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Plasma Clozapine Levels and the Treatment of L-DOPA-Induced Psychosis in Parkinson's Disease

A High Potency Effect of Clozapine

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The purpose of this study was to determine the plasma level of clozapine and its metabolite, N-desmethylclozapine, in Parkinson's disease patients with L-DOPA-induced psychosis responsive to clozapine. The psychotic symptoms of the three patients studied responded to low doses of clozapine with plasma levels of clozapine between 4.5 and 16.1 ng/ml and N-desmethylclozapine between 2.6 and 6.1 ng/ml, much below the plasma clozapine levels usually found in clozapine-treated refractory schizophrenia or affective disorders (range 100 to 687 ng/ml). Possible mechanisms that may account for clozapine's antipsychotic action in dopaminomimetic-induced psychosis in Parkinson's disease, including serotonin$_{2A}$ (5-HT$_{2A}$) and dopamine D$_4$ receptor blockade, at plasma levels that would be ineffective in refractory schizophrenia, are discussed. It is suggested that 5-HT$_{2A}$ receptor blockade is the most likely basis for the effectiveness of clozapine in L-DOPA psychosis.
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KEY WORDS: *Clozapine; L-DOPA; Parkinson's Disease; Psychosis*

There is now extensive evidence that clozapine is an effective treatment of the delusions, visual hallucinations, and other psychotic symptoms such as thought disorder, produced by L-DOPA or bromocriptine in patients with Parkinson's disease (Scholz and Dichgans 1985; Freedman and Lannon 1989; Pfeiffer et al. 1990; Freedman 1991; Pinter and Helscher 1993). Typical neuroleptic drugs, even thioridazine, which produces the least pseudoparkinsonism of any antipsychotic drug, can also alleviate psychotic symptoms in these patients, but are rarely used because they cause an intolerable exacerbation of extrapyramidal symptoms (Scholz and Dichgans 1985; Freedman and Lannon 1989; Pfeiffer et al. 1990; Freedman 1991). Clozapine has been found to be extremely effective in reducing L-DOPA psychosis in Parkinson's disease in nearly all cases, at doses ranging from 6.25 to 150 mg/day (median 62.5 mg/day; Scholz and Dichgans 1985; Ostergaard and Dupont 1988; Freedman and Lannon 1989; Roberts et al. 1989; Kahn 1990; Pfeiffer et al. 1990; Freedman 1991; Pinter and Helscher 1993; Factor et al. 1994). The effect of clozapine is persistent (Factor et al 1994). This dose range is nearly an order of magnitude less than the 130 to 900 mg/day (mean 465 mg/day) of clozapine required in the treatment of neuroleptic refractory schizophrenia (Meltzer 1992) and manic psychoses refractory to mood stabilizing drugs and neuroleptics (Calabrese and Meltzer 1991; Suppes et al. 1992). This difference in dosage required to treat psychosis in the common forms of se-

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vere mental illness and dopamine agonist-induced psychosis could be the result of pharmacokinetic or pharmacodynamic differences, or both.

Plasma levels of clozapine have been reported to predict clinical response in schizophrenia in two recent studies (Perry et al. 1991; Hasegawa et al. 1993). The mean plasma levels of clozapine in patients with schizophrenia who responded to clozapine were 404 ± 199 (range 100 to 687) ng/ml (Hasegawa et al. 1993). Mean N-desmethylclozapine plasma levels were 30.2% (Perry et al. 1991) and 75.0% (Hasegawa et al. 1993), of plasma clozapine levels. Dose was positively correlated with plasma levels in one study (Hasegawa et al. 1993). The lowest effective doses in these two studies were 350 mg/day (Perry et al. 1991) and 75 mg/day (Hasegawa et al. 1993).

The purpose of this study was to determine the relationship, if any, between plasma clozapine levels and clinical response in patients with Parkinson's disease receiving clozapine for L-DOPA-induced psychosis. Plasma levels of the major metabolite of clozapine, N-desmethylclozapine, were also studied.

