Clozapine Treatment And Risk Of Unplanned Pregnancy

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With recent advances in the medical treatment of chronic psychiatric patients who are capable of living productive lives in their communities, follow-up of these patients is often carried out by their family physicians. These family physicians are also generally responsible for family planning.

Many schizophrenic patients have preserved sex drives, but their judgments and responsibilities with respect to contraception are impaired. Often the family physician has to deal with lack of cooperation from these patients when they are asked to use common forms of contraception. Some family physicians rely on the infertility secondary to hyperprolactinemia caused by traditional antipsychotic agents. Clozapine is a new antipsychotic medication, the use of which is increasing rapidly, but not all physicians realize that it does not cause hyperprolactinemia-induced infertility. We present a case of a schizophrenic patient who became pregnant shortly after her antipsychotic treatment was changed to clozapine. The purpose of our report is to increase the awareness of physicians treating patients with clozapine of the possibility of undesired pregnancy when no contraceptive is used.

Case Report

A 37-year-old woman, born in Israel, has been schizophrenic from the age of 17 years; her brother also suffers from paranoid schizophrenia. During childhood and adolescence she was shy and passive and performed as an average student at school. At the age of 17 years she was hospitalized for the first time and was found to be suffering from schizophrenia with paranoid delusions, accompanied by auditory and visual hallucinations and a labile and inappropriate affect. She was treated with antipsychotic drugs and discharged from the hospital after a month. She did not serve in the army because of her illness but studied teaching. After graduating, she worked as a teacher for 2 years. She married at the age of 20 years, but her marital, social, and occupational life gradually deteriorated, and after 2 years of childless marriage she divorced her husband. Since then, she has been hospitalized eight times because of psychotic paranoid states. She attempted suicide several times by swallowing psychiatric drugs and was once hospitalized in coma in an intensive care unit. Between hospitalizations she did not function normally; she was independent but lived close to her parents in a supervised setting. She maintained some social relationships with her family. As a result of impairment in her social judgment, she has suffered from disinhibition of her sexual drives and has had many sexual relations with unfamiliar men. She did not use any contraceptives but nevertheless did not conceive during all these years, perhaps as a result of hyperprolactinemic amenorrhea.

She was prescribed lithium, up to 900 mg/d, trifluoperazine, up to 40 mg/d, and from 1990 to 1993 with haloperidol, up to 10 mg/d, and sulpiride, up to 1600 mg/d, without any noteworthy improvement in the paranoid delusions. In 1991 she agreed for the first time to the insertion of an intrauterine device (IUD), but it was removed after a half-year because of metrorrhagia. At that time she did not agree either to reinsertion of an IUD or to other contraceptive methods. In 1992 while in the hospital, her treatment was changed to clozapine, 400 mg/d, which was subsequently lowered later to 200 mg/d because of somnolence. All other medications were stopped. A weekly hematologic evaluation was carried out for 18 weeks. Her psychiatric condition improved considerably — she was less disturbed by delusions and hallucinations, and her affect was less paranoid

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and irritable. There was also some improvement in her routine daily activities as a housekeeper. Two months after the switch to clozapine treatment, a pregnancy was diagnosed. Abortion was induced and an IUD was reintroduced. Clozapine treatment, 300 mg/d, continued regularly.

Two months after the abortion a sonographic examination was performed to observe ovulatory activity; it showed normally growing follicles and ovulation — a clear indication of fertility. The patient also had a regular menstrual cycle of 30 days with a menstruation of 5 days. In addition, a 2 months' hormonal evaluation was carried out (Table 1), which indicated normal ovulation. Unfortunately prolactin levels were not determined before the change in her medication.

Discussion

Clozapine (8-chloro-11[4-methyl-1-piperazinyl]-5H-dibenzo[b,e][1,4] diazepine) is a unique antipsychotic drug that differs a great deal from the classical neuroleptic drugs. It is a strong antagonist of the D-1, 5-HT2 cholinergic, α-adrenergic, and histaminergic receptors and modulates GABA(γ-aminobutyric acid)ergic neurotransmission.[3-8] The mechanism responsible for the antipsychotic activity in drug-resistant schizophrenic patients is unclear. Clozapine is considered more effective than haloperidol or chlorpromazine in the treatment of resistant psychotic patients.[1] Furthermore, it has been effective in schizophrenic patients resistant to classical neuroleptic medications.[2]

Table 1. Endocrinologic Results during Clozapine Treatment.

