To comparatively study of the Clozapine drug used as anti-aggressive properties.

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Abstract

Aggressive behaviour is very common in the hospital setting. Simple aggression may unpredictably progress to overt aggression by any patient in the emergency centres (ECs). Aggressive behaviour often manifests in forms of verbally abusive language, verbal threats and intimidating physical behaviour. Physical and/or psychic threats generate stress and may therefore lead to offensive or defensive aggression. Stress has to be considered in its physiological dimension (biological stress responses) and psychological dimension (perceived stress). While half of the variance in childhood aggression is attributed to genetic factors, the biological mechanism and the interplay between genes and environment that results in aggression remains elusive. Although its mechanism of action in anxiety disorders is unclear, it is thought to act by enhancing serotonergic neurotransmission and down-regulating central receptors. In comparison with other SSRIs, fluoxetine has a long elimination half-life (4 days).Fluoxetine (usual dosage ≈20 mg/day) for ≥8 weeks was as effective as citalopram. Aggressive rats are an interesting model for studying fear-induced aggression.

Keywords

Antipsychotic, clozapine, violence,psychotropic,DSM-5, suicidality

Introduction

The first problem is to define aggression. Aggression has been defined as behaviour deliberately aimed at inflicting physical damage to persons or property. Assessment tools used currently in psychiatry to measure aggression are based on diverse definitions of aggression. For some, it is defined by uncontrollable anger.[1]for others, objects have to be destroyed. Still others require physical aggression toward people. The term aggression does not even appear in the glossary of the DSM-5[2]. Buss defined aggression as a response that delivers noxious stimuli to another organism. The noxious stimuli may be physical (e.g., hitting, punching, stabbing or shooting) or verbal (e.g., cursing or threatening) [3].

With their general aggression model (GAM), Anderson and Bushman provided an integrative framework that incorporates different theoretical aspects to explain the occurrence of aggressive behaviour[4]. The original article has been cited over 6900 times and within the past 20 years, the GAM has been updated and applied to explain aggression in a variety of different contexts currently, findings suggest that up to 50% of patients with psychiatric disorders show aggressive symptoms, as compared to less than 2% of the general population[5]. Likewise, recent studies hint at an increased risk of aggression among patients affected by mental disorders admitted to the hospital.

Although aggression can take on different forms and behaviours, researchers categorize aggression into two main categories: proactive and reactive aggression. Proactive aggression represents aggressive behaviours that are predatory and have premeditated purposes to harm others for external or internal personal gains[6].

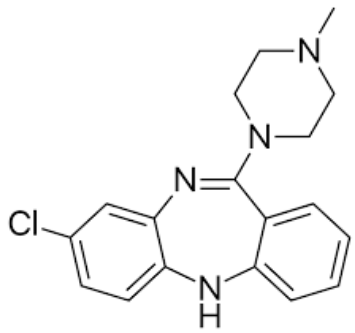
Aggression triggers

- Physical fear of others
- Family difficulties
- Learning, neurological, or conduct/behaviour disorders
- Psychological trauma

Drug Profile

Clozapine is an atypical or second-generation antipsychotic drug used in treatment-resistant schizophrenia and to decrease suicide risk in schizophrenic patients[7].

Structure:



IUPAC Name

6-chloro-10-(4-methylpiperazin-1-yl)-2,9-diazatricyclo[9.4.0.0^{3,8}]pentadeca-1(15),3,5,7,9,11,13-heptaene

Brand Names

Clozaril, Fazaclo, Versacloz

Generic Name

Clozapine

Weight:

Average:-326.823

Monoisotopic: 326.129824335

Chemical Formula

$C_{18}H_{19}ClN_4$

Volume of distribution

The median volume of distribution of clozapine was calculated to be 508 L (272-1290 L).

Protein binding

Clozapine is approximately 97% bound to serum proteins

Half-life

The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4 to 12 hours), compared to a mean elimination half-life of 12 hours (range: 4 to 66 hours), after achieving a steady state with 100 mg twice daily dosing[8].