METHODS

Two male patients, ages 71 and 77, and one female, age 69, with L-DOPA-induced psychoses and their guardians gave written informed consent to participate in this trial. The duration of Parkinson's disease and L-DOPA treatment were 6.1 ± 0.3 and 1.8 ± 0.2 years, respectively. The three patients had each developed a syndrome characterized by paranoid delusions and visual or auditory hallucinations that had been present for 4, 18, or 24 months, respectively. Two were moderately cognitively impaired and one severely cognitively impaired. The doses of carbidopa-L-DOPA (Sinemet®) at the time of initiating treatment with clozapine were 10/100 t.i.d., in one patient and 12.5/50 t.i.d. mg/day in the other two patients. No other relevant psychotropic drugs were administered.

Clozapine treatment was initiated at a dose of 12.5 (n = 1) or 25 (n = 2) mg/day and was titrated up to doses of 25 (n = 1) and 50 (n = 2) mg/q.h.s. The dose of carbidopa/L-DOPA was increased 25 to 50% in all three patients 1 to 2 weeks after clozapine treatment was initiated and the psychosis decreased in order to further improve motor function. Compliance with taking clozapine was assured because caregivers gave clozapine to the three patients each night at bedtime.

Psychopathology, including mental status, was assessed by one of the authors (J.K., a psychiatrist), using the Schedule for Affective Disorders and Schizophrenia-Change rating scale (Endicott and Spitzer 1978) and the Mini-Mental Status examination (Folstein et al. 1975). Motor symptoms were assessed by a neurologist (D.R.) using the Unified Parkinson's Disease Rating Scale.

Blood for plasma clozapine levels was obtained at 9:00 A.M. after 6 weeks or more of treatment when patients were receiving the doses described above. Each patient was studied at least twice. Plasma clozapine and N-desmethylclozapine levels were determined by high pressure chromatography by a modification of the method of Lovdahl et al. (1991). All determinations were done in duplicate.

RESULTS

Case Histories

Case 1: G.R. is a 71-year-old male with a two-year history of Parkinson's disease. Twenty months after beginning treatment with carbidopa, L-DOPA, and bromocriptine, he developed visual and olfactory hallucinations that caused anxiety and agitation. Psychotic symptoms persisted even after stopping the bromocriptine. He had moderate-severe cognitive impairment (MiniMental State Exam [MMSE] = 6). At the time of starting clozapine, he was receiving Sinemet® 10/100 t.i.d. Clozapine was started at 25 mg/day, with improvement noted during the first week. At a dose of 50 mg/day, the visual and olfactory hallucinations as well as the associated agitation ceased. Motor symptoms also improved when the dose of Sinemet® was increased to 15/100 mg/q.i.d., but cognitive function did not improve. No side effects of clozapine were noted. The patient's wife stated that clozapine prevented the need for nursing home placement.

Case 2: K.T. is a 77-year-old male with a 4-year history of Parkinson's disease. Treatment with intermittent carbidopa-L-DOPA provided some relief of motor symptoms but had to be stopped because of confusion and paranoia. Two trials of different neuroleptics at low doses were terminated because of severe rigidity. He was also unable to tolerate addition of trihexyphenidyl because of confusion. He was receiving 10/100 Sinemet® q.i.d. but was severely bradykinetic and rigid. Prior to admission, he resided in a nursing home because of unmanageable aggressive behavior and had auditory hallucinations, severe depressive symptoms, and severe dementia (MMSE = 2). With the first dose of clozapine (25 mg), aggressive behavior stopped. Within several days of reaching a dose of 50 mg/day, dramatic improvement in delusions and hallucinations was noted. The dose of Sinemet® was increased to 15/100 q.i.d. after 4 weeks without effect on mental status. Over a two-month period, there was marked decrease in depressive symptoms, and Hamilton Depression Scale total ratings decreased from 33 to 14. No change in MMSE occurred. Slight motor improvement was also noted. There were no side effects of note.

Case 3: S.J. is a 69-year-old female with a 20-year history of Parkinson's disease. She developed psychotic symptoms when given either amantadine or Sinemet® 12.5/50 t.i.d. At the time of admission, she had visual hallucinations, paranoid delusions about her husband, depression, and severe dementia (MMSE = 2). Clozapine was begun at 12.5 mg/day and increased to 25 mg/day. Full remission of delusions was noted within the first week, and almost complete disappearance of the visual hallucinations was noted within three weeks. There were no side effects of clozapine noted. The dose of Sinemet® was increased to 25/100 t.i.d. at 3 months and 37.5/150 t.i.d. at 6 months. Improvement in depression was noted with the Hamilton Depression scale score decreasing from 25 at baseline to 12 at 6 months. Motor symptoms improved. There was no change in MMSE. The patient's husband noted marked improvement in quality-of-life (i.e., more rational communication and independent living), for both the patient and himself.

