The Effect of Clozapine on Plasma Norepinephrine: Relationship to Clinical Efficacy

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Clozapine is an atypical neuroleptic medication with superior efficacy to conventional antipsychotic agents for patients with chronic, symptomatic schizophrenia. Neurochemical characteristics that distinguish clozapine from other neuroleptics and contribute to its differential efficacy are not known. We assessed the effects of clozapine on plasma levels of norepinephrine (NE) in a double-blind, parallel groups comparison of clozapine (n = 11) and haloperidol (n = 15) in chronic schizophrenic outpatients who had been previously treated with fluphenazine. Simultaneous measurements were obtained for plasma levels of the catecholamine precursor dopa, the dopamine metabolite dihydroxyphenylacetic acid (DOPAC), the NE metabolite 3,4-dihydroxyphenylglycol (DHPG), adrenocorticotropin (ACTH), cortisol, and hemodynamic parameters. Clozapine produced marked increases (471%) in plasma NE levels, whereas haloperidol had no significant effects on plasma NE levels. Clozapine also increased dopa and tended to increase DOPAC levels, without effects on DHPG, ACTH, or cortisol levels and without consistent changes in blood pressure. Across patients, the magnitude of clozapine-induced increments in plasma NE levels was positively related to improvement in positive symptoms and global symptomatology and was unrelated to the occurrence of extrapyramidal symptoms. The results suggest that clozapine differs importantly from other neuroleptics in increasing plasma NE levels, with the peripheral noradrenergic stimulation related to its superior efficacy profile. The unchanged DHPG levels and absence of hypertension suggest a more complex mechanism of action of clozapine than heightened NE release alone. [Neuropsychopharmacology 10:1–7, 1994]

Clozapine is an atypical neuroleptic with superior antipsychotic efficacy in patients with schizophrenia who are refractory to conventional treatments (Kane et al., 1988; Meltzer et al., 1990; Pickar et al. 1992; Breier et al. 1993). Intensive investigational efforts are aimed at identifying the biochemical characteristics of clozapine that produce its superior efficacy. This study reports that clozapine produces a striking peripheral neurochemical profile, including very high plasma levels of norepinephrine (NE), and that this profile is related to clozapine's clinically beneficial effects.

The neurochemical effects of clozapine differ in several ways from those of conventional neuroleptics. These properties include a high ratio of serotonergic 5-HT$_2$ receptor to dopamine D$_2$ receptor binding (Melt-

zer 1989) and relatively high affinity for the newly
cloned D_4 receptor (Van Tol et al. 1991). Clozapine also
has higher affinity for noradrenergic α_1- and α_2-
adrenoceptors than do many conventional neurolep-
tics (Baldessarini and Frankenberg 1991; Cohen and
Lipinski 1986; Richelson and Nelson 1984). In rats,
clozapine increases the activity of noradrenergic neu-
rons and noradrenergic turnover (Baldessarini et al.,
1992). Clinical studies have demonstrated that chronic
clozapine treatment increases cerebrospinal fluid (CSF)
and plasma NE levels, whereas conventional neurolep-
tics do not (Pickar et al., 1992; Liberman et al., 1991;
Ackenheil 1989). No study to date has reported a
significant relationship between clozapine's noradren-
ergic effects and its superior clinical efficacy.

The present study used a double-blind, parallel
groups design to compare the effects of clozapine with
those of haloperidol on plasma levels of NE in patients
who had been previously treated with fluphenazine.
Plasma levels of dopa, the precursor of the catechola-
mines; dihydroxyphenylacetic acid (DOPAC), a dopa-
mine metabolite; 3,4-dihydroxyphenylglycol (DHPG),
the intraneuronal metabolite of NE; and hemodynamic
parameters were also measured. These indices reflect
specific aspects of NE synthesis and metabolism and,
therefore, provide information about mechanisms of
changes in NE levels. Plasma cortisol and adrenocor-
ticotropin (ACTH) were measured to assess the spec-
ificity of noradrenergic effects. Relationships between
clozapine's effects on plasma NE levels and symptom
ratings were examined.

