

# Study of the Correlation between clozapine levels and clinical findings in acutely intoxicated patients admitted to Poison Control Center-Ain Shams University Hospitals: 6 months (A prospective Study)

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## Abstract

**Background:** Clozapine (CLZ) superior efficacy compared to other antipsychotics is well established. Unlike other antipsychotic medications, a safe therapeutic blood level range for clozapine has not been clearly established.

**Objective:** This study was undertaken as a trial to evaluate the potential correlation between clinical findings and CLZ blood levels in patients with acute CLZ toxicity.

**Methodology:** A prospective study was conducted on all patients of both sexes with history of acute clozapine overdose, admitted to Poison Control Center of Ain Shams University Hospitals (PCC-ASUH) from the first of March 2019 to the end of August 2019. The total number of acutely intoxicated clozapine cases in this study was 25 patients, number admitted in 6 months period. The data collected for each patient included socio-demographic data, clinical data (intoxication data and clinical examination), laboratory investigation (including blood clozapine level), ECG, treatment, and outcome.

**Results:** The results showed that there was no statistically significant correlation between the blood level of clozapine and any of the studied parameters, except with the level of consciousness, where there was statistically significant increase in the level of clozapine in comatose patients compared to conscious ones.

**Conclusion:** It was concluded that the study suggests that there could be a potential benefit of blood clozapine level as a predictor and prognostic marker of coma in acute clozapine overdose.

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## Key words

Clozapine, antipsychotic, blood level, acute poisoning

## Introduction

Clozapine (CLZ) has a superior efficacy compared to other antipsychotics is well established (Oyewumi *et al.*, 2002; Sandson *et al.*, 2007; Couchman *et al.*, 2010). Although it is possible to measure plasma levels of other antipsychotics, CLZ is the only antipsychotic where routine monitoring of levels is not routinely available (Couchman *et al.*, 2010; Flanagan *et al.*, 2005).

The clinical findings like agranulocytosis and ECG changes correlation with CLZ metabolite level has been suggested as it has been found that N-desmethylclozapine, the major CLZ metabolite, might be the cause of agranulocytosis because it is more toxic to WBC precursors than CLZ itself. Nonetheless, the CLZ plasma level associated with toxicity remains unclear (Cormac *et al.*, 2010).

Higher CLZ levels (> 600 mcg/L) or doses (> 600 mg/day) and faster rate of upward titration are associated with increased risk of seizure activity. Higher CLZ levels may also be associated with hypersalivation, tachycardia, QTc prolongation,

myocarditis, and cardiomyopathy (Greenwood-Smith *et al.*, 2003; Couchman *et al.*, 2010).

Plasma CLZ levels above 2000 mcg/L were reported to be usually associated with acute toxicity. However, there have been reports of patients with CLZ levels over 3000 mcg/L with no evidence of associated toxicity (Flanagan *et al.*, 2005), because of these conflicting reports, this study was undertaken as a trial to evaluate the potential correlation between clinical findings and CLZ blood levels in patients with acute CLZ toxicity.

## Patients and Methods

This was a prospective study that was conducted at the Poison Control Centre, Ain Shams University Hospitals (PCC-ASUH) for six months from the first of March to the end of August 2019.

### Study Population

With the approval of the Ethical Committee Ain Shams University, this study included 25 patients of both sexes and different age groups (14-36) presenting with history of acute CLZ toxicity, after an informed consent was taken from each patient or their guardian.

**Inclusion Criteria:** Patients of both sex and different age groups presenting with acute clozapine toxicity to Poison Control Center of Ain Shams University Hospitals with history of acute clozapine toxicity.

**Exclusion Criteria:** Patients with history of mixed ingestion, including co-ingestion of other antipsychotic or CNS acting drugs.

