

리스페리돈이 심혈관계에 미치는 영향

최세진* · 전진숙*[†] · 최영태**

The Cardiovascular Effect of Risperidone

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ABSTRACT

Objectives : Risperidone is a new antipsychotic drug developed to overcome the therapeutic limitation of conventional antipsychotics. It responds to negative as well as positive symptoms by blocking both dopaminergic and serotonergic receptors, causing no significant side effects such as agranulocytosis and seizure. It is, however, not known whether it induces any serious cardiovascular side effects as evoked by other conventional antipsychotic drugs. The aims of this study were to evaluate the effect of risperidone on cardiovascular function, and to discuss the factors affecting the cardiovascular function.

Methods : For 42 patients(22 males and 20 females) diagnosed as schizophrenia, schizophreniform disorder or schizoaffective disorder according to the DSM - classification, the cardiovascular functions such as heart rate, systolic and diastolic blood pressure, PR interval, QRS interval and QT interval were successively checked before and after 2 weeks and 4 weeks risperidone administration. Furthermore, variables such as body weight, Brief Psychiatric Rating Scale(BPRS), Clinical Global Impression(CGI), Extrapyramidal Symptom Rating Scale(ESRS), Anticholinergic Rating Scale(ARS), serum cholesterol level, serum triglyceride level, serum high - density - lipoprotein level, serum WBC, serum Hb, serum platelet level, prothrombin time and partial thromboplastin time were also analyzed before and after 2 weeks and 4 weeks risperidone administration.

Results :

- 1) Risperidone treatment resulted in a significantly decreased heart rate and increased QT interval after 4 weeks administration($p < 0.005$ respectively).
- 2) The scores of BPRS and CGI were significantly decreased after 2 weeks and 4 weeks risperidone administration as compared with baseline($p < 0.001$ respectively). The scores of ESRS and ASRS were significantly increased after 2 weeks and 4 weeks risperidone administration as compared with baseline($p < 0.001$ respectively).
- 3) There were positive correlations between heart rate after 4 weeks and total dose($P < 0.05$). Blood pressure was significantly($p < 0.05$) correlated with sex(higher in male) and significantly($p < 0.05$) positive correlated with body weight. QT interval was significantly($p < 0.05$) correlated with sex(longer in female) and smoking history(shorter in smokers).

Conclusions : Risperidone could induce significant change in heart rate and Q - T interval. Therefore, the cardiovascular safety for risperidone should be reconsidered according to the duration and dosage increase.

KEY WORDS : Risperidone · Heart rate · QT interval · Dose.

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서론

19 Delay Deniker chlorpromazine (Moriarty 1984). dopamine(DA) 가 dopamine - D2 (Cohen 1994 ; Keefe Harvey 1994 ; Melzer Stahl 1976).

가 가 (Andreasen Olsen 1982 ; Crow 1980 ; Mackay 1980), (tardive dyskinesia) (compliance) (Putten 1974).

DA , 가 DA adrenergic, cholinergic, histaminergic receptor

(atypical neuroleptics) clozapine 가 1 2% plan Sadock 1991).

Risperidone benisoxazol serotonin - S2 dopamine - D2 가 1988 risperidone

(Gelders 1990 ; Castelao 1989 ; Mesotten 1989 ; Roose 1988). risperidone 가

azine 가, 가 1 -adrenergic 가 (Cohen 1994). risperidone

대상 및 방법

1. 연구대상

1999 6 2000 5 DSM - (American Psychiatric Association 1994) , , (schizophreniform) risperidone 42 (22 , 20) Risperidone , Risperidone , Risperidone 1 , ,

(±) 33.83 ± 11.49 , 28.31 ± 10.75 . (±) 11.71 ± 3.74 , (±) 61.63 ± 11.98kg, 165 ± 8.03cm . 20 (48%) , 2 (5%) 가 .

가 4 (10%) . 26 (62%) , 13 (31%) , 3 (7%) .

