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Case report

Clozapine re-trial in a patient with repeated life threatening pneumonias

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Summary. *Background and aim of the work:* There has been an increasing amount of evidence to suggest a link between Clozapine and pneumonia. Whilst an exact mechanism for disease causation has not been identified excess salivation, impaired swallowing and abnormalities within the immune system have all been implicated. Within forensic services there is often a need to treat complex patients with Clozapine, even when a past history of pneumonia is present. *Methods:* We present a case report on a forensic inpatient who has suffered repeated episodes of Clozapine associated pneumonia and highlight methods for good practice. *Results:* Where appropriate, Clozapine can still be used in complex patients who have suffered previous pneumonias and have additional risk factors for chest infections, provided that robust risk reduction, infection surveillance and treatment interventions are employed. *Conclusions:* Practical measures can be employed to enable safe treatment of forensic patients with Clozapine, this includes risk factors for chest infections being carefully controlled such as asthma, Chronic Obstructive Airways Disease or diabetes. Patients should be carefully monitored for signs of infection by way of regular physical examinations and appropriate tests when required. Should signs of pneumonia arise the dose of Clozapine may need to be reduced and the infection aggressively treated with antibiotic medication.

Key words: Schizophrenia, Violence, Clozapine, Pneumonia

Introduction

Many patients within forensic services present with treatment resistant schizophrenia complicated by high levels of aggression and violence. Clozapine is often the drug of choice within this patient group but has a complex side effect profile which can be seen in Table 1. Given the risk of potentially fatal agranulocytosis, it is only recommended in the United Kingdom in cases that have not responded to other antipsychotic drugs (1). Research within the last decade initially identified an association between elderly patients being treated with Clozapine and fatal complications such as pneumonia (2,3,4). More recent studies have started to identify an association between Clozapine and pneumonia within adult patients. This includes a retrospective analysis by Taylor *et al.* (5) on the reasons for Clozapine discontinuation, which identified that the most common cause of Clozapine discontinuation was death with the most frequent cause of death being pneumonia. In particular they cite 5 cases of fatal pneumonia in patients being treated with Clozapine.

Table 1. Side effects of Clozapine

Constipation, tachycardia, nausea, sedation, hypersalivation, postural hypotension, agranulocytosis, convulsions, blurred vision, dry mouth,	restless legs, muscle stiffness, temperature derangement, urinary retention or incontinence, neuroleptic malignant syndrome, weight gain, confusion,	diabetes, swallowing problems, pneumonia, pancreatitis and cardiac problems including pericarditis, myocarditis and death.

Within the literature, further case reports include fatal pneumonia in a 43 year old diabetic patient treated with Clozapine (6) and a case of non-fatal pneumonia with Clozapine toxicity in a 42 year old man (7). The most robust evidence available is provided by a case control study nested in a population of 33,024 adult patients receiving atypical antipsychotic drugs. This study found an association between many antipsychotics and pneumonia including Clozapine, Quetiapine, Olanzapine, Zotepine and Risperidone. Importantly, Clozapine was the only drug found to have a significant dose-dependent association with pneumonia (8).

