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Clonazepam Effective Against Antipsychotic Effect

Abesh Das[1]; Samar Dule[2]; Amit Kumar Bittu[3*]; Sandip Panda[4*]; Souradeep Sarkar[5*].

[1]Kolkata Institute of Pharmaceutical Science.
[2]Radiant Institute of Pharmaceutical Sciences
[3*,4*,5*] Sai College of Pharmacy

ABSTRACT

A benzodiazepine medication called clonazepam is used to treat epilepsy, panic disorder, and nonconvulsive status epilepticus acutely. Numerous off-label uses of the medication include tardive dyskinesia, severe mania, sleeplessness, and restless leg syndrome. Clonazepam functions as over lasting-acting, high-potency benzodiazepine. By increasing the frequency of chloride channel opening, benzodiazepines promote the activity of GABA-A by causing neurons to become hyperpolarized and fire less frequently. This reduces neuronal excitability and has a calming impact on the brain. By boosting the synthesis of serotonin, clonazepam also exhibits serotonergic action. Mechanism of action, administration, adverse event profile, contraindications, monitoring, and toxicity of clonazepam in relation to interprofessional team members treating patients with panic and seizure disorders will be the main emphasis of this study.

Keywords: Benzodiazepine, clonazepam, GABA, seizure, serotonergic

Introduction

While tolerance may develop, benzodiazepines are used to treat a variety of seizures, such as absence seizures, photosensitive epilepsy, and myotonic or atonic seizures. Treatment for panic disorder has also been suggested with this medication. It seems that the increase of gamma-aminobutyric acid receptor responses is the mechanism of action. Clonazepam has a long history of use in the management of the aforementioned illnesses since it was initially invented in 1960 and brought to the US market by Roche in 1975. Millions of prescriptions for the drug are written annually, both domestically and abroad, despite the agent's availability as a generic version. Unfortunately, clonazepam use has also been linked to drug misuse and recreational use, just like most benzodiazepines. However the exact mechanism by which clonazepam prevents seizures and calms anxiety is unclear. Pentylenetetrazol-induced convulsions in rats and, to a lesser degree, electrical stimulation-induced convulsions in sensitive baboons are both antagonistic. Additionally, muscular weakness, hypnosis, and a taming effect in aggressive monkeys are induced. Clonazepam can reduce the frequency, intensity, length, and spread of discharge in small motor seizures in humans as well as the spike and wave discharge in absence seizures.

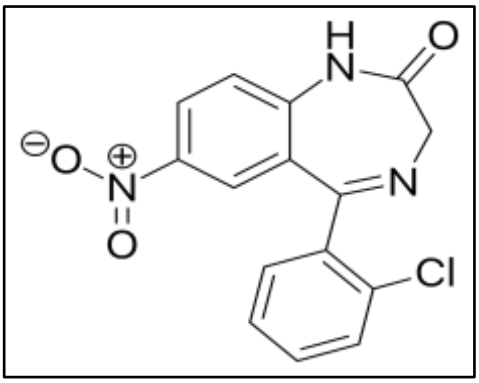

Figure 1: Structure of Clonazepam.

Pharmacokinetics

Upon oral administration, clonazepam is absorbed quickly and entirely. Regarding clonazepam, its absolute bioavailability is roughly 90%. After oral treatment, clonazepam reaches its maximum plasma concentrations 1–4 hours later. About 85% of clonazepam is bound to plasma proteins. clonazepam is extensively digested, less than 2% of it remains unaltered and is eliminated in the urine. The primary process of biotransformation is the reduction of

the 7-nitro group to the 4-amino derivative. It is possible to acetylate, hydroxylate, and glucuronidate this derivative. Cytochrome P-450, which includes CYP3A, might be crucial for the oxidation and reduction of clonazepam. Usually, clonazepam has an elimination half-life of thirty to forty hours. The pharmacokinetics of clonazepam are dose-independent across the whole dosage range. There is no proof that clonazepam alters a person's metabolism or that of other medications.