가 1 가 14 (33%) , 28 (67%)

2. 연구방법

risperidone 1 risperidone , 2 , 4

Table 1. Demographic characteristics of patients(N = 42)

Age(Yr)*	33.83 ± 11.49
Sex(F/M)	20(48%)/22(52%)
Period of education(Yrs)*	11.71 ± 3.74
Marital status	
Single	26(62%)
Marrited	13(31%)
Divorce	3(7%)
Family history of cardiovascular disease	
Yes	2(5%)
No	40(95%)
Weight(kg)*	61.63 ± 11.98
Height(cm)*	165.49 ± 8.03
Onset age(Yr)*	28.31 ± 10.75
Smoking history	
Yes	20(48%)
No	22(52%)
History of diabetes mellitus	
Yes	4(10%)
No	38(90%)

*These data represent Mean ± SD

결 과

1. Risperidone 투여 후 심혈관계 기능의 변화

risperidone (±)
 2 3.43 ± 1.17mg/day , 4 4.19 ± 1.23
 mg/day .
 Risperidone (2). (±)
 81.19 ± 11.03 / , 2 77.05 ± 8.28
 / , 4 74.26 ± 6.70 / ,
 4 (p<0.005).
 (±) 125.71 ± 12.91mmHg
 , 2 122.14 ± 11.80mmHg, 4 120.71
 ± 10.22mmHg . (±)
 81.43 ± 9.77mmHg, 2 78.57 ± 9.52mmHg, 4
 77.62 ± 7.26mmHg
 . (±) PR 153.90 ± 25.94 msec,
 2 159.80 ± 24.82msec , 4 158.93 ±
 23.90msec . (±) QRS 87.
 79 ± 19.00msec, 2 90.69 ± 16.90msec, 4
 92.71 ± 19.04msec . (±) QT
 357.10 ± 37.29msec, 2 373.14 ± 35.17msec,
 4 382.14 ± 30.25msec , 4
 가 (p<0.005).

2. 심혈관계 기능에 영향을 미치는 요인의 변화

(2).
 (±) 61.63 ± 12.05kg, 2
 63.24 ± 11.73kg, 4 64.61 ± 11.54kg ,
 가
 BPRS 54.14 ± 5.70 ,
 2 40.90 ± 6.80 , 4 30.81 ± 8.78 , CGI
 5.21 ± 0.81 , 2 4.05 ± 0.96 ,
 4 3.17 ± 1.25 . BPRS CGI
 2 , 4 , 2
 4 가
 (p<0.001). ESRS 2 1.79 ± 1.
 54 , 4 3.29 ± 2.18 , ASRS 2
 2.36 ± 1.38 , 4 4.31 ± 2.25 .
 2 , 4 , 2
 4 (p<0.001).

(PR
 , QRS , QT)
 , , , , , , , ,
 , , , , , , , ,
 Anticholinergic Symptom
 Rating Scale(ASRS)(McEvoy 1991) Extrapyramidal
 Symptom Rating Scale(ESRS)(Chouinard 1980), ch-
 olesterol, triglyceride, (high density
 lipoprotein, HDL), , ,
 Clinical Global Impression(CGI)(Guy
 1976), Brief Psychiatric Rating Scale(BPRS)(Kaplan
 Sadock 1995) 가 .
 Windows SPSS
 (frequency an-
 alysis) , , 2 , 4 , ,
 , , PR , QRS , QT
 (one - way ANOVA) Tukey
 HSD
 (correlation analysis)
 p - value 0.05 .

Table 2. Comparison of changes in cardiovascular function and variables after risperidone administration

