

만성 정신분열증 환자에서 Clozapine의 치료반응과 혈장 Homovanillic Acid 및 5-Hydroxyindoleacetic Acid 농도와의 관계

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Relationship between Clozapine-Induced Therapeutic Responses and Plasma Homovanillic Acid and 5-Hydroxyindoleacetic Acid Levels in Patients with Chronic Schizophrenia

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ABSTRACT

This study was done to examine changes of plasma homovanillic acid(HVA), 5-hydroxyindoleacetic acid(5-HIAA), and HVA/5-HIAA ratio during an 8-week clozapine trial and to investigate the relationship between the plasma monoamine metabolites and treatment responses.

Twenty-seven chronic schizophrenic patients were treated for 8 weeks with clozapine. The psychopathology was assessed at baseline just clozapine trial and then every 2 weeks until the end of 8-week clozapine treatment using the Positive and Negative Syndrome Scale(PANSS) and the Clinical Global Impression scale(CGI). The plasma HVA and 5-HIAA levels were measured also biweekly using high performance liquid chromatography with electrochemical detection method.

Plasma HVA and 5-HIAA levels were significantly decreased during a 8-week clozapine treatment, although plasma HVA/5-HIAA ratio showed no significant change. The changes of plasma HVA levels were in significant correlations with the changes of PANSS positive scores, of general psychopathology scores, and changes of total scores. The changes of plasma 5-HIAA levels were in significant correlations with the changes of PANSS negative scores. But the changes of plasma HVA/5-HIAA ratio had no significant correlation with any PANSS subscale score changes. 48% of the patients treated with clozapine was categorized as responders, who showed at least a 20% decrease in PANSS total score and a CGI severity score of mildly ill or less (3) at the end point of the study. The baseline plasma HVA levels and HVA/5-HIAA ratio were significantly higher in responders(N=13) than in nonresponders(N=14). But no significant difference in baseline levels of plasma 5-HIAA was found between responders and nonresponders. At the end point of the study, there was significant difference in the change of plasma HVA between responders(40.3% decrement) and nonresponders(3.1% increment). But no significant differences in the change of plasma 5-HIAA and the change of plasma HVA/5-HIAA ratio between responders and nonresponders were observed.

These results suggest that the antipsychotic effect of clozapine on positive symptoms may be associated with dopaminergic blocking activity, and that on negative symptoms may be associated with serotonergic blocking activity. The baseline plasma HVA levels and the change of HVA levels from baseline may be useful predictors of treatment response with clozapine.

KEY WORDS : Clozapine · Therapeutic response · Plasma HVA · Plasma 5-HIAA · Chronic schizophrenia.

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서론

1950 chlorpromazine 가 가 paradigms (An - den 1970 ; Carlsson Lindqvist 1963) D₂ Clozapine dibenzodiazepine 가 가 (atypical) clozapine 가 (clinical potency) (Creese 1976 ; Seeman 1975) (overactivity) (Juul - Povlsen 1985 ; Meltzer 1989). 가 clozapine 가 (1993 ; Kane 1988 ; Meltzer 1989) . Clozapine chlorpromazine haloperidol catalepsy , prototype (Meltzer 1989). clozapine homovanillic acid(HVA) (Bowers Heninger 1981 ; Post 1975 ; Sharma 1989) 가 HVA 가 (Berger 1980 ; Rimon 1971), (Sharma 1989). 1980 가 가 (typical antipsychotic drugs) 1993). 가 (Meltzer 1989 ; Szymanski 1993). 가 HVA 가 가 (Davidson 1987 ; Davila 1988), HVA/5 - HIAA(5 - hydroxyindoleacetic acid) HVA/ MHPG 가 (Bowers 1989 ; Chang 1990 ; Davidson 1991 ; Pickar 1986), HVA (positive) (Pickar 1990) 가 (Hsiao 1993 ; Szyman - ski 1993). Hsiao (1993) HVA 5 - HIAA HVA/5 - HIAA (Crow 1979 ; Haberland Hetey 1987) (Widerlov 1988) D₂ 20 30% (Davis 1980 ; Kane 1989), 가 (Andreasen Olsen 1982) 가 가 가

