Graylands Hospital Drug Bulletin

Clozapine Initiation Chart - *A new medication chart for clozapine commencement*

North Metropolitan Health Service - Mental Health June 2014 Vol 21 No.2 ISSN 1323-1251

Introduction

In 2012, a new medication chart was trialled for all in-patients initiated on clozapine at Graylands hospital (Clozapine Initiation Chart, CIC). The chart was developed by pharmacists at Graylands and Fremantle hospitals under the support of the office of safety and quality, based on current clozapine manufacturer, TGA and hospital guidelines to manage the pre-treatment screening, monitoring, prescribing and administration of clozapine titration. The chart also contains support material to assist in the safe prescribing and administration of clozapine and decision support for managing side effects. The chart can be found at: http://www.safetyandquality.health.wa.gov.au/medication/standardised_charts.cfm

A retrospective review on the adherence to treatment guidelines when initiating clozapine was conducted on patient records before and after introducing the chart. The data was collected using a standardised data collection tool designed by the Office of the Chief Psychiatrist. Results of the review showed the introduction of the chart had a large improvement in compliance with the requirements for pre-treatment screening, monitoring of vital signs and the administration of clozapine. The purpose of this bulletin is to provide an in-depth explanation behind all the requirements described in the CIC for pre-commencement, screening, monitoring, prescribing and administration of clozapine.

Who should get clozapine?

Clozapine is indicated for Treatment Resistant Schizophrenia (TRS), i.e. those with schizophrenia who are non-responsive to, or intolerant of, other antipsychotic drugs[1]. Non-responsiveness is defined as lack of satisfactory clinical improvement despite sequential treatment with two different antipsychotics at adequate dose, duration and adherence. Intolerance is defined as the impossibility to achieve adequate benefit with other antipsychotic drugs because of severe and untreatable neurological adverse effects. As an appropriate trial with an antipsychotic is considered to be 4-6 weeks, clozapine could be initiated after a minimum of eight weeks of poor response (or poor tolerability) for some patients. However, this is rarely the case and long delays in initiating clozapine have been reported. For example, a recent UK study found that the average delay in initiating clozapine was four years[2], while literature from New Zealand reports a delay of over nine years from first contact with services[3]. Reasons proposed explaining such a delay include concern over adverse effects, mandatory blood testing, unfamiliarity and lack of active marketing[4].

Registration

Because of the risk of agranulocytosis, clozapine has had certain restrictions placed on its use. Individuals cannot commence treatment with clozapine until the following steps have been completed.

1. Clozapine registration form is required for new patients, completed by the psychiatrist. The patient cannot start clozapine therapy until the clozapine centre (at this time ClopineConnect™) has approved their registration & supplied the patient with a Clozapine Patient Number.

2. PBS eligibility - clozapine is PBS for schizophrenia, there are also other criteria that must be met. http://www.pbs.gov.au

3. Continuation of supply - this is extremely important as not all personnel, clinics and pharmacies are registered to prescribe or dispense clozapine. Doctor, pharmacist, centre & patient must all be registered with the clozapine centre.

4. Patients, carers and/or family need to view the Patient Notification Form and be provided with Consumer Medicine Information Leaflets and information regarding their treatment including the weekly blood tests for the first 18 weeks of treatment, followed by 4 weekly blood tests, and other ongoing monitoring.

5. Patient consent is required. Where this is not applicable a second opinion by a psychiatrist needs to be obtained.

6. Pre-clozapine baseline tests must be performed within 10 days of commencement of clozapine treatment.

7. Patient consent form for inclusion on clozapine database needs to be completed.

Clozapine titration schedule

Many of the adverse effects of clozapine are predictable, dose-dependant and often related to the speed of titration. Adverse effects also tend to be more common and severe at the beginning of therapy. Standard maintenance doses may even prove fatal in clozapine-naïve subjects[5]. To minimise these problems, it is important to start treatment at a low dose and to increase dosage slowly. An example of a 14-day clozapine titration schedule is included on the third page of the CIC. This schedule serves as a guide only and dose titration should be individualised. The dose of clozapine to be prescribed each day for any patient should be recorded on the 28-day blank prescription chart found on the second page of the CIC.

