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Elevated clozapine levels associated with infection: A systematic review

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ABSTRACT

Clozapine is the most effective anti-psychotic medication for treatment refractory schizophrenia. A growing number of case reports have linked infection to high clozapine levels and associated adverse outcomes. We present a systematic review of published cases to clarify the relationship between infection and elevated clozapine levels. The case reports were located through PubMed and Embase. In addition, 8 new cases from two Australian states were included. Demographics, psychiatric diagnoses and medical morbidities, medications, clinical symptoms, clozapine levels, inflammatory markers and final clinical outcome were extracted. 40 cases were identified in 23 publications that demonstrated elevated clozapine levels associated with infection. Infections were commonly respiratory in origin. Adverse events, typically sedation, were associated with raised clozapine levels during infection. In many cases the signs of infection such as fever and white blood cell count were reduced. Severe adverse effects were uncommon, with one case each of seizure, myocarditis and neutropenia. The relationship between infection, clozapine levels and adverse events is complex and multi-factorial. Monitoring of clozapine levels is essential during hospitalisation for infection and consideration should be given to gradual dose reduction to minimise dose related side effects.

1. Introduction

Clozapine is the most effective anti-psychotic medication for treatment refractory schizophrenia (Siskind et al., 2016). The use of clozapine is however limited to third line due to an increased incidence of agranulocytosis and neutropenia (Nielsen et al., 2013). Clozapine also has a range of other serious side effects including myocarditis, seizures, gastrointestinal hypomotility and diabetic ketoacidosis (Cohen et al., 2012; Williams and Park, 2015; Young et al., 1998). Only some of these side effects are thought to be related to the clozapine serum level, including sedation, delirium, seizures, arrhythmias, hypotension, aspiration, and respiratory depression (Stark and Scott, 2012). The concept of 'clozapine toxicity' is widely used despite difficulty in clearly defining the clinical presentation of toxicity and the clozapine level at which this occurs (Stark and Scott, 2012; VanderZwaag et al., 1996). The risk of seizures increases from 600 mcg/L, with 1000 mcg/L often quoted as the threshold beyond which risk of seizures, sedation and delirium outweighs treatment benefit (Bell et al., 1998; Stark and Scott, 2012; Williams and Park, 2015). In saying this, there is a significant inter-personal variability in clozapine levels, response and adverse events. This variability may be explained by pharmacogenomic variation as well as alteration to its metabolism through effect on Cytochrome P450 (CYP450) enzymes by drug interactions, smoking cessation, excessive caffeine and the more recently identified risk of infection and inflammation (Stark and Scott, 2012; Williams and Park, 2015).

A growing number of case reports have linked infection and its treatment to elevated clozapine levels (Leung et al., 2014; Nielsen et al., 2016). Patients with chronic psychosis are known to be more at risk of infection though factors such as elevated smoking rates, metabolic disorders, dental caries and poorer relationships to community health providers (Kisely et al., 2015). Clozapine treatment has been shown to be associated with increased rates of single incidence and recurrent pneumonia (Abdelmawla and Ahmed, 2009; Hung et al., 2016; Kuo et al., 2013). Systemic infection and inflammation may also inhibit CYP450 enzymes, potentially leading to risk of raised clozapine levels in people hospitalised for severe infections (Leung et al., 2014).

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There are no relevant cross-sectional, cases - control or cohort studies in the literature dealing with this potentially high risk phenomenon, with only single case reports or small series currently published. We thus aimed to consolidate and expand upon currently published literature by performing a systematic review including eight new cases of elevated clozapine level associated with infection identified in patients treated in Australian public psychiatry services in two states.

2. Methods

This study was registered with PROSPERO, (registration number: CRD42016037536), an international database of prospectively registered systematic reviews (Booth et al., 2012). Articles were located through a search of PubMed (1964 to April 2016) and Embase (1974 to April 2016), with search terms: *clozapine, toxicity, infection*. All languages were included and translated into English. Identified records and abstracts were screened independently by authors (NW, SC, GK). References were checked to identify other eligible studies. Due to the difficulty in clearly defining the serum level of clozapine at which toxicity occurs we determined inclusion criteria as either having clozapine levels >1000 mcg/L, or >600 mcg/L with clinical symptoms of clozapine level elevation. Cases with a diagnosis of infection as reported by the author were included. Cases of inflammation without a diagnosis of infection and those with an identifiable non-infectious cause for elevated clozapine levels, such as liver failure and fluvoxamine use, were excluded. Data was abstracted independently by authors (NW, SC, GK) including: case demographics, psychiatric diagnoses, medical comorbidities, medications (including treating antibiotics), clinical signs and symptoms of infection, clozapine levels (baseline, peak and ratio clozapine and norclozapine), inflammatory markers (WBC and CRP), evidence for smoking cessation and final clinical outcome. Clozapine levels were reported as ng/mL, mcg/L, and nmol/L across studies, and were converted to mcg/L to aid comparison. One report included two separate incidences of raised clozapine level with separate infections in the same patient. These were included as separate cases (Takahashi et al., 2015).

