International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 30, Issue 9, September 2024 **ijppr.humanjournals.com** ISSN: 2349-7203

A Review on Doxepin Hydrochloride as an Antidepressant Drug

Madhavan K*, Dr.Kamalakkannan Venkatachalam, Dr.Sangameswaran Balakrishnan, Dr.Parthiban Ganeshan

Department of Pharmaceutics, SSM College of Pharmacy, Erode, Tamil Nadu, India

Received: 2024-09-03 Revised: 2024-09-11 Accepted: 2024-09-15

ABSTRACT

A medicine called Doxepin Hydrochloride is used to treat major depressive disorder, anxiety and sleeplessness. It belongs to the group of drugs known as tricyclic antidepressants. Some of the other antidepressant drugs increase the risk of suicidal thinking and behavior(suicidality) in children, adolescents, and young adults. Doxepin hydrochloride is a drug that reduces suicidal thinking in children, adolescents, and young adults. This activity explains doxepin's uses, dosage, adverse effects, and contraindications as a useful depression treatment tool. The mechanism of action, side effects, toxicity, dosage, and significance of employing a team-based strategy to treat patients with severe depressive disorder will all be emphasized in this exercise.

Keywords: doxepin hydrochloride, antidepressants, Young adults

INTRODUCTION

Anxiety, major depressive disorder, urticaria, and insomnia are all treated with the antidepressant doxepin. This medication is a member of the tricyclic antidepressant pharmacological class. This exercise describes the usage, dose, side effects, and contraindications of doxepin, a medicine that is helpful in treating depression. This exercise will focus on the mechanism of action, side effects, toxicity, and dose of major depressive disorder patients, as well as the need of managing them through a team-based approach.[1]

Since their discovery in the 1990s, tricyclic antidepressants have been used to treat depression as well as other diseases. These days, depression has grown to be a serious issue. To ensure the highest quality in pharmaceutical manufacture and to determine the optimal therapeutic doses, drug compound studies are crucial. Tricyclic antidepressants, a class of antidepressant medications, are frequently used for therapeutic treatment. Therapeutic drug monitoring (TDM) is crucial when patients are not responding as expected to CYP450 inducers or inhibitors, when non-compliance occurs, and when patients are at risk, such as the elderly, those with poor metabolization, or those with liver damage.[2]

DRUG PROFILE

Doxepin hydrochloride (DOX) is chemically known as benzoxepin-11-ylidene (3E)-3-(6H-benzo[C][1])-N,dimethylpropan-1-amine. Doxepin is a tricyclic antidepressant and anxiolytic psychotropic agent. It is used to treat depression, anxiety disorders, and chronic idiopathic urticarial as a second line treatment [3]. It has various brand names, including Aponal, Adapine, Doxal (orion), Deptran, Sinquan, Spectra, Doxin, Doxetar and Sinequan. Doxepine is also used for sleep maintenance treatment. For such an indication, Silanor is the trade name. Doxepin has a following structure of the drug which is shown in fig-1.[4]

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Volume 30, Issue 9, September 2024 ijppr.humanjournals.com ISSN: 2349-7203

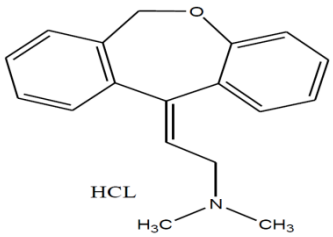

Figure No. 1: Structure of doxepin hydrochloride.

IUPAC Name :3-(dibenzo) [b,e]oxepin -11(6H) -ylidene)-N,N-dimethylpropan-1-amine

Mol Formula : C19H21ClNO

Mol Weight :279.376 g/ mol

Solubility :Water and alcohol

Melting point : 192-193ºC

Category : Tricyclic antidepressant

Route : Oral

Storage : 20 to 25ºC

Pka : 8.96 [5].

PHARMACODYNAMICS

Similar to other tricyclic antidepressants, doxepin was shown, in preclinical trials, to decrease the electrical activity of the brain, prolong the hexobarbital-induced sleep and block avoidance behavior without affecting the conditioned emotional response. At high doses, it also produces symptoms of central nervous system depression.[6]

Doxepin is known to cause antidepressant, sedative, and anticholinergic effects. At high doses, its anticholinergic and antiadrenergic properties are the most prevalent which limit its efficacy. These effects are observed at high doses where its affinity for H1 histamine receptor is lost and its binding to other receptors is observed.[7]

The maximal antidepressive effects of doxepin are present around two weeks following initiation of therapy.[8] However, the sedative effects of doxepin, usually used for the treatment of insomnia or anxiety, are observed immediately after administration.[9]

PHARMACOKINETICS[10]

Absorption

Doxepin is moderately absorbed following oral ingestion with a bioavailability of 30%. The median peak concentration of doxepin ranges from 8.8-45.8 ng/ml and it is achieved 3.5 hours after initial administration. Its absorption is increased with concomitant administration of a high-fat meal.

