SHORT COMMUNICATON

Clin Drug Invest 2002; 22 (5): 341-346
1173-2563/02/0005-0341/$25.00/0

Reduction of Suicidality in Patients with Schizophrenia Receiving Clozapine

Michael J. Reinstein, Maxim A. Chasonov, Kathleen D. Colombo, Lynne E. Jones and *John G. Sonnenberg*

Uptown Research Institute, Chicago, Illinois, USA

Suicide, suicidality and ideation of suicide are serious problems associated with the course of disease in patients with schizophrenia. This, along with the adverse effects and ineffectiveness of typical antipsychotic agents, has made it necessary for clinicians to find treatment modalities that will address symptoms and reduce adverse effects.

A number of studies have shown that clozapine has a significant positive impact on the reduction of the incidence of suicidality in schizophrenic and schizoaffected patients.[1-7] This retrospective study reports on the results of clozapine therapy and suicidality in 295 patients who were antipsychotic-resistant. All individuals were outpatients residing in two long-term care facilities for the mentally ill in Chicago, Illinois, USA.

Clozapine was the only antipsychotic medication administered to these patients during the course of the study. Length of therapy ranged from 7 to 78 months [average 43.8 months, standard deviation (SD) 21.4 months]. These study results indicate that there is demonstrable reduction in suicidality with clozapine therpay in antipyschotic-resistant patients. Additionally, we have found, in our clinical experience and in this study, that clozapine helps avert the suicidal urges of psychotic patients better than other antipsychotics. This study cohort comprised a majority of African-Americans. To confirm our results, future studies will need to be undertaken to review and establish a suicide-clozapine link among ethnically diverse populations.

Clinical Picture of Suicidality

Prevalence of Schizophrenia-Associated Suicidality

The annual incidence rate of schizophrenia is estimated to be between 0.1 and 0.5 per 1000,[8] with the lifetime risk of developing schizophrenia estimated between 7.0 and 9.0 per 1000.[9] The onset of schizophrenia typically occurs between the ages of 15 and 45 years. The disease occurs equally in men and women, with the mean age of onset about 5 years earlier for men.[10] The relatively young age of onset, coupled with the realisation that one will likely lose the ability to hold a job, have meaningful relationships, and function as a productive member of society, along with the disease process of schizophrenia, leads many patients to attempt and succeed in committing suicide. Indeed, suicide is a significant cause of death among patients with schizophrenia and schizoaffective disorder, affecting some 10 to 15% of patients.[11]

Clinical Picture of Schizophrenia and Suicidality

The predominant clinical features of acute schizophrenia include positive symptoms, e.g. delusions, hallucinations and interference with normal thinking. Some patients recover from the acute illness while others progress to the chronic stage. These latter patients experience positive and negative symptoms, which include apathy, slowness and social withdrawal. Once the chronic

syndrome is established, few patients recover completely.[8]

Between 20 and 40% of patients with schizophrenia receiving typical antipsychotic medications attempt suicide,[12,13] and the completed suicide rate ranges from 9 to 12.9%[14] over the course of the illness. Approximately 1 to 2% of all schizophrenic patients who attempted suicide were reported to complete suicide within a year after their initial attempt, with an additional 1% doing so each year thereafter.[15,16] Thus, the risk of death by suicide among patients with schizophrenia is significant and nearly equivalent to the risk of developing clinically manageable agranulocytosis and agranulocytopenia for clozapine therapy.

A number of studies also suggest that the suicide rate of patients with schizophrenia is comparable to that seen in patients with severe depression.[17,18] However, beyond co-morbid depression, there are other reasons for the increased risk of suicide in schizophrenic patients. In lucid moments, these patients may realise that their illness will have devastating consequences on the quality of their lives. Furthermore, the positive symptoms may make death an attractive alternative.[11] In addition, many of these patients are prone to substance abuse, with the attendant risk of overdose or unsafe behaviour leading to potentially lethal consequences.

