بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

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MONA MAGHRABY

Correlation of clinical findings and clozapine levels in patients with acute clozapine toxicity admitted in a 6 months period to Poison Control Center – Ain Shams University Hospitals (A prospective Study)

Thesis

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Nada Amgad

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List of Abbreviations

Abb.	Full term
ABG	Arterial blood gases
ANC	Absolute neutrophil count
CBC	Complete Blood Cunt
CNS	Central nervous system
CYP1A2	Cytochrome P450 enzyme 1A2
DBP	Diastolic blood pressure
EEG	Electroencephalography
GC	Gas Chromatography
HPLC	High-Performance Liquid Chromatography
ME	Medication error
PCC-ASUH	Poison Control Centre, Ain Shams University Hospitals
SBP	Systolic blood pressure
SSRIs	Selective serotonin reuptake inhibitors
WBC	White blood cell

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INTRODUCTION

Clozapine's superior efficacy compared to other antipsychotics is well established ***(Oyewumi et al., 2002; Sandson et al., 2007; Raedler et al., 2008; Couchman et al., 2010).***

Unlike other antipsychotic medications, a safe therapeutic dosage range for clozapine has not been clearly established ***(McKean et al., 2008).***

Although it is possible to measure plasma levels of other antipsychotics ***(Nazirizadeh et al., 2010; Sparshatt et al., 2011),*** clozapine is the only antipsychotic where routine monitoring of levels is recommended ***(Couchman et al., 2010; Flanagan et al., 2005; Perry, 2001; Taylor, 1997).***

The clinical findings like agranulocytosis and ECG changes correlation with clozapine metabolite level has been suggested as it has been found that N-desmethylclozapine, the major clozapine metabolite, might be the cause of agranulocytosis because it is more toxic to WBC precursors than clozapine itself ***(Gerson and Meltzer 1992; Gerson et al. 1994).***

The clozapine blood level associated with toxicity remains unclear ***(Cormac et al., 2010).***

Higher clozapine levels (> 600 µg/L) or doses (> 600 mg/day) and faster rate of upward titration are associated with

increased risk of seizure activity ***(Greenwood-Smith et al., 2003; Couchman et al., 2010).*** Higher clozapine levels may also be associated with hypersalivation, tachycardia, QTc prolongation, myocarditis and cardiomyopathy ***(Couchman et al., 2010; Simon et al., 2009).***

Flanagan et al. (2005) reported that plasma clozapine levels associated with acute toxicity are usually above 2000 µg/L; however, there have been reports of patients with clozapine levels over 3000 µg/L with no evidence of associated toxicity.

AIM OF THE WORK

This study is a trial to find the correlation between clinical findings with clozapine blood levels in patients with acute clozapine toxicity admitted to Poison Control Center – Ain Shams University to evaluate the value of clozapine blood levels in assessing severity of clozapine toxicity.

REVIEW OF LITERATURE

Clozapine has been found to be superior to traditional neuroleptics in the treatment ***(Kane et al., 1988)*** and is increasingly being used to treat affective disorders ***(Zarate et al., 1995),*** some neurological disorders ***(Safferman et al., 1994),*** and aggression ***(Ratey et al., 1993; Cohen and Underwood, 1994).***

Despite its demonstrated efficacy in psychosis and the expanding indications for its use, widespread use of clozapine has been limited by the potential for adverse effects. In addition to the risk of life-threatening agranulocytosis, clozapine can cause seizures, hypotension, tachycardia, weight gain, sialorrhea, and many other significant adverse effects ***(Kikuchi, et al., 2014).***

Adverse effects also limit the rate at which the dose can be increased, as well as the maximum dose that can be tolerated by some patients. For many patients, clozapine is their best hope for successful treatment of a disabling mental illness. However, full benefit can be achieved only if the adverse effects can be controlled.

Clozapine Pharmacokinetics

Clozapine is a lipophilic drug with a high volume of distribution (6 L/kg). It is 95–97% bound to plasma proteins and has a mean terminal half-life of 12 hours (range 4–66

hours), reaching peak blood levels in 0.4–4.2 hours. Steady state is attained in 5–7 days.

Clozapine is primarily metabolized by the cytochrome P450 enzyme 1A2 (CYP1A2), but P450 enzymes 2D6, 3A4, 2C9 and 2C19 also contribute to its metabolism ***(Cormac et al., 2010; Couchman et al., 2010; Lowe and Ackman, 2010).***

Clozapine's metabolism demonstrates dose-dependent saturation, resulting in disproportionate increases in clozapine blood levels with relatively small increases in dose above plasma levels of 600 µg/L in some patients ***(Couchman et al., 2010).***

Clozapine Pharmacodynamics

This product is a kind of major tranquilizer which has well therapeutic effect on treating acute and chronic schizophrenia. Its mechanism of action is probably playing a pharmacological effect on central dopamine nerve. It can selectively block dopamine receptors in the limbic system with small effect on nigrostriatal dopamine receptor, so it has a strong anti-psychotic effect. The extrapyramidal side effects are rare. Its function also has no dependence on the activity of adenylate cyclase. Clozapine is a second-generation antipsychotic with antagonist activity at numerous receptors, including dopamine (D_1, D_2, D_3, D_4, D_5), serotonin (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}), muscarinic (M_1, M_2, M_3, M_5), α_1- and α_2-adrenergic, and histamine (H_1) receptors. In addition, clozapine