MATERIALS AND METHODS

Subjects

Twenty-six outpatients of the Maryland Psychiatric Re-
search Center participated in a double-blind, parallel
groups efficacy study of clozapine compared to halo-
peridol for chronic schizophrenia. The complete admis-
sion criteria and results of the efficacy study have been
reported previously (Breier et al. 1993). In brief, patients
who met DSM III-R (American Psychiatric Association)
criteria for chronic schizophrenia as determined by a
Structured Clinical Interview for DSM III R (SCID) (Spit-
zer et al. 1989) and by a best-estimate diagnostic con-
ference led by two research psychiatrists were included
in the study. Patients with concurrent drug abuse, al-
coholism, organic brain disorders, mental retardation,
or a medical condition in which clozapine is contrain-
dicated were excluded from the study of the patients.
The age range of the patients was 18 to 55 years. In ad-
dition, patients had a history of partial responsiveness
to conventional neuroleptics and had residual positive
and/or negative symptoms at the time of admission to
the study. Eleven patients were assigned randomly to

Table 1. Demographic and Clinical
Characteristics[a] of 26 Patients

Patient Characteristic	Clozapine (n = 11)	Haloperidol (n = 15)
Age (yr)	34.7 ± 5.9	36.8 ± 9.3
Sex (M/F)	7/4	13/2
Race (W/B)	7/4	10/5
SES	4 ± 1	4 ± 1
Age of onset (yrs)	17.3 ± 5.75	22.7 ± 5.69
Duration of illness (yrs)	17.4 ± 5.9	14.2 ± 7.1
No. of hospitalizations	6.0 ± 7	9.6 ± 11
BPRS positive symptom score		
Baseline	13.6 ± 4.6	13.4 ± 4.7
10 weeks	11.3 ± 5.14	12.4 ± 4.2
BPRS total score		
Baseline	36.7 ± 9.0	38.0 ± 8.7
10 weeks	33.5 ± 8.3	35.1 ± 7.6

[a] Data are presented as means ± standard deviations.

receive clozapine and 15 were assigned to receive halo-
peridol. Their sociodemographic and illness character-
istics are presented in Table 1.

Study Design

Patients underwent a 6-week prospective, open-labeled
trial of fluphenazine (20 mg/day) to confirm the pres-
ence of neuroleptic partial responsiveness and to es-
tablish clinical stability. Patients were than randomly
assigned to either clozapine or haloperidol groups dur-
ing a 10-week double-blind trial. Haloperidol-assigned
patients received a fixed dose of double-blind cogentin
(4 mg/day). Blood was drawn during the last week of
fluphenazine treatment (baseline) and after 5 weeks of
either clozapine or haloperidol treatment. Pulse rates
and blood pressures were obtained at baseline and af-
ter 5 weeks of treatment. Daily doses of clozapine and
haloperidol were increased progressively in a fixed
manner to 400 mg/day and 20 mg/day, respectively, by
the 4th treatment week and were then held constant
through the 5th week. Thus, blood was drawn at sta-
ble doses of comparable potencies of the two drugs.

The night before blood sampling, patients abstained
from food and drink except water and reported to the
clinic between 8:00 AM and 9:00 AM. An intravenous
catheter was inserted into the antecubital fossa and kept
patent with a heparin lock. After the subjects had been
supine (resting) for 75 minutes, blood samples were
drawn.

Assaying Procedure

Blood for assays of NE, dopa, DOPAC, and DHPG con-
centrations was collected in heparinized tubes and im-
mediately placed on ice, centrifuged within 30 minutes

of collection, and the plasma stored at −70°C. Plasma catechol levels were assayed simultaneously using liquid chromatography with electrochemical detection, as described previously (Eisenhofer et al. 1986). Briefly, after addition of an internal standard (dihydroxybenylamine) to the plasma, the catechols were extracted by absorption on alumina. After elution from the alumina, they were separated by reverse-phase, ion-pairing liquid chromatography and quantified by the current produced on exposure of the column effluent to a series of oxidizing electrodes and then a reducing electrode. The limits of detection were approximately 10 pg/ml. Blood for assays of cortisol and ACTH concentrations was collected in ethylenediaminetetraacetic acid–containing tubes, immediately placed on ice, centrifuged within 30 minutes of collection, and the plasma was stored at −70°C. Cortisol and ACTH levels were assayed in duplicate by radioimmunoassay (Chrousos et al. 1984). The approximate limit of detection for ACTH was 1 pg/ml and for cortisol it was 1 μg/dl.