Day of Menstruation	Result	Normal Range
Follicular phase		
Day 8		
Prolactin (ng/mL)	3.7	up to 30
Progesterone (ng/mL)	0.3	up to 1
Estradiol (pg/mL)	88	25–75
Follicle-stimulating hormone (mIU/mL)	5.5	5–20
Lutenizing hormone (mIU/mL)	4.6	5–20
DHEA-S (μg/dL)	150	up to 250
Thyroxine, free (ng/dL)	1.1	0.8–2.4
Luteal phase		
Day 21		
Prolactin (ng/mL)	13	up to 30
Progesterone (ng/mL)	4.6	5–20
Estradiol (pg/mL)	130	50–300
Day 30		
Prolactin (ng/mL)	4.0	up to 30
Progesterone (ng/mL)	6.4	up to 1
Estradiol (pg/mL)	144	75–150
DHEA-S (μg/dL)	112	up to 250
Thyroxine, free (ng/dl)	1.0	0.8–2.4

DHEA-S=dehydroepiandrosterone sulfate.

Clozapine has fewer neurologic side effects than do classical neuroleptics,[1,9,10] and since 1972 no cases of tardive dyskinesia in patients receiving it have been reported.[11] The most serious side effect, however, is agranulocytosis, which has an incidence of 20 cases per 1000 patients during 1 treatment-year[1,12]; therefore, careful patient selection and weekly hematologic measurements must be carried out. Additional side effects are a possible rise in liver enzymes and body temperature, increased salivation, weight gain, and somnolence.[13] Furthermore, clozapine influences the cardiovascular system (orthostatic hypotension, sinus tachycardia, PR shortening, and ST flattening) and the central nervous system (hyperthermia and hallucinations), and it can cause death when combined with other medications.[2,14,15]

Classical neuroleptic medications induce hyperprolactinemia.[16,17] This effect can result in impotence, gynecomastia, and galactorrhea in male patients, and breast engorgement, galactorrhea, anorgasmia, and amenorrhea in female patients. Increased plasma prolactin concentrations are accompanied by cyclic disturbances, ranging from irregular menstrual bleeding or inappropriate luteal function to anovulatory periods and cessation of menses. The mechanism by which prolactin exerts its antiovulatory effect is not yet clear. The possibilities are suppressive effect at the level of the gonadostat, interference with ovarian progesterone synthesis,[18] and suppression of gonadotropin-releasing hormone. Dopamine, which is blocked during classical neuroleptic treatment, has an inhibitory effect on prolactin secretion through the tuberoinfundibular dopaminergic tract.[19]

The results of the gynecologic endocrine study in our patient support the hypothesis that clozapine treatment does not elevate plasma prolactin levels and does not affect other hormonal levels sufficiently to inhibit fertility, but there is a need for a case-control study to prove that assumption. These findings are in agreement with two recent studies showing that clozapine does not affect prolactin secretion.[20,21] In the first study[20] prolac-

tin levels were measured serially in two male schizophrenic patients during 7 weeks of treatment with up to 450 mg of clozapine daily. Marked clinical improvement, as assessed by the Brief Psychiatric Rating Scale, was observed, while prolactin levels remained unaltered. In the second study,[19] morning serum prolactin levels were measured in 13 schizophrenic patients of both sexes during treatment with up to 800 mg of clozapine daily. Morning serum prolactin levels did not differ from corresponding levels during a placebo period. In another 6 patients without a placebo treatment period, there was no difference in prolactin levels compared with other patients. The conclusion from these findings is that clozapine does not interfere with prolactin secretion, unlike the hyperprolactinemic effect of classical neuroleptic drugs. The results in the present and the above studies contradict those of Ackenheil,[8] who found an elevation of prolactin levels during clozapine treatment in 4 healthy volunteers. The lack of effect of clozapine on prolactin levels could result in regular ovulation.

