Adverse Drug Reactions of Clozapine and Their Management in a Tertiary Care Hospital in Kelantan

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Abstract

Introduction: Clozapine remains as the most effective antipsychotic for the treatment of resistant schizophrenia. However, it has a wide range of adverse drug reactions (ADRs) which may cause significant distress and affects treatment outcome.
Objective: We aimed to identify ADRs associated with clozapine and their management among patients at outpatient psychiatric clinic in Hospital Raja Perempuan Zainab II, Kelantan.
Methods: A secondary data review was conducted from November 2016 to April 2017. The inclusion criteria were all adult patients on long term clozapine treatment with at least 3 regular follow-ups. Patients with incomplete medical records were excluded from the study.
Results: A total of 50 patients were involved with 199 ADRs recorded. Subjects were mostly male (70%, n=35), Malays (84%, n=42) with mean age of 38.7 (SD 9.4) years old. The mean duration of treatment with clozapine was 61.1 (SD 29.9) months. It was noted that majority of the patients developed weight gain (66%, n=33) as there was a statistically significant difference between baseline and current body mass index (p=0.015). Other common ADRs were sedation (52%, n=26), followed by upper respiratory tract infection (48%, n=24), constipation (36%, n=18) and hypersalivation (34%, n=17). No incidence of agranulocytosis or thrombocytopenia was observed in our study. This was consistent with the laboratory findings since no statistically significant differences were noted between baseline and current total white blood cells as well as platelet count (p=0.770 and p=0.201, respectively).
Conclusion: Our study added to the existing information on the patterns of ADRs following clozapine treatment at a local facility. Fortunately, all ADRs reported were tolerable and manageable. Nevertheless, a careful increase in clozapine dosage and regular laboratory monitoring are strict requirements.

Keywords: clozapine, adverse drug reactions, antipsychotics, schizophrenia

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Introduction

Schizophrenia is one of the most complex and debilitating mental illnesses. It interferes with one's ability to think clearly, manage emotions, make decisions and relate to others. It represents a heterogeneous syndrome of hallucinations, delusions, negative symptoms and cognitive issues. Antipsychotics have been the mainstay of therapy and amongst them is clozapine[1]. Clozapine has existed for more than half a century since it was first synthesised in 1956[2]. Early clinical trials had confirmed its efficacy which led to the introduction of clozapine into clinical practice in Europe in the 1970s. Clozapine was, however, withdrawn from the market after fatal cases of agranulocytosis were reported in Finnish patients. It was then reintroduced in 1990 after the results of a major clinical trial were published in favour of clozapine[3]. Other studies later also demonstrated that clozapine was proven to be superior to other antipsychotics for treatment-resistant schizophrenia[4,5]. Treatment-resistant schizophrenia occurs in approximately 30% of patients with schizophrenia. There are various definitions; but usually patients are diagnosed with treatment-resistant schizophrenia when they have at least moderate impairment in functioning as a result of failure to respond to any two antipsychotics administered at adequate dosage and duration. At this point, they may benefit from clozapine which is the only antipsychotic indicated for treatment-resistant schizophrenia[6,7].

In spite of its reputation as the most effective antipsychotic, clozapine has many adverse drug reactions (ADRs) which may limit its use[8]. Prescribers are usually hesitant to start their patients with clozapine for fear of the ADRs[2,8–10]. These ADRs ranges from annoying to noxious and potentially harmful[2]. They can occur in many organ systems with the most affected are central nervous system (sedation, dizziness, headache and tremor), cardiovascular system (tachycardia, hypotension and syncope), autonomic nervous system (hypersalivation, weight gain, sweating, dry mouth and visual disturbances) and gastrointestinal system (constipation and nausea)[10]. In the long run, patients can develop metabolic syndrome and type 2 diabetes mellitus. It also predisposes patients to rare but life-threatening events of agranulocytosis, cardiomyopathy and myocarditis[11–13]. Apart from that, there are cases of adverse cutaneous drug reactions (ACDRs) reported among patients commencing clozapine[10].