Behavioral Assessments

Positive symptoms were assessed using the sum of the following four Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1961) items: hallucinations, conceptual disorganization, suspiciousness, and bizarre thoughts. The sum of the 18-item BPRS (total BPRS scores ranged from 18 to 126) was used as a general measure of symptomatology. The instrument was administered by masters and doctoral level clinicians with extensive experience with schizophrenia. Interrater reliability for the BPRS was 0.87. These two measures were selected for this study because they were significantly reduced by clozapine in our efficacy study (Breier et al. 1993) and in recent controlled studies (Kane et al. 1988; Pickar et al. 1992). In addition, extrapyramidal symptoms were assessed at baseline and after 10 weeks of treatment, using the Simpson–Angus Scale (scores ranged from 0 to 51) (Simpson and Angus, 1970).

Statistical Analyses

All plasma indices were first analyzed in a two-factor multivariate analysis of variance (MANOVA) using Hotelling's statistic, with the factors DRUG (clozapine or haloperidol) and TIME (baseline and 5-week treatment points). If a significant TIME versus DRUG interaction was found, each clozapine versus haloperidol week 5 plasma measure was then analyzed with an analysis of covariance, using baseline plasma levels as the covariate. Effects on physiologic parameters (heart rate, blood pressure) were determined by comparing values at 5 weeks of treatment using baseline (fluphenazine) values as covariates. Five-week treatment minus baseline change values for plasma and physiologic variables and 10-week (endpoint) minus baseline change values for BPRS scores and Simpson–Angus scores were calculated and used in correlative analyses.

RESULTS

The MANOVA for all neurochemical data revealed significant effects for DRUG ($F = 5.6$; $df = 6,18$; $p = .002$), TIME ($F = 4.9$; $df = 6,18$; $p = .004$), and DRUG versus TIME interaction ($F = 5.1$; $df = 6,18$; $p = .003$).

Norepinephrine Levels

Plasma NE levels in clozapine-treated patients were almost fivefold greater than those in the same patients treated with fluphenazine and almost fivefold greater than in haloperidol-treated patients (Fig. 1). Haloperidol treatment did not significantly affect plasma NE levels.

Dopa, DOPAC, and DHPG Levels

Clozapine, in comparison to haloperidol, produced significant elevations in plasma dopa levels and tended to increase plasma DOPAC levels (Table 2). There were, however, no significant differences between clozapine and haloperidol treatment in plasma DHPG levels (Table 2). Changes in dopa levels during clozapine treatment were significantly related to changes in NE levels ($r = .75$, $p = .008$). Change in NE was not significantly related to change in DOPAC and DHPG.

Cortisol and ACTH Levels

There were no significant differences between clozapine and haloperidol for plasma cortisol and ACTH levels (Table 3). Change in plasma NE was not significantly related to changes in cortisol and ACTH.
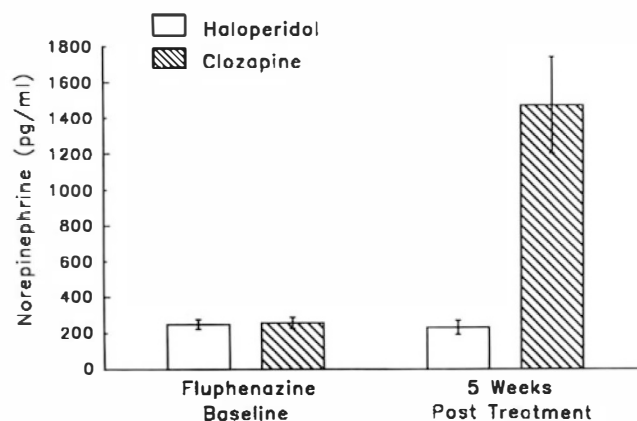

Figure 1. The effects of clozapine ($n = 11$) and haloperidol ($n = 15$) on plasma NE levels (mean ± SD).