Descriptive statistics were calculated for age, gender, diagnosis, clozapine dose at the time of infection, clozapine levels prior and during infection, clozapine to norclozapine ratio (CLZ:NCLZ) at the time of infection, time on clozapine, white blood cell count (WBC), C – Reactive Protein (CRP), presence/absence of fever and type of adverse effects.

3. Results

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed (Fig. 1) (Moher et al., 2009). There were 412 non-duplicate studies identified in the databases, with a further seven identified through hand searching of references. Following screening of the title and the abstracts, a further 39 studies were excluded at full text as they did not contain adequate information to indicate a diagnosis of infection or the elevated clozapine levels were clearly related to an external factor (e.g. liver failure, clozapine overdose), leaving 23 studies describing 32 cases. An additional eight new cases of elevated clozapine levels associated with infection were included from clinical services associated with the authors (SC, DJ, NW).

A total of 40 cases were included (Table 1), of which 31 described people with treatment resistant schizophrenia, five described people with schizoaffective disorder, and four cases were without a documented diagnosis. Average age at presentation was 48.9 years (standard deviation 12.3, range 23 to 68 years) and 58% were male. Medical comorbidities were common, including type 2 diabetes (12.5%), chronic obstructive airways disease (10%) and gastro-oesophageal reflux disease (10%). Clozapine dose ranged from 200 mg–900 mg/day and the baseline clozapine level was a median of 550 mcg/L. The mean time on clozapine was four years. In five cases the clozapine dose had been increased within the last month and one case was in the titration phase. The reporting of variables such as baseline clozapine and norclozapine level, smoking status, renal and liver function was inconsistent.

The majority of infections were identified as respiratory (57.5%), with the remainder as urinary (32.5%), gastrointestinal (7.5%) and orthopaedic (5%). In three cases there was both a respiratory and urinary source and in two cases no source was identified. The presence or absence of fever was documented in 95% of cases. Fever was absent in 12 cases (30%). WBC count was reported in 25 (62.5%) cases. There was an absence of elevated WBC with infection seen in 10 cases (25%), the average WBC was 13.2×10^9/L. CRP was reported in 22 (55%) cases. The average elevation of CRP was 130 mg/L. Again, the reporting of these variables was inconsistent, limiting the ability to generalise results. Six patients were treated with antibiotics likely to increase clozapine levels (ciprofloxacin and erythromycin).

Mean clozapine levels during infection were 1811 mcg/L (range 744 mcg/L–4740 mcg/L) with mean CLZ:NCLZ ratio of 3:1. Baseline clozapine levels were reported in 25 (62.5%) cases. Sedation was recorded in 48% of cases, 20% recorded delirium and speech and gait were disturbed in 15% and 12.5% of cases. In the 11 cases with levels >2000 mcg/L, dizziness, gait disturbance, sedation, weakness, tremor and dysarthria were the predominant symptoms. Interestingly, in five cases it was documented that there were no signs of neurological disturbances, despite having clozapine levels >1000 mcg/L. Seven cases developed myoclonus, four documented as negative myoclonus. A seizure occurred at a clozapine level of 1300 mcg/L in one case. There was pre-infection use of anti-epileptic medication in 10 cases. In four cases intensive care treatment was required; the clozapine level in these cases was widely spread (1400 mcg/L, 1542 mcg/L, 2663 mcg/L and 4318 mcg/L). There was one case in which myocarditis developed and one case of neutropenia. No deaths were recorded.

In all cases clozapine dose reduction or cessation resulted in the resolution of symptoms in days to weeks. Nearly half of cases (43%) were then treated longer term on a reduced dose of clozapine, and clozapine was ceased completely in two cases. The impact of the infection, neurological disturbances and medication changes to the mental state of the patients was frequently not documented, and few cases reported addition of other anti-psychotics.

4. Discussion

We identified 40 cases where elevated clozapine levels have been associated with infection. When documented prior to infection, baseline clozapine level was under 600 mcg/L, with no reported symptoms of dose dependent clozapine side effects. With the onset of infection a significantly elevated clozapine level was recorded as well a clinical deterioration. The most commonly documented adverse events were prominent sedation or delirium; however other gross neurological signs such as speech and gait impairment were noted in over 20% of cases. Altered conscious state is a common complication of severe infection, though neurological disturbance is less likely to be primarily related to the infection and is consistent with an independent effect due to raised clozapine levels. Serious events such as seizures, neutropenia and death were uncommon. An elevation of clozapine levels occurred with a wide range of bacterial and viral infections, though most frequently in association with respiratory and urinary sources, perhaps reflecting the incidence of these in the community. Fever and raised WBC were absent in 25 to 30% of cases, suggesting that the clinical presentation of infections may be somewhat masked by the elevated clozapine levels. Awareness, communication and motivation to act on symptoms of infection are likely to be impaired in patients with sedation associated with high clozapine levels. Sedation may in turn decrease the frequency of smoking, further increasing clozapine levels. Together these factors may increase the risk of late presentation with more severe illness.

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