	Baseline	Risperidone administration		p-Value*	
		After 2wks	After 4wks	ANOVA	Tukey HSD
Heart rate/min	81.19 ± 11.03	77.05 ± 8.28	74.26 ± 6.70	p = 0.002	p = 0.001 (-)
Systolic BP(mmHg)	125.71 ± 12.91	122.14 ± 11.80	120.71 ± 10.22	N.S**	
Diastolic BP(mmHg)	81.43 ± 9.77	78.57 ± 9.52	77.62 ± 7.26	N.S	
PR interval(msec)	153.90 ± 25.94	159.80 ± 24.82	158.93 ± 24.82	N.S	
QRS interval(msec)	87.79 ± 19.00	90.69 ± 16.90	92.71 ± 19.04	N.S	
QT interval(msec)	357.10 ± 37.29	373.14 ± 35.17	382.14 ± 30.25	p = 0.004	p = 0.002 (-)
Body weight(kg)	61.63 ± 12.05	63.24 ± 11.73	64.61 ± 11.54	N.S	
BPRS1	54.14 ± 5.70	40.90 ± 6.80	30.81 ± 8.78	p = 0.000	p = 0.000
CGI2	5.21 ± 0.81	4.05 ± 0.96	3.17 ± 1.25	p = 0.000	(- ,
ERS3	0	1.79 ± 1.54	3.29 ± 2.18	p = 0.000	- ,
ASRS4	0	2.36 ± 1.38	4.31 ± 2.25	p = 0.000	-)
Cholesterol(mg/dl)	170.88 ± 33.48	174.48 ± 37.19	183.14 ± 28.47	N.S	
Triglyceride(mg/dl)	114.29 ± 64.76	134.19 ± 68.49	146.71 ± 70.33	N.S	
HDL5(mg/dl)	41.81 ± 14.69	41.29 ± 11.41	41.40 ± 10.82	N.S	
WBC(10e3/ul)	7.84 ± 2.87	6.21 ± 1.31	6.16 ± 1.68	p = 0.000	p = 0.001 (- , -)
Hb(g/dl)	13.06 ± 1.79	12.86 ± 1.70	12.74 ± 1.61	N.S	
Platelet(g/dl)	243.40 ± 73.11	229.29 ± 77.06	215.31 ± 59.04	N.S	
PT6(secs)	11.79 ± 1.09	11.90 ± 0.95	11.80 ± 0.86	N.S	
PTT7(secs)	34.55 ± 4.04	36.42 ± 3.54	36.69 ± 3.35	p = 0.016	P = 0.020 (-)

*One-way ANOVA with Tukey HSD, **N.S = statistically non-significant

¹Brief Psychiatric Rating Scale

²Clinical Global Impression

³Extrapyramidal Symptoms Rating Scale

⁴Anticholinergic Symptoms Rating Scale

⁵High Density Lipoprotein

⁶Prothrombin Time

⁷Partial Thromboplastin Time

cholesterol (±) 170.88 ± 33.48mg/dl, 2 174.48 ± 37.19mg/dl, 4 183.14 ± 28.47mg/dl . Triglyceride (±) 114.29 ± 64.76mg/dl, 2 134.19 ± 68.49mg/dl, 4 146.71 ± 70.33mg/dl . HDL (±) 41.81 ± 14.69mg/dl, 2 41.29 ± 11.41mg/dl, 4 41.40 ± 10.82mg/dl . WBC (±) 7.84 ± 2.87 10³/ul, 2 6.21 ± 1.30 10³/ul, 4 6.16 ± 1.68 10³/ul, 2 , (p<0.005). Hb (±) 13.06 ± 1.79g/dl, 2 12.86 ± 1.70g/dl, 4 12.74 ± 1.60g/dl . Platelet (±) 243.40 ± 73.11 10³/ul, 2 229.29 ± 77.06 10³/ul, 4 215.31 ± 59.04 10³/ul . prothrombin time (±) 11.79 ± 1.09secs, 2 11.90 ± 0.95secs, 4 11.80 ± 0.86secs, 2

partial thromboplastin time (±) 34.55 ± 4.04secs, 2 36.42 ± 3.54secs, 4 36.69 ± 3.35secs, 2 가 (p<0.05). 3. 심혈관계 기능과 여러 변인과의 상관성 (3). 4 (= 0.334, p<0.05). 2 4 : 2 = - 0.339, p<0.05 ; 4 = - 0.351, p<0.05, : 2 = - 0.362, p<0.05 ; 4 = - 0.415, p<0.01), (: 2 = 0.408, p<0.01 ; 4 = 0.313, p<0.05, : 2 = 0.343, p<0.05 ; 4 = 0.305, p<0.05). QT (= 0.421, p<0.01) 4 (= 0.313, p<0.05) 2 (= 0.424, p<0.01) 4 (= 0.392, p<0.05) QT .