Plasma Clozapine and N-Desmethylclozapine Levels

Plasma clozapine levels in patients 1 to 3 were 16.1, 6.8, and 4.5 ng/ml, at doses of 50, 50, and 25 mg/day, respectively. Plasma N-desmethylclozapine levels were 5.1, 4.9, and 2.6 ng/ml, respectively.

DISCUSSION

The major finding of this study is that clozapine was very rapidly effective in reducing paranoid delusions and visual or auditory hallucinations in three L-DOPA-treated patients with Parkinson's disease at doses of clozapine that produced plasma levels of clozapine and N-desmethylclozapine of less than 25 ng/ml. These levels are 40- to 50-fold lower than those usually required to treat refractory schizophrenia or mania (e.g., 300 to 500 ng/ml). They are also significantly lower than those plasma levels generally necessary to treat nontreatment-resistant schizophrenic patients (150 to 200 ng/ml; Haring et al. 1990; Meltzer et al. unpublished data). It is extremely unlikely that noncompliance was the cause of low clozapine levels in these patients because of caregiver assistance. Thus, it seems likely that the rapid and robust response of psychotic symptoms resulting from L-DOPA in patients with Parkinson's disease occurred at plasma clozapine levels that are far below those usually needed to ameliorate positive psychotic symptoms (i.e., delusions and hallucinations) in refractory schizophrenia or mania. This has been found to be ≥350 ng/ml in most patients but can be as low as 100 ng/ml (Perry et al. 1991; Hasegawa et al. 1993). It is noteworthy that the response to clozapine in the cases reported here as well as those in previous reports of clozapine treatment of Parkinson's disease with L-DOPA-induced psychosis (Freedman and Lannon, 1989; Freedman 1991) is so much more rapid than that generally observed in schizophrenic patients (Kane et al. 1988).

These findings raise a number of important questions. The first issue is how closely these plasma levels reflect brain levels. In the rodent, brain levels of clozapine have been reported to be fivefold higher than plasma levels in one study (Gauch and Michaelis 1970). In a second study, clozapine levels were 7.2-fold higher in brain than serum at brain clozapine levels lower than or equal to 5 μg/g, whereas for all brain clozapine levels, the brain clozapine levels were 24.3 times higher than serum levels (Baldessarini et al. 1993). The higher brain clozapine levels were attributed to effect of free plasma clozapine, lipophilicity and penetration of the blood brain barrier, binding to cellular elements in brain, and local brain metabolism (Baldessarini et al. 1993). It is unknown if similar differences between brain and serum clozapine levels exist for humans. Presumably, there is some degree of concentration of clozapine in human brain as well. However, unless this effect differs in Parkinson's disease patients and patients with schizophrenia, it is still the case that the plasma and presumably brain clozapine levels needed for an antipsychotic effect are much lower in Parkinson's disease.

The rapid response of positive symptoms to clozapine in L-DOPA-induced psychosis suggests a direct antagonist effect on a receptor for which clozapine has a relatively high affinity and which might be related to psychosis (e.g., the D_1, D_2, or D_4 DA receptor), a serotonin (5-HT) receptor (e.g., the 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, or 5-HT_7 receptors); or some presynaptic effect (e.g., decreased release of DA), which might lead to decreased postsynaptic dopaminergic activity. Antipsychotic effects mediated by actions at the $alpha_1$ adrenergic (Baldessarini et al. 1992) or muscarinic receptors (Bolden et al. 1991, 1992) are also possible. More slowly developing adaptive effects on the density of receptors or second messenger systems cannot be excluded because a single dose of clozapine can downregulate 5-HT_2 receptors (Matsubara and Meltzer 1989). Chronic clozapine treatment has usually been reported not to alter the number of D_1 or D_2 receptors in mesostriatal DA regions (Rupniak et al. 1984; Ashby et al. 1989b), but a recent autoradiographic study reported 21 days treatment with clozapine downregulated DA D_2 receptor density in several mesolimbocortical areas (Giardino et al. 1991).