Suicidality may also be increased when the prescribed medication is not effective. Inadequate efficacy of antipsychotic drugs results in a host of problems, including poorly controlled symptoms, heightened social and personal problems, and an unstable disease course. In addition, adverse effects (particularly when typical antipsychotics are being used), such as tardive dyskinesia (TD), add to the patient's frustration and to an outlook of hopelessness.

Previous Studies of Clozapine and Suicidality in Patients with Schizophrenia

In their prospective study, Meltzer and Okayli[14] treated 88 antipsychotic-resistant patients with clozapine for periods from 6 months to 7 years. There were no successful suicides in this group of patients, only three suicide attempts that were considered to have a low probability of success, and seven patients who experienced suicidal ideation. The authors concluded that clozapine treatment of antipsychotic-resistant schizophrenic patients markedly reduced suicidality during the study period.

Reid et al.[11] examined annual suicide rates over a two-year period (1993-95) among 30 000 patients with schizophrenia and schizoaffective disorder in the Texas mental health system. They compared simple rates of suicide in three populations: all severely and chronically mentally ill patients in the system; patients with a primary diagnosis of schizophrenia or schizoaffective disorder; and the subset of the latter group of patients who were treated with clozapine. They found that the suicide rate in the first two groups was approximately five times that of the general population, or 63.1 and 60.2 per 100 000, respectively, versus 12 per 100 000 in the United States. The suicide rate for the clozapine-treated group was 12.74 per 100 000. These investigators noted that while the data do not prove a direct causal relationship, they seem to support the theory that clozapine reduces suicide risk in these patients.

However, not all researchers have found that clozapine is associated with reduced suicide risk. Sernyak et al.[19] studied 1415 patients in the VA Hospital system who were treated with clozapine over a 4-year period. They compared the suicide rate of this group with a control group of patients with schizophrenia (n = 2380) who were not given clozapine. These investigators found that while there were significantly fewer deaths in the clozapine group, these were entirely attributable to the fact that these patients had a much lower rate of respiratory disorders. There were no significant differences in the rates of suicide or accidental death between the two groups studied.

The authors explained their findings by noting that previous studies failed to provide a control group in their protocols (also a limitation in the study we report on here). The researchers created

their control group using 'propensity scoring': a statistical method, they stated, which is widely accepted but rarely used in psychiatric studies. These investigators further noted that even in the 1998 Reid et al.[11] study, the results were equivocal, since the 'equivalence of the comparison group to the clozapine group on even basic demographic characteristics such as age, gender or race, was not systematically established.' As in the group of patients we studied, many clinicians feel that there is an ethical responsibility to provide desperately ill patients with effective care, which may preclude strict adherence to the creation and maintenance of a 'control group.'

Effects of Clozapine

In 1990, the US Food and Drug Administration approved the marketing of clozapine, the first new antipsychotic medication approved in over a decade. Clozapine, a dibenzodiazepine, is substantially different from other, typical antipsychotic medications. It is chemically related to loxapine, but has a very different pharmacological profile, and is considered an atypical antipsychotic agent.[13]

Clozapine reacts with dopamine D_1 and D_O receptors in the limbic region of the brain rather than in the striatal areas of the motor cortex, the site of action of other antipsychotic drugs. For this reason, clozapine is much less likely to cause extrapyramidal symptoms (EPS), tardive dyskinesia or neuroleptic malignant syndrome, although these adverse events may occur.[1] Kane et al.[1] conducted a formal clinical trial comparing clozapine with chlorpromazine in patients who met carefully defined criteria for poor responsiveness to at least three other antipsychotic medications, and who further failed to respond to a six-week trial of haloperidol. After six weeks, 30% of clozapine-treated patients met improvement criteria in both positive and negative symptoms of schizophrenia, whereas only 4% of chlorpromazine-treated patients showed improvement, and then in only the positive symptoms of the illness.