These ADRs generally take place during the initial stage of therapy which can prompt patients to withdraw from the treatment[14]. Often the main reason for discontinuation of clozapine is its intolerable ADRs. In a retrospective cohort study, it was found that 45% of patients discontinued their first trial of clozapine within 24 months of therapy. It was observed that the risk of treatment withdrawals due to ADRs was highest in the first few months of clozapine initiation[8]. Therefore, it is important to maintain the appropriate management of ADRs to ensure that treatment outcome is not affected. Dosage adjustment can greatly help in minimising the occurrence of ADRs[15]. Patients who experienced frequent but non severe ADRs of increased appetite, sedation, enuresis and hypersalivation usually do not require reduced doses or drug intervention[14]. Nevertheless, it is always recommended that regular assessment and blood monitoring should be done prior to and after initiation of clozapine to prevent complications and fatal incidences of ADRs[2,4,12].

There is an abundance of literature published in the 80's and 90's but little is documented on the local practice of clozapine. Therefore, we aimed to identify ADRs associated with clozapine and their management among psychiatric patients in a tertiary care hospital in Kelantan. It was hoped that the findings can shed some light on the current clinical experience with this drug as compare to other practices.

Methods

A secondary data review was conducted for a duration of 6 months which was from November 2016 to April 2017 at the outpatient psychiatric clinic in Hospital Raja Perempuan Zainab II, Kelantan. The inclusion criteria were all adult patients on long term clozapine treatment with at least three regular visits. Patients with incomplete medical records were excluded. The list of the patients prescribed with

clozapine was obtained from outpatient psychiatric clinic. Data collection form was used to collect demographic characteristics of patients, types and frequencies of ADRs as well as their management from all available medical records at the time.

Data was entered and analysed using IBM SPSS Statistics version 20.0. All categorical data in the demographic characteristics were presented as frequencies (n) and percentages (%) while continuous variables were expressed as mean and standard deviation (SD). Descriptive statistics were also used to explain ADRs associated with clozapine and their management among psychiatric patients. Paired t-test was applied to check the differences between baseline and current body mass index, total white blood cells and platelet count. A *p*-value of <0.05 was considered as statistically significant.

This research was submitted to Medical Research and Ethical Committee (MREC) for ethical approval and was granted with National Medical Research Registry (NMRR) identity number of NMRR-16-2654-33392. Permission to conduct the study at the site was obtained from the Director of Hospital Raja Perempuan Zainab II. The research was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Subject's confidentiality was protected with no reference to a specific individual.

Results

A total of 102 medical records were reviewed. After exclusion, only 50 subjects were included in the study. Patients were mostly male (70%), Malays (84%) with mean age of 38.7 (SD 9.4) years old. Many of them were prescribed with initial and maintenance clozapine dose of between 100 to 200mg daily. The mean duration of clozapine treatment was 61.1 (SD 29.9) months (Table 1).

A total of 199 ADRs was recorded. A majority of patients developed weight gain (66%, n=33) and the difference between baseline and current body mass index was statistically significant ($p<0.05$). Other common ADRs were sedation (52%, n=26), upper respiratory tract infection (48%, n=24), constipation (36%, n=18) and hypersalivation (34%, n=17). Skin reaction (32%, n=16), headache (30%, n=15) and palpitation (26%, n=13) were also prevalent among our study population. Some even complained of having rigidity (18%, n=9), blurred vision (12%, n=6) and restlessness (10%, n=5) during the course of clozapine treatment. Only a minority reported ADRs of hyperglycaemia (4%, n=2), cardiovascular effect (4%, n=2) and seizure (4%, n=2) (Table 2).

No incidence of agranulocytosis or thrombocytopenia was observed. This was consistent with the laboratory findings since no statistically significant differences were noted between baseline and current values for total white blood cells and platelet count ($p=0.770$ and $p=0.201$, respectively) (Table 3).