Clozapine should normally be started at a dose of 12.5 mg once a day. On days 2 and 3 the dose can be increased to 25 mg daily. If the patient is tolerating clozapine, the dose can be increased by 25-50 mg a day, until a dose of 300 mg a day is reached. This can usually be achieved in 2-3 weeks. Further dosage increases should be made slowly in increments of 50-100 mg each week. Slower titration may be necessary where sedation is severe. If the patient is not tolerating a particular dose, decrease to one that was previously tolerated. If the adverse effect resolves, increase the dose again but at a slower rate.

Table 1: Recommended physical monitoring during dose titration whilst in hospital.

Day	monitoring
1	Temperature, respiration rate, pulse & blood pressure should be monitored hourly for 6 hours, then every six hours for the first 24 hours
2-7	Temperature, respiration rate, pulse and blood pressure should be monitored twice daily
8-126	Temperature, respiration rate, pulse and blood pressure should be monitored daily

Clozapine levels

Clozapine levels are best performed after the initial titration stage, once the dose has been stable for at least a week[6]. For meaningful results, the sample should be taken as a trough level immediately before the next dose or in the morning after an evening dose. Although clozapine plasma levels are broadly related to daily dose[7], there are significant differences between individuals (a coefficient of variation of 53% has been suggested[8]), which appears largely due to differences in absorption and metabolism[7].

Interpreting clozapine plasma levels

A plasma level of 350mcg/L should be aimed for to ensure an adequate trial, but response may occur at lower plasma levels[6,9]. The average (there is substantial variation) 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].

Norclozapine (N-desmethylclozapine) one of the major metabolites of clozapine, is often reported alongside clozapine plasma levels. Although there are limited data, it is considered to be at least partially active and potentially responsible for some of clozapine's unique efficacy[11]. On average, the clozapine to norclozapine ratio is suggested as 1.32 across all dose ranges. Thus, at a clozapine level of 350mcg/L, the average norclozapine level would be 265mcg/L[12].

Clozapine metabolism (via cytochrome P4501A2) may, however, become saturated as the clozapine to norclozapine ratio appears to increase at higher plasma levels[7]. A similar reduction in the clozapine to norclozapine ratio has been shown when fluvoxamine (a potent cytochrome P4501A2 inhibitor) is added to clozapine, which also supports a potential saturation of the metabolising enzyme[13].

Recommencing therapy after interruption

Along with the rapid decline in plasma levels upon clozapine discontinuation, tolerability to adverse effects rapidly falls away. Patients who have missed clozapine for 48 hours or more should be gradually re-titrated from 12.5mg once or twice daily on the first dose. The speed of the titration depends on the original acceptance and tolerability of clozapine and can often be more rapid than the original titration. Hypotension, tachycardia and seizures are particular risks when re-starting clozapine but so is relapse, so re-titration should be as rapid as possible. Depending on how long clozapine is missed, the frequency of FBC monitoring may need adjusting.

Monitoring check list

Monitoring of physical health is essential for those receiving clozapine. The table on page 3 of the CIC provides a baseline and on-going monitoring checklist for patients commencing clozapine. This also includes a section to record the smoking status of the patient.

Metabolic monitoring

Clozapine is well known to cause a variety of metabolic adverse effects including weight gain, impaired fasting glucose, diabetes and dyslipidaemia. Therefore monitoring weight, blood glucose and lipids is recommended.

