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CLOZAPINE AND OBSESSIVE-COMPULSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

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Summary

Clozapine differs from typical neuroleptics in its potent serotonin blockade and weak D_2 receptor blockade. This paper consists of a series of three brief case vignettes describing patients with schizophrenia and obsessive-compulsive symptoms who were treated with clozapine. Two of the patients manifested an exacerbation of their obsessive-compulsive symptoms, while the third manifested no change. The findings are interpreted in the light of previous work and theories on the pathophysiology of obsessive-compulsive symptoms, which has been linked to abnormal serotonin as well as dopaminergic activities. The differential effect of clozapine on obsessive-compulsive symptoms may be a reflection of the heterogeneity of the pathophysiology of obsessive-compulsive symptoms.

Keywords: clozapine; schizophrenia; obsessive-compulsive symptoms; serotonin; dopamine

INTRODUCTION

Clozapine is an atypical antipsychotic which may be effective in the treatment of schizophrenic patients whose symptoms do not respond to traditional typical anti-psychotics (Kane,1988, Meltzer, 1990). Unlike the typical antipsychotics, clozapine is a more potent antagonist of serotonin 5-HT_2 receptors than of dopamine D_2 receptors (Seeman, 1990).

There are reported cases of either an exacerbation or development of obsessive-compulsive (OC) symptoms in patients with chronic psychosis treated with clozapine (Baker,1992, Earles,1994, Patil,1992). The impression from these reports is that exacerbation or development of OC symptoms seems more likely with clozapine than with typical antipsychotics although this adverse effect has also been reported with risperidone, another atypical neuro-leptic (Remington,1994).

Reported here are three patients who suffered from schizophrenia (according to DSM III-R criteria). In two of the patients, there were worsening of OC symptoms while in the third patient with pre-existing OC symptoms there was no exacerbation of her OC symptoms. Clozapine therefore may not invariably cause an exacerbation of pre-existing OC symptoms. We interpret our findings in light of previous work and theories regarding the pathophysiology of OC symptomatology.

CASE 1

S.S., a 32 year old Chinese male, had suffered from schizophrenia since the age of 17. Despite continuous treatment with typical antipsychotics, there was no lessening of his symptoms which included persistent auditory hallucinations, paranoid delusions, thought disorder and a range of negative symptoms. He was treated with clozapine which was maintained at 550 mg/day. His Brief Psychiatric Rating Scale (BPRS) score prior to clozapine was 40 and 29 after 18 weeks of treatment. Auditory hallucinations and delusions remitted over time. There was a significant improvement in his self-grooming and volition. However, he began to complain of intrusive and repetitive thoughts of a sexual theme. He identified them as his own thoughts and was very distressed by them. Although he had experienced this prior to treatment with clozapine, he had not complained as it was not as severe and had even remitted while he was on chlorpromazine. Because of the worsening of his obsessive thoughts, he asked to be taken off clozapine and reinstated on chlorpromazine. A subsequent reduction of clozapine to 300 mg/day resulted in a self-reported reduction of his obsessive thoughts.

CASE 2

L.C.H., a 26 year old Chinese woman, had a 5 year history of schizophrenia with prominent persecutory delusions and ideas of reference. Shortly after the onset of her psychotic symptoms, she developed certain compulsive rituals which consisted of checking light switches, and doing household chores ritualistically. She knew that it was ridiculous to do so, but felt uncomfortable when she resisted. Typical oral and depot antipsychotics were ineffective in relieving her psychotic features. She was started on clozapine which was subsequently maintained at 125 mg/day. Her persecutory delusions disappeared whilst her ideas of reference were reduced. However, her compulsive rituals worsened within 3 months of clozapine treatment, and she even began to ruminate on anything that came to her mind. She found these thoughts irrational and distressing but was unable to resist them. Addition of clomipramine 50 mg/day resulted in resolution of her obsessive thoughts and a decrease of her compulsive checking.