clozapine HVA 8
 5 - HIAA HVA/5 - HIAA PANSS 가
 가 가 , ,
 HIAA HVA/5 - HIAA HVA , 5 -
 가 가 , clozapine ndrome Scale”(PANSS) 가 . PANSS
 HVA HVA/5 - HIAA , 5 - HIAA 가 Kay (1987)
 , HVA/5 - HIAA , clozapine 8 가 video tape Kay PANSS
 HVA , 5 - HIAA 가 가 (inter - rater reliability)가 0.8
 HVA/5 - HIAA 가 가 CGI 가
 가 clozapine CGI(Clinical Global Impression ; Guy 1976)
 가 가

apine 가 2
 가 가 .
 “ Positive and Negative Sy -
 ndrome Scale”(PANSS) 가 . PANSS
 Kay (1987)
 Kay PANSS
 video tape
 가 가 (inter - rater reliability)가 0.8
 CGI 가
 CGI(Clinical Global Impression ; Guy 1976)
 가

대상 및 방법

1. 연구대상

, 1) , 2)
 18 45 , 3) 2
 , 4) DSM - III - R(American Psychiatric Associa -
 tion 1987)
 , 1) , , 2)
 가 , 3) 가 5000/mm³
 가 2500/mm³ , 4)
 , 5)
 , 6) , 7)
 , 8) (8) depot

2. 연구방법

1) 치료약물 투여

clozapine 가 가
 clozapine . Clozapine
 25mg 1 2 50mg bid 2 ,
 75mg tid 2 , 100mg tid 2 ,
 (2)
 8

2) 임상증상의 평가

가 1 cloz -

Kane (1988)

PANSS 가 20%
 CGI 가 (mild)

3) 혈장 HVA 및 5-HIAA 농도측정

tryptophan
 2 ,
 8 ()
 (15cc) EDTA - tube
 - 70
 HVA 5 - HIAA Seegal (1986)
 (electrochemical deceptor)가
 (high pressure liquid chromato -
 graphy ; HPLC)
 HPLC
 HPLC Waters (Waters Associates, Milford, MA,
 USA) model 510 pump, model 717 plus autosampler,
 model M460 amperometric detector, Temperature control
 module(TCM)
 Bus LAC/E card Millenium™ 2010 Chr -
 omatography Manager software가 IBM PC
 column Shiseido (Tokyo, Japan) 250
 × 4.6mm I.D., 5 μm particle size, reversed phase C₁₈ colu -
 mn column temperature 30
 sodium phosphate
 (monobasic), citric acid, 1 - outane sulfonic acid(sodium salt),
 isovanillic acid, EDTA(ethylene diamine tetra - acetic acid)
 Sigma (St. Louis, MO, USA), methyl alcohol, tetrahy -

drofuran Burdick and Jackson (Muskegon, MI, USA), lyophilized serum Biorad (Segrate, Italy), perchloric acid Wako Pure Chemical (Osaka, Japan), phosphoric acid E. Merck (Darmstadt, Germany), Milli-A water system(Millippre Corp, Bedford, MA, USA)

3 Sigma HVA
5 - HIAA , Stock 2
1mg/ml - 70

가

HVA 5 - HIAA
HVA 5 - HIAA perchloric acid

1ml sample 4
, internal standard isovanillic acid 100
vortex mixing , 100 µl perchloric acid

vortex mixing 30 4
13,000×g 15 4

40 µl HPLC
system

0.08M sodium phosphate, 0.01M citric acid, 5mM 1 - Octane sulfonic acid, 0.1mM EDTA가

phosphate buffer 945ml 50ml methyl alcohol 5ml tetrahydrofuran 1L pH 3.1

0.22 µm pore size filter ultra - son - icator 30 1.2ml/ min , amperometric detector +

850mV vs Ag/AgCl electrode potential 1.5×1nA
HVA, 5 - HIAA

int -

ernal standard가 가 drug free serum (ratio)