Table 3. Correlation between cardiovascular function and variables

	Baseline				Risperidone administration							
					After 2wks				After 4wks			
	HR1	Systolic BP ²	Diastolic BP	QT interval	HR	Systolic BP	Diastolic BP	QT interval	HR	Systolic BP	Diastolic BP	QT interval
Sex	-0.017	-0.128	-0.042	0.218	-0.221	-0.339*	-0.362*	0.421**	-0.095	-0.351*	-0.415**	0.313*
Body weight	-0.121	0.308*	0.237	0.063	-0.121	0.408*	0.343*	0.002	-0.112	0.313*	0.305	-0.067
Smoking history	-0.058	0.166	0.190	0.303	-0.437**	-0.193	-0.193	0.424**	-0.272	-0.216	-0.184	0.392*
Total dose	0.175	0.275	0.141	-0.103	0.160	0.120	0.040	-0.187	0.334*	0.068	-0.035	-0.178
Cholesterol 0	-0.017	0.091	0.106	0.075	-0.162	0.169	0.170	0.017	0.078	0.236	0.320*	-0.051
Cholesterol 2	0.070	0.156	0.112	0.137	-0.014	0.209	0.254	0.073	0.095	0.223	0.332*	0.046
Cholesterol 4	0.142	0.221	0.221	0.060	-0.151	0.326*	0.314*	-0.028	0.091	0.295	0.372*	-0.150
Triglyceride 0	0.083	0.036	0.043	-0.099	0.056	0.262	0.256	-0.093	0.068	0.232	0.199	-0.061
Triglyceride 2	0.113	0.097	0.082	-0.149	0.007	0.224	0.219	-0.123	0.044	0.179	0.244	-0.120
Triglyceride 4	0.073	0.127	0.094	-0.185	0.018	0.117	0.056	-0.191	0.034	0.078	0.169	-0.161
Hemoglobin 0	-0.033	0.240	0.245	0.028	0.047	0.318*	0.411**	-0.188	-0.005	0.481**	0.396*	-0.192
Hemoglobin 2	-0.111	0.267	0.258	0.056	-0.066	0.329*	0.369*	-0.300	0.048	0.508**	0.445**	-0.324*
Hemoglobin 4	-0.076	0.239	0.148	-0.018	0.080	0.280	0.303	-0.296	0.024	0.379*	0.400**	-0.287
Platelet 0	0.162	0.103	0.194	-0.027	-0.027	-0.107	-0.055	-0.103	0.213	-0.060	-0.020	-0.181
Platelet 2	0.177	0.062	0.135	-0.119	0.058	-0.010	0.082	-0.161	0.144	0.024	-0.099	-0.212
Platelet 4	0.163	0.102	0.095	-0.072	-0.038	0.014	0.111	-0.204	0.168	0.111	-0.142	-0.189

. These data represent correlation coefficients(g)

*p<0.05 **p<0.01

¹HR = heart rate

²BP = blood pressure

0 : baseline

2 : 2 weeks after risperidone administration

4 : 4 weeks after risperidone administration

고 찰

clozapine (Leysen 1988). risperidone 5-HT_{2A} ritanserine halo-peridol 200, DA D₂ haloperidol (Ereshefsky Lacombe 1993 ; Janssen 1988). Risperidone 가 . Serotonin(5-HT)₂ 가 . 가 clozapine , , , 가 (Hippus 1989 ; McKenna Bailey 1993) serotonin 가 prolactin 가 , , , (Bleich 1988). (D₁, D₂, D₃, D₄) 가 (hot flush) (Kaplan Sadock 1995). 1-adrenergic risperidone (Melzer Fatemi 1996 ; Remington 1996). (Cohen 1994 ; risperidone benzisoxazole 5-HT₂, Leysen 1992). Risperidone DA D₂, 1-adrenergic QT QRS 가 (Ken 2-adrenergic, histamine H₁ 1996 ; Richard Robert 1996). , DA D₁ muscarinic cholinergic QT 가 (Kevin 1982 ; Leysen 1988 ; Sc-hatzberg 1997). 5-HT_{2A} D₂ QRS QT 가가 Titusville(1994) D₂ 5-HT_{2A} 25 Drici (1988) risperidone ser-

tindole QT (p<0.05).
 , (p<0.05),
 Cohen(1994) Owen(1994) (p<0.05). QT
 가
 , risperidone
 (1994) QT , risperidone
 가
 (Claus
 1992 ; Meco 1989 ; Mesotten 1989 ; Putten 1974).
 가
 risperidone 가
 (1966 ; 1994 ; 1998 ; Owen
 1994). BPRS, CGI