Physiochemical Properties

S. NO.	**PHYSICAL AND CHEMICAL PROPERTIES**	
1	Molecular weight	315.71 g/mol
2	Physical appearance	Off-white to light yellow crystalline powder
3	Melting point	237.5°C
4	Solubility	Insoluble in benzene; slightly soluble in acetone, methanol, chloroform
5	Octanol/water partition coefficient	2.41
6	Presence of ring	Diazepine
7	Number of chiral centers	Not present

Mechanical of Action

One very strong long-acting benzodiazepine is clonazepam. GABA-A receptors, clonazepam produces pharmacological effects. A ligand-gated chloride ion selective channel, the GABA-A receptor is activated by the endogenous ligand known as gamma-aminobutyric acid, or GABA. By increasing the frequency of chloride channel opening, benzodiazepines promote the activity of GABA-A by causing neurons to become hyperpolarized and fire less frequently. This reduces neuronal excitability and has a calming impact on the brain. Benzodiazepines have no effect on GABA-A receptor activity when GABA is not present.

In the limbic system and cortex, GABA is a neurotransmitter that has a strong inhibitory effect. A, B, and C are the three GABA receptors. BZDs, however, exclusively affect GABA-A receptors. Each receptor complex is made up of five subunits: two alpha, two beta, and one gamma. It also contains two GABA-binding sites and one BZD-binding site. BZDs bind to different BZD-binding sites located at the interface between the alpha and gamma subunits on the receptor complex rather than the same receptor site as the endogenous neurotransmitter GABA. The binding causes the chloride channel of the GABA-A receptor to alter shape, which causes the cell to become hyperpolarized and explains why GABA has an inhibitory effect on the central nervous system. Based on the alpha subunit isoforms, GABA receptors are further divided into several BZD receptor subtypes. The anticonvulsant and sedative properties of benzodiazepines are attributed to their alpha-1 subunit-containing benzodiazepine type-1 receptors (BZ1).

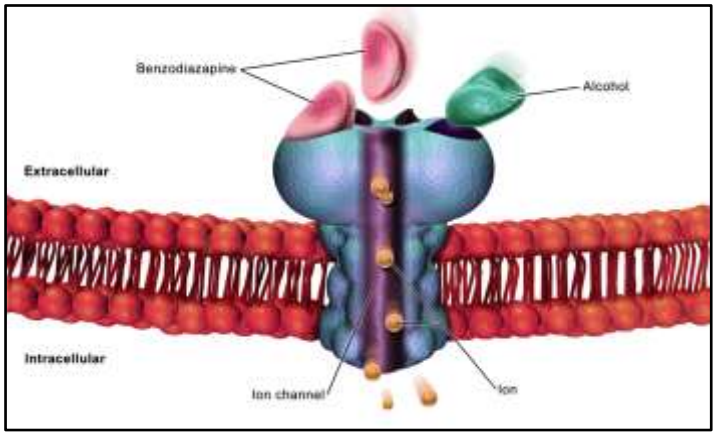

Figure 2: Mechanism of Action of Clonazepam

ADME of Clonazepam

- **Absorption:** After oral dosing, clonazepam is rapidly absorbed. After oral administration, the maximal plasma concentration is attained one to four hours later.
- **Distribution:** Around 85% of clonazepam is bound to plasma proteins. Comparing clonazepam to other high-potency benzodiazepines, it is less prone to cause anterograde amnesia and has a lower lipid solubility.
- **Metabolism:** The liver's cytochrome P-450, especially CYP3A, extensively metabolizes clonazepam in a dose-dependent manner.
- **Excretion:** The elimination half-life of clonazepam is thirty to forty hours. The primary metabolite of clonazepam, 7-amino-clonazepam, is primarily excreted in urine.