CASE 3

W.F.K., a 30 year old Chinese woman, suffered from schizophrenia since the age of 13. Her illness was characterized by auditory hallucinations, persecutory delusions, thought disorder, and unpredictable and aggressive behaviour. About ten years into her schizophrenic illness, she developed a fear of contamination and an obsession with cleanliness with compulsive hand washing and bathing. She would also wash anything that she considered contaminated. Despite high doses of typical antipsychotics, her illness deteriorated and she had to be hospitalized for nearly a year before clozapine was started. Clozapine was eventually increased to 450 mg/day and her schizophrenic illness improved significantly. From a pre-clozapine score of 71, her BPRS score fell to 31 after 18 weeks of treatment. After more than a year of continuous treatment with clozapine however, her OC symptoms remained in status quo.

DISCUSSION

It has been suggested that clozapine, an atypical neuroleptic, is effective in treatment refractory schizophrenia because, in contrast to typical neuroleptics, it also blocks serotonin (5-HT) receptors with the highest affinity for 5-HT_{2C} receptors (Kahn,1993).

Serotonin has been implicated in the pathophysiology of obsessive-compulsive disorder (OCD) as evidenced by the efficacy of serotonin reuptake blocker (clomipramine) and selective serotonin reuptake inhibitors (fluvoxamine, fluoxetine) in the treatment of OCD (Barr,1992). Selective serotonin reuptake inhibitors have also been reported to be effective in the treatment of OC symptoms resulting from clozapine therapy (Cassady,1992, Allen,1994) and clomipramine was effective in reducing the OC symptoms in case 2. Administration of meta-chlorophenylpiperazine (MCPP) which binds to all 5-HT receptors but most potently to the 5-HT_{2C} subtype, causes an exacerbation of OC symptoms in patients with OCD (McDougle,1994). It would be expected that cloza-pine (a 5-HT_{2C} antagonist) would improve these symptoms but clozapine actually appeared to worsen these OC symptoms. Furthermore, the lack of an exacerbation of obsessive-compulsive features in case 3, and a reported case of refractory OCD that responded to clozapine alone (Young,1994) suggests the possibility that different 5-HT receptor subtypes are involved in the pathophysiology of OC symptomatology. In additional, dopaminergic mechanism has also been implicated in OCD (Goodman,1990). Interestingly, the first patient reported that his obsessive thoughts remitted while he was treated with chlorpromazine. If dopaminergic activity is linked to expression of OC symptoms, the OC symptoms of this patient may have emerged due to the discontinuation of this typical neuroleptic. Monotherapy with typical neuroleptics have been reported to be effective in some cases of OCD (Thethown,1955, O'Regan,1970). Typical neuroleptics produce a more potent blockade of D_2 receptors in contrast to clozapine which has a weak affinity for D_2 receptors but a higher affinity for D_1 and D_4 receptors (Kerwin,1994). This may suggest that different dopamine receptor subtypes may also be involved in the pathophysiology of OC symp-tomatology.

It is also possible that serotonergic-dopaminergic interactions may play a part. There is considerable preclinical evidence of such interactions. Schmidt et al (1991) found that the 5-HT_2 receptor antagonist, MDL11,939, blocks acute stimulation of striatal dopamine synthesis induced by 3,4-methylenedioxy-methamphetamine (MDMA). Sorensen (1992) also demonstrated that amphetamine-induced reduction in firing rate of A 10 dopamine neurons in chloral hydrate-anaesthetized rats is blocked in animals pretreated with the selective 5-HT_2 receptor antagonists MDL 23,133A and ritanserin.

It is still far too premature for any firm explanation of OC pathophysiology. It may involve receptor subtype selectivity or specific ratios of receptor antagonism. These or none of these mechanisms may contribute to some extent in explaining the effect that clozapine has on OC symptoms.

Furthermore, caution should be exercised in interpreting findings from the pooling together of several case reports. The limitations of this report as in previous reports are that it consists of isolated cases with no structured assessment, and they raised more questions than answers. However, such observations do offer a glimpse of the neuro-biological heterogeneity involved in the expression of OC symptoms in schizophrenia, and also gives support to the heuristic validity of using treatment response to define subgroups of schizophrenia (Buckley,1994).

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