4) 자료분석

Clozapine PANSS , HVA ,
5 - HIAA , 5 - HIAA , HVA/5 - HIAA

가 Bonferroni's t - test

. Clozapine HVA ,
5 - HIAA , HVA/5 - HIAA

PANSS , PANSS
, PANSS

Pearson's correlation test

(%) [(-)/
× 100]

(PANSS , PANSS , CGI) , PANSS , PANSS , CGI) ,

(HVA , 5 - HIAA , HVA/5 - HIAA) Student's t - test

Clozapine 8 Student's t - test

SPSS/PC⁺(ver 5.0) 0.05

결 과

1. 인구사회학적 자료

29 clozapine 2
1 1
27 22
5 27.3±6.6
18.7±4.4 , 8.6±5.6 . DSM - III - R 18 (68%) 가
4 , 3 , 1

1 (Table 1).

2. Clozapine 치료에 따른 혈장 HVA 농도, 5-HIAA 농도 및 HVA/5-HIAA 농도비의 변화

Clozapine HVA 5 - HIAA 가
, HVA/5 - HIAA 가 . Bo - nferoni's t - test HVA 가 ,
8 가 ,
5 - HIAA 6 , 8

Table 1. Demographic data and schizophrenic subtypes(N=27)

Variables	Value
Age(years)	27.3± 6.6
Sex(frequency)	
Male	22
Female	5
Onset age(years)	18.7± 4.4
Duration of illness(years)	8.6± 5.6
Number of hospitalization	3.9± 2.8
Weight(kg)	66.8± 11.4
Subtype of schizophrenia	
Undifferentiated type	18
Residual type	4
Paranoid type	3
Catatonic type	1
Disorganized type	1

3. Clozapine 치료에 따른 PANSS 하위척도점수의 변화

Clozapine PANSS 가 Bonferroni's t-test 가 PANSS 2 8 가 PANSS 4 8 가 (Table 3).

4. Clozapine 치료에 따른 혈장 대사물의 변화율과 치료반응과의 상관관계

Clozapine 8 PANSS HVA 5 - HIAA HVA/5 - HIAA PANSS (r=0.587, p=0.002), PANSS (r=0.539, p=0.004), PA - NSS (r=0.648, p<0.001)

Table 2. Changes of plasma monoamine metabolite levels during an 8-week clozapine treatment in chronic schizophrenia

	Duration of clozapine treatment(week)					p ^a
	Baseline	2nd week	4th week	6th week	8th week	
HVA(ng/ml)	10.37 (2.54)	8.71 (2.53)	8.88 (2.15)	8.96 (3.41)	7.45 (2.64) ^b	0.018
5-HIAA(ng/ml)	6.36 (1.62)	5.84 (1.54)	5.37 (1.31)	4.57 (1.81) ^b	4.58 (1.87) ^b	0.005
HVA/5-HIAA	1.75 (0.73)	1.52 (0.57)	1.75 (0.50)	2.13 (1.17)	2.10 (2.62)	0.225

Each value represents mean(standard deviation)

^a : Repeated measures one-way ANOVA

^b : p<0.05 compared to baseline by post-hoc Bonferroni's t-test

Table 3. Changes of PANSS scores during an 8-week clozapine treatment in chronic schizophrenia

	Duration of clozapine treatment(week)				
	Baseline	2nd week	4th week	6th week	8th week
PANSS scores					
Positive ^a	26.26 (6.65)	21.22 (7.44)	19.15 (5.70)	17.74 (4.70)	17.15 (4.56)
Negative ^b	36.19 (7.71)	33.59 (7.88)	31.19 (11.64)	27.26 (6.65)	27.37 (6.18)
General ^a	65.52 (10.04)	56.41 (1.54)	50.67 (9.10)	45.11 (8.50)	44.26 (7.25)
Total ^a	127.96 (20.11)	111.22 (21.58)	101.00 (22.19)	90.11 (17.13)	88.78 (14.18)

Each value represents mean(standard deviation)

^a : p<0.05 by repeated measures one-way ANOVA and p<0.05 compared to baseline from 2nd week through 8th week by post-hoc Bonferroni's t-test

^b : p<0.05 by repeated measures one-way ANOVA and p<0.05 compared to baseline from 4th week through 8th week by post-hoc Bonferroni's t-test

(Table 4). 5 - HIAA PAN - (r=0.659, p<0.001)(Table 4).