Synthesis of Clonazepam

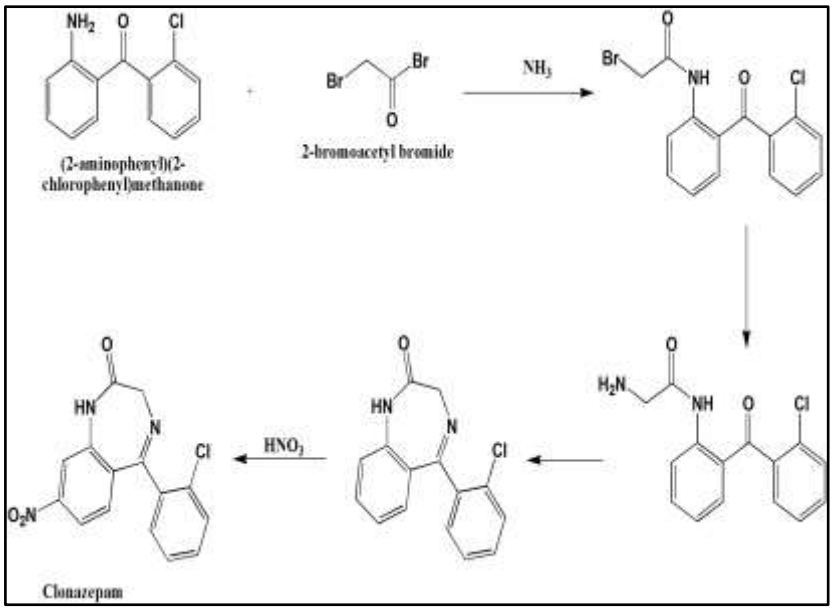

Figure 3: Synthesis of clonazepam

INDICATIONS AND USAGE

Seizure Disorders: Klonopin is helpful in treating akinetic, myoclonic, and Lennox-Gastaut syndrome (petit mal type) seizures either on its own or in combination with other medications. Klonopin may be helpful in people with absence seizures (petit mal) who are not responding to succinimides.

As clonazepam is being used, there could be some decrease of effect.

Panic Disorder*:* The DSM-V states that panic disorder, with or without agoraphobia, can be treated with Klonopin. The characteristics of panic disorder include unanticipated panic attacks, anxiety about having more attacks, concern over the consequences or ramifications of the attacks, and/or a discernible shift in behavior related to the attacks.

CONTRAINDICATIONS

Clonazepam is contraindicated in patients with the following conditions:

- History of sensitivity to benzodiazepines
- Clinical or biochemical evidence of significant liver disease
- Acute narrow-angle glaucoma (it may be used in patients with open-angle glaucoma who are receiving appropriate therapy).

INDICATIONS AND USAGE

Seizure Disorders: When treating akinetic, myoclonic, and Lennox-Gastaut syndrome (petit mal variety), clonazepam can be used either alone or in conjunction with other medications. Clonazepam may be helpful in absence seizure patients who have not responded to succinimides.

Panic Disorder: According to the DSM-V, clonazepam is recommended for the treatment of panic disorder, whether or not agoraphobia is present. Unexpected panic episodes, worry about having more attacks, worry about the implications or repercussions of the attacks, and/or a noticeable change in behavior connected to the attacks are the hallmarks of panic disorder.

WARNINGS

Risks from Concomitant Use with Opioids: The combined use of opioids and benzodiazepines, such as Clonazepam, can cause fatalities as well as severe sedation, respiratory depression, and coma. Reserving concurrent prescriptions of opioids and benzodiazepines for individuals for whom alternative treatment choices are insufficient is advised due to these hazards.

Compared to using opioids alone, observational studies have shown that using benzodiazepines and opioid analgesics concurrently raises the risk of drug-related mortality. In the event that it is decided to give Clonazepam along with opioids, the lowest effective dosages and shortest possible durations of concomitant usage should be used. Patients should also be continuously monitored for signs and symptoms of drowsiness and respiratory depression.

Interference with Cognitive and Motor Performance: Patients on clonazepam should be advised not to engage in risky jobs requiring mental alertness, such as operating machinery or operating a motor vehicle, as this medication causes CNS depression. Additionally, they ought to be cautioned about using alcohol or other CNS-depressants concurrently with clonazepam medication.