Adverse Effects of Clozapine

Despite its therapeutic properties and reduced likelihood of the usual adverse effects of antipsychotic medications, clozapine can induce granulocytopenia (2.8% risk) and/or agranulocytosis (0.6% risk),[21] with most cases occurring in the first 18 months of treatment.[22] Bi-weekly blood examinations are required to monitor for adverse effects. These adverse effects, when they occur, can be controlled by reducing the dosage of clozapine or by halting the drug temporarily or, if necessary, permanently. Additionally, filgrastim is an agent capable of immediately and dramatically reversing agranulocytosis, thus reducing the incidence of serious complications and deaths.

Given the risk of agranulocytosis, clozapine is generally reserved for treatment-resistant schizophrenia, schizophrenia with prominent negative symptoms, and psychotic patients with severe TD or EPS.[17]

Methods

Patient Recruitment and Characteristics

All patients in the present retrospective study were considered antipsychotic-resistant according to the following criterion: patients were severely ill schizophrenic patients who failed to show an acceptable response to adequate courses of standard antipsychotic drug treatment, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs.

Schizophrenia was defined using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), diagnostic criteria. All patients were under our care, and consequently we made the diagnoses ourselves. 'Severity of illness' was limited to an examination of the incidence of suicide. This was determined by establishing whether the patient had active intent to harm him- or herself. Only those individuals who committed an act that could be linked to self-harming tendencies were considered suicidal. For example, a superficial cut to the wrist or ingestion of more

than the prescribed amount of medication – even if this was not life-threatening – was considered to be suicidal behaviour. Merely having a plan or a fantasy was not sufficient.

Each patient was given at least two trials with two different standard antipsychotic medications at an adequate dose and for an adequate duration. Indeed, most of these patients had far more than the minimum criterion of two trials of standard antipsychotic drug without a complete or acceptable response. Many patients remained clinically unstable, requiring frequent repeated hospitalisations to achieve psychiatric stabilisation prior to initiation of clozapine therapy.

Patients participating in the present study were outpatients residing in two long-term care facilities for the mentally ill located in Chicago, Illinois, USA. Of 833 patients treated with clozapine since the drug was approved for treatment-resistant schizophrenia in 1990, 295 patients were determined to have received clozapine for at least 6 months. The 295-patient group comprised the study population.

Clozapine was the only antipsychotic medication administered long-term to this group of patients during the study period. The extant statistics on suicidality in patients with schizophrenia served as the control for this study. Charts of all patients who were hospitalised during the period of continuous clozapine administration were reviewed to determine whether the cause of admission was attempted suicide or suicidal ideation.

Patient Demographics

Of the 295 patients, 102 were female and 193 were male. Their ages on first administration of long-term clozapine therapy ranged from 20 to 76 years (mean 41.7 years, SD 11.1 years). The length of time these patients received clozapine therapy ranged from 7 to 78 months with an average of 43.8 months and a SD of 21.4 months. Racial distribution was as follows: three Asians, 210 African-Americans, 64 Caucasians, and 18 Hispanics (see table I).

Diagnosis was based on information gained from the listed psychiatrist's review and on DSM-IV diagnostic criteria. As is our standard procedure, we queried patients for suicidal ideation. In addition, patients were seen on a regular basis (monthly) for the duration of this study.

Results

There was a total of 41 nonpsychiatric (non–suicide-related) hospitalisations (table I). Based on the general observations reported above (that 1 to 2% of schizophrenic patients complete suicide within 1 year after initial attempts with an additional 1% doing so each year thereafter), during the mean long-term exposure to clozapine of 43.8 months (3.65 years) we would have expected as many as 10 or 11 successful suicides or suicide attempts. In fact, none were observed.