Symptomatic treatments were given for ADRs of upper respiratory tract infection, constipation, skin reaction and epigastric pain. These ADRs were adequately managed with over-the-counter drugs. Antipyretic, antihistamine, mucolytic agent and cough syrup were prescribed for upper respiratory tract infection. Laxatives were given for constipation while antifungal and topical corticosteroids were endorsed for skin reaction. As for epigastric pain, it was treated with antacid and oral histamine-2 blocker. All ADRs were either mild or moderate and were successfully intervened without dosage adjustment (Table 4).

Table 1: Demographic characteristics of study population (N=50)

Characteristics	n (%) / mean (SD)
Age, year, mean (SD)	38.7 (9.4)
Gender, n (%)	
Male	35 (70)
Female	15 (30)
Ethnicity, n (%)	
Malay	42 (84)
Others	8 (16)
Initial clozapine dose, n (%)	
100 – 200 mg	36 (72)
> 200 – 300 mg	9 (18)
> 300 mg	5 (10)
Current clozapine dose, n (%)	
100 – 200 mg	25 (50)
> 200 – 300 mg	13 (26)
> 300 mg	12 (24)
Duration of clozapine treatment, month, mean (SD)	61.1 (29.9)

Table 2: ADRs of clozapine among study population (N=199)

ADR	n (%)
Weight gain	33 (66)
Sedation	26 (52)
Upper respiratory tract infection	24 (48)
Constipation	18 (36)
Hypersalivation	17 (34)
Skin reaction	16 (32)
Headache	15 (30)
Palpitation	13 (26)
Epigastric pain	11 (22)
Rigidity	9 (18)
Blurred vision	6 (12)
Restlessness	5 (10)
Hyperglycaemia	2 (4)
Cardiovascular effect	2 (4)
Seizure	2 (4)

Table 3: Comparison of baseline and current laboratory parameters

Laboratory parameter	Indication	Baseline, mean (SD)	Current, mean (SD)	*p*-value*
Body mass index, kg/m^2	Weight gain	25.0 (5.6)	28.4 (14.0)	0.015
White blood cell, x10/L	Agranulocytosis	8.7 (2.1)	8.7 (2.1)	0.770
Platelet, x10/L	Thrombocytopenia	273.3 (64.4)	278.7 (66.2)	0.201

* Paired t-test, normality assumed

Table 4: Pharmacological management of ADRs among study population

ADR	Management
Upper respiratory tract infection	Paracetamol tablet Chlorpheniramine tablet Bromhexine tablet Diphenhydramine syrup
Constipation	Lactulose syrup Glycerine enema
Skin reaction	Miconazole cream Betamethasone cream
Epigastric pain	Mixture magnesium trisilicate Ranitidine tablet

Discussion

Clozapine continues to be the gold standard and cornerstone therapy for treatment-resistant schizophrenia. It has been proven to successfully treat symptoms and improve the condition of these patients. Evidence also clearly showed that clozapine has the advantage of reducing the risk of mortality and aggression over other available antipsychotics[3]. Despite its effectiveness, it causes the worst metabolic disturbances among antipsychotics. Like many other reports, we found that clozapine was strongly associated with weight gain[16]. An increase of at least 7% of baseline weight gain was considered as clinically significant, which was in agreement with our study population[17]. It was said that this ADR is time-related, whereby weight and body mass index increase significantly over time. There were patients who put on up to 9.2 kg[18] and 13.5 kg[17] during the course of their treatment. In order to overcome this problem, Siskind and colleagues suggested that prescribing metformin could promote weight loss for people with obesity on clozapine[16].

There are many other common ADRs associated with clozapine. Most of our patients complained of a high rate of sedation and headache upon taking clozapine. Both were frequent but troubling adverse events involving the central nervous system[2,3,10]. Sedation seems to be multifactorial[19] and can be associated with the fact that clozapine is a strong histamine H1 receptor antagonist[20]. The management is still unclear but reducing the dose of clozapine may alleviate the effect[19]. Prescribers should discuss and negotiate the dosing schedule with patients. Treatment augmentation with drugs such as aripiprazole may help to reduce the required clozapine dose and thus decrease sedation, but should not be prescribed without the consultation of a psychiatrist[7].