Clearance

The median clearance of clozapine is calculated to be 30.3 L/h (14.4–45.2 L/h)

Solubility

Clozapine is considered poorly soluble in water, with a solubility of around **0.1889 mg/L** at 25°C. It is more soluble in organic solvents like acetone, chloroform, and ethanol. For example, its solubility in methanol is 10 mg/mL, in ethanol is 11 mg/mL, and in DMSO is 4.8 mg/Ml[9].

Bioavailability

Between 27 and 47% due to highly variable first pass metabolism and is 95% bound to plasma proteins. The time to achieve peak concentration is around 2.5 h following oral dosing[10].

BCS Classification:

BCS Class II drugs: are characterized by low solubility and high permeability.

- **Low aqueous solubility**: means clozapine dissolves poorly in water, which can affect its absorption in the gastrointestinal tract.
- **High intestinal permeability**: suggests that clozapine is readily absorbed across the intestinal wall if it's in a dissolved state

Pharmacokinetics

Absorption: Clozapine tablets are bioequivalent to a clozapine solution. The peak plasma concentrations are attained at 2.5 hours (1 to 6 hours)[10]. Food does not seem to influence the bioavailability of clozapine; clozapine may be administered with or without food.

Distribution: Clozapine exhibits approximately 97% plasma protein binding. Clozapine is transported across the blood-brain barrier[11].

Metabolism: The uptake of clozapine in the liver is mediated by SLC22A1, SLC22A2, and SLC22A3 (solute carrier (SLC) family)[12]. Clozapine is extensively metabolized in the liver by cytochrome P450 isozymes, particularly CYP1A2, CYP2D6, and CYP3A4. CYP3A4 and CYP1A2 are the major enzymes responsible for demethylation, with CYP2D6 playing a minor role. The desmethyl-norclozapine is an active metabolite of clozapine[13].

Excretion: The mean elimination half-life ranges from 8 to 12 hours; the elimination half-life increases after multiple dosing. Approximately 50% of clozapine is excreted in the urine and 30% in the feces[14].

Mechanism of Action

Clozapine is part of a group of drugs known as second-generation antipsychotics or atypical antipsychotics. Antipsychotic drugs are vital in treating the core symptoms of aggressive behaviour. As an atypical antipsychotic, clozapine is an antagonist to dopamine and serotonin receptors. Clozapine binds to the dopamine D4 receptor with a higher affinity than the dopamine D2 receptor, contributing to decreased adverse events and extrapyramidal symptoms. Clozapine is a partial 5-HT1A agonist that reduces adverse and extrapyramidal symptoms and a muscarinic M1, M2, M3, M5, histamine, and alpha-1 adrenergic-receptor antagonist. Norclozapine, the metabolite of clozapine, actively works on the M1 and M4 receptors[15].

Clinical Trial Data

(Reducing the Risk of Recurrent Suicidal Behaviour in Patients withSchizophrenia or Schizoaffective Disorder Who are Judged to be at Risk of ExperiencingSuicidal Behaviour)The effectiveness of CLOZARIL in reducing the risk of recurrent suicidal behaviour was assessedin the International Suicide Prevention Trial (InterSePT™)[16], which was a prospective, randomized, international, parallel-group comparison of CLOZARIL vs. Zyprexa®* (olanzapine)in patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be atrisk for re-experiencing suicidal behaviour[17]. Only about one-fourth of these patients (27%) wereconsidered resistant to standard antipsychotic drug treatment, and the remainder were not.

Patients met one of the following criteria:

●They had attempted suicide within the 3 years prior to their baseline evaluation.

●They had been hospitalized to prevent a suicide attempt within the 3 years prior to theirbaseline evaluation.

●They demonstrated moderate-to-severe suicidal ideation with a depressive componentwithin 1 week prior to their baseline evaluation[18].

●They demonstrated moderate-to-severe suicidal ideation accompanied by commandhallucinations to do self-harm within 1 week prior to their baseline evaluation[19].

Dosing regimens for each treatment group were determined by individual investigatorsand were individualized by patient. Dosing was flexible, with a dose range of 200-900 mg/dayfor CLOZARIL and 5-20 mg/day for Zyprexa. For the 956 patients who received CLOZARIL orZyprexa in this study, there was extensive use of concomitant psychotropic: 84% withantipsychotics; 65% with anxiolytics; 53% with antidepressants, and 28% with mood stabilizers[20].