Table 2. The Effects of Clozapine (n = 11) and
Haloperidol (n = 15) on Plasma Catecholaminergic
Precursors and Metabolites (pg/ml)[a] in
Schizophrenic Patients

Drug	Baseline[b]	5 Weeks Posttreatment	%D	F[c]	p
DOPA					
Clozapine	1811.4 ± 745	2288.7 ± 1007	+26		
Haloperidol	1636.9 ± 518	1633.9 ± 363	0	8.6	.007
DOPAC					
Clozapine	1083.3 ± 359	1503.4 ± 795	+38		
Haloperidol	1087.6 ± 257	1129.2 ± 305	+4	2.8	.10
DHPG					
Clozapine	836.3 ± 300	768.0 ± 224	−8		
Haloperidol	700.3 ± 126	717.0 ± 201	+2	.6	.43

[a] All levels determined while patients were at rest.
[b] All patients were stabilized on fluphenazine 20 mg/day.
[c] Clozapine versus haloperidol week 5 comparisons with baseline
levels as covariates.

Heart Rate and Blood Pressure

There were significant increases in heart rate (beats per
minute) produced by clozapine (baseline: 70.2 ± 11 and
week 5: 101.8 ± 9), compared with haloperidol (base-
line: 69.4 ± 15 and week 5: 73.4 ± 10) (F = 62.3; df =
1,20; p < .0001). Systolic blood pressure (mg Hg) was
not significantly different between clozapine (baseline:
119 ± 15 and week 5: 120 ± 15) and haloperidol (base-
line: 122 ± 15 and week 5: 126 ± 13) (F = 1.4; df = 1,20;
p = .23). Similarly, diastolic blood pressure was not
significantly different between clozapine (baseline: 72 ±
10 and week 5: 76 ± 9) and haloperidol (baseline: 70 ±
7 and week 5: 76 ± 7) (F = 0.4; df = 1,20; p = .5). There
were no significant correlations between change on
plasma NE and change in heart rate or systolic or di-
astolic blood pressure.

Norepinephrine and Symptom Changes

Changes in plasma NE levels were significantly cor-
related with clozapine-related changes in BPRS posi-

Table 3. The Effects of Clozapine (n = 11) and
Haloperidol (n = 15) on Plasma ACTH and
Cortisol Levels[a] in Schizophrenic Patients

Drug	Baseline[b]	5 Weeks Posttreatment	%D	F[c]	p
ACTH (pg/ml)					
Clozapine	21.7 ± 20	21.7 ± 19	0		
Haloperidol	18.5 ± 10	17.5 ± 10	−5	.27	.60
Cortisol (µg/dl)					
Clozapine	9.5 ± 3	9.6 ± 4	0		
Haloperidol	9.7 ± 4	10.0 ± 4	0	0	.99

[a] All levels determined while patients were supine and at rest.
[b] All patients were stabilized on fluphenazine 20 mg/day.
[c] Clozapine versus haloperidol week 5 comparisons with baseline
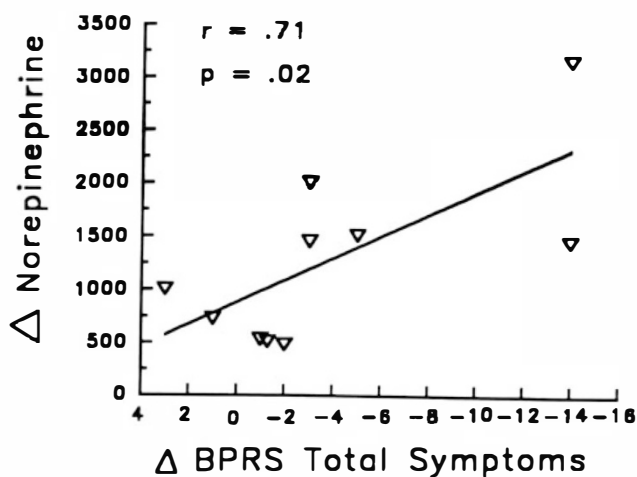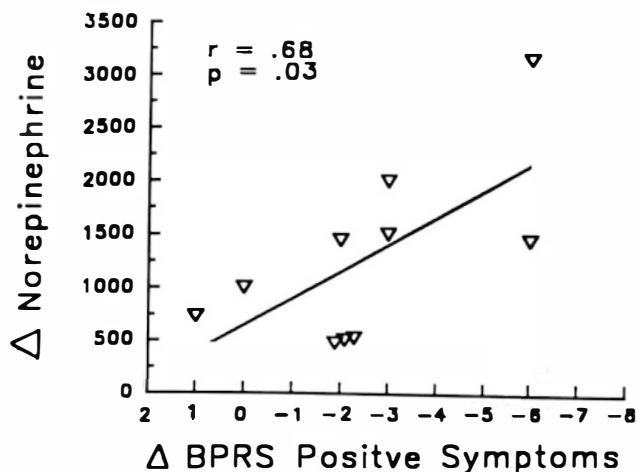levels as covariates.

