Section A -Research paper

Clozapine: A review Shed Light on It's Pharmacological Properties, Clinical Uses and Toxicological Aspects

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Abstract:

Background: Clozapine, a tricyclic dibenzodiazepine, is an atypical antipsychotic drug. It has the best effect among all antipsychotic drugs and has a strong antagonistic activity on D4-dopaminergic receptors, serotonergic, noradrenergic, histamine and cholinergic M2 receptors. Clozapine is uniquely effective and the only licensed agent for treatment-resistant schizophrenia. It reduces symptoms of psychosis by 40%, It significantly decreases psychiatric-related hospital admissions and mortality. However, clozapine is associated with agranulocytosis, metabolic side effects like insulin resistance with increased risk of type II diabetes and a variety of cardiovascular problems, including myocarditis.

Aim: The current review provides the evaluation of clozapine, outlining its pharmacological properties, clinical applications, mechanism of action as well as its toxic effects and management.

Conclusion: In summary, researchers have frequently emphasized the significance of clozapine therapy as the cornerstone of the treatment of psychosis.

Keywords: Atypical antipsychotic drug; Clozapine; Toxicity.

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Introduction:

Clozapine (CLZ), the progenitor of second-generation antipsychotic drugs, was first synthesized at Wander Laboratories in Bern, Switzerland in 1956. Clozapine was the earliest member of this family and was approved for treatment of schizophrenia in 1989 **(Ellington, 2023).** Introduction of clozapine was in 1970s in response to limited efficacy and intolerable adverse effects of first-generation antipsychotics particularly extrapyramidal side effects which were the main reason for their ineffectiveness **(Levine and Burns, 2007).**

Clozapine has the best effect among all antipsychotic drugs. However, currently, about 30% to 60% of patients with schizophrenia have poor efficacy in conventional antipsychotic treatment; 60% of patients in this population (refractory schizophrenia) are treated with clozapine

and their condition improve **(Gong et al.,2021).**

Chemical structure:

Clozapine is 8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4] diazepine **(Nair et al., 2020).**

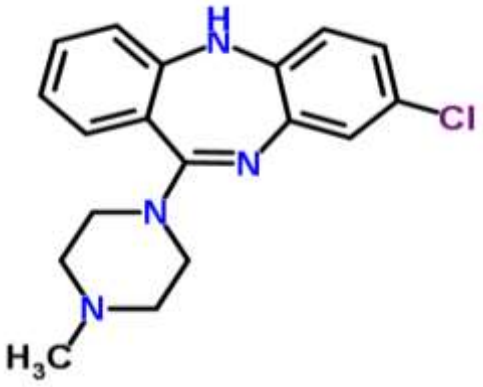

Figure (1): Chemistry of clozapine **(Nair et al., 2020).**

Physical properties:

Clozapine is a yellow crystalline powder, odorless or with a weak characteristic odor. It has a melting range of 182.0°-186.0°C. clozapine is slightly soluble in water, freely soluble in methylene chloride, soluble in ethanol, acetone and highly soluble in chloroform **(Hopfinger et al., 2009).**

Drug preparations:

Haidary and Padhy (2018) reported that Clozapine is available as oral tablets, oral disintegrating tablets, and oral suspension. Choice of dosage form depends on patient acceptability and tolerability.

- Oral tablet dosages of 25 mg, 50 mg, 100 mg, and 200 mg.
- Orally disintegrating tablet dosages of 12.5 mg, 25 mg, 100 mg, 150 mg, and 200 mg.
- Oral suspension dosage of 50 mg/mL (100 mL).

Tablets are round, pale yellow, uncoated, easy-to-break, scored, and can be divided into equal halves **(Lobos et al., 2010).**

Pharmacology:

Pharmacokinetics:

Absorption

Clozapine is rapidly absorbed from the gastrointestinal tract (90-95%) and has moderate first pass metabolism so the oral bioavailability is only 50% to 60%. The time to reach the peak concentration after oral dosing is about 2.5 hours. Neither the rate nor the extent of absorption of clozapine is influenced by food **(Rostami-Hodjegan et al., 2004**).

