International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 6, Issue 1, pp: (372-375), Month: April - September 2018, Available at: www.researchpublish.com

Low Dose Clozapine with Lamotrigine Augmentation in Treatment Resistance Schizophrenia: A Case Report

Alkhamees Abdulmajeed, MBBS

Demonstrator, College of Medicine, Qassim University, Saudi Arabia

Abstract: **The initial clozapine dose is 12.5 mg, increasing gradually to 300-400 mg/d, up to a licensed maximum of 900 mg/d. A plasma level of 350 µg/L should be aimed for to ensure an adequate trial, but response may occur at lower plasma level, depending on many factors including augmentation and Ethnicity, here we present the case of a 24-year-old Saudi male with refractory schizophrenia who responded to low dose of clozapine and lamotrigine augmentation.**

Keywords: **clozapine; lamotrigine; Treatment Resistance Schizophrenia.**

1. INTRODUCTION

The second generation or "atypical" antipsychotic clozapine is effective in some 30%-60% of patients with schizophrenia who do not respond fully to other medicines, and is better tolerated by others who could not take older drugs. The UK National Institute for Health and Clinical Excellence guidelines [1] for the treatment of schizophrenia promote the use of clozapine in such patients despite the need for regular hematological monitoring due to the risk of neutropenia and/or agranulocytosis[2].

The initial clozapine dose is 12.5 mg, increasing gradually to 300-400 mg/d, up to a licensed maximum of 900 mg/d. There is a risk of hypotension leading to renal failure and seizure, tachycardia, and coma in overdose; a single dose of 200-400 mg may be life threatening in a clozapine-naive adult. Side effects of clozapine that may be dose-related include the following: drowsiness, headache, sedation, dizziness, hypersalivation, tachycardia, postural hypotension, tremor, hyperthermia, weight gain, constipation, myocarditis, cardiomyopathy, and seizures[3,4]. Very rarely, there have been deaths from clozapine-induced liver failure. Often morbidity can be minimized by careful dose escalation or alleviated by reducing the dose, although weight gain might be an exception to this. Alternatively, appropriate additional medication may be required. The enhanced risks of diabetes and dyslipidemia associated with clozapine, and with other atypical, are related to weight gain/obesity, among other factors[5].

Pharmacokinetic studies of antipsychotics have found that Asians generally have a higher plasma concentration than Caucasians given the same weight-adjusted dose [6]. For example, Chang et al. (1997) found clozapine plasma concentrations were 30–50% higher in 162 patients with refractory schizophrenia in Taiwan than those reported for Caucasian patients, despite use of comparable doses[7].

Clozapine is the only antipsychotic agent with proven efficacy in treatment-resistant schizophrenia [8], However, a substantial minority of patients fail to respond or have only a partial response to clozapine, leading clinicians to search for potential augmentation strategies to improve outcomes.

Here we present the case of a 24-year-old Saudi male with refractory schizophrenia who responded to low dose of clozapine and lamotrigine augmentation.

2. CASE REPORT

A 24-year-old Saudi male with no significant past medical history, besides heavy smoking and abusing marijuana, diagnosed with schizophrenia with onset at the age of 17 years, when he experienced auditory hallucinations and delusional ideas of persecution and reference. Over the previous years, he had presented chronic and resistant psychotic symptoms despite treatment with several atypical antipsychotics at therapeutic dosages for adequate durations , one of the trial included clozapine which he discontinue Early due to the suspicion of myocarditis , patient was maintained on quetiapine 800 mg and paroxetine 40 mg with reasonable responses except for attenuated auditory hallucinations , 1 week before coming to the hospital he started having paranoid ideation toward his father and try to attack him at one time , after the attack, the father who is a physician decided to decrease his quetiapine to 200 mg twice daily and his paroxetine to 20 mg once daily and added clozapine 25 mg at night in addition to lamotrigine 100 mg once daily , patient was seen at the hospital and was admitted , at admission he was positive for cannabinoids and his WBC count (11,900 cells/µl) and neutrophils (7,170 cells/µl) , on Day 5 of the Admission his clozapine was increased from 75 mg at night gradually to the target of 150 mg which he reached after 8 days ,his WBC count after he reached 150 mg was (16,700 cells/µl) and his neutrophils (12,200 cells/µl) which was increased , and he started having persistent tachycardia (pulse rate 115-130 bpm) but there was no sign of fever , so the team decided to discontinue his quetiapine and paroxetine which was done gradually , on the day 15 his WBC decreased to (12,800 cells/µl) and his neutrophils (8,240 cells/µl) and his pulse rate started decreasing to less than (110 bpm) , on day 22, patient was in his best status since the start of the illness According to his Family , he had no clear psychotic symptoms , and no significant mood or Anxiety symptoms and he was insightful about his illness , his WBC count was (10,500 cells/µl) and neutrophils (6,290 cells/µl) and his pulse rate was less than (110 bpm)