The patient population in this study was predominantly African-American (210 of 295 patients, or 71%). Earle et al.[24] reported that African-Americans are less likely (by about 50%) to commit suicide than the general population of psychiatric patients. Even adjusting for the expected number of suicides based on this observation, we would still have expected to find six to seven successful suicides or serious suicide attempts (table II). Furthermore, none of the 295 patients

Table I. Patient demographics

Females (no.)	102
Males (no.)	193
Age on entry to study (years)	
Range	20-76
Mean ± SD	41.7 ± 11.1
Months in study	
Range	7-78
Mean ± SD	43.8 ± 21.4
Race (no.)	
Asian	3
African-American	210
Caucasian	64
Hispanic	18
Hospitalisations (no.)	
Nonpsychiatric	41

Table II. Suicidality in patients with schizophrenia receiving clozapine

Expected	Actual
10-11[a]	0
6-7[b]	0

a 295 patients × 3.65 years × 1% per year suicide rate.

b (210 African-American patients × 3.65 years × 0.5% per year suicide rate) + (85 non-African-American patients × 3.65 years × 1% per year suicide rate).

demonstrated agranulocytosis or granulocytopenia while taking clozapine.

Discussion

A potential weakness of this study was the fact that we did not create a proper control group. In their important paper, Serynak et al.[19] created a control group and found a negative effect of clozapine and completed suicide. However, our findings are consistent with numerous studies[11,14,17,28] that have shown that clozapine has a beneficial effect on the rate of suicidality in antipsychotic-resistant patients. There are various theories as to why this is so. One theory centres on the mechanism of action of clozapine. Some researchers have noted that clozapine is an effective treatment for patients with major depression, and is an effective mood stabiliser in bipolar and schizophrenic patients.[25] Clozapine also reduces hopelessness associated with TD as well as aggressiveness and substance abuse; two other factors for suicide.[21]

Some investigators[25] also point to the fact that patients taking the medication must come into the clinic for weekly white blood cell level monitoring during the first 18 weeks of therapy. However, on closer examination, this may not be a significant factor. Meltzer[19] cited programmes that involve close monitoring of patients receiving clozapine. These programmes did not have a reduced rate of suicide. Moreover, programmes in Europe and China[25] that have reduced such monitoring have not reported appreciable increases in suicide rates.

There is also some uncertainty as to whether the effect of clozapine is important because patients who are resistant to antipsychotics are more prone to commit suicide. However, this hypothesis has not been borne out. In one study,[14] long-term incidence and current episodes of suicidal thoughts, plans and attempts were comparable between antipsychotic-resistant and -responsive patients. Furthermore, antipsychotic treatment does not appear to contribute to suicidality. Indeed, one study[20] found that the patients who committed suicide had lower levels of antipsychotics than those who did not.

Walker et al.[27] found that there was a marked decrease in suicidality among 'current users' of clozapine compared with 'past users' and 'recent users'. The incidence of suicide in the current cohort was 19% of overall mortality. Indeed, most of the patients who committed suicide were those who had stopped taking clozapine. These patients were antipsychotic-resistant, and thus at a higher risk for suicide. Conversely, patients who responded to clozapine tended to continue to take the medication, which became a realistic management strategy. Interestingly, it is the control of psychosis that may be the cause of a reduction in suicide rates.

Unlike the demographics of schizophrenic patients and patients who attempt to commit suicide,[28] our study consisted of a majority of African-American patients. Although studies[24] indicate that this group of patients is less likely to attempt suicide, we found a remarkably low incidence of suicide in this group and indeed in all the groups we studied.

Conclusions

In addition to being an effective therapy for antipsychotic-resistant schizophrenic patients, clozapine also reduces the rate of suicidality during continuous drug administration. The results of the present study confirm previously reported findings of reduced suicidality with clozapine therapy in antipsychotic-resistant schizophrenic patients.[7]

Acknowledgements

Funding support for this study was provided by Novartis Pharmaceuticals.

