The effects of clozapine on levels of total cholesterol and related lipids in serum of patients with schizophrenia: a prospective study

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Objective: To investigate the effects of 12 weeks of clozapine treatment on levels of cholesterol and related lipids in patients with schizophrenia. **Design:** Prospective study. **Setting:** University department associated with a teaching hospital. **Participants:** Eight patients (6 women and 2 men) with a clinical diagnosis of schizophrenia consistent with DSM-IV criteria. The patients were classified as treatment-resistant and had not responded to treatment with at least 2 conventional antipsychotics. **Interventions:** Current antipsychotic medications were tapered and treatment with clozapine was initiated. **Outcome measures:** Cholesterol and serum lipid levels, as well as Brief Psychiatric Rating Scale (BPRS) scores were measured before and after 12 weeks of treatment with clozapine. **Results:** Clozapine treatment significantly improved the BPRS scores but did not significantly alter serum lipid levels, except triglyceride levels, which increased. **Conclusion:** The previously reported lower levels of cholesterol in treatment-resistant patients with schizophrenia cannot be attributed to the effects of clozapine administration. Further research is required to support and clarify the effects of antipsychotic drugs on lipid levels.

Objectif : Étudier les effets d'un traitement à la clozapine d'une durée de 12 semaines sur les taux de cholestérol et de lipides connexes chez les patients atteints de schizophrénie. **Conception :** Étude prospective. **Contexte :** Service universitaire associé à un hôpital d'enseignement. **Participants :** Huit patients (six femmes et deux hommes) chez lesquels on a posé un diagnostic clinique de schizophrénie conformément aux critères DSM-IV. Les patients résistaient au traitement et n'avaient pas réagi au traitement administré au moyen d'au moins deux neuroleptiques classiques. **Interventions :** On a réduit graduellement les neuroleptiques administrés pour entreprendre un traitement à la clozapine. **Mesures de résultats :** Taux de cholestérol et de lipides sériques, et résultats selon l'échelle d'évaluation psychiatrique BPRS (Brief Psychiatric Rating Scale) avant et après 12 semaines de traitement à la clozapine. **Résultats :** Le traitement à la clozapine a amélioré considérablement les résultats BPRS mais n'a pas modifié de façon significative les taux de lipides sériques, sauf les taux de triglycérides, qui ont augmenté. **Conclusion :** Les taux moins élevés de cholestérol indiqués auparavant chez les patients atteints de schizophrénie résistant au traitement ne peuvent être attribués aux effets de l'administration de clozapine. Des recherches plus poussées s'imposent pour appuyer et clarifier les effets des neuroleptiques sur les taux de lipides sériques.

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Medical subject headings: cholesterol; clozapine; lipids; schizophrenia

J Psychiatry Neurosci 1999;24(5):453-5.

Submitted July 20, 1998
Revised Dec. 23, 1998
Accepted Jan. 4, 1999

Introduction

There is evidence that changes in the serum level of total cholesterol (TC) may affect central nervous system neurotransmission and thus influence the development of psychiatric disorders.[1] Many studies have reported that patients with schizophrenia have lower cholesterol levels than control patients, with the exception of patients who are agitated, who have cholesterol levels higher than can be accounted for by increased autonomic arousal due to agitation (reviewed in Boston et al[1]). Lowering serum cholesterol levels can decrease central serotonin (5-HT) receptor function, possibly through a membrane effect.[2] In patients with schizophrenia, 5-HT receptors appear to be involved in the presentation of symptoms;[3] some antipsychotic drugs, such as clozapine, are potent 5-HT receptor antagonists. We previously reported, in a cross-sectional study, lower serum TC levels in patients with schizophrenia treated with clozapine than in patients treated with other typical antipsychotic drugs.[4] This might indicate that treatment resistance to typical antipsychotics may be related to lower TC levels; alternatively, the lower TC levels may be the result of clozapine treatment. To further investigate this latter hypothesis, the effects of clozapine on serum TC levels and related lipid levels, and on clinical psychopathology, were assessed in patients with schizophrenia.

Methods

Eight patients (6 women and 2 men) with a clinical diagnosis of schizophrenia consistent with the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria, were included in the study. Patients had a duration of illness since first diagnosis of at least 2 years and were classified as treatment-resistant, defined as having no clinical response to at least 2 conventional antipsychotics. Patients were excluded if they had a history of recent significant changes in appetite or weight, hypothyroidism, or known disorders of lipoprotein metabolism.