Figure 2. Relationship between clozapine-induced changes
in plasma NE (pg/ml) and changes in positive and total BPRS
Symptoms.

tive symptom and BPRS total symptom scores (Figure
2). There was no significant relationship between change
in NE and change in symptoms during haloperidol
treatment. Simpson–Angus scores of extrapyramidal
symptoms were low at baseline and after 10 weeks of
treatment with clozapine (baseline: 1.5 ± 1 and week
10: 1.6 ± 2.1) or haloperidol (baseline: 1.6 ± 2 and week
10: 2.6 ± 1.8). There was no significant relationship be-
tween change in Simpson–Angus scores and change
in NE levels.

DISCUSSION

The results of this study show that clozapine treatment
elicits robust increases in plasma NE levels and that
these changes are related to the clinical efficacy of cloza-
pine in patients with chronic schizophrenia.

The finding of elevated plasma NE levels agrees

with previous clinical studies reporting clozapine-induced increases in plasma and CSF NE levels in schizophrenic patients (Lieberman et al. 1991; Pickar et al. 1992; Ackenheil 1989; Sarafoff et al. 1979). These elevations have been interpreted in terms of increased NE release in the brain and periphery; however, increased NE release alone cannot easily explain the lack of concurrent increases in plasma levels of DHPG, the main neuronal metabolite of NE, in the present study, and the lack of concurrent increases in CSF levels of MHPG, a major metabolite of NE in the brain, in the study by Pickar et al. (1992). Additional possible mechanisms of clozapine-induced increases in NE levels are discussed below.

The significant relationship between clozapine's effects on positive and global symptoms and changes in plasma NE levels suggests the possibility that clozapine's superior efficacy profile results from effects on noradrenergic function in the brain. Although most research about catecholamines and schizophrenia has focused on the pathophysiologic role of dopamine, several lines of evidence from postmortem studies (Farley et al. 1978; Bird et al., 1979a, 1979b; Crow et al. 1979; Kleinman et al. 1979) or responses to pharmacologic challenges (Sternberg et al. 1982; Glazer et al. 1987) and CSF and plasma (Breier et al. 1990; van Kammen et al. 1989, 1990; Gomes et al. 1980; Lake et al. 1980; Sternberg et al. 1981; Kemali et al. 1982; Gattaz et al. 1983; Castellani et al. 1982; Naber et al. 1980; Albus et al. 1982) have suggested a noradrenergic mechanism. Circulating NE does not cross the blood-brain barrier (Leimdorfer et al. 1947; Liljedahl and Von Euler 1954; Weil-Malherbe et al. 1959), but drugs that affect NE synthesis, release, reuptake, metabolism, or adrenoceptor function in the periphery, and which enter the central nervous system, generally produce the same effects in the brain, accounting for directionally similar changes in CSF and plasma NE levels (Goldstein et al., 1987).

Treatment with haloperidol and fluphenazine was not associated with plasma NE levels above those normally observed in healthy volunteers (Goldstein 1987; Kagedal and Goldstein 1988). The low rate of extrapyramidal symptoms and the lack of correlation between these symptoms and NE levels suggests that the relationship between improvement in positive symptoms and global symptomatology and change in plasma NE is not secondary to the influences of extrapyramidal symptoms.