Other than that, clozapine also affects the autonomic nervous system which causes hypersalivation (sialorrhea) and visual disturbances[10]. We found that one third of our patients experienced drooling which was consistent with previous systematic review[21]. However, this figure was far lower than Maher *et al.*'s study in 2016 who reported that over 90% of their study population suffered from hypersalivation[22]. This ADR can be troublesome as it interrupts sleep which eventually influences quality of life[21,22]. Hypersalivation, particularly while sleeping can be embarrassing and stigmatising to the patients. Sublingual anticholinergic drugs may have some effect on the ADR[7]. As for visual disturbances, clozapine has been listed as one of the drugs that can cause difficulty with focusing at near and blurred vision[23]. This could explain why some of our study population complained of blurred vision. If left untreated, it may lead to worsening eye problems which may cause permanent damage to the sight[24].

Patients who are prescribed with clozapine are prone to fever, cold and flu-like symptoms due to viral upper respiratory tract infections. In most situations, patients do not require adjustment of therapy. This might be the reason our prescribers resorted to over-the-counter medications such as

paracetamol and antihistamines for symptomatic relief. However, it is wise not to ignore these signs and symptoms as they may indicate something far serious, for instance myocarditis or secondary infections due to neutropenia. Full blood count must be checked so that these conditions can be ruled out[7]. Clozapine also increases the risk of pneumonia, although its relationship is said to be complex. Ironically, among possible indirect mechanisms that predispose clozapine-treated patients to infection is the ADR of hypersalivation itself [25].

Gastrointestinal reactions are prevalent with clozapine which explain the rationale behind our findings. It can affect the whole gastrointestinal system and has varying degrees of impairment. The incidence of constipation was reported between 22% and 33%, and up to 60% of patients with clozapine[10]. This problem causes patients to be highly dependent on laxatives[26], as seen in our patients. In worst circumstances, there has been reports of deaths due to severe gastrointestinal hypomotility[10,13]. Preventative actions need to be taken at the first sign of constipation. Patients should be encouraged to maintain consistent intake of sugar-free fluid and practise regular exercise[7]. It is suggested that prescribers should use the lowest effective dose of clozapine and avoid concomitant drugs that have effect on bowel motility[26], such as drugs with significant anticholinergic effects like oxybutin and amitriptyline [7].

Our least reported ADRs were hyperglycaemia, cardiovascular effect and seizure. Hyperglycaemia is considered as a rare metabolic ADR[10] but the incidence is closely related to weight gain as well as clozapine-induced insulin resistance[2,27]. Paradoxically, cardiovascular events such as tachycardia are not uncommon in patients prescribed with clozapine. A fast pulse rate often leads to palpitations which can be treated with beta-blockers and calcium-channel blockers[28]. The risk of developing myocarditis or cardiomyopathy as severe cardiac problems, however, is very low (0.015% to 0.188%)[2,10,13].

Although seizure and rigidity are considered as common ADRs[10,13], our results corresponded to the work by Maher *et al*. (2016), whereby only a small number of cases were recorded. Clozapine has been associated with seizures with a cumulative one-year risk of approximately 3 to 5%. These seizures include a wide variety of epileptic activity and not just generalised tonic-clonic seizures. Patients who have seizures while taking clozapine must be referred to emergency department immediately. Clozapine concentrations, testing for illicit drugs, brain imaging and neurology review may be required. An accurate diagnosis of seizures is essential before the decision to stop clozapine is made. Prescribers may consider adding antiepileptic drug such as sodium valproate or lamotrigine to the patient's regime. Nevertheless, it is important to consult the psychiatrist before commencing any changes to a patient's standard care[7,11]. On the other hand, rigidity or muscular stiffness should not be taken lightly at any time. It may indicate a bigger concern if accompanied by other symptoms like hyperthermia and instability of cardiorespiratory parameters, which are the symptoms of neuroleptic malignant syndrome. It is an uncommon and lethal neurological disorder, attributed to the administration of antipsychotics, for example clozapine[29].