### Methodology

The following data were collected:

1. Sociodemographic data: Age and gender
2. Intoxication data: Amount of ingested CLZ, mode of poisoning, time delay, and pre-consultation management.
3. Past history
  - a. Duration of CLZ treatment in case of previous ingestion of CLZ in both therapeutic and toxic doses.
  - b. Psychiatric illness including history of drug dependence.
4. Clinical data on admission
  - a. General examination
    - i. Vital data: Body temperature, heart rate, and blood pressure.
    - ii. Pupil size
    - iii. Skin changes
  - b. Neurologic status
    - i. Level of consciousness using Reed's classification of coma
    - ii. Autonomic dysfunction signs
    - iii. Extrapyramidal manifestations
5. Investigations
  - a. Laboratory: Blood and urine samples were withdrawn on admission and immediately tested for:
    - i. Arterial blood gases (ABG)
    - ii. Complete Blood Count (CBC)
    - iii. Kidney function profile: Serum urea and creatinine
    - iv. Urine samples were analyzed for drugs of abuse testing: Opiates, tramadol, cannabinoids, and benzodiazepines (BDZ). Remaining serum (1-1.5ml) was kept refrigerated until GC analysis was undertaken for clozapine blood level:
      1. Three-mL venous blood samples were withdrawn from each patient 12 hours after ingestion and daily thereafter. After complete clotting, samples were centrifuged, and 1 to 1.5 mL serum were saved for CLZ blood assay.
      2. CLZ level was measured by Gas Chromatography:  
The therapeutic reference range of CLZ is 250 to 350 mcg/L (17–51 µmol/L)<sup>8</sup>.
  - b. ECG: A twelve-lead ECG was done on admission and then repeated twice a day for as long as patient stayed in hospital; to assess PR interval, QRS width, QTc, and arrhythmias

### Statistical analysis

- A. Descriptive statistics: These were made to quantitatively describe the main features of collected data, including frequencies, percentages, maximum, minimum, means, and standard deviations.
- B. Inferential statistics: Mann-Whitney test: was used to compare between two groups with quantitative data non-parametric distribution. Kruskal-Wallis test: was used to compare between more than two independent groups with quantitative data non-parametric distribution. Spearman correlation coefficients: were used to assess the correlation between two quantitative parameters in the same group.

### Results

This study enrolled 25 patients, average age of whom was 24.6 years, ranging from 14-36 years. Fifty six percentages (56%) of whom were females (Table 1).

All studied patients had no previous history of CLZ treatment. All studied patients exposed to toxicity through ingesting tablets in 2 concentrations: 25 & 100 mg. Most of patients ingested the higher-concentration 100 mg tablets (64%), with average number of 8.5 tablets per patient. The resulting median total dose was 500 mg per patient with a median delay of 4 hours between exposure and emergency room (ER) presentation. Of all studied cases, only one patient received pre-hospital treatment with flumazenil (Table 2).

Table 3 shows that 20% of studied patients had history of previous psychiatric illness. All patients were vitally stable with no skin changes. Pupils were constricted in 24% of cases, pinpoint observed in one case (4%), and normal in the remaining cases. As regards to neurological manifestations, coma was the predominant one, being present in 92% of cases, followed by slurred speech in 2 cases (8%), then ataxic gate, hallucination, and drowsiness by one patient showing each.

Regarding lab findings (Table 4), only 2 patients came positive in drug screening, 1 for tramadol and the other for opiates. Kidney function tests (urea and creatinine) were normal for all cases. CLZ blood level ranged from 0-80 µg/ml with a median of 0.65 µg/ml (650 mcg/L). None of the studied patient had changes in TLC in their CBC tests. Only 12% of patients developed respiratory acidosis compared to 1 case (4%) developed metabolic acidosis.

Table 5 shows that average heart rate was 93 bpm with a range of 70-124 bpm. Rhythm was regular in all cases and 40.7% of patients developed prolonged QTc interval.

Tables 6 to 10 show that there was no statistically significant correlation between blood CLZ level and any of the studied parameters, except with coma, where CLZ blood levels were significantly higher in comatose patients compared to non-comatose ones (Table 8).

