CLINICAL REFLECTION

Clozapine rapid retitration in the community: an assertive approach can prevent admissions

Nikola Nikolić, Kevin Kilbride & Patrick Preston

Nikola Nikolić is an advanced specialist mental health pharmacist with HSE Dublin North East and a credentialled member of the College of Mental Health Pharmacy in the UK. He is associated with the Programme for the Homeless, Dublin, Ireland. He has a wide range of experience in psychiatric therapeutics, in particular adult general psychiatry **Kevin Kilbride** is a consultant psychiatrist at the Programme for the Homeless, Dublin, Ireland with decades of experience in general adult psychiatry. He specialises in assertive outreach in the community, working with the homeless people with severe and enduring illness, including dual diagnoses **Patrick Preston** is a senior mental health nurse at Dublin North City HSE Mental Health Services, Ireland, with experience in a wide range of mental health specialties, from intensive care to assertive outreach in the community. **Correspondence** Nikola Nikolić, HSE Dublin North East, c/o St Mary's Hospital, Acres Road, Dublin 20, Ireland. Email: nik.nikolic@sussexpartnership.nhs.uk

SUMMARY

Rapid retitration of clozapine may be necessary to reduce the known high risk of mental state destabilisation in patients who have had a 48 h treatment break. It may carry a high risk of complications, including seizures and myocarditis. We reflect on the literature on standard and rapid retitration and present a case of rapid retitration in the community. In this case, of a 54-year-old homeless man with treatment-resistant schizophrenia and polysubstance misuse, we safely retitrated clozapine in a community setting four times during a 6-month period; each retitration was completed over 4 days. We used a specific protocol based on his psychiatric history. We are now more confident in delivering clozapine retitration to other patients, thus preventing unnecessary admissions.

DECLARATION OF INTEREST

N. N. has received honoraria from Janssen Pharmaceuticals.

Background

Clozapine (CLZ) is considered to be the gold standard in the treatment of refractory schizophrenia. There is a known high risk of mental state destabilisation in patients who have had a 48 h treatment break. The literature on clozapine titrations, including various local guidelines, focuses on initial titration and retitration over a non-standardised duration (SrT), and there is a paucity of evidence examining rapid retitration (RrT) (Nielsen 2011; Ronaldson 2012; Ifteni 2014a, b; Medicines.ie 2016; Poyraz 2016; Taylor 2016) (in this article we use RrT to denote a retitration period shorter than 7 days). The available evidence on RrT is from in-patient rather than community settings (Ronaldson 2012; Ifteni 2014b; Poyraz 2016).

Could this lack of evidence be due to the estimated 3% incidence of myocarditis in the Australian population (Ronaldson 2015), which dissuades clinicians worldwide from conducting trials on CLZ RrT because of the perceived high risk?. It has been argued that the risk in the non-Australian population may in fact be as low as 0.07–0.6 per 1000 (Cohen 2012). In a Finnish 5-year follow-up of patients with first-onset schizophrenia, the adjusted odds ratio (OR) for cardiovascular death associated with CLZ was found to be 0.23 (95% CI 0.05–1.02) (Kiviniemi 2013); and in a Swedish schizophrenia cohort study, CLZ showed an adjusted OR for all deaths of 0.92 (95% CI 0.70–1.22) (Leon 2015). In the USA between 1989 and 1999, there were 17 confirmed cases of myocarditis among a total of 189 405 persons treated with CLZ (Grenade 2001). Another retrospective cohort study observed a risk of cardiac mortality, mainly due to myocarditis and cardiomyopathy, in schizophrenia of 1.1% and 2.7% at 5- and 10-year follow-up in people aged under 55, with a further significantly higher risk in the those aged 55 and over (Kelly 2010).

Ronaldson *et al* (2012) demonstrated that initial titrations in which cumulative doses above 920 mg were given in the first 9 days of treatment were associated with more than twice the risk of myocarditis in comparison with cumulative doses of less than 500 mg. Each additional 250 mg resulted in an added risk of 26% (OR 1.26; 95% CI 1.02–1.55; $P = 0.03$). Concomitant use of valproate, older age and change in the patient's smoking status were significantly correlated with risk. Ronaldson *et al* (2011) quantified the threshold limits of troponin T (TropT) (at least twice the upper limit of normal) or C-reactive protein (CRP) (>100 mg/L) beyond which CLZ discontinuation should be considered in order to prevent cardiac damage. Compliance with their suggested monitoring protocol may be formidably challenging in community mental health settings.