References

1. Kane JM, Honigfeld G, Singer J, et al. Clozapine for treatment-resistant schizophrenia. Arch Gen Psychiatry 1988; 45: 789-96
2. Meltzer H, Burnett S, Bastani B, et al. Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. Hosp Community Psychiatry 1990; 41: 892-7
3. Pickar D, Owen RR, Litman RE, et al. Clinical and biological response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. Arch Gen Psychiatry 1992; 49: 345-53
4. Breier A, Buchanan RW, Irish D, et al. Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. Hosp Community Psychiatry 1993; 22: 1145-9
5. Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on postiive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 1994; 151: 20-6
6. Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and preditctors of outcome. Am J Psychiatry 1994; 151: 1744-52
7. Rosenheck R, Cramer J, Xu W, et al. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. A comparison of clozapine and haloperidol in hospitalised patients with refractory schizophrenia. N Engl J Med 1997; 337: 809-15
8. Gelder M. Gath D, Mayou R, et al. (editors) Schizophrenia and schizophrenia-like disorders. In: Oxford Textbook of Psychiatry. 3rd ed. New York: Oxford University Press, 1996: 246-293
9. Jablensky A. Epidemiology of schizophrenia: a European perspective. Schizophr Bull 1986; 12: 52-73
10. Hafner H, Riecher A, Maurer K, et al. How does gender influence age at first hospitalization of schizophrenia. Psychol Med 1989; 19: 903-18
11. Reid WH, Mason M, Hogan T. Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. Psychiatr Serv 1998; 49 (8): 1029-33
12. Schuttler R, Huber G, Gross G. Suizid and Suizidversuch im Verlauf schizophrener Erkrankungen. Psychiatr Clin (Basel) 1976; 9: 97-105
13. Modestin J. Suizid in der psychiatrischen Klinik. Stuttgart: Enke, 1987
14. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995; 152: 183-90
15. Ehrlinger R. Evaluation of suicide prevention after attempted suicide. Acta Psychiatr Scand Suppl 1975; 260: 64-124
16. Kreitman N, editor. Parasuicide. New York: John Wiley & Sons, 1977
17. Westermeyer JF, Harrow M, Marengo JT. Risk for suicide in schizophrenia and other psychotic and non-psychotic disorders. J Nerv Ment Dis 1991; 179: 259-66 (as cited in Reid[4])
18. Caldwell CB, Gottesman II. Schizophrenics kill themselves too: A review of risk factors for suicide. Schizophr Bull 1990; 16: 571-89 (as cited in Reid[4])
19. Sernyak MJ, Desi R, Stolar M, et al. Impact of clozapine on completed suicide. Am J Psychiatry 2001; 158: 931-7
20. Ereschefsky L, Watanabe MD, Tran-Johnson TK. Clozapine: an typical antipsychotic agent. Clin Pharm 1989-8: 691-709
21. Lieberman JA, Alvir JMJ. A report of clozapine-induced agranulocytosis in the United States. Incidence and risk factors. Drug Saf 1992; 7: 1-2
22. Reinstein MJ, Sirotouskaya LA, Mohan SC, et al. Incidence and treatment of side effects with clozapine treatment [poster]. Presented at the Annual Meeting of the American Psychiatric Association, Chicago, 8 May 2000
23. Marder SR, Van Putten T. Who should receive clozapine? Arch Gen Psychiatry 1988; 45: 865-7
24. Earle KA, Forquer SL, Volo AM, et al. Characteristics of outpatient suicides. Hosp Community Psychiatry 1994; 45: 123-6
25. Meltzer HY. Suicide and schizophrenia: Clozapine and the InterSePT study. J Clin Psychiatry 1999; 60 Suppl. 2: 47-50
26. Taiminen TJ, Kujari H. Antipsychotic medication and suicide risk among schizophrenic and paranoid inpatients. Acta Psychiatr Scand 1994; 90: 247-51 (as cited in Meltzer[25])
27. Walker AM, Lanza LL, Arellano F, et al. Mortality in current and former users of clozapine. Epidemiology 1997; 8: 671-7 (as cited in Meltzer[25])
28. Meltzer HY. Suicide in schizophrenia: Risk factors and clozapine treatment. J Clin Psychiatry 1988; 59 Suppl. 3: 15-20

Correspondence and offprints: Dr *John G. Sonnenberg*, Uptown Research Institute, LLC, 4755 N. Kenmore Avenue, Chicago, IL 60640, USA.