**Table (1):** Distribution of patients regarding age and gender among the studied patients

Age (years) (No.= 25)		Gender (No.= 25)	
Mean $\pm$ SD	Range	Female	Male
24.56 $\pm$ 6.27	14 – 36	14 (56.0%)	11 (44.0%)

*SD standard deviation*

**Table (2):** Distribution of intoxication data among the studied patients.

Parameter	Findings (No.= 25)	
CLZ tablet concentration (mg)	25 mg	9 (36.0%)
	100 mg	16 (64.0%)
Number of Tablets	Mean $\pm$ SD	8.52 $\pm$ 4.80
	Range	2 – 20
Total dose	Median (Inter Quartile Range)	500 (250 – 1000)
	Range	50 – 2000
Route of intoxication	Oral	25 (100.00%)
Delay (Hours)	Median (IQR)	4 (3 – 7)
	Range	1 – 24
Previous CLZ treatment	No previous CLZ treatment	25 (100.00%)
Prehospital treatment	No	24 (96.00%)
	Flumazenil	1 (4.00%)

*SD standard deviation*

**Table (3):** Distribution of history and physical finding among the studied patients.

Parameter	Findings (No.= 25)	
Psychiatric illness	No	20 (80.00%)
	Yes	5 (20.00%)
Vital data	Stable	25 (100.00%)
Pupil	Normal Equal Reactive	18 (72.00%)
	Constricted Equal Reactive	6 (24.00%)
	Pinpointed Equal	1 (4.00%)
Skin changes	No	25 (100.00%)
Neurological manifestations	Coma	23 (92.00%)
	Slurred speech	2 (8.00%)
	Ataxic gait	1 (4.00%)
	Hallucination	1 (4.00%)
	Drowsy	1 (4.00%)

*SD standard deviation*

**Table (4):** Distribution of laboratory results among the studied patients.

Parameter	Findings (No.= 25)	
Drug screen	Opiates	Positive 1 (4.0%)
	Tramadol	Positive 1 (4.0%)
	Cannabis	Positive 0 (0.0%)
	BDZ	Positive 0 (0.0%)
Kidney function tests	Urea	Mean $\pm$ SD 13.32 $\pm$ 4.71
		Range 7 – 24
	Creatinine	Mean $\pm$ SD 0.76 $\pm$ 0.20
		Range 0.1 – 1.12
CLZ blood level (mcg/ml)	Median (IQR)	0.65 (0.41 – 1.80)
	Range	0 – 80
CBC	No agranulocytosis	25 (100.0%)
ABG	Normal	21 (84.0%)
	Respiratory acidosis	3 (12.0%)
	Metabolic acidosis	1 (4.0%)

*SD standard deviation*

**Table (5):** Distribution of ECG finding among the studied patients.

Parameter	Findings (No.= 25)	
	Rate	Mean $\pm$ SD
	Range	70 – 124
Rhythm	Regular	25 (100.00%)
QTc	Mean $\pm$ SD	0.47 $\pm$ 0.09
	Range	0.34 – 0.69

SD standard deviation

**Table (6):** Mann Whitney statistical to Correlate of CLZ blood level to some studied parameters

Parameter	Correlation with CLZ blood level ( $\mu$ g/ml)	
	r	P-value*
Age	-0.236	0.256
Number of Tablets	-0.100	0.633
Total dose of CLZ (mg)	0.135	0.520
Delay (Hours)	-0.221	0.289
Urea	-0.125	0.552
Creatinine	0.079	0.708
Rate	0.289	0.161
QTc	0.211	0.310

\* $P > 0.05$ : Nonsignificant;  $P < 0.05$ : Significant;  $P < 0.01$ : Highly significant.

**Table (7):** Correlation of CLZ blood level to gender, concentration, psychiatric illness, and previous consultation treatment using Mann Whitney test.

Parameter		CLZ blood level ( $\mu$ g/ml)		Test value	P value*	Sig.
		Median (IQR)	Range			
Gender	Female	0.78 (0.43 – 18.25)	0.06 – 80.0	-0.986*	0.324	NS
	Male	0.52 (0.20 – 0.87)	0.00 – 50.00			
CLZ dose (mg)	25 mg	0.43 (0.09 – 0.65)	0 – 25.9	-1.755	0.079	NS
	100 mg	0.87 (0.45 – 10.13)	0 – 80			
Psychiatric illness	No	0.57 (0.34 – 10.03)	0.00 – 80.0	-0.034*	0.973	NS
	Yes	0.86 (0.52 – 0.90)	0.00 – 2.00			
Pre-consultation treatment	No	0.59 (0.34 – 1.90)	0.00 – 80.0	-0.277*	0.781	NS
	Flumazenil	0.86 (0.86 – 0.86)	0.86 – 0.86			

\* $P$ -value  $> 0.05$ : Non-significant (NS);  $P$ -value  $< 0.05$ : Significant (S);  $P$ -value  $< 0.01$ : highly significant (HS).