Clozapine 8 HVA 5 - HIAA PANSS (r=0.713, p<0.001), PA - NSS (r=0.516, p=0.007) HVA PANSS (r=0.481, p=0.013), (r=0.644, p<0.001) HVA/5 - HIAA PANSS (Table 5).

5. 치료반응군과 치료비반응군 간의 clozapine 투여전 인구사회학적 자료 및 기준 임상변수의 비교

Clozapine 8 13 (48%), 14 (52%) Clozapine 가 (5.2 ± 3.2) (2.5 ± 1.3) (p = 0.008)(Table 6). 22 11 5 2 clozapine PANSS 가 (Table 6).

6. 치료반응군과 치료비반응군 간의 clozapine 투여전 기준 대사물 농도와 clozapine 투여 8주 후 대사물 농도 변화율의 비교

Clozapine HVA HVA/5 - HIAA 5 - HIAA

Table 4. Correlation between the percentile changes of plasma monoamine metabolites levels and the percentile change of PANSS subscale scores from baseline at the end of study

	HVA	5-HIAA	HVA/5-HIAA
PANSS scores			
Positive	0.587(0.002) ^a	-0.029(0.889)	-0.052(0.805)
Negative	0.372(0.061)	0.659(0.000) ^a	0.135(0.520)
General	0.539(0.004) ^a	-0.074(0.721)	-0.331(0.106)
Total	0.647(0.000) ^a	0.148(0.472)	-0.166(0.427)

Each value represents correlation coefficient(P value)

^a : p<0.05 by pearson's correlation test

Table 5. Correlation between the percentile changes of plasma monoamine metabolites levels and the percentile change of PANSS each item scores from baseline at the end of study

	HVA	5-HIAA	HVA/5-HIAA
Positive subscale			
Delusion	0.3940.046 ^a	0.0530.796	0.0520.806
Conceptual disorganization	0.2990.138	-0.3590.071	-0.1580.450
Hallucinatory behavior	0.7130.000 ^a	0.0170.934	-0.1930.355
Excitement	0.2010.324	0.2460.226	0.1750.040
Grandiosity	0.1170.570	-0.0360.862	0.1640.433
Suspiciousness/persecution	0.2960.142	0.0150.940	0.1560.458
Hostility	0.2560.206	0.0790.701	-0.1430.495
Negative subscale			
Blunted affect	0.3320.098	0.4810.013 ^a	0.2400.249
Emotional withdrawal	0.0920.654	0.1430.487	-0.0300.887
Poor rapport	0.0850.680	0.6440.000 ^a	0.1670.425
Passive/apathetic social withdrawal	0.3480.082	0.3070.128	0.1500.475
Difficulty in abstract thinking	-0.0260.900	-0.1730.398	-0.2700.192
Lack of spontaneity and flow of conversation	0.5160.007 ^a	0.2830.162	-0.2810.174
Stereotyped thinking	0.3860.052	0.3560.075	0.0750.723

Each value represents correlation coefficient (P value)
^a : p < 0.05 by Pearson's correlation test

Table 6. Comparison between responders and non-responders in demographic data and baseline clinical assessment scores

Variables	Responders (N=13)	Non-responders (N=14)	p ^a
Demographic data			
Age (years)	26.2 ± 6.4	28.4 ± 6.8	0.413
Sex (frequency)			-
Male	11	11	
Female	2	3	
Onset age (years)	19.7 ± 5.0	17.9 ± 3.8	0.288
Duration of illness (years)	6.5 ± 5.7	10.5 ± 4.8	0.062
No. of hospitalization	2.5 ± 1.3	5.2 ± 3.2	0.008
Baseline clinical assessment scores			
PANSS positive	35.0 ± 8.6	38.1 ± 6.2	0.284
PANSS negative	27.6 ± 6.1	25.0 ± 7.1	0.317
PANSS total	128.6 ± 18.2	128.2 ± 22.0	0.959
CGI severity	6.2 ± 1.0	6.2 ± 1.1	0.879