Ifteni *et al* (2014a) evaluated an RrT method ($n = 111$, average CLZ dose during first 24 h: 25–400 mg) for hospital in-patients, in which no patients experienced seizures, syncope due to hypotension, agranulocytosis or any other major complication. A retrospective study (Poyraz 2016), also conducted in an in-patient setting, comparing RrT with SrT regimes, found an association of the former with shorter hospital stays, albeit with higher rates of hypotension.

Here we reflect (with the patient's consent) on our clinical experience of RrT and its proactive delivery

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in a community outreach service for the homeless, where patients are seen according to severity and endurance of illness, up to several times a day. Our service places emphasis on patients with low levels of engagement and a high risk of causing harm to self and others owing to mental destabilisation, through planned community visits.

Case presentation

This 54-year-old homeless man has a 30-year history of paranoid schizophrenia complicated by polysubstance misuse. He has an unremarkable medical history despite his 'dual diagnoses'. He has a history of self-harm, drug overdoses and impulsive dangerous behaviour. Over the course of his illness he has incurred over 30 mental health admissions. Since commencing CLZ in 2013, a significant clinical improvement, enhanced well-being and risk management have been noted.

He is currently prescribed 450 mg of CLZ daily. Owing to a chaotic lifestyle, often too disorganised to allow him to adhere to treatment, 48 h treatment breaks with clinical deterioration have been frequently noted. To manage these, a 4-day RrT protocol was designed based on the history of his clinical presentation. For treatment breaks longer than 48 h but less than 96 h, CLZ was to be retitrated in single daily doses as follows: day 1, 100 mg; day 2, 200 mg; day 3, 300 mg; day 4, 450 mg. Minimum monitoring requirements for this protocol were blood pressure (BP), heart rate (HR) and temperature, measured before each dose of CLZ. In addition, the risk of myocarditis would be assessed using TropT and CRP tests (as available), with results accessible within hours of requesting, thus allowing prompt changes to the treatment.

CLZ was retitrated on 24 June (RrT_1), 31 July (RrT_2), 26 August (RrT_3) and 1 November 2017 (RrT_4) after 48 h treatment breaks, each time following the above protocol. The patient's temperature never exceeded 37.1°C. The highest recorded BP was 140/77 mmHg on day 3 of RrT_1 and the lowest was 100/65 mmHg on day 3 of RrT_3 (mean BP = 120/72 mmHg, $n = 12$). The highest recorded HR was 99 bpm on day 3 of RrT_3 (mean HR = 90, $n = 12$). Postural hypotension was suspected in RrT_1 and RrT_2, and the patient experienced transient syncope on day 1 of RrT_1 only. Seven days after initiation of RrT_3 and RrT_4, TropT and CRP levels were obtained. Although the TropT result was negative (<14 ng/L), CRP levels were elevated (90.72 mg/L after RrT_3 and 19.69 mg/L after RrT_4 where a normal range would be 0–10mg/L). In RrT_3 only, the CRP test was repeated 7 days later (14 days after initiation) and then again 19 days after; these two tests showed a marked reduction (63.34 mg/L and 9.62 mg/L respectively). No changes were made to the patient's treatment, as he was otherwise asymptomatic. Clinical observation indicated that he was under the influence of multiple illicit substances on all four occasions. Overall, there was no destabilisation in his mental state. He did not have any hospital admissions in this period.

Conclusions

We safely and rapidly retitrated CLZ for a high-risk and 'chaotic' patient in a community setting four times in 6 months, each time over 4 days. To ensure safety and prevent major complications, we put in place basic monitoring. This case shows that RrT can be delivered even to a patient with severe and complex difficulties. We are now more confident in offering rapid CLZ retitration to other patients. RrT of CLZ in the community can prevent admissions to hospital.

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