Volume of distribution

The volume of distribution of clozapine is 6 L/kg **(Stark and Scott, 2012).**

Protein binding

Clozapine is approximately 95 % bound to plasma proteins **(Stark and Scott, 2012).**

Route of elimination

Clozapine is extensively metabolized in the liver, via the cytochrome p450 system to polar metabolites. These metabolites are suitable for elimination in urine or in feces **(Raggi et al., 2004).**

Half-life

The typical plasma half-life of clozapine is between 14 and 16 hours, depending on the daily dose **(Flanagan et al., 2005).**

Mechanism of action:

Clozapine has unique effects on a variety of central nervous system receptors. It has a strong affinity for dopaminergic D4 receptors and potent serotonergic, noradrenergic, histaminergic, cholinergic M2 receptor blocking abilities. Moreover, clozapine also has significant effects on GABA-ergic and glutamatergic systems **(De Berardis et al., 2012).**

It is distinguished from typical antipsychotics by its greater efficacy and reduced tendency to cause extrapyramidal movement disorders **(Abbas and Abbas, 2016).**

Therapeutic uses:

Clozapine is used for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder. It is also used in Treatment of resistant schizophrenic patients who are non-responsive or intolerant to conventional antipsychotic drugs. It can be used in Parkinson's disease with drug-induced psychosis without worsening Parkinsonism. Clozapine helps to induce remissions of substance use disorder in schizophrenic patients. Clozapine is also used in developmental disorders e.g., Autism **(Rezaie et al., 2022).**

Recent study also points out that clozapine is an effective treatment for negative symptoms like emotional withdrawal, apathy poverty of speech, flat affect, lack of insight and judgment and positive symptoms like delusions, hallucinations and thought disorder **(Bangwal et al., 2020).**

Other benefits of clozapine include improvement of cognitive functioning, social functioning, quality of life, decrease need for hospitalization, compliance with treatment and reduction of aggressive behavior **(De Berardis et al., 2012).**

Dosage:

Due to risk of serious side effects, clozapine treatment is begun at a very low dose usually 12.5 mg once or twice on the first day and increased slowly until a therapeutic dose is reached **(Mustafa, 2020).** Most patients respond to clozapine doses in the range of 200–450 mg/day **(Nielsen et al., 2011).** In the meta-analysis performed by **Davis and Chen (2004)** the dose necessary for optimal treatment of many patients with treatment-refractory schizophrenia was over 400 mg daily. The maximum dose recommended for clozapine is 900 mg/day **(Nielsen et al., 2011).**

Due to the wide dose range and the variable clinical response to different doses, plasma levels are important in guiding clozapine treatment. The therapeutic response to clozapine has been shown to be closely associated with serum concentrations **(Lenk et al., 2023).** Clozapine levels thought to be effective in most patients range from 350– 420 ng/ml (**Remington et al., 2013).**

Side effects:

Clozapine commonly causes sedation, postural hypotension and tachycardia,

nausea, vomiting, constipation, elevation of liver enzymes, sialorrhoea, confusion or delirium, incontinence or urinary retention and benign hyperthermia **(Correll et al., 2022).**

However, Clozapine use had been associated with agranulocytosis, a life-threatening condition characterized by abnormally low levels of white blood cells **(Lorenzo-Villalba et al., 2020).** This led to its withdrawal in most countries. It then was reintroduced in the early 1990s after evidence established its clinical superiority in refractory schizophrenia **(Crilly, 2007).** Mandated guidelines were implemented requiring regular monitoring of patient's blood profile **(Schulte et al., 2023).**

Acute clozapine toxicity:

Clozapine toxicity has been very frequent in the recent years, especially in male young adults with history of substance abuse as it is used widely to prevent relapse **(Zhornitsky et al ., 2010).**

Stanworth et al. (2012) stated that clozapine is very toxic and death may occur because clozapine has a narrow therapeutic index.

A safe therapeutic dosage range for clozapine has not been clearly established, due to large variations in individual responses (**Lowe and Ackman, 2010).**

Children may develop severe symptoms of intoxication with a relatively small exposure (>100 mg) **(Pillay, 2013).**

Toxic and lethal doses:

The ingestion of a single tablet of clozapine may cause significant toxicity in a toddler. overdose of 300-400 mg of clozapine may result in coma in a nonhabituated adult. Adult fatalities have been reported following the ingestion of >2 g of clozapine **(Dubois, 2005).**

Signs and symptoms of acute clozapine toxicity:

Stark and Scott (2012) reported that the most serious toxicity involves the central nervous system causing lethargy, confusion, slurred speech, sedation and coma. Seizures occur in aproximately 5-10% of patients. Extra-pyramidal side-effects are more common in children.

Also **Li et al. (2021)** reported that the cardiovascular effects of acute clozapine intoxication include Sinus tachycardia, mild hypotension, rarely, QT prolongation , arrhythmias and congestive heart failure. However, clozapine, particularly in a relatively high dose has a clear cardiotoxic effect that can lead to sudden death.