Each value represents mean ± S.D. of frequency
^a : p value by Student's t-test

Table 7. Comparison between responders and non-responders in baseline plasma monoamine metabolites levels and the percentile change of monoamine metabolites levels

Variables	Responders	Non-responders	p ^a
Baseline metabolites levels			
HVA level (ng/ml)	11.7 ± 2.5	8.4 ± 2.1	<0.001
5-HIAA level (ng/ml)	6.1 ± 1.3	6.6 ± 1.9	0.423
HVA/5-HIAA	2.0 ± 0.5	1.4 ± 0.7	0.037
8 monoamine metabolites			
HVA	40.3 ± 28.8	31.1 ± 19.1	<0.001
5-HIAA	16.5 ± 34.7	11.9 ± 39.2	0.755
HVA/5-HIAA	22.7 ± 33.0	70.9 ± 85.5	0.099

Each value represents mean ± S.D.
^a : p value by Student's t-test

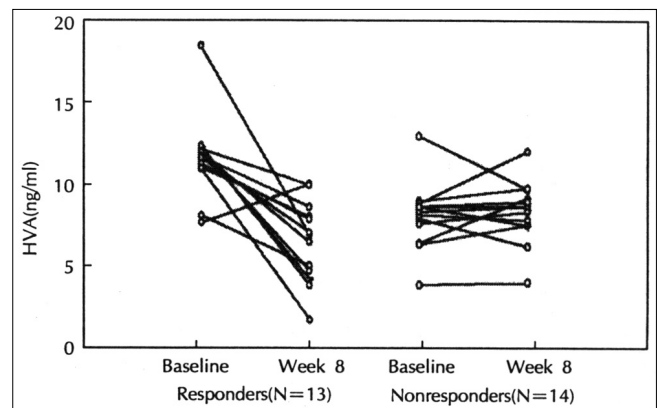


Fig. 1. Mean plasma homovanillic acid at baseline and at end of study (week 8) for responders and nonresponders.

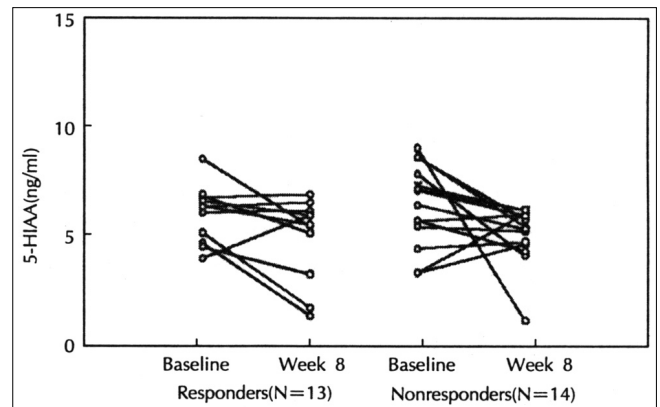


Fig. 2. Mean plasma 5-HIAA at baseline and at end of study (week 8) for responders and nonresponders.

가 (Table 7).
 8 HVA 가 40.3% ,
 HVA 가 3.1% 가
 (Table 7, Fig. 1). 5 - HIAA
 (16.5%) (11.9%)

가 (Table 7, Fig. 2). HVA/5 - HIAA
 가
 (Table 7).