There was significantly greater use of concomitant psychotropic medications among the patientsin the Zyprexa group.The primary efficacy measure was time to a significant suicide attempt, including acompleted suicide, hospitalization due to imminent suicide risk (including increased level ofsurveillance for suicidality for patients already hospitalized), or worsening of suicidalityseverity as demonstrated by “much worsening” or “very much worsening” from baseline in theClinical Global Impression of Severity of Suicidality as assessed by the Blinded Psychiatrist(CGI-SS-BP) scale[21]. A determination of whether or not a reported event met criterion 1 or 2above was made by the Suicide Monitoring Board (SMB, a group of experts blinded to patientdata).A total of 980 patients were randomized to the study and 956 received study medication.Sixty-two percent of the patients were diagnosed with schizophrenia, and the remainder (38%)were diagnosed with schizoaffective disorder. Only about one-fourth of the total patientpopulation (27%) was identified as

"treatment resistant" at baseline. There were more males thanfemales in the study (61% of all patients were male). The mean age of patients entering the studywas 37 years (range 18-69). Most patients were Caucasian (71%), 15% were Black, 1% wereOriental, and 13% were classified as being of "other" races.Data from this study indicate that CLOZARIL had a statistically significant longer delay in thetime to recurrent suicidal behaviour in comparison with Zyprexa. This result should be interpretedonly as evidence of the effectiveness of CLOZARIL in delaying time to recurrent suicidalbehaviour and not a demonstration of the superior efficacy of CLOZARIL over Zyprexa.The probability of experiencing (1) a significant suicide attempt, including a completed suicide, or (2) hospitalization due to imminent suicide risk (including increased level of surveillance forsuicidality for patients already hospitalized) was lower for CLOZARIL patients than for Zyprexapatients at Week 104: CLOZARIL 24% vs. Zyprexa 32%; 95% C.I. of the difference: 2%, 14%[22]

Fig 01- Kaplan-Meier survival curve for the cumulative probability of suicide risk[23]

Anti-aggressive effects of clozapine in involuntarily committed black patients with severe mental illness

Clozapine should be considered as a treatment option in the forensic or involuntarily committed psychiatric population given their risk for aggression. Additionally requirements, the evidence supporting use of clozapine in this population is limited to a few small trials. These trials evaluated clozapine's ability to reduce the number of seclusion and restraint (S/R) episodes[24]. Many of these studies were designed as retrospective trials and most participants were of European ancestry. Despite representing a disproportionately high percentage of incarcerated people in the US with mental clozapine are underutilized in Black patients. The higher rates of benign ethnic neutropenia (BEN) observed among Black patients may play a role[25]. Analyzing the anti-aggressive effects of clozapine in this population is important given the sparsity of evidence of clozapine in forensic or court order patients, and furthermore the lack of prospective clinical trial data in Black patients who are often under-prescribed this important medication[26]. His purpose of this study is to evaluate clozapine's effect on aggressive behaviors exhibited in the largest group of involuntarily committed Black patients studied to date.

Anti-aggressive efficacy of the second-generation antipsychotics

The greater anti-aggressive efficacy of the second-generation antipsychotics may be explained by their pharmacological action. They have lower affinity for dopamine D_2 receptors and greater affinities for serotonin ($5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_3$, $5\text{-}HT_6$, and $5\text{-}HT_7$)[27] and norepinephrine α_1 and α_2 neuro receptors than first-generation antipsychotics. Norepinephrine and serotonin have been implicated in violent behaviour. Deficiency or dysregulation of serotonin has been associated with violence. Drugs that block the $5\text{-}HT_{1A}$ and $5\text{-}HT_2$ receptors appear to have selective anti-aggressive effects in animals.

Clozapine's anti-aggressive effect has been linked to its serotonergic action in animal models. The greater limbic selectivity of clozapine , shared also to some extent by olanzapine, may also play a role in this antiaggressive effect. Thus, second-generation antipsychotics, and in particular clozapine, might be effective even in patients with conduct disorder.

The overall treatment comparisons of the study indicated that clozapine had a stronger anti-aggressive effect than olanzapine and that the latter was superior to haloperidol. The anti-aggressive effect was separate from the antipsychotic or sedative action of these medications, as there were no significant differences among the three medication groups in improvement of psychotic symptoms.