QT , risperidone
 가
 중심 단어 : QT
 참고문헌

, risperidone
 4
 Cohen
 (1994) Risperidone
 가 triglyceride 가
 , risperidone 가가
 가
 가

강대엽 · 이충순 · 최진숙 · 김형섭 · 한광수 · 황태연 · 김용희 · 이정식(1966) : 만성정신분열증 환자에 대한 리스페리돈 효과 및 안전성 비교시험. 용인정신의학보 3 : 61-77
 백운수 · 강병조 · 김승팔(1994) : Risperidone의 임상적 안전성. 신경정신의학 33 : 453-461
 이민수(1998) : 정신분열병에 대한 risperidone의 효과 및 안전성. 신경정신의학 37 : 60-74
 이홍식(1992) : 비전형적 항정신병 약물 ; clozapine과 기타 새로운 약물. 대한정신약물학회지 3 : 96-104
 Andreasen NC, Olsen S(1982) : Negative vs positive schizophrenia : defenition and validation. Arch Gen Psychiatry 39 : 789-794
 American Psychiatric Association(1994) : Diagnostic and statistical manual of mental disorder 4th ed, Washington DC, American Psychiatric Press, pp273-290
 Bleich A, Brown SL, Kahn R, van Praag HM(1988) : The role of serotonin in Schizophrenia. Schizophr Bull 114 : 297-315
 Castelao JF, Ferreira L, Gelders YG, Heylen LE(1989) : The efficacy of the D 2 and 5-HT 2 antagonist risperidone(R 64 766) in the treatment of chronic psychosis. Schizophr Res 2 : 411-415
 Chouinard G, Ross-Chouinard A, Annable L, Jones BD(1980) : Extrapyramidal symptom rating scale. Can J Neurol Sci 7 : 233
 Claus A(1992) : Risperidone versus haloperidol in the treatment of chronic schizophrenic patients ; a multicentre double-blind comparative study. Acta Psychiat Scand 85 : 295-305
 Cohen LJ(1994) : Risperidone. J human Pharmacol and drug therapy 14 : 253-265
 Crow TJ(1980) : Positive and negative schizophrenic symptoms and role of dopamine. Br J Psychiatry 137 : 379-386
 Drici, Milou-Daniel, Wang, Wen X, Liu, Xioake, Woosley, Raymond L, Flockhart, David A(1988) : Prolongation of QT Interval in Isolated Feline Hearts by Antipsychotic Drugs. J Clin Psychopharmacol 18 : 477-481
 Ereshefsky L, Lacombe S(1993) : Pharmacological profile of risperidone. Can J Psychiatry 38(Suppl 3) : S80-88
 Gelders YG, Heylen SLE, Vanden Bussche G, Reyntjens AJM, Janssen PAJ(1990) : Pilot clinical investigation of risperidone in the treatment of psychotic patients. Pharmacopsychiatry 23 : 206-211
 Guy W(1976) : Assessment manual for psychopharmacology. Roc-

결론

1999 6 2000 5
 DSM -
 42 risperidone 가
 Risperidone 2
 4 , 가
 ESRS ASRS 가
 1) Risperidone 4
 , QT 가 (p<
 0.005).
 2) BPRS, CGI
 2 4
 (p<0.001), ESRS, ASRS
 2 4 가 (
 p<0.001).
 3) 4 risperidone