고찰

clozapine , clozapine 38
. Clozapine 8 PANSS 가 20% 63% D₂ . Clozapine
CGI 가 (mild) D₁ D₂
27 13 (48.1%) D₁
30 50% clozapine D₂ D₄
(Kane 1988 ; Lindström 1988 ; Na-ber 1989 ; Small 1987) (Van Tol 1991).
Clozapine HVA 5 - HIAA D₂ HVA 가
clozapine 4 9 (Meltzer 1989 ; Pickar 1992 ; Potter 1989) HVA D₂ D₁
HVA 가 HVA, 5 - HIAA D₄ .
HVA, 5 - HIAA가 가 clozapine 5 - HIAA
가 가 가 . Clozapine 5 - HT
가 가 가 (Meltzer 1989), Nordström (1993)
가 가 가 PET colapine 5 - HT
가 가 가 HT HT clozapine 5 -
HVA HVA HVA HVA 5 - HIAA 5 - HIAA
(Bacopoulos 1979 ; Kendler Davis 1984) debrisq - 5 - HIAA
uine HVA (1995 ; Alfredsson
(Massemnd 1993) HVA Wiesel 1989) 5 - HIAA
HVA (Degrell Nagy 1990) ,
HVA HVA 5 - HIAA
(Kahn Davidson 1993) 가 clozapine, risperidone - (se-
가 가 가 rotonin - dopamine antagonists ; SDAs)
가 가 가 가
Haloperidol, fluphenazine HVA 가 HVA, 5 - HIAA HVA/5 - HIAA
(Bowers 1989 ; Pickar 1986) cloza - (Pickar 1992 ; Szymanski
pine HVA 1993), haloperidol (Hsiao
HVA/5 - HIAA 1993)
HVA 가 HVA, 5 -
(Bowers 1984 ; Chang 1988) HIAA HVA/5 - HIAA clozapine
clozapine HVA 가 clozapine
가 가
clozapine (positron emi-
ssion tomography ; PET) (Farde 1992) 가 가
70 80% D₂ 가 (Hsiao 1987). 가

(HVA, 5-HIAA, MHPG) PANSS, HVA
 (bala- 5-HIAA)
 HVA/5-HIAA HVA/MHPG
 (Hsiao 1993). HVA PANSS
 (Lieberman 1994), HVA/5-HIAA, clozapine
 HVA/5-HIAA HVA/5-HI-
 HVA/5-HIAA HVA/5-HIAA PA-
 NSS, CGI, PANSS, clozapine
 1980 HVA
 5-
 (Andreasen Olsen 1982; Crow HIAA, clozapine 8
 (delusion), (hallucination), HIAA HVA/5-HIAA 5-
 (bizzar, agitated behavior), HVA 가
 (conceptual disorganization) (productive) HVA 가 clozapine
 (blunted affect), HVA 5-HI-
 (poor contents of speech and thought), AA 가
 (apathy), (anhedonia), (blocking), AA 가
 (lack of motivation), (social withdrawal),
 (cognitive defect) (deficit)
 clozapine HVA/5-HIAA
 (Crow 1980; Johnstone 1978; Meltzer HVA/5-HIAA가
 (Pickar 1992; Szymanski 1993)
 1986). Clozapine (Kane) clozapine HVA/5-HIAA
 1988; Meltzer 1989) HVA가
 HVA PANSS 5-HT, 5-HT
 5-HIAA PANSS 가 가 5-HIAA
 cloz- 가 5-HT 가

clozapine 가 . Clozapine 8 HVA
 가 40.3% , HVA 가 3.
 clozapine 1% 가 . Clozapine
 HVA HVA/5 - HIAA 8 5 - HIAA HVA/5 - HIAA
 가 , 가
 HVA/5 - HIAA 가
 가 HVA/5 - HIAA 가
 가
 요 약
 27
 clozapine 8
 (PANSS CGI) (HVA ,
 5 - HIAA HVA/5 - HIAA)
 , clozapine
 clozapine 8
 가 clozapine
 가 가
 , 5 - HIAA 가 , HVA/
 5 - HIAA 가 . HVA/
 clozapine 8 HVA , 5 - HIAA
 , HVA/5 - HIAA 8
 (PANSS , ,
 ,) HVA
 PANSS , ,
 5 - HIAA PANSS
 . clozapine
 8 HVA PANSS
 , PANSS
 5 - HIAA PANSS
 . Clozapine 8 PANSS 가 20%
 CGI 가
 , 27 48%(13)가
 . Clozapine (N = 13)
 (N = 14) HVA
 HVA/5 - HIAA
 , 5 - HIAA 가

중심 단어 : Clozapine . HVA . 5 - HIAA .

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