Clozapine is of benefit in reducing the clinical severity of ASPD. It improved all symptom domains, especially impulsive-behavioraldyscontrol and anger, and reduced levels of aggression and violence, especially at lower doses (serum levels <350 ng/m). To our knowledge, this is the first account of clozapine treatment in patients with ASPD and high psychopathy.

Clozapine is also widely known for its anti-aggressive effects, which have most commonly been demonstrated among schizophrenia patients. In a randomized control trial comparing clozapine, olanzapine, and haloperidol, all 3 drugs showed similar antipsychotic effects; however, clozapine showed a significantly better effect in reducing violent incidents, thus

Neurobiological basic and Neuroimaging evidence

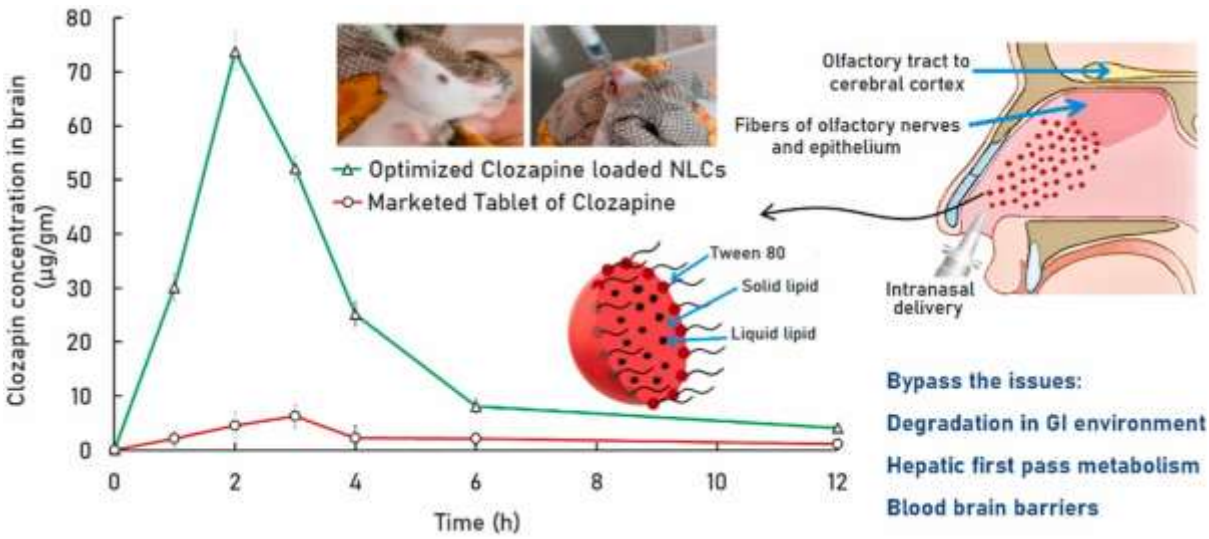


Fig 01- Designing tailored clozapine loaded nanostructured lipid carriers (NLCs) and deliver them to the brain via intranasal pathway.

In the present study an attempt was made to optimize the clozapine loaded nanostructured lipid carriers and delivered them to the brain through the nose-to-brain pathway. The recent studies suggest that the drug loaded NLCs have significant potential to penetrate (transcellular diffusion) the blood brain barrier to manage brain diseases. Thus, NLCs was selected as nanocarriers to deliver drug to the brain tissue. indicating its specific anti-aggressive effects.

Conclusion

Clozapine is an atypical antipsychotic that has shown to be of benefit in reducing the risk of violence in schizophrenia. To the best our knowledge, this is the first time that clozapine has been shown to be of benefit in patients with ASPD with comorbid high psychopathy. An ability of clozapine to reduce risk of suicides and attempts in schizophrenia patients appears to be a unique effect not shared with other modern medicines indicated for schizophrenia or bipolar disorder.Clozapine have high efficiency it's acting on brain thinking

power and changes in thinking. Clozapine showed the better act as anti-aggressive action and giving the effective changes in aggressive behaviour as well as suicide mood.

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