• Mann-Whitney test.

**Table (8):** Correlation of CLZ blood level to neurological manifestations.

Parameter		CLZ blood level ( $\mu$ g/ml)		Test value	P value*	Sig.
		Median (IQR)	Range			
Pupil	Normal Equal Reactive	0.47 (0.20 – 1.80)	0.00 – 80.0	1.312 $^{\ddagger}$	0.519	NS
	Constricted Equal Reactive	0.89 (0.76 – 2.00)	0.27 – 50.00			
	Pinpointed Equal	0.52 (0.52 – 0.52)	0.52 – 0.52			
Coma	No	0.04 (0.00 – 0.09)	0.00 – 0.20	-2.054*	0.040	S
	Yes	0.76 (0.43 – 2.00)	0.00 – 80.0			
Slurred speech	No	0.65 (0.41 – 1.80)	0.00 – 80.0	-0.050*	0.960	NS
	Yes	34.13 (0.00 – 68.25)	0.00 – 68.25			
Ataxic gait	No	0.71 (0.42 – 1.90)	0.00 – 80.0	-1.595*	0.111	NS
	Yes	0.00 (0.00 – 0.00)	0.00 – 0.00			
Hallucination	No	0.59 (0.34 – 1.74)	0.00 – 80.00	-1.664*	0.096	NS
	Yes	68.25 (68.25 – 68.25)	68.25 – 68.25			
Drowsy	No	0.71 (0.42 – 1.90)	0.00 – 80.0	-1.110*	0.267	NS
	Yes	0.20 (0.20 – 0.20)	0.20 – 0.20			

\*  $P$ -value  $> 0.05$ : Nonsignificant (NS);  $P$ -value  $< 0.05$ : Significant (S);  $P$ -value  $< 0.01$ : highly significant (HS)

• Mann Whitney test

$\ddagger$  Kruskal Wallis test

**Table (9):** Kruskal Wallis statistical analysis to Correlate CLZ blood level to ABG findings.

Parameter		CLZ blood level (ug/ml)		Test value	P value*	Sig.
		Median (IQR)	Range			
ABG	Normal	0.65 (0.41 – 1.68)	0 – 68.25	0.944	0.624	NS
	Respiratory acidosis	0.52 (0 – 80)	0 – 80			
	Metabolic acidosis	2 (2 – 2)	2 – 2			

\* *P*-value >0.05: Nonsignificant (NS); *P*-value <0.05: Significant (S); *P*-value < 0.01: highly significant (HS)

**Table (10):** Mann Whitney statistical to Correlate CLZ blood level to drug tests and outcome.

Parameter		CLZ blood level (ug/ml)		Test value	P value*	Sig.
		Median (IQR)	Range			
Opiate	Negative	0.71 (0.34 – 1.9)	0 – 80	-0.139	0.890	NS
	Positive	0.52 (0.52 – 0.52)	0.52 – 0.52			
Tramadol	Negative	0.71 (0.34 – 1.9)	0 – 80	-0.555	0.579	NS
	Positive	0.43 (0.43 – 0.43)	0.43 – 0.43			
Outcome	Consented discharge	0.81 (0.42 – 1.35)	0.06 – 80.00	-0.435	0.663	NS
	Recovery	0.48 (0.20 – 2.00)	0.00 – 68.25			

\* *P*-value >0.05: Nonsignificant (NS); *P*-value <0.05: Significant (S); *P*-value < 0.01: highly significant (HS)

## Discussion

The present study showed that there was no statistically significant correlation between the level of CLZ and genders among the studied patients, agreeing with *Bowskill et al., (2010)*. The present generalization is that females tend to have relatively higher CLZ blood level (*Castberg et al., 2017*). However, this understanding is related to patients on regular CLZ treatment rather than acute overdose patients. Also, many other factors such as smoking, caffeine intake, co-treatment with other metabolites inducers, BMI, and inflammation may affect the clozapine blood level (*Taylor et al., 2015*).

This study also found no correlation between CLZ level and age. Another study found that CLZ blood concentration was higher after age of 65 even with decreasing therapeutic dose. The current study was limited to young and middle-aged patients (14-36 y, mean = 24.6) with no significant comorbidities, so results could have been different if older patients were included (*Bowskill et al., 2010*).

The study at hand shows that there was no statistically significant correlation between the blood level of CLZ and either number of tablets, concentration, or total dose of CLZ ingested. This could be attributed to the wide variation between patients in the rate at which they metabolize CLZ into norclozapine (50-fold). This was opposite to another study that stated that there is a definite relationship between the dose of CLZ and the plasma CLZ and norclozapine concentrations (*Yusufi et al., 2007*). Other previous studies have reported that the oral CLZ dose is insufficient to explain the high interindividual variability of serum levels (*Rostami-Hodjegan et al., 2004; Lane et al., 1999*).

The present study showed that there was no statistically significant correlation between the blood level of CLZ among the studied patients and the time-delay between exposure and presentation to the PCC. This is attributed to the delayed absorption due to gastrointestinal hypomotility induced by CLZ; CLZ does not follow single-compartment model of metabolism; in addition to the previously mentioned

different factors affecting its metabolism (*Fang et al., 2014*). In our study, the time interval between CLZ consumption and blood level testing has been variable and may have contributed to the lack of correlation.

In the current study, there was no statistically significant correlation between the level of CLZ among the psychiatric patients and non-psychiatric patients. Higher serum CLZ levels have been reported to be associated with greater cognitive impairment in patients with chronic schizophrenia after adjusting for the effects of age, sex, and oral dose (*Adler et al., 2002; Rajji et al., 2010*). Again, great interpersonal variability exist depending on the previously mentioned factors and may considerably change the plasma levels. Regarding the neurological manifestations, there was statistically significant increase in the level of CLZ in comatose patients compared to conscious patients. The clear indications for the therapeutic drug monitoring (TDM) of CLZ are signs of central nervous system toxicity, which can be linked to serum level. Most sources suggest levels greater than 600 mcg/L related to serious side effects. The risk of developing seizures appears to increase with higher concentrations (>1000 mcg/L) (*Zernig et al., 2007*).

There was no statistically significant correlation between CLZ level and ECG rate, rhythm, or the prolongation of QTc interval. A retrospective study enrolled patients with acute psychotropic drug overdose showed that QTc prolongation occurred in 40.5% of patients (*Miura et al., 2015*), similar to the results of our study. The potential mechanism underlying QTc prolongation of antipsychotic drugs is based on their ability to block the rapidly activating delayed rectifier potassium current (IKr), which leads to lengthening of cardiac repolarization (*Kim et al., 2018*). Absence of correlation could be explained considering that QTc prolongation is determined not only by the medication, but also by other patient's risk factors, which include old age, female sex, congenital long QT syndrome, heart conditions, electrolyte abnormalities, and concurrent use of medications that

prolong the QT interval or inhibit the metabolism of a drug that prolongs the QT interval (Leung et al., 2012). The current study shows no statistically significant correlation between CLZ level and ABG changes among studied patients. In a previous study, authors showed that psychotropic medications, especially CLZ, were the most common cause of poisoning associated with mixed respiratory alkalosis and metabolic acidosis (Hamdi et al., 2016). Metabolic disturbances associated with CLZ treatment could be related to its ability to bind wide range of receptors including muscarinic and adrenergic receptors, leading to potential autonomic dysfunctions (Yuen et al., 2018). The reported respiratory acidosis in the current study can be explained by impaired ventilation following central nervous system depression. Myocardial impairment/hypotension results in reduced tissue perfusion and the production of lactate leading to metabolic acidosis.

The study at hand shows no correlation between the plasma level of CLZ among the studied patients and drug screening of tramadol, cannabis, opiate, or benzodiazepine. Comorbid substance use disorder is common in patients with schizophrenia (Regier et al., 1990) and is associated with a variety of serious adverse consequences such as hospitalization (Swofford et al., 1996). Several reports suggest that CLZ may have the effect of decreasing the use of alcohol or/and other drugs of abuse among patients with schizophrenia (Drake et al., 2000). However, several investigators have in fact argued that abuse of alcohol and other drugs may worsen adherence to antipsychotic pharmacotherapy, including CLZ (Werner and Covenas, 2017). Based on this, the findings of the current study were not unexpected considering that only 20% patients gave history of previous psychiatric illness, 4% were positive in drug screening, and none have history of previous CLZ treatment.

The present study detected no statistically significant correlation between the level of CLZ among the studied patients and their mean urea and creatinine values. Acute interstitial nephritis (AIN) is a rare, but potentially fatal, adverse reaction to CLZ (Hunter et al., 2009). Acute renal failure due to neuroleptic malignant syndrome is well known as well (Strawn et al., 2007). The relatively small number and low severity of the studied cases in the present study may explain why such result was reached.

Since 100% of patients enrolled in the present study had full recovery, we found no statistically significant correlation between CLZ level and the outcome. This came in agreement with Paksu et al. (2014) who found that the majority of patients with psychotropics toxicity recover well with supportive therapy. Similarly, Elhady et al., (2016) pointed that acute overdose with antipsychotics seldom results in death. Again, the relatively small number and low severity of the studied cases in the present study may explain why such result was reached.

## Conclusion

The current study concluded that there was statistically significant increase in the level of CLZ in comatose patients compared to conscious ones. This

suggests that the potential benefit of blood CLZ level as a predictor of coma in acute CLZ overdose needs to be assessed.

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## دراسة الارتباط بين مستوى الكلوزابين و النتائج السريرية في حالات التسمم الحاد للمرضى المحجوزين بمركز السموم الإكلينيكي بمستشفيات جامعة عين شمس

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### الملخص العربي

#### المقدمة:

إن فعالية عقار الكلوزابين أمر لا شك فيه، بخلاف بقية أدوية مضادات الذهان لم يحدد بوضوح مجال أمن للجرعات العلاجية للكلوزابين، وما يزال مستوى الكلوزابين المصاحب للسمية مبهمًا.

#### الهدف من الدراسة :

وإنما تهدف هذه الدراسة لتقصي الارتباط بين التظاهرات السريرية ومستويات الكلوزابين في الدم لدى مرضى التسمم الحاد بالكلوزابين، لتقدير أهمية مستويات الكلوزابين في تقييم شدة التسمم.

#### منهجية الدراسة:

وقد أجريت دراسة وصفية مستقبلية على كل مرضى التسمم الحاد من كلوزابين من كلا الجنسين والذين قد أدخلوا مركز علاج التسمم بمستشفيات جامعة عين شمس ما بين آذار (مارس) ٢٠١٩ حتى آب (أغسطس) ٢٠١٩.

بلغ إجمالي عدد حالات التسمم الحاد بالكلوزابين في هذه الدراسة ٢٥ مريضًا أدخلوا على فترة ستة أشهر. تم تحصيل بيانات العمر و الجنس و البيانات السريرية و المختبرية بما فيها مستوى الكلوزابين بالدم و تغيرات رسم القلب الكهربائي و العلاج و النتيجة لكل منهم.

#### نتائج الدراسة :

ما من زيادة ذات دلالة إحصائية تذكر بين مستوى الكلوزابين لدى المرضى محل الدراسة وبين البيانات المدروسة ما عدى في المرضى الذين يعانون من الغيبوبة حيث ان زيادة إحصائية مهمة قد وجدت في مستوى الكلوزابين لدى المرضى اللذين يعانون من الغيبوبة مقارنةً بالواعين منهم.

#### الخلاصة :

وقد استنتج من الدراسة انه من المرجح وجود فائدة من قياس مستوى الكلوزابين بالدم لتوقع نتائج مرضى الغيبوبة في حالات التسمم الحاد بالكلوزابين.