

Tardive dyskinesia on clozapine treatment

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Antipsychotic-induced tardive dyskinesia is a potentially irremediable and debilitating condition with the onset most commonly associated with the use of first-generation antipsychotics.¹ The development of tardive dyskinesia on clozapine, a second-generation antipsychotic, is uncommon, and the drug is therefore a treatment option for those patients who develop the syndrome following treatment with first-generation agents. I report on the case of a 27-year-old man who developed severe tardive dyskinesia following initiation of clozapine treatment. To the best of my knowledge, this is the first case of tardive dyskinesia associated with clozapine use reported in South Africa.

Case presentation

A 27-year-old single man was admitted to a psychiatric hospital for the first time in June 2006, with a diagnosis of substance-induced psychosis. He had a history of regular illicit polysubstance abuse from the age of 14 years (mostly cannabis and methaqualone (Mandrax) and methamphetamine (tik) abuse from 2005.

He was discharged on chlorpromazine following his first hospital admission of 3 weeks after an initial unsuccessful trial of haloperidol. Although there was no history of continued substance abuse after his first hospital admission, he relapsed 6 months later and was re-admitted to hospital. The diagnosis was revised to schizophrenia. Clozapine was initiated and titrated up to 200 mg/day over a period of 2 weeks. His psychotic symptoms improved but depressive symptoms emerged, including dysphoria and suicidal ideation. Fluoxetine was commenced with good effect. Investigations, including a computed tomography (CT) head scan, full blood count, HIV ELISA test, thyroid function test and rapid plasma reagin (RPR) screen were done but the results were unremarkable. He was discharged after 4 months – euthymic, a psychotic and with no extrapyramidal features. He maintained regular community clinic reviews with good medication compliance and no evidence of ongoing substance abuse, and no adverse effects were reported.

In March 2007, onset of orobuccal dyskinesia was noted. Fluoxetine was immediately stopped but he continued on clozapine 200 mg/daily. The dyskinesia progressively worsened over the following 4 months. In July 2007, he was re-admitted to hospital, overtly distressed by severe orofacial dyskinesia with involvement of the oesophagus, as well as upper- and lower-limb dyskinesia. His symptoms were incapacitating as he struggled to chew and swallow and he also complained of a re-emergence of suicidal thoughts, auditory hallucinations and feeling dysphoric. The severity of his dyskinesia was rated as 30 (severe) on the Abnormal Involuntary Movement Scale (AIMS). Apart from severe dyskinesia, his physical examination was unremarkable. Clozapine was stopped and regular oral diazepam was administered, with significant improvement of symptoms within days. Diazepam was thereafter substituted with a regular dose of clonazepam 1 mg twice daily. A repeat full blood count (FBC), HIV screen, thyroid screen, RPR, caeruloplasmin and antistreptolysin O titre (ASOT) were done. Results were within normal limits. A repeat CT head scan and an EEG were non-contributory. However, a SPECT scan showed left basal ganglia hypoperfusion, as well as decreased perfusion in the left thalamus, left parietal area and striatum. The abnormal limb movements improved after discontinuation of clozapine but he remained distressed by the ongoing orofacial dyskinesia. At the time of reporting, he had been on clonazepam for 7 weeks and a gradually increasing dosage of quetiapine. His AIMS score 8 weeks after stopping clozapine had improved to 19 (moderate) and, although the mood symptoms resolved, the psychosis had worsened.

Discussion

The atypical or second-generation antipsychotic agents (SGAs) are often drugs of choice in the treatment of psychotic illness, based on evidence of their reduced risk for associated acute extrapyramidal side-effects and tardive dyskinesia, compared with the first-generation antipsychotics (FGAs).¹⁻³ The pathophysiology of the antidyskinetic properties of atypical antipsychotics, as well as the pathophysiology of tardive dyskinesia itself, remains unclear.⁴

The clinical benefits of the use of SGAs in patients with tardive dyskinesia appear to be twofold. They may ameliorate the symptoms of pre-existing tardive dyskinesia, and are also less likely to induce tardive dyskinesia. Evidence for the lower

incidence of tardive dyskinesia associated with the SGAs is highlighted in a recent systematic review. The authors concluded that the annual incidence of tardive dyskinesia associated with the use of second-generation antipsychotics is 3.9%, as compared with an incidence of 5.5% for the first-generation agents.²

It is difficult to determine whether clozapine induces tardive dyskinesia, because treatment with the agent is often initiated only after a patient has had prolonged exposure to other psychotropic agents, including high-dose FGAs. Furthermore, the paucity of prospective clinical trial data has not provided any statistically significant proof of increased risk for tardive dyskinesia with clozapine use and, in some studies, results have been equivocal.^{5,6} Evidence for clozapine-induced tardive dyskinesia has therefore largely been based on case reports in the literature.^{6,7}

In this case, it could be argued that previous methamphetamine abuse might have predisposed the patient to developing tardive dyskinesia. Methamphetamine abuse has been implicated in the onset of hyperkinetic disorders including chorea.⁸ One could further speculate on whether our patient developed tardive dyskinesia on the basis of exposure to fluoxetine. However, the onset of the dyskinesia was 20 months after his last methamphetamine exposure, and the dyskinesia increased in severity for a period of 4 months after fluoxetine had been withdrawn and while he was still on clozapine. A marked

improvement in the dyskinetic movements was observed after clozapine was discontinued, however, which therefore suggests that clozapine was the most likely causative agent.

This report highlights the possibility of the emergence of tardive dyskinesia with the use of clozapine. Although the occurrence rate is lower than that associated with the use of first-generation antipsychotics, it is important for clinicians to be aware of the potential risk of tardive dyskinesia in patients being treated with clozapine.

I thank Drs T Henderson and R Steyn for their clinical contribution, and Professor Denise White for assistance with the manuscript.

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