After giving consent, the dosage of the patients' current typical antipsychotic medications were tapered; all antipsychotics and mood stabilizers being taken were gradually reduced and discontinued after 4 weeks following the initiation of the study. Patients were allowed to take other medications, including benzodiazepines and anticholinergic drugs. After an overnight fast and 24 hours before beginning treatment with clozapine, a single blood sample was taken and the Brief Psychiatric Rating Scale (BPRS) was used to rate clinical psychopathology. From the blood sample, serum levels of TC, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (TRI), total protein (TP) and albumin (ALB), were measured as described previously.[4] Blood work and BPRS were repeated after 12 weeks of treatment with clozapine.

Statistical analysis of the data was performed using two-tailed paired Student's *t*-test.

Results

The 6 women and 2 men had a mean age of 35.9 (standard deviation [SD] 7.3) years. At the end of 12 weeks, patients were taking a mean dosage of 352 (SD 73) mg per day of clozapine. Following clozapine treatment, the severity of the schizophrenic symptoms was attenuated; mean BPRS scores were reduced from 43.7 (SD 3.1) to 25.0 (SD 3.9). Changes in lipid levels are shown in Fig. 1. Except for a small (11%) increase in TRI levels, there were no significant changes in plasma lipid levels as a result of clozapine administration. Specifically, there was no significant change in TC, HDL or LDL. Neither TP nor ALB levels were significantly altered.

Discussion

Clozapine treatment improved the BPRS score of patients with schizophrenia but did not significantly

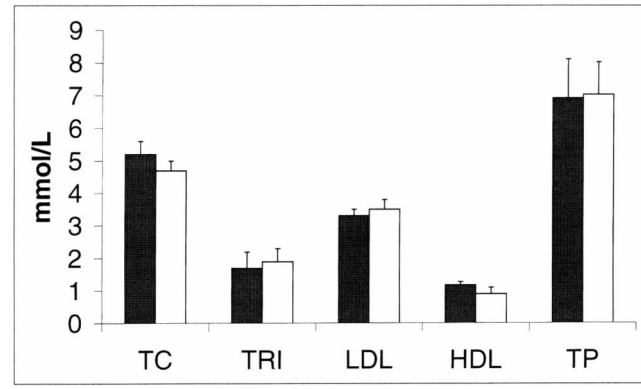

Fig. 1: Mean serum lipid levels before (black bars) and after (white bars) clozapine treatment. *$p < 0.05$. TC = total cholesterol; TRI = triglycerides; LDL = low-density lipoproteins; HDL = high-density lipoproteins; TP = total protein. Normal serum lipid levels are as follows: TC 3.9 to 6.5 mmol/L; TRI 0.0 to 0.2 mmol/L; LDL > 0.9 mmol/L; HDL > 0.9 mmol/L; TP 6 to 8 mmol/L.

alter serum levels of TC and other lipids, with the exception of TRI. Our findings are consistent with those from a comparative study examining lipid levels in patients treated with clozapine or other atypical antipsychotics.[5] In results similar to those of our study, Ghaeli and Dufrense[5] found no significant differences in cholesterol levels between groups, with the exception of higher levels of TRI after treatment with clozapine. These results are contrary to a case study reported by Vampini et al,[6] in which a patient had a gradual increase in TRI and cholesterol levels during clozapine treatment; these results have not been replicated.

The results of our study suggest that the previously reported lower levels of cholesterol in patients with schizophrenia who are treatment-resistant[4] cannot be attributed to the effects of clozapine administration. This supports the possibility that lower cholesterol levels represent an intrinsic abnormality in metabolic function in these patients. Such a decrease may be clinically important in light of evidence that lowered cholesterol may reduce serotonergic neuronal activity.[2,7] If this is the case, then the ability of clozapine to reduce schizophrenic symptoms in patients who are resistant to the effects of typical antipsychotics may be attributable to its impact on serotonergic function.[8]

In summary, within 12 weeks treatment with clozapine produced significant decreases in the BPRS scores but did not alter levels of cholesterol in serum of patients with schizophrenia. Higher levels of TRI were the only significant effect on lipid levels after treatment. Further research is required to clarify the relation among neurotransmission, cholesterol, sex-related effects and drug-related effects.

Acknowledgements

We are grateful to the Schizophrenia Research Fund (UK) for financial support and to Dr. James R. Blackburn, Diane Bird and Helen Tremayne for their critical reading of the manuscript.

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