Case Report

We report with the patient's consent, on a Caucasian man in his early 20s who suffers from treatment resistant paranoid schizophrenia. Prior to his current admission, he had no past history of pneumonia or other physical health problems. Following a further relapse in mental state he was admitted to a general adult hospital but was promptly transferred to a low secure forensic service due to the emergence of high frequency assaults. Routine physical examination, blood tests and ECG performed on admission were unremarkable. Given his lack of response to other antipsychotic drugs, he was commenced on Clozapine 12.5mg, and Sodium Valproate. His Clozapine was gradually increased over 3 months to 400mg per day in divided doses. This led to a significant improvement in his mental state and cessation of violent assaults on others. He made gradual progress but after 5 months of starting Clozapine and coinciding with his first winter at the hospital, whilst still remaining on Clozapine 400mg, he suffered from his first serious episode of pneumonia. He required emergency transfer to the acute medical hospital's intensive care ward. The pneumonia began with general malaise, swinging fever, rigors and productive cough. Respiratory examination revealed bronchial breathing and dullness. Chest X-Ray showed changes suggestive of pneumonia. A number of further specialist tests including microbial and viral cultures, CT-Chest, Echocardiogram and bronchoscopy were performed and found to be negative. Interestingly, no significant neutropenia was present but his liver function tests were slightly deranged. His Clozapine and Sodium Valproate were stopped as precautionary measures. He was diagnosed with pneumonia and treated with a range of highly potent antibiotic drugs including Gentamycin, Vancomycin and later Meropenem. His condition improved and after 2 weeks he was transferred back to his psychiatric ward. Given his complications on Clozapine, he was switched to Risperidone but after 8 months he suffered from a further relapse in mental state and a return to assaultive behaviour. After careful consideration a re-trial on Clozapine was attempted. He was commenced on Clozapine 12.5mg, which was increased over 2 months to 275mg per day in divided doses. This led to an improvement in mental state and cessation of assaults. After a further 12 months of progress on the ward, whilst still being treated with Clozapine 275mg, he suffered from a second episode of pneumonia with high fever, requiring re-admission to the acute medical hospital for aggressive antibiotic treatment. Again, there was no neutropenia but his Clozapine was immediately stopped as a precautionary measure. He made a good physical recovery but within 2 days his mental state deteriorated and the assaults recurred. Given concerns regarding Clozapine and potentially fatal pneumonia he was initially treated with Haloperidol 15mg per day in divided doses without success. 4 days later, a clinical decision based on risks and benefits was made to re-trial Clozapine treatment for a second time with specific plans to reduce risks, monitor for signs of infection and intervene at an early stage to prevent infections such as pneumonia. Upon returning to Clozapine the patient was able to make progress and work towards discharge without any further serious chest infections occurring.

Discussion

Whilst this case report cannot rule out the possibility of drug interactions, the temporal relationship between commencing Clozapine and subsequent episodes of pneumonia, combined with the recent literature on the topic suggests that Clozapine is likely to have caused the patients pneumonias. During each acute episode of illness, the possibility of Neuroleptic Malignant Syndrome (NMS) was excluded by way of physical examination and investigations including

white blood cell count which was not significantly raised. We did not measure phosphokinase levels but strongly recommend that this should be undertaken given recent evidence, suggesting that this NMS can occur during Clozapine therapy (9,10,11,12).

The mechanism for Clozapine linked pneumonia has not been confirmed and remains relatively speculative. An early case report by Hinkes et al (13) suggested that Clozapine induced hyper salivation may cause pneumonia though aspiration. This would be consistent with reports of antipsychotic induced dysphagia caused by oro-pharyngeal dyskinesia (14). In our patient, we have reduced his swallowing related problems by treatment with antimuscarinic medication to reduce extrapyramidal side effects and hyoscine hydrobromide to reduce his reports of excess salivation. An alternative theory, which is not applicable to our patient is that the anticholinergic effects of Clozapine can lead to dryness of the mouth increasing the risk of impaired oesophageal transit and subsequent aspiration pneumonia (3).

Maddalena (15) postulates that antipsychotic medication may cause oesophageal dilation and reduced motility thus impairing swallowing and again causing aspiration pneumonia. We attempted to assess our patients swallowing by completing a bed side swallowing assessment by a Dysphagia Speech and Language Therapist. This concluded that normal swallowing was present and suggested pneumonia would be unlikely to be caused by aspiration as a result of the above mechanisms.

