Psychopharmacology for the Clinician
Psychopharmacologie pratique

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

Do serum lipids predict response to clozapine treatment?

R.P. was a 26-year old man with a 9-year history of schizophrenia.[1] Refractory to previous trials of antipsychotics, he was prescribed clozapine. After 3 weeks of 225 mg/d on clozapine, we noted a remarkable improvement in his clinical status; 2 weeks later (5 weeks after initiating clozapine), we found his total cholesterol and triglyceride levels to be substantially elevated compared with preclozapine levels. Unable to reduce his lipid levels through dietary management over a 2-week period, we prescribed a lipid-lowering agent (atorvastatin). Over the next 7 weeks, his lipid levels fell substantially toward preclozapine values. He then relapsed into a psychotic episode. Apart from the addition of atorvastatin, we had not changed his pharmacological regimen (including dose of clozapine). Given that his lipid levels had reduced, we decided to discontinue the atorvastatin 2 days after the psychotic episode. Over the next 6 weeks, R.P.'s lipid levels increased, coinciding with improvement in his clinical status; he no longer experienced delusions or heard voices.

The changes in lipid levels could have influenced clozapine's pharmacological activity. In vitro studies show that increasing lipid concentrations results in the redistribution of clozapine from the lipoprotein-deficient fraction of serum (where it is usually 95% protein bound) to the low-density (LDL) and very low-density lipoprotein (VLDL) fractions.[2] This partitioning of clozapine into the lipoprotein fraction of serum in itself could modify its pharmacokinetics, tissue distribution and pharmacological activity in a manner that has been documented for other lipophilic drugs.[3]

Although some clinical data (mostly circumstantial) suggest a relation between lipid levels and clinical response to clozapine, the reports almost always draw attention to an apparent association between weight gain and response. To control for weight gain, we performed multiple regression analysis on a group of 55 patients treated with clozapine for 8 weeks and independently examined the association between lipid concentrations and symptoms using Positive and Negative Syndrome Scale (PANSS)[4] scores.[5] The analyses showed

1) that changes in lipid concentration predicted changes in symptoms over that of change in weight,
2) that an increase in triglyceride concentration was associated with a significant decrease in total PANSS score, and
3) that an increase in either total cholesterol or triglyceride concentration was associated with a significant decrease in PANSS negative subscale scores.

Data from our patient's case and the clinical trial[5] suggest that changes in lipid concentration from whatever cause could be responsible for some variations in symptoms over time among patients treated with clozapine. To explain the association between lipid concentration and symptoms, the following hypotheses have been put forward.

1) Lipids have a direct effect on symptoms independent of clozapine.
2) The partitioning of clozapine into the LDL and VLDL fraction of serum creates a "physiological depot" for clozapine. As such, clozapine is released from the lipoprotein fraction of serum in a sustained manner comparable to other depot antipsychotic medications.
3) The redistribution of clozapine into the lipoprotein fraction facilitates its penetration across the blood–brain barrier either by passive diffusion or by a receptor-mediated process.

Alternatively, the mechanism by which lipids influence clozapine's therapeutic response may be a combination of these hypotheses. Taken together, psychiatric symptoms should be monitored when treating dyslipidemia in a patient currently taking clozapine.

Although this case and clinical trial highlight an important clinical issue, they also raise questions that currently remain unanswered. Is the increase in lipids an acceptable risk? If so, how much of an increase is acceptable and for how long? Are there patients whose symptoms are improved by clozapine and who have normal lipid levels (either unchanged or controlled by lipid-lowering agents)? Further research is necessary to help answer these and other important questions.

Ric M. Procyshyn, PhD
William G. Honer, MD
BC Mental Health and Addictions Research Institute
Vancouver, BC
Alasdair M. Barr, PhD
Department of Anesthesiology, Pharmacology and Therapeutics
University of British Columbia
Vancouver, BC

Competing interests: Dr. Procyshyn is a paid consultant for and has received speaker fees from AstraZeneca, Janssen and Eli Lilly. Dr. Honer is a paid consultant for AstraZeneca, InSilico, Wyeth, Janssen and Pfizer, and has received speaker fees from AstraZeneca and Janssen and travel assistance from AstraZeneca and Eli Lilly. None declared for Dr. Barr.

Psychopharmacology for the Clinician columns are usually based on a case report that illustrates a point of interest in clinical psychopharmacology. They are about 500–650 words long and do not include references. Columns can include a bibliography which will be available only on the journal website and can be accessed through a link at the bottom of the column.
Please submit appropriate columns online at http://mc.manuscriptcentral.com/jpn; inquiries may be directed to jpn@cma.ca.

References

1. Pande S, Procyshyn RM, Nazerali M, et al. Do triglycerides modulate the effectiveness of clozapine? A case study. *Int Clin Psychopharmacol* 2002;17:197-9.
2. Procyshyn RM, Kennedy NB, Marriage S, et al. Plasma protein and lipoprotein distribution of clozapine. *Am J Psychiatry* 2001;158:949-51.
3. Wasan KM. Modifications in plasma lipoprotein concentration and lipid composition regulate the biological activity of hydrophobic drugs. *J Pharmacol Toxicol Methods* 1996;36:1-11.
4. Kay SR, Fiszbein A, Opler LA.The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-76.
5. Procyshyn RM, Wasan K, Thornton AE, et al. Changes in serum lipids, independent of weight, are associated with changes in symptoms during chronic clozapine. *J Psychiatry Neurosci* 2007;32: 331-8.