Clozapine toxicity is associated with many serious life shortening side effects including metabolic syndrome, dyslipidemia, glucose intolerance and type 2 diabetes mellitus **(Gautam and Meena, 2011).**

Possible mechanisms of the clozapine-associated metabolic side effects especially those concerning impaired glucose homeostasis may be indirect through induction of peripheral insulin resistance. However, direct impairment of pancreatic beta-cell function by histaminic or α2-adrenergic receptor antagonism, direct

suppression of insulin secretion by selective impairment of cholinergic-stimulated insulin release **(Abdelrahim, 2013).**

Other reported manifestations include aspiration and respiratory depression **(Kramer et al., 2010).** Anti-muscarinic effects as agitation, restlessness, delirium, mydriasis but often have miosis, dry, warm skin, tachycardia, ileus, urinary retention and hypersalivation (sialorrhea) which is a characteristic and paradoxical effect of clozapine toxicity. Those antimuscarnic effects delay gastric emptying, potentially resulting in prolonged toxicity **(Minns and Clark, 2012).**

While neuroleptic malignant syndrome (NMS) rarely complicates clozapine toxicity and manifested by hyperthermia, autonomic instability, neuromuscular rigidity, and altered mental status, laboratory abnormalities such as elevated serum creatinine kinase and elevated white blood cell counts **(Minns and Clark, 2012).**

Causes of death:

Clozapine may cause death by a variety of mechanisms including agranulocytosis, neutropenia, arrhythmia, myocarditis/cardiomyopathy, convulsions, diabetic ketoacidosis, fulminant hepatic failure, circulatory collapse and thromboembolism **(Stanworth et al., 2012).**

Management of acute toxicity:

- **Diagnosis:**

Clozapine toxicity can be diagnosed by clinical history, physical examination, ECG, continuous Cardiac monitoring, measurement of cardiac biomarkers and Serum electrolytes **(Ronaldson et al., 2011).** Also Complete blood count monitoring as an initial leukocyte count with differential should be obtained at admission then to be monitored once or twice weekly for four weeks following overdose **(Pillay, 2013).** Co-ingestion is common in overdose patients with access to psychiatric medications, so screening for common available co-ingestion such as serum acetaminophen, salicylate, ethanol, lithium should be considered based on the history, physical examination **(Minns and Clark, 2012).** Monitoring of liver function is advisable as Clozapine has been associated with a rise in liver enzymes, renal function must also be monitored **(Pillay, 2013).**

- **Therapeutic drug monitoring:**

Plasma concentrations of specific atypical antipsychotic agents are not widely available and not useful in the acute management of an overdose **(Minns and Clark, 2012).** However clozapine is the only antipsychotic where routine monitoring of levels is recommended **(Remington et al., 2013).**

Treatment:

Treatment is primarily supportive, No available antidote. First as emergency stabilization. Airway and advanced cardiac life support should be instituted as necessary. All patients require continuous cardiac and respiratory monitoring, intravenous access, and a 12-lead ECG. Patients with altered mental status or seizures should receive empiric intravenous dextrose, naloxone,

oxygen, and thiamine **(Minns and Clark, 2012).**

Then gastrointestinal decontamination through administration of activated charcoal is recommended within the first 6 hours after the ingestion of the drug, as long as no contraindications exist, such as the presence of sedation or vomiting. Gastric lavage is not routinely recommended, as the risk of death is very low. Symptomatic and supportive treatment are used **(Minns and Clark, 2012).**

Hypotension should be treated initially with intravenous fluids, plasma expanders and vasopressors (dopamine or noradrenaline), adrenaline is contraindicated. In refractory cases, vasopressin has been used with good effect **(Rotella et al., 2014).**

Sinus tachycardia does not require specific treatment **(Ronaldson et al., 2011).** If persistent, **Rostagno et al. (2008)** suggested using of β-Blockers and ACE inhibitors to decrease the risk of clozapine-induced tachyarrhythmias, cardiomyopathies, and sudden death. Prolongation of the QTc requires no specific treatment other than the correction of potential contributing causes such as hypokalemia and hypomagnesemia **(Minns and Clark, 2012).**

Benzodiazepines are usually sufficient for treatment of seizures, phenytoin or valproic acid may also be given but carbamazepine is contraindicated **(Pillay, 2013).**

Physostigmine can safely and effectively reverse clozapine-induced delirium. The most important aspect of treatment of NMS is withdrawal of the drug and supportive care, with particular attention to fluid and electrolyte balance and cooling **(Minns and Clark, 2012).** Available Pharmacologic interventions are benzodiazepines and paralytic agents if needed, oral dopamine agonists, such as bromocriptine, amantadine and Dantrolene **(Troller et al., 2009).**

