trazodone has a biphasic elimination process, with a half-life of 4.1 to 14.6 hours for the elimination phase and 3 to 6 hours for the distribution phase. Extended-release trazodone has an elimination half-life of 9.1 to 13.2 hours. Trazadone's elimination half-life is less than that of mCPP, which ranges from 2.6 to 16.0 hours. Within 72 hours, it was shown that 70–75% of the 14C-labelled trazodone was eliminated in the urine. Metabolites are conjugated to glutathione or gluconic acid. Through biliary clearance, the residual medication and its metabolites are eliminated in the feces. The medication is excreted in less than 1% of its original form.

Synthesis

Trazodone, 2-[3-[4-(m-chlorophenyl)-1-piperazineyl] propyl]-s-triazolo[4,3-a] Piridine-3(2h)-one, is synthesized from 2-chloropiridine, the reaction of which with semi carbazide gives S-triazolo-3-one[4,3-a] pyridine. Alkylation of this product using 1-(3-chloropropyl)-4-(3-chlorophenyl) piperazine gives Trazodone**.**



Uses

Depression is treated using this drug. It could lessen depression-related anxiety and insomnia while also enhancing your mood, appetite, and energy level. Trazodone functions by aiding in the restoration of serotonin, a naturally occurring neurotransmitter, to its proper balance in the brain.

Side effects:

Nausea, vomiting, diarrhea, drowsiness, dizziness, tiredness, blurred vision, changes in weight, headache, muscle ache/pain, dry mouth, bad taste in the mouth, stuffy nose, constipation, or change in sexual interest/ability may occur. This medication may increase serotonin and rarely cause a very serious condition called serotonin syndrome/toxicity. To relieve dry mouth, suck on (sugarless) hard candy or ice chips, chew (sugarless) gum, drink water, or use a saliva substitute.

Inform your doctor or pharmacist about all the medications you take, as there is an increased risk if you also take other prescriptions that raise serotonin (see Drug Interactions section). If you have any of the following symptoms, get medical attention right away: rapid heartbeat, jerking muscles, unexplained fever, hallucinations, loss of coordination, extreme dizziness, nausea, vomiting, or diarrhea.

Rarely, this medication might cause a very dangerous adverse reaction. However, if you have any of the following signs of a significant allergic response, obtain medical attention right away: rash, breathing difficulties, extreme dizziness, itching or swelling, especially in the face, tongue, or neck.

Dosage:

Adults who want to treat depression should take 150–600 mg of regular pills daily.

Usually, the first dose is 150 mg per day, and every three to seven days, the dose is increased by 50 mg per day.

Doses of 25-75 mg are prescribed for insomnia .

Patients taking DESYREL along with other CNS depressant medications (alcohol, alcohol and chloral hydrate and diazepam, amobarbital, chlordiazepoxide, or meprobamate) have died from overdose.

The most serious side effects that have been linked to DESYREL overdose alone include priapism, respiratory arrest, seizures, and abnormalities in the ECG, including QT prolongation. The most commonly reported responses have been nausea and sleepiness. Any of the documented adverse events may occur more frequently or with greater severity if a dosage is exceeded.

An overdose of trazodone hydrochloride does not have a specific counteragent. When controlling an overdose, take into account the potential for multiple drug involvement. An overdose of trazodone hydrochloride does not have a specific counteragent. When controlling an overdose, take into account the potential for multiple drug involvement..

Interactions:

Trazodone is metabolized by many liver enzymes, including CYP3A4, CYP2D6, and CYP1A2. Meta-chlorophenyl piperazine (mCPP), its active metabolite, is known to be produced by CYP3A4 and metabolized by CYP2D6

Trazadone and/or mCPP metabolism may be changed by the inhibition or activation of the aforementioned enzymes by different substances, resulting in changes to blood concentrations..

Since many drugs, plants, and foods are known to promote or inhibit the aforementioned enzymes, trazodone may interact with these compounds.

Smokers have larger ratios of mCPP to trazodone and lower trazodone levels. While mCPP concentrations were the same in smokers and non-smokers, smokers had 30% lower trazodone levels and a 1.29-fold higher mCPP to trazodone ratio. It is well known that smoking induces CYP1A2, which could account for these results.

- It is not recommended to take MAO-inhibitors with any antidepressant, including trazodone, that raises serotonin levels in the brain. A few medications in the MAO-inhibitor class are:
- isocarboxazid (Marplan)
- phenelzine (Nardil)
- tranylcypromine (Parnate)
- procarbazine
- Trazadone and digoxin and phenytoin increase in blood concentration of digoxin and phenytoin.
- Carbamazepine trazadone decrease the blood levels of trazadone by increasing elimination from the body.

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