Recently, remoxipride, a relatively specific D_2 receptor antagonist with some sigma receptor blocking properties (Köhler et al. 1990) was also reported to reduce visual hallucinations and psychotic thinking in four of five Parkinson's disease patients receiving L-DOPA with or without bromocriptine or selegiline

(Eriksson and Olsson 1993). One patient whose psychosis had responded to clozapine did not respond to remoxipride. The dose of remoxipride that was effective was 150 mg/day (n = 3) and 50 mg/day (n = 1). The usual clinical dose of remoxipride in schizophrenia is 300 to 400 mg/day (Lewander et al. 1980). Thus, the clinically effective dose of remoxipride in L-DOPA-induced psychosis is nearly comparable to that in schizophrenia, especially if one adjusts for the likelihood of lower dose requirement in the elderly. The effect of remoxipride in L-DOPA psychosis is most likely a result of its potent D_2 receptor blockade, although sigma antagonism, a property it shares with clozapine, cannot be ruled out. Remoxipride has no affinity for the D_1 receptor, which has been suggested to be the basis for the ability of clozapine to block L-DOPA-induced psychosis (Pinter and Helscher 1993). Like clozapine, remoxipride did not worsen parkinsonian symptoms in these patients, suggesting that it did not produce effective blockade of D_2 receptors in the striatum or inactivate nigrostriatal dopaminergic neurons. Clozapine has been shown to be a relatively weak antagonist at human striatal D_2 receptors, at least in the striatum (Fardé et al. 1992). However, it has been shown that clozapine blocks D_2 receptors to a greater extent in the rat limbic system than the striatum (Stockmeier et al. 1993). It is possible that clozapine and remoxipride could be much more effective in blocking mesolimbic D_2 receptors than striatal D_2 receptors.

The 5-HT_3 receptor antagonist, ondansetron, has also recently been reported to completely block L-DOPA-induced visual hallucinations in three patients and partially in four patients with Parkinson's disease (Zoldan et al. 1994). This effect was rapidly reversible with temporary discontinuation of ondansetron. The basis for this effect was suggested to be blockade of the effect of 5-HT released from serotonergic nerve terminals by DA formed in these terminals from L-DOPA. However, visual hallucinations are most likely the result of 5-HT_{2A} or 5-HT_{2C} receptor stimulation (Sadzot et al. 1989). Antagonism of 5-HT_3 receptors might be expected to decrease the release of DA by antagonizing 5-HT_3 heteroreceptors that enhance the release of DA (Blandina et al. 1988). Ondansetron also decreases the effect of intraaccumbens amphetamine on DA-mediated behaviors (Costall et al. 1987) and amphetamine-induced hunger in man (Silverstone et al. 1992). Thus, ondansetron might be effective in this syndrome by decreasing the release of DA. Clozapine is an effective 5-HT_3 antagonist in vivo, but its potency is relatively weak (Ashby et al. 1989a). Thus, it seems unlikely that 5-HT_3 antagonism could explain the action of clozapine at the low concentrations observed in this study.

Clozapine has been reported to block D_4 DA receptors at concentrations 15.3 times lower than that required to block D_2 receptors (Van Tol et al. 1991). It is possible that stimulation of supersensitive D_4 receptors by DA derived from L-DOPA may be the basis for the psychotic symptoms in Parkinson's disease. If so, antagonists selective for D_4 as compared to D_2 receptors might be effective in patients with Parkinson's disease who develop L-DOPA-induced psychotic symptoms. It may also be possible that supersensitive DA receptors of various types develop in the limbic as well as the striatal system in some patients with Parkinson's disease. The affinity of clozapine for the supersensitive D_4 receptors in limbic regions might be sufficiently augmented so that they are capable of being occupied by very low concentrations of clozapine that are ineffective in schizophrenia or mania. It has previously been demonstrated that atypical antipsychotics, including clozapine, sulpiride, and thioridazine, have increased potency at supersensitive postsynaptic DA receptors (see Meltzer 1991 for review).