Suicidal Behavior and Ideation Patients: using antiepileptic medicines (AEDs), such as Clonazepam, for any reason are more likely to experience suicidal thoughts or behaviors. Patients receiving treatment with any AED for any reason should be closely watched for any unusual changes in mood or behavior, suicidal thoughts.

PRECAUTIONS

General:

Worsening of Seizures: Grand mal seizures, or generalized tonic-clonic seizures, may occur more frequently or more quickly in patients with multiple seizure disorders when clonazepam is administered. This can need increasing the dosages of the prescribed anticonvulsants or adding more of them. Valproic acid and Clonazepam used together may result in absent status.

Loss of Effect: Up to 30% of patients in certain trials who had reacted at first had a loss of anticonvulsant activity, frequently within three months of treatment. A change in dosage may occasionally restore efficacy.

Laboratory Testing During Long-Term Therapy: It is recommended to perform routine liver function tests and blood counts when on long-term clonazepam medication..

Psychiatric and Paradoxical Reactions: It is known that using benzodiazepines might result in paradoxical effects, including agitation, irritability, aggression, anxiety, wrath, nightmares, hallucinations, and psychoses (see ADVERSE effects: Psychiatric). If this happens, the drug should be gradually stopped (see to DRUG ABUSE AND DEPENDENCE: Physical and Psychological Dependency and PRECAUTIONS: Risks of Abrupt Withdrawal). Older people and children are more prone to experience paradoxical reactions.

Risks of Abrupt Withdrawal: Abrupt cessation of Clonazepam use may cause status epilepticus, especially in individuals receiving high-dose therapy for an extended period of time. Consequently, it's crucial to taper off Clonazepam gradually. The slow withdrawal of clonazepam may necessitate the concurrent use of another anticonvulsant.

Caution in Renally Impaired Patients*:* Since the kidneys eliminate clonazepam's metabolites, patients with reduced renal function should take extra care when administering the medication to prevent excessive accumulation of these metabolites.

Hypersalivation: Salivary flow may rise while using clonazepam. Before administering the medication to patients who have trouble managing secretions, this should be taken into account.

Respiratory Depression: Patients with impaired respiratory function, such as those with chronic obstructive pulmonary disease or sleep apnea, should use clonazepam with caution as it may produce respiratory depression.

Porphyria: Patients with porphyria should use clonazepam with caution since it may have a porphyrogenic effect.

Clonazepam Maximum Daily Dose						
Adverse Event by Body System	<1mg n=96 %	**1<2mg n=129 %**	**2<3mg n=113 %**	≥3mg n=235 %	**All Klonopin Groups N=574 %**	**Placebo N=294 %**
Central & Peripheral Nervous System						
Somnolence†	26	35	50	36	37	10
Dizziness	5	5	12	8	8	4
Coordination Abnormal†	1	2	7	9	6	0

Ataxia†	2	1	8	8	5	0
Dysarthria†	0	0	4	3	2	0
Psychiatric						
Depression	7	6	8	8	7	1
Memory Disturbance	2	5	2	5	4	2
Nervousness	1	4	3	4	3	2
Intellectual Ability Reduced	0	2	4	3	2	0
Emotional Lability	0	1	2	2	1	1
Libido Decreased	0	1	3	1	1	0
Confusion	0	2	2	1	1	0
Respiratory System						
Upper Respiratory Tract Infection†	10	10	7	6	8	4
Sinusitis	4	2	8	4	4	3
Rhinitis	3	2	4	2	2	1
Coughing	2	2	4	0	2	0