Conclusion

The present case confirms the reports that clozapine treatment does not elevate prolactin levels sufficiently to inhibit ovulation. It also points out the danger of unplanned pregnancy when clozapine treatment is given to female schizophrenic patients without contraceptive treatment. With traditional neuroleptic therapy there could be association between hyperprolactinemia and interference with ovulation. Conversely, when a patient is prescribed clozapine, there is not an associated hyperprolactinemia that can contribute to infertility. Pregnancy in clozapine-treated women might be even more problematic, inasmuch as the teratogenic effect of clozapine is as yet unclear.

References

1. Kane J, Honigfeld G, Singer J, Metzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; 45:789-96.
2. Fisher-Cornelssen KA, Ferner UJ. An example of European multicenter trials: multispectral analysis of clozapine. Psychopharmacol Bull 1976; 12:34-9.
3. Farde L, Weisel FA, Halldin C, Sedvall G. Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatry 1988; 45:71-6.
4. Fink H, Morgenstern R, Oelssner W. Clozapine — a serotonin antagonist? Pharmacol Biochem Behav 1984; 20:513-7.
5. Coward DM. Classical and non-classical neuroleptics induce super sensitivity of nigral GABA-ergic mechanisms in the rat. Psychopharmacology Berl 1982; 78:180-4.
6. Coward DM, Imperato A, Urwyler S, White TG. Biochemical and behavioural properties of clozapine. Psychopharmacology Berl 1989; 99(Suppl):S6-S12.
7. Markianos E, Nystrom I. Studie uber die dopamine beta hydroxylase in serum. Arzneimittelforschung/ Drug Research 1974; 24:1021-3.
8. Ackenheil M. Clozapine-pharmacokinetic investigations and biochemical effects in man. Psychopharmacology 1989; 99(5):32-7.
9. Claghorn J, Honigfeld G, Abuzzahab FS Sr, Wang R, Steinbook R, Tuason V, et al. The risks and benefits of clozapine versus chlorpromazine. J Clin Psychopharmacol 1987; 7:377-84.
10. Small JG, Milstein V, Marhenke JD, Hall DD, Kellams JJ. Treatment outcome with clozapine in tardive dyskinesia, neuroleptic sensitivity, and treatment-resistant psychosis. J Clin Psychiatry 1987; 48:263-7.
11. Lindstrom LH. The effect of long-term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for up to 13 years. Acta Psychiatr Scand 1988; 77:524-9.
12. Krupp P, Barnes P. Leponex-associated granulocytopenia: a review of the situation. Psychopharmacology Berl (Suppl) 1989; 99(S):S118-S21.
13. Cohen S, Chiles J, MacNaughton A. Weight gain associated with clozapine. Am J Psychiatry 1990; 147:503-4.
14. Panteleeva GP, Kovskaya MY, Bellyaev BS, Minsker EL, Vyner D, Ceskova E, et al. Clozapine in the treatment of schizophrenic patients: an international multicenter trial. Clin Ther 1987; 10:57-68.
15. Gaertner HJ, Fischer E, Hoss J. Side effects of clozapine. Psychopharmacology Berl 1989; 99(Suppl):S97-S100.
16. Rubin RT. Prolactin and schizophrenia. In: Meltzer HY, editor. Psychopharmacology: the third generation of progress. New York: Raven Press, 1987:803-8.
17. Smith S. Neuroleptic-associated hyperprolactinemia. Can it be treated with bromocriptine? J Reprod Med 1992; 37:737-40.
18. Del Pozo E, Wyss H, Tolis G, Alcaniz J, Campana A, Naftolin F. Prolactin and deficient luteal function. Obstet Gynecol 1979; 53:282-6.
19. Hokfelt T, Fuxe K. Effects of prolactin and ergot alkaloids on the tubero-infundibular dopamine (DA) neurons. Neuroendocrinology 1972; 98:100-22.
20. Kane JM, Cooper TB, Sachar EJ, Halpern FS, Bailine S. Clozapine: plasma level and prolactin response. Psychopharmacology Berl 1981; 73:184-7.
21. Meltzer HY, Goode DJ, Schyne PM, Young M, Fang VS. Effect of clozapine on human serum prolactin levels. Am J Psychiatry 1979; 136:1550-5.