Weight gain

Clozapine is considered to have the greatest potential to induce weight gain in patients treated with antipsychotic medications[14]. However, the average weight gained and incidence of weight gain with clozapine vary greatly between studies. One review suggests the average initial weight gain with clozapine is 1.7kg per month[15], whereas earlier meta-analyses reported the mean weight increase as 4.45kg over 10 weeks[16]. Long-term naturalistic studies report lower rates of weight gain with clozapine and suggest the mean change is from around 3kg over three years[17] to 11.6kg over five years[18]. Body mass index (BMI) and waist circumference are useful measures to assess the risks from being overweight. These measurements should be recorded on the CIC at baseline and then again at monthly intervals.

Diabetes mellitus

In case reports clozapine has been associated with transient hyperglycaemia, diabetic ketoacidosis (including fatalities)[19], new onset diabetes mellitus and exacerbation of pre-existing diabetes[20]. Diabetes with clozapine can occur at any time, although over half of all cases are reported in the first three months of therapy[21]. In naturalistic studies of clozapine patients, the cumulative incidence of new onset diabetes with clozapine was reported to be 37% at five years[17] and 43% at 10 years[18]. Fasting plasma glucose should be monitored and recorded on the CIC at baseline, and then again at 6 monthly intervals.

Dyslipidaemia

Clozapine has also been shown to increase total cholesterol and triglyceride levels[22], with triglyceride levels doubling following long-term therapy[22]. Total cholesterol, LDL, HDL and triglycerides (all fasting) should be monitored at baseline on the CIC, and then again at 6 monthly intervals.

Liver function tests (LFTs)

Clozapine commonly increases LFTs, usually in the first six weeks of treatment[23]. This increase is largely transient and asymptomatic[23]. There are however, rare reports of toxic hepatitis and liver failure associated with clozapine[24,25] so any liver enzyme elevated beyond three times the normal level should prompt a dose reduction or discontinuation of clozapine. LFTs should therefore be routinely monitored before starting clozapine and repeated 6-monthly or earlier if clinically indicated.

Neutropenia and agranulocytosis

Clozapine can cause a number of blood dyscrasias. Neutropenia and agranulocytosis are the best recognised and are the reason for mandatory monitoring. Neutropenia is defined as a neutrophil count of 0.5-1.5 x 10^9 /L, agranulocytosis as a neutrophil count of less than 0.5 x 10^9/L.

The overall incidence of neutropenia is around 2.7%[26] and agranulocytosis is between 0.7 and 0.8%[27].The peak incidence for both occurs between 6-18 weeks of clozapine treatment and the risk considerably declines after the first year. The second year incidence rate is quoted in one study as 0.7% for neutropenia and 0.07% for agranulocytosis[26]; an incidence similar to that seen with the phenothiazines. Both neutropenia and agranulocytosis are generally reversible on discontinuation of clozapine.

The manufacturer of clozapine has developed a robust monitoring service which records white blood cell counts before clozapine can be supplied. A colour-coded system for results is used to highlight those patients who should stop clozapine because of neutropenia, or who require extra monitoring.

Table 2: Blood results cloured-coded system

Colour	WBC 10x9/L	Neutrophil 10x9/L	Action
Green	>3.5	>2.0	Continue standard blood tests
Amber	3.0-3.5	1.5-2.0	Twice-weekly full blood counts until in green range
Red	<3.0	<1.5	Stop clozapine and repeat FBC daily until in green range.

Eosinophilia

Eosinophilia (>0.7x10^9/L) is commonly seen with clozapine, with an incidence of around 13%[28]. Eosinophilia generally occurs in the first four weeks of treatment and usually resolves spontaneously without intervention and may occur more frequently in women[29]. In the majority of cases eosinophilia is benign, but there are occasional reports linking this blood dyscrasia with eosinophilic cardiomyopathy[30]. As a result of this possible association, manufacturers of clozapine recommend that clozapine should be discontinued if eosinophilia count rises above 3.0x10^9/L and should not be restarted until the count is below 1x10^9/L[31].

Myocarditis and cardiomyopathy

Myocarditis and cardiomyopathy are serious and potentially fatal adverse effects that have been connected to clozapine therapy[32]. Estimates of the incidence of clozapine-related myocarditis have ranged from 1 in 500 patients[33] to 1 in 10 000[34].