The possibility that Clozapine has a direct effect on the immune system leading to increased susceptibility to pneumonia remains speculative. Whilst, Clozapine is known to cause agranulocytosis this has not been associated with the development of pneumonia according to the literature. In particular, Taylor et al (5) found that neutropenia was not present at the time of death, in any of its 5 cases of fatal pneumonia; which is consistent with the absence of neutropenia in our patient. Instead, several studies have identified that during an infection the serum level of Clozapine and its metabolites can rise to toxic levels (16,17,18). Therefore during a significant infection serum Clozapine levels should be assessed. In addition, clinical signs of Clozapine toxicity such as sedation, confusion, respiratory depression, speech dysfluency, myoclonus, agitation and hypotension should be monitored. Identification or suspicion of Clozapine toxicity should lead to urgent consideration of Clozapine dose reduction or temporary discontinuation (19). Drugs that can increase serum Clozapine levels should also be avoided such as Omeprazole, Theophylline, Modafinil and Fluvoxamine in addition to caffeine which can also increase Clozapine levels (7).

It is also worth noting suggestions in the literature that Clozapine related pneumonia can develop silently. Liana & Hsieh (20) describe the case of a 60 year old female who relatively silently developed non febrile pneumonia. Her only presenting symptom was myoclonus indicative of Clozapine toxicity. Despite the absence of respiratory symptoms her Chest X-Rays revealed lobar shadowing that later resolved with antibiotic treatment. Whilst anecdotal, the potential for non symptomatic pneumonia to develop heightens the degree of clinical suspicion required and suggests a low threshold for performing Chest X-Rays.

Implications for clinical practice

We suggest that when managing complex patients with clozapine, general risk factors for respiratory infections should be identified and controlled including asthma, chronic obstructive pulmonary disease, diabetes and smoking. Our patient did not suffer from these conditions; whilst he is a smoker we could not encourage him to cease this habit. Instead, we are mindful that should he suffer from a chest infection, his smoking capacity could reduce, effectively increasing his serum Clozapine levels which should therefore be monitored both during infections and changes in smoking habit.

The decision to prescribe Clozapine, cannot be taken lightly given its serious side effect profile. In treatment resistant cases some patients may present with distressing symptoms or problems such as illness driven violence that appear to mandate the use of Clozapine. In such cases, the decision to continue Clozapine where there has been previous pneumonias, must involve a careful balance of risks and benefits. We postulate, that where modifiable risk factors can be reduced and robust monitoring enabled then a deci-

sion to continue Clozapine may still be justified. Risk reduction should include use of minimum therapeutic doses of Clozapine and avoidance of medications that can increase the risk of dysphagia or aspiration. Where patients have a past history of pneumonia there should be a low threshold for requesting medical assessments including infection screening, Clozapine levels and Chest X-Rays. When pneumonia is identified the patient may require transfer to an acute medical hospital, Clozapine may need to be reduced or stopped and the pneumonia aggressively treated with antibiotic medication after careful liaison with the microbiology department. A summary of implications for clinical practice including risk reduction, infection surveillance and appropriate interventions are highlighted in Table 2.

Conclusion

An increasing evidence base suggests a possible link between Clozapine and pneumonia. Our case study highlights the need for judicious and evidence based decision making when prescribing Clozapine within forensic services and highlights that in appropriate cases robust risk reduction, infection surveillance and appropriate treatment interventions can enable the risk of pneumonia to be safely reduced.

Table 2. Implications for Clinical Practice

Risk reduction
• Lowest therapeutic dose of clozapine • Optimise co morbid physical conditions especially respiratory problems • Encourage controlled cessation of smoking • Avoidance of medications and substances that increase Clozapine levels • Consider yearly flu vaccination
Infection surveillance
• Monitor temperature, heart rate, blood pressure, respiratory rate • Awareness of the potential for silent presentations of pneumonia • Regular physical examination • Additional blood tests if chest infection is suspected • Low threshold for Chest X-Ray • Monitoring for clinical signs of Clozapine toxicity
Treatment Interventions
• Consider urgent transfer to the Accident and Emergency Department • Urgent serum Clozapine level • Explain potential risk of Clozapine associated pneumonia to the medical team • Consider dose reduction or discontinuing Clozapine • Consider stopping medications that can increase Clozapine levels • Early and aggressive treatment with antibiotic medication

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