- kville MD, US Department of Health Education and Welfare, pp218-222
- Hippus H(1989)** : *The history of clozapine. Psychopharmacology (Suppl99)* : S3-5
- Janssen PAJ, Niemegeers CJE, Awouters F, Schelenkens KHL, Megens AAHP, Meert TF(1988)** : *Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin S₂, and dopa-mine D₂ antagonistic properties. J Pharmacol Exp Ther 244* : 685-693
- Kaplan HI, Sadock BJ(1991)** : *Synopsis of psychiatry. 6th ed, Baltimore, Williams & Wilkins, pp606-669*
- Kaplan HJ, Sadock BJ(1995)** : *Comprehensive textbook of psy-chiatry. Williams and Wilkins, Baltimore, pp624-627*
- Kaplan HJ, Sadock BJ(1995)** : *Comprehensive textbook of psy-chiatry. 6th ed. Baltimore, Williams and Wilkins, pp2016-2018*
- Keefe RSE, Harvey PD(1994)** : *Understanding schizophrenia ; A guide to the New Research on Causes and treatment. New york, The Free Press, 41, pp97-128*
- Ken Brown, Howard Levy, Cynthia Brenner, Stephen Leffler, Ellen Hamburg(1993)** : *Overdose of Risperidone. Ann Emergency Med 22* : 1908-1910
- Kevin FB, Douglas PZ, James JH, Eric NP(1982)** : *Influence of the autonomic nervous system on the Q-T interval in man. Am J Cardiol 50* : 1099-1103
- Leysen JE, Gommerren W, Eens A, DenChaffoy de Courcelles D, Stoof JC, and Janssen PAJ(1988)** : *The biochemical profile of risperidone, a new antipsychotic. J Pharmacol Exp Ther 247* : 661-670
- Leysen JE, Janssen PMF, Gommerren W(1992)** : *In vitro and in vivo receptor binding and effects of monoamine turnover in rat brain regions of the novel antipsychotics risperidone and oca-peri-done. Mol Pharmacol 41* : 494-508
- Leysen JE, Janssen PMF, Megens AAHP, Schotte A(1994)** : *Risperidone ; a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharm- acological profile. J Clin Psychiatry 55 (Suppl 5)* : 5-12
- Lieberman JA(1996)** : *Atypical antipsychotic drugs as a first-line treatment of schizophrenia ; A rationale and hypothesis. J Clin Psychiatry (Suppl 11)* 57 : 68-71
- Mackay AVP(1980)** : *Positive and negative schizophrenic symptoms and the role of dopamine. Br J Psychiatry 137* : 379-383
- McEvoy JP, Hogarty GE, Steingard S(1991)** : *Optimal dose of neuroleptic in acute schizophrenia. Arch Gen Psychiatry 48* : 739-745
- McKenna PJ, Bailey PE(1993)** : *The strange story of clozapine. Br J Psychiatry 162* : 32-37
- Meco G, Bedini L, Bonifati V, Sonsini U(1989)** : *Risperidone in the treatment of chronic schizophrenia with tardive dyskinesia. Curr Ther Res 46(5)* : 876-883
- Melzer HY, Fatemi SH(1996)** : *The role of serotonin in schizophrenia and the mechanism of action of antipsychotic drugs. In : Serotonin in Antipsychotic Treatment ; Mechanism and Clinical Practice. Ed by Kane JM, Moller HJ, Awters F, New York, Marcel Dekker, Inc, pp77-107*
- Melzer HY, Stahl SM(1976)** : *The dopamine hypothesis of schizo- phrenia ; A review. Schizophr Bull 2* : 16-76
- Mesotten F, Suy E, Pietquin M, Burton P, Heylen S, Gelders Y (1989)** : *Therapeutic effect and safety of increasing doses of risperidone (R 64 766) in psychotic patients. Psychopharma- cology 99* : 445-449
- Moriarty KM, Alagna SW, Lake CR(1984)** : *Psychopharmacology ; An Historical Perspective. Psychiatr Clin North Am 7* : 411-434
- Owens D(1994)** : *Extrapyramidal side effects and tolerability of risperidone ; A review. J Clin Psychiatry 55(Suppl 5)* : 29-35
- Remington GJ(1996)** : *Schizophrenia ; Changing concepts and the development of novel antipsychotics. J Biol Psychiatry 3* : 22-29
- Richard JH, Robert JH(1