Kilian *et al*[33] identified 15 cases of myocarditis (5 deaths) and 8 cases of cardiomyopathy (1 death) from 8000 clozapine patients in Australia. All 15 cases of myocarditis presented within 3 weeks of starting treatment (mean: 15 days, range: 3 – 21 days), whereas onset of cardiomyopathy was generally longer (mean: 12 months, range: 2 – 36 months).

Troponin I - The troponin test measures the levels of the protein, troponin I, in a blood sample. This protein is released when the heart muscle has been damaged. The more damage there is to the heart, the greater the amount of troponin I there will be in the blood. **CRP-** 'C- reactive protein'- is produced by the liver. The level of CRP rises when there is inflammation throughout the body. CRP is generally a non-specific marker of inflammation; however, studies indicate that elevated CRP is an early diagnostic indicator of the presence of myocarditis where other cardiac biomarkers are elevated.

Monitoring for clozapine-induced Myocarditis

Intensive monitoring of biochemical, functional and patient parameters is essential during the first month of clozapine treatment if myocarditis is to be detected and death to be avoided. Baseline assessment is critical as this serves as the reference point to future measurements. Monitoring of vital signs, asking about key symptoms (chest pain, fever, cough, shortness of breath) and testing levels of troponin 1 and CRP are essential for the safe use of clozapine.

Troponin 1 and CRP assay should be recorded at baseline and then repeated on days 7, 14, 21 and 28. The ECG and medical assessment should be done at baseline and then repeated at day 7 and 14 and then as clinically indicated.

- If clinical features of myocarditis/infective illness (e.g. fever, tachycardia, SOB) develop the troponin 1, CRP and ECG should be repeated daily. An echocardiogram and assessment by a physician or cardiologist should be requested.
- If CRP>100mg/L or troponin 1 > 2x ULN stop clozapine and repeat echocardiography

Cardiomyopathy

By 2013 there were 58 cases of suspected clozapine-induced cardiomyopathy reported in the literature. In Australia the actual incidence of cardiomyopathy in people taking clozapine is 0.1%[33]. Cardiomyopathy occurs late in treatment and is much less common than myocarditis. Cardiomyopathy usually presents with dyspnoea and reduced exercise capacity occurring up to seven years after starting clozapine[35].

Fever

Clozapine-induced fever is common in the first three weeks of starting clozapine and continues for between one and five days[36]. In the majority of cases, the fever spontaneously resolves, either upon a temporary suspension of clozapine or by cautiously continuing treatment. In all cases of clozapine-induced fever, it would be prudent to rule out a more sinister cause such as an underlying infection, neuroleptic malignant syndrome (NMS), agranulocytosis or myocarditis.

Smoking and clozapine

Cigarette smoking significantly induces the metabolism of clozapine, resulting in lower plasma concentrations. Smoking as few as 7-12 cigarettes per day may be sufficient for maximum induction of clozapine metabolism[37]. Consequently, giving up smoking can cause an increase in clozapine levels between 50 and 72%, which can lead to severe adverse effects such as seizures[38]. The interaction usually occurs gradually between two and four weeks and can be especially difficult to predict in those sporadically stopping and starting smoking. Clinicians should monitor clozapine levels before stopping smoking, reduce the dose gradually by approx. 25% and recheck levels four weeks after stopping smoking[39].

Conclusion

Clozapine remains the most effective antipsychotic drug for treatment-resistant schizophrenia. However, due to the complexity associated with its use, and problematic adverse effects, long-term monitoring is essential. Consequently, establishing and maintaining patients on clozapine is not straightforward and requires a high level of commitment and persistence on the part of all concerned.

In this edition of the bulletin, we have shown that the CIC can provide a suitable mechanism for ensuring the safe initiation and long-term monitoring for patients who require this important medication.

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