Because clozapine has large volume of distribution and extensive protein binding, enhanced elimination techniques such as multiple-dose charcoal, hemodialysis, urinary alkalinization and hemoperfusion are unlikely to be of benefit and not recommended **(Pillay, 2013).** Close medical supervision is necessary for at least five days because of the possibility of delayed reactions **(Kramer et al., 2010).**

Chronic toxicity:

- **Haematotoxicity:**

The most serious toxic effects of clozapine is agranulocytosis and neutropenia **(Corbeil et al., 2023).**

Clozapine manufacturer Novartis defines severe neutropenia by a white blood cell (WBC) count < 2000 per mm3, whereas agranulocytosis is indicated by a WBC count below 1000 per mm3 or by an absolute neutrophil count of < 500 per mm3. Clozapine is associated with a 0.5–2% risk of agranulocytosis and 3% risk of neutropenia . The risk of agranulocytosis seems to peak by the third month of therapy and declines significantly after the sixth month, but never reaches zero **(Choudhury et al., 2021).**

Agranulocytosis is thought to occur more often in persons < 21 years of age, the

elderly and in women, with mortality rate estimated at 3 – 4% of identified cases **(Fitzsimons et al., 2005).**

The pathogenesis of clozapine-induced agranulocytosis is controversial whether immunological, genetic or toxic mechanisms (bio-activation to reactive nitrenium ion) or a multistep phenomenon are responsible for this life-threatening side effect. To reduce the occurrence of agranulocytosis, centralized mandatory haematological monitoring for patients on clozapine was introduced in many countries **(Mijovic and MacCabe, 2020).**

Patients should be advised to inform of any new onset fever or infection (sore throat, weakness etc.) to ensure early detection of this potentially life-threatening adverse event. Severe neutropenia and agranulocytosis are both considered medical emergencies. Clozapine treatment must be ceased immediately if either is diagnosed with haematological consultation **(Micheletto et al., 2020).**

- **Cardiotoxicity:**

Clozapine may be associated with cardiovascular risks including cardiomyopathy, potentially fatal myocarditis, heart failure and pericarditis. The mechanisms by which clozapine causes cardio-toxicity remain unclear, however it can be explained by increased catecholamine levels **(Patel et al., 2019),** increased release of pro-inflammatory cytokines, IgE-mediated hypersensitivity reaction and oxidative stress **(Abdel-Wahab et al., 2014).**

The gold standard for diagnosis of myocarditis is an endomyocardial biopsy, but this is not a practical initial approach. Transthoracic echocardiography is a valuable and widely available tool to assist in diagnosis of clozapine-induced cardiotoxicity **(Magnani and Dec, 2006).**

The mainstay of treatment of clozapine-induced myocarditis is cessation of clozapine and provision of supportive care **(Micheletto et al., 2020).**

- **Endocrine system:**

Use of atypical antipsychotics has been linked to the development of hyperglycemia, ketoacidosis, hyperosmolar coma, and death. So we should monitor patient's fasting blood sugar at baseline and periodically, especially in individuals with a high risk of developing diabetes **(Micheletto et al., 2020).** Also Clozapine has been reported to cause dyslipidemia, increase in triglyceride levels (use with caution in patients with diabetes), and weight gain **(Xiong et al., 2019).**

- **Neurotoxicity:**

Central nervous system (CNS) abnormalities are often problem with clozapine treatment. Electroencephalogram (EEG) abnormalities have been reported in 50–60% of cases and the incidence of seizures ranges from 1–5%. The risk has been shown to increase in a dose-dependent manner **(Hatano et al., 2023).**

Patients with a history of convulsive disorder have also been reported to be more likely to have seizures, even with low doses of clozapine. In addition, other risk factors for CNS abnormalities include concomitant use of lithium **(Kitagawa et al., 2021).**

- **Others:**

Also, clozapine causes eosinophilia, hepatotoxicity, pulmonary embolism and rebound psychosis after withdrawal **(Micheletto et al., 2020).**

Conclusion: In summary, specialists have frequently emphasized the significance of clozapine therapy as the cornerstone of the treatment of psychosis. Strong evidence from research has shown that clozapine is the best treatment of resistant schizophrenia. clozapine administration induces many toxic effects and has avery narrow therpeutic index so it needs close monitoring.

Recommendations:

On the light of the information provided by the current review, the following guidelines are recommended: Widespread public education regarding the health hazards of clozapine, close monitoring of potential toxicity in patients treated with clozapine is required with routine periodical check and investigations and clinicians should be highly alert when patients on clozapine therapy display any signs of toxicity. Further studies are needed to identify other mechanisms of clozapine-induced toxicity.

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