Clozapine has high affinity for the α_1-adrenoceptor with three times greater potency at this receptor than haloperidol (Cohen and Lipinski 1986; Richelson and Nelson 1987; Baldessarini and Frankenberg 1991). In addition, clozapine treatment upregulates α_1-adrenoceptors, with particularly marked effects in forebrain areas (Cohen and Lipinski 1986). In contrast, clozapine has little effect on dopamine D_2 receptor density, whereas haloperidol and other conventional neurolep-

tics upregulate D_2 receptors (Cohen and Lipinski 1986). One may propose that blockade of α_1-adrenoceptor-mediated effects in the brain is the basis for the clinical benefit of clozapine treatment, and that clozapine-induced blockade of α_1-adrenoceptors may produce secondary increases in NE release.

Clozapine also antagonizes α_2-adrenoceptors (Souto et al. 1979). Other neuroleptics bind to this receptor as well, although neuroleptics generally bind more avidly to α_1- than α_2-adrenoceptors (Baldessarini et al. 1992). In the brain and periphery, α_2-adrenoceptor blockade increases NE release, probably by interfering with modulation by α_2-adrenoceptors on noradrenergic cells or terminals.

Combined blockade of α_1- than α_2-adrenoceptors would be expected to produce high plasma NE levels, due to vasodilation-induced reflexive increases in sympathoneural outflow, combined with the above-noted blockade of modulatory α_2-adrenoceptors on sympathetic nerves. Blockade of α_1- and α_2-adrenoceptors also helps to explain the lack of increase in blood pressure in clozapine-treated patients, despite marked increases in plasma NE levels sufficiently large to evoke vasoconstriction and hypertension in healthy volunteers (Goldstein et al. 1986).

This mechanism of increases in NE levels cannot explain, however, the lack of increase in DHPG levels in the present study, because both reflexive stimulation of sympathetic outflow and blockade of α_2-adrenoceptors increases reuptake of endogenously released NE. Analogously, clozapine has been reported not to affect CSF MHPG levels, despite significant increases in CSF NE levels (Pickar et al. 1992). The latter finding excludes augmented O-methylation as the basis for the lack of increase in DHPG levels.

These unexpected results force consideration of other mechanisms by which clozapine may increase NE concentrations in extracellular fluid in the brain and periphery without concurrent increases in concentrations of its neuronal metabolite. The most straightforward additional mechanism is blockade of NE reuptake. The combination of reuptake blockade and α_2-adrenoceptor blockade produces marked increases in plasma NE levels in healthy volunteers (Goldstein et al. 1986, 1988). Because blood pressure also increases acutely in this setting, combined reuptake blockade and α_2-adrenoceptor blockade would not account for the hemodynamic data. The combination of high plasma NE levels, the absence of changes in DHPG levels, and the absence of hypertension during clozapine treatment therefore seem to require a complex mechanism that includes blockade of both subtypes of α-adrenoceptors and blockade of the NE transporter. We are unaware of research findings testing the latter putative effect of clozapine. The increases in plasma DOPA and DOPAC levels are consistent with increased catecholamine biosynthesis in sympathetic nerves, to match increases in noradren-

ergic turnover. Analogous changes in DOPA and DOPAC levels have been reported in noradrenergic centers in the brain in animals undergoing clozapine treatment (Baldessarini et al. 1992). It will be important to examine the time course of clozapine's effects on noradrenergic function to determine if data gleaned from acute dosing studies apply to chronic treatment conditions.

The failure of clozapine to change plasma ACTH and cortisol levels supports the contention that the elevations in plasma NE levels are not secondary to generalized arousal or distress. Previous clinical studies have reported that chronic clozapine treatment decreases plasma cortisol levels (Pickar et al. 1992; Meltzer 1989). It is possible that reductions in cortisol previously observed were secondary to clozapine's effects on reducing stress and arousal, compared with levels in the untreated control condition. Because our subjects were stable outpatients and did not participate in neuroleptic washout (which may increase arousal, activation and stress) prior to clozapine treatment, they would have been less likely to experience stress-reducing effects from clozapine.

In summary, clozapine treatment markedly increases plasma NE levels, with the increases related to clinical effects of the drug. The mechanism of noradrenergic activation appears to be complex, possibly involving a combination of adrenoceptor blockade and blockade of the NE transporter. The findings generally lead one to reconsider the role of endogenous NE in the pathophysiology of schizophrenia, with central noradrenergic systems a potential new target of antipsychotic drug action.

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