It is possible that the L-DOPA-induced psychosis in Parkinson's disease is related to an excess of D_2 receptor-mediated dopaminergic neurotransmission because it also occurs with the direct-acting DA agonist bromocriptine, which is a mixed D_1/D_2 agonist and is effectively antagonized by the selective D_2 antagonist remoxipride. Because clozapine produced only weak blockade of DA D_2 receptors, the possibility must be considered that some nondopaminergic mechanism(s) are involved in the antipsychotic action of clozapine in both L-DOPA-induced psychosis and schizophrenia, for example, antagonist effects on 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7, α_2-adrenergic, muscarinic, or sigma receptors, or enhancement of glutamatergic function (Meltzer 1991; Roth et al 1994), and that these effects may occur at much lower concentrations in L-DOPA-induced psychosis than in schizophrenia or mania. The recent demonstration that very low doses of risperidone also block L-DOPA-induced visual hallucinations in Parkinson's disease suggests that both clozapine and risperidone are primarily acting via 5-HT_{2A} receptor blockade because risperidone is a potent 5-HT_{2A} antagonist with relatively weak D_2, D_4, and 5-HT_{2C} affinities (Roth et al. 1992; Schotte et al. 1993; Megens et al. 1994). Schremmer et al. (1990) demonstrated that ritanserin, a selective 5-$HT_{2A/2C}$ antagonist, and cyproheptadine, a nonselective 5-HT antagonist, were, like clozapine, able to block the supersensitive component of apomorphine-induced locomotor activity in 6-OH-DA-pretreated rats. Because haloperidol, which lacks 5-HT antagonist properties, was relatively ineffective in this model, it was suggested that 5-$HT_{2A/2C}$ receptor stimulation might enhance dopaminergic supersensitivity.

Nausieda et al. (1983) previously suggested that L-DOPA-induced psychosis may occur via a serotonergic mechanism. They proposed that L-DOPA may induce a decrease in brain 5-HT concentration (by com-

petition for L-tryptophan transport and displacement of 5-HT from nerve terminals following uptake of L-DOPA into 5-HT neurons) or an increase in 5-HT receptor sensitivity, or both. We suggest this might be the 5-HT_{2A} receptor. Blockade of 5-HT_{2A} receptors might lead to a suppression and normalization of mesolimbic and mesocortical dopaminergic activity (Ugedo et al. 1989; Sorensen et al. 1993). Blockade of 5-HT_{2A} receptors may be the basis of the action of clozapine in schizophrenia, mania, and psychotic depression as well. The difference in potency of both clozapine and risperidone in Parkinson's disease and these other psychoses may be a result of the need for only minimal interference with 5-HT_{2A} receptor stimulation in Parkinson's disease.

Nausieda and colleagues also suggest the importance of enhanced and dysregulated activity of the hypothalamo-pituitary-adrenal axis in L-DOPA psychosis, especially if accompanied by sleep disruption (Nausieda et al. 1982a, c). They proposed that glucocorticoids may enhance behavioral supersensitivity to 5-HT (Nausieda et al. 1982b). We have reported that clozapine decreases plasma glucocorticoid levels (Meltzer 1989). It is possible that this may be a factor in clozapine-induced suppression of L-DOPA- or bromocriptine-induced psychosis.

Other possible sensitive antipsychotic actions that could block L-DOPA psychosis of clozapine include modulation of glutamatergic function. Clozapine has recently been reported to block the locomotor activity and stereotypy produced by the NMDA receptor antagonist MK-801 in the rat at doses 11.2-fold lower than those required to block D_2-mediated behavior exhibited in the climbing mouse assay (Wettlaufer et al. 1993). Thus, clozapine appears to be much more potent against an NMDA-receptor mediated model of psychosis than a dopaminomimetic mechanism.

In conclusion, it has been found that clozapine is an effective treatment of L-DOPA-induced psychosis in Parkinson's disease at doses that produce plasma clozapine or N-desmethylclozapine levels $\leq$25 ng/ml. The basis for its antipsychotic action may be 5-HT_{2A} receptor blockade, although an inhibitory effect at D_4 receptors, decrease in glucocorticoid output, and enhancement of glutamatergic function are also possibilities. Further study of the L-DOPA or bromocriptine psychoses in Parkinson's disease might provide new insights into the role of DA and other neurotransmitters in several types of psychosis as well as the basis of the antipsychotic action of clozapine.

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