Other observed ADRs were epigastric pain (gastrointestinal upset), restlessness (agitation) and skin reactions[22]. Gastrointestinal problem is a common and dose-related ADR of clozapine. They can be treated with proton pump inhibitors and in our setting, antacid and histamine-2 blocker were used. Although there were reports of omeprazole affecting clozapine concentrations, all proton pump inhibitors are generally considered to be safe to use in patients taking clozapine[7]. Agitation is often exhibited as ADR in patients treated with antipsychotic. However, only a few cases were associated with clozapine[22,30]. Interestingly, we observed a high number of ACDRs in our study population. For these ADRs, antifungal and steroid cream were prescribed. This was worth noting as skin reaction is always regarded as an uncommon ADR in patients with clozapine. Minor ACDRs had occurred in 2% to 5% of patients, with only a few reports on severe skin reactions[10,31].

None of our study population experienced any serious ADR during the course of their treatment. Most cases were adequately managed by symptomatic treatments. This may be due to the

fact that physical health assessment and blood monitoring are mandatory requirements in our setting. Our study revealed that the management were only for upper respiratory tract infection, constipation, skin reaction and epigastric pain. A structured approach to clozapine monitoring is vital to prevent the risk of rare but deadly ADRs such as agranulocytosis[7,13]. Even though it was postulated that its incidence decreases over time of clozapine treatment, cases of late-onset of agranulocytosis have been witnessed[32].

Routine assessment is a must at baseline and should be made compulsory to be repeated at constant intervals. Full blood count, urea and electrolytes as well as liver function test are required at the start of clozapine treatment and once per year. It is recommended that physical health monitoring which includes cardiovascular risk assessment to be done on patients diagnosed with schizophrenia annually. Weight, body mass index and waist circumference should be checked at baseline, 1 month, 3-monthly and then yearly. Blood pressure monitoring is advised before starting therapy and frequently during dose titration of clozapine. Also, patients with medical history of cardiovascular disease should be subjected to regular electrocardiogram. Other than that, fasting blood glucose needs to be measured at baseline, 1 month and then 4 to 6-monthly. As for lipid profile, it is advised that it is checked at baseline, 3-monthly in the first year and then annually. Electroencephalogram is not essential but may be indicated for patients with pre-existing compromised brain function or seizures. In addition to the investigations and specific assessments for clozapine, there is an urge for usual monitoring relevant for any other medications concurrently prescribed for the patient. Monitoring for ADRs must be done regularly during each follow up[7,9,13].

Our study had several limitations. Due to the nature of retrospective design, we may miss out some of the important clinical characteristics and were unable to pinpoint all management for ADRs. We were unable to determine causal relationship and factors associated with ADRs in clozapine-treated patients. Furthermore, some assumptions were made when the description of ADRs were written vaguely. These issues can be resolved by utilising research with prospective study design. Another way is by opting for qualitative approach to provide in-depth details on the subject matter. The small sample size also limited us from generalising the findings to the entire population. Therefore, caution should be exercised when interpreting the results. A multicentre study involving more facilities from other regions in Malaysia which incorporates probability sampling method is recommended to avoid potential bias. Notwithstanding these limitations, the results are still worthy of further research.

Conclusion

Our study adds to the existing information on the pattern of ADRs following clozapine treatment at a local facility. Fortunately, all ADRs reported were tolerable and manageable. It is important to bear in mind that appropriate management of ADRs can facilitate maximum outcome of clozapine treatment. Physicians and patients alike should be aware that the benefit of clozapine use is wider than its risk. Nevertheless, a careful increase in clozapine dosage and regular laboratory monitoring are strict requirements.

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Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

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