Table 1: Clonazepam dosage

Clonazepam Maximum Daily Dose						
Adverse Event by Body System	<1mg n=96 %	**1<2mg n=129 %**	**2<3mg n=113 %**	≥3mg n=235 %	**All Klonopin Groups N=574 %**	**Placebo N=294 %**
Pharyngitis Bronchitis	1 1	1 0	3 2	2 2	2 1	1 1
Gastrointestinal System						
Constipation†	0	1	5	3	2	2
Appetite Decreased	1	1	0	3	1	1
Abdominal Pain†	2	2	2	0	1	1
Body as a Whole Fatigue Allergic Reaction	9 3	6 1	7 4	7 2	7 2	4 1
Musculoskeletal Myalgia	2	1	4	0	1	1
Resistance Mechanism Disorders Influenza	3	2	5	5	4	3
Urinary System Micturition Frequency Urinary Tract Infection†	1 0	2 0	2 2	1 2	1 1	0 0
Vision Disorders Blurred Vision	1	2	3	0	1	1
Reproductive Disorders‡ Female						
Dysmenorrhea	0	6	5	2	3	2
Colpitis Male	4	0	2	1	1	1
Ejaculation Delayed	0	0	2	2	1	0
Impotence	3	0	2	1	1	0

Table 2: Dosage of clonazepam

DOSAGE AND ADMINISTRATION

Adults: The first dose for adults with seizure disorders should not exceed 1.5 mg/day, divided into three doses. Until the seizures are properly under control or until the adverse effects prevent an increase, the dosage can be increased by 0.5 to 1 mg every three days. The maintenance dosage for each patient must be tailored to their individual reaction. The recommended daily dosage is 20 mg or less.

Pediatric Patients: Clonazepam can be ingested orally. To reduce drowsiness, the initial dose for babies and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day, but not exceeding 0.05 mg/kg/day given in two or three distinct doses. The dosage should be increased by no more than 0.25 to 0.5 mg every third day until a daily maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached, unless seizures are under control or side effects preclude further increases. If possible, the daily dosage should be divided into three equal amounts. If the dosages are not split evenly, the maximum dosage ought to be given prior to retirement.

Drug Interactions

Clonazepam's Impact on Other Drugs' Pharmacokinetics. The pharmacokinetics of phenytoin, carbamazepine, or phenobarbital do not seem to be affected by clonazepam. It has not been studied how clonazepam affects the metabolism of other medications. Influence of Additional Medication on Clonazepam's Pharmacokinetics According to observations in the literature, the pharmacokinetics of clonazepam are not significantly changed by ranitidine, an agent that lowers stomach acidity. There is no effect of fluoxetine on the pharmacokinetics of clonazepam. Clonazepam metabolism is induced by cytochrome P-450 inducers, including phenytoin, carbamazepine, and phenobarbital. This results in a 30% reduction in plasma clonazepam levels. Based on the role of the cytochrome P-450 3A family in the metabolism of clonazepam, despite the lack of clinical data, inhibitors of this enzyme system.

Overdose Management

Treatment consists of urgent gastrointestinal lavage, general supportive measures, and monitoring of blood pressure, pulse, and breathing. Administering intravenous fluids and maintaining a sufficient airway are important. Levarterenol or metaraminol can be used to treat hypotension. There is no recognized value to dialysis.

When a benzodiazepine overdose is known or suspected, flumazenil, a particular benzodiazepine-receptor antagonist, can be used to reverse the sedative effects of benzodiazepines completely or partially. The appropriate steps should be taken to secure the airway, ventilator, and intravenous access before flumazenil is administered. The goal of flumazenil is to supplement appropriate benzodiazepine overdose therapy, not to replace it. For a suitable amount of time following treatment, patients receiving flumazenil should be observed for signs of reversibility, and respiratory depression.

Conclusion

The current study compared the safety and effectiveness of clonazepam, lorazepam, and alprazolam in patients with anxiety disorder who are also taking an antidepressant concurrently. All three BZDs demonstrated statistically significant improvements in anxiety symptoms as compared to baseline, which is consistent with other research; however, there were no differences observed between the drugs. The lowest dosage is advised because BZDs are occasionally seen as a "necessary evil." This makes it noteworthy that clonazepam had considerably lower mean and maximum doses as well as baseline and week 6 prescription doses than the other two BZDs. Although the most well-known psychiatry textbook served as the basis for our equivalency conversion criteria (alprazolam 0.25 mg=clonazepam 0.5 mg=lorazepam 1.0 mg), there is disagreement over these computations. As such, care should be taken while interpreting our results.

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