Volume of Distribution

The mean apparent volume of distribution of doxepin is reported to be of 20 L/kg.

Protein binding

Equilibrium dialysis indicates a mean protein binding of 75.5% for doxepin and 76% for desmethyldoxepin.

Metabolism

Doxepin is extensively metabolized to N-desmethyldoxepin which is a biologically active metabolite and other inactive metabolites. The first-pass metabolism accounts for 55-87% of the administered dose.5 After, the secondary metabolism is driven by the transformation of N-desmethyldoxepin to its glucuronide conjugates.

The main metabolic enzymes involved in the transformation of doxepin are the members of the cytochrome P450 family, CYP2C19 and CYP2D6 with minor involvement of CYP1A2 and CYP2C9.

Route of elimination

The elimination profile of doxepin is presented as biphasic. It is excreted in the urine mainly in the form of glucuronide conjugates. Less than 3% of a doxepin dose is excreted in the urine as parent compound or nordoxepin.

Half-life

The mean elimination half-life is reported to be of 15 hours.

Clearance

The mean total apparent plasma clearance of a single oral dose of 50 mg doxepin in healthy individuals is 0.93 l/hr/kg.

Mechanism of Action

A chemical imbalance and a deficiency of neurotransmitters in the brain seem to be the cause of depression. Different kinds of antidepressants have been developed to target distinct receptors and increase neurotransmitter availability in order to accomplish specific objectives. Doxepin belongs to the class of medications known as tricyclic antidepressants (TCAs), which function by raising the brain's concentration of the neurotransmitters norepinephrine (NE) and serotonin (5-HT). This prevents the neurotransmitters 5-HT and NE from being reabsorbed into the presynaptic terminal, extending their availability inside the synaptic cleft and improving neurotransmission.

Additionally, doxepin exhibits antagonistic effects in the central nervous system by inhibiting the histamine (H1), alpha-1 adrenergic, and muscarinic receptors. Additionally, it blocks the potassium and sodium channels in cardiomyocytes.[11][12] Doxepin's antipruritic effect is explained by its ability to block H1 and H2 histamine receptors.

Pharmacokinetics for Oral Formulation[13]

- Time for peak plasma concentration: 3.5 hours
- Food effects: AUC increased by 41% and Cmax by 15% after a high-fat meal
- Distribution: Highly distributed in other body tissue compartments, the apparent volume of distribution is about 11,930 L for tablets
- Plasma protein bindings: approximately 80%
- Metabolism: Hepatic; active metabolite is desmethyldoxepin
- Apparent terminal half-life: Doxepin: approximately 15 hours; desmethyldoxepin: 31 hours
- Excretion: Less than 3% urine as unchanged drug or N-desmethyldoxepin

Pharmacokinetics for Topical Formulation[13]

• Absorption: Percutaneous absorption

• Plasma concentration : Nondetectable to 47 ng/mL

• Metabolism: Hepatic; primary metabolite is desmethyldoxepin (active)

• Half-life elimination: Doxepin: 28 to 52 hours for desmethyldoxepin

Administration

• Commercial versions of the antidepressant doxepin are offered as oral pills, capsules, and liquids. Patients with depression most frequently use oral administration.

• There are two strengths of doxepin tablets: 3 mg and 6 mg.

• Oral capsules are available in 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg.

• Oral solutions are available as 10 mg/mL.

• Other forms available include topical creams (5%) and transdermal patches.

• Although transbuccal delivery of doxepin has been studied, little information has been provided to substantiate its efficacy.[14] Techniques like rectal, sublingual, and intranasal delivery need more research.[15]

Adult Dosing

Tablets: For a brief period of time (less than 4–8 weeks), 3–6 mg of doxepin tablets are taken once daily, 30 minutes before bedtime, to cure insomnia.

Oral Concentrate and Capsule: The first dose for treatment-resistant depression and major depressive disorder (unipolar) is 25–50 mg before bed. Every third day or more, the dosage is increased by 25–50 mg, for a total daily dose of 100–300 mg. It is best to provide it in divided doses, two to three times total.

Withdrawal: Due to its lengthy half-life, doxepin normally does not cause symptoms when abruptly stopped, although it should be weaned down gradually like other antidepressants.

Specific Patients Population

Patient with Hepatic Impairment: The manufacturer's label does not provide instructions for dose adjustments for patients with hepatic impairment. However, the medicine should be administered cautiously in these patients since doxepin is being converted in the liver into the active metabolite desmethyldoxepin.

Patient with Renal Impairment: The manufacturer's label does not provide dose adjustment instructions for people with renal impairment.

Pregnant women: It is under category C medication for pregnancy.

Breastfeeding Women: Since doxepin and its active metabolite are available in breast milk, it is not advised for nursing women to take this medication.[16]

Pediatric Patients: Doxepin efficacy and safety in younger patients are unknown. Use in pediatric patients younger than 12 years old is not advised, per box warnings.

Geriatric Patients: There is a lack of comprehensive research on the safety and effectiveness of doxepin in adult versus geriatric patients. It is classified as a potentially inappropriate medication that individuals 65 years of age and older should avoid taking.However, because elderly patients are more likely to experience reduced renal, cardiac, or hepatic functions, the beginning

dose for them should typically be at the low end of the dosing range. Additionally. Close observation is advised as doxepin may cause disorientation and oversedation in elderly people.

ADVERSE EFFECTS

• The reason doxepin is different from other antidepressants is that its side effects vary according to which receptors it binds to.Three distinct receptors are antagonistic to doxepin: histamine, adrenergic, and muscarinic.

• The FDA has approved low-dose doxepin, 3 mg, and 6 mg dosages to be used as a first-line treatment in depressed patients with sleep difficulties and depression associated with anxiety. Doxepin inhibits the histamine H1 receptor and induces drowsiness and somnolence. In order to stop patients from overdosing on these medications and self-medicating, proper education is required.[17][18]

• In a trial including 329 individuals receiving doxepin plus amitriptyline, the potential for a notable gain in weight associated with doxepin was evaluated.[19]

• Doxepin blocks alpha-adrenergic receptors and should be carefully monitored in those with cardiovascular disordersbecause it can cause orthostatic hypotension.[20]

• Finally, doxepin causes anticholinergic side effects such constipation, dry mouth, dizziness, lightheadedness, tachycardia, and extended QT interval by blocking muscarinic receptors.In [21]In [22][23]

• Patients on antidepressants, including doxepin, need to be closely monitored because of the black box warning about a potential rise in suicidality.[24]

• Doxepin has severe medication interactions that need to be managed with dose adjustments, frequency modifications, or temporary avoidance. Treat doxepin and MAO Inhibitors (selegiline, phenelzine, etc.) separately every 14 days.

CONTRAINDICATIONS

• Before prescribing drugs like antidepressants, doctors need to collect a complete medical history as well as a medication history from their patients. When taken with other drugs, including opioids, alcohol, herbal remedies, psychedelics, or even other antidepressant classes, antidepressants can have very negative side effects. Overselectivity of serotonin in the central nervous system may result from an interaction between two distinct kinds of antidepressants. Serotonin syndrome, also referred to as serotonin poisoning, is the result of this impact. Changes in mental status, autonomic stimulation, and neuromuscular excitement are among the symptoms of serotonin poisoning. Anger, disorientation, tachycardia, heat, flushing, tremor, and neuromuscular abnormalities such rigidity, heightened reflexes, and clonus are among the symptoms that patients encounter.[25][26]

• Patients having a history of cardiovascular conditions, such as bundle branch blockages, should not be prescribed doxepin. Atrioventricular heart block, orthostatic hypotension, and anomalies in conduction have all been documented in literature-based case studies involving doxepin patients.[27][28]

• Finally, because of its sedative and respiratory depressant properties, doxepin has a poor safety profile in postpartum breastfeeding moms and should not be used while nursing.[29][30]

• Patients who are at risk of purposeful overdose or who have a history of suicidal thoughts should not use as overdose can be lethal.

• Individuals who are allergic to excipients or doxepin should also refrain from using doxepin.

CONCLUSION

Doxepin Hydrochloride is a tricyclic antidepressant (TCA) frequently prescribed to treat anxiety and depression and has antihistaminic properties. Some of the other antidepressant drugs increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of the doxepin hydrochloride drug or any other antidepressant in a child, adolescent, or young adult must balance this risk of suicidal thinking.This decreases serotonin reuptake and noradrenaline reuptake while exhibiting active core anticholinergic action. Those with serious depression and other mental illnesses, such as panic disorder, obsessive-compulsive disorder, eating disorders, and hyperactivity disorder, are the main patients treated with TCAs.

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How to cite this article:
Madhavan K et al. Ijppr.Human, 2024; Vol. 30 (9): 1-7.

Conflict of Interest Statement: All authors have nothing else to disclose.