At follow-up, on day 38, the patient was in a good condition and his blood tests were within normal range.

3. DISCUSSION

There are problems with using clozapine in addition to its adverse effects. Firstly, the full therapeutic benefit may take weeks or months to become apparent. Secondly, adherence and impaired gastrointestinal mobility may be issues. Thirdly, although its effect on the white cell count is unpredictable to an extent, its therapeutic benefit is dose related. However, people vary dramatically (some 50-fold) in the rate at which they metabolize clozapine and, thus, identifying the correct dose in individual patients is not easy. Although hepatic clearance is substantial, there is indirect evidence that presystemic metabolism in the gut may make a large contribution to total clozapine clearance[9]. A further complication is that the clozapine dose requirement varies with smoking habit, increasing by approximately 50% on average in smokers, and vice versa[10]. There may be serious complications such as convulsions if a patient stops smoking and the clozapine dose is not reassessed promptly[11].

A plasma level of 350 µg/L should be aimed for to ensure an adequate trial, but response may occur at lower plasma level. The average dose at which this plasma level is reached varies according to gender and smoking status. The range is approximately 250 mg/day (female non-smoker) to 550 mg/day (male smoker) [10]

The clozapine concentrations of Asian patients reported in previous studies appear to be higher than those in Caucasian patients [12,13]. A large study from the Clozaril Patient Monitoring Service in the UK found a mean plasma clozapine plasma level of 430 ng/ml for a mean dose of 460 mg/day from a sample of more than 3000 patients [10] Such variations may indicate essential ethnic differences in clozapine pharmacokinetics. In addition, there may be pharmacodynamic differences between Caucasian and Asian populations. A study of Korean–American patients found that the Asians showed greater improvement than Caucasians with lower mean doses of clozapine[14]. Although the dose corrected clozapine concentration was lower in the Koreans compared to Caucasians, they were more likely to experience adverse effects. Of note were 11 Korean subjects who responded with plasma concentrations less than 200 ng/ml. Several studies in Caucasians have indicated a greater likelihood of therapeutic response with levels above 350 ng/ml [15]. The authors suggested that Asian patients might be treated effectively and safely with lower doses of clozapine than used for Caucasians.

To date, augmentation strategies with clozapine have generally proved dis- appointing. Although data are limited[16], Dursun *et al.* (1999) concluded that improvement in psychiatric symptoms may be obtained when lamotrigine is added to clozapine in resistant schizophrenia. , Tiihonen *et al.* (2003) found that adding lamotrigine to the clozapine treatment was more effective in reducing positive and general psychopathological symptoms in treatment-resistant schizophrenia. And

his finding also were similar to Zoccali et al., (2007) who concluded that lamotrigine augmentation of clozapine treatment is well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in treatment-resistant schizophrenia.[17]

Lamotrigine Augmentation May be useful in partial or non-responders. Further evidence support that clozapine plus lamotrigine may be helpful in reducing alcohol consumption and craving among patients with schizophrenia and comorbid alcohol dependence..[18], a meta-analysis was conducted by Tiihonen J (2009) suggests that lamotrigine augmentation may be an effective treatment for patients with clozapine-resistant schizophrenia [19]

In our case the patient responded to low dose of clozapine (150 mg) with Augmentation of Lamotrigine, with no apparent side effect, although he is A heavy smoker with A big body built.

Unfortunately, the plasma level could not be obtained because of the unavailability of the Test in the Local labs and this present a limitation of our case report. The response the patient showed could be related to the Augmentation or his Ethnicity, or other unknown factors .and we report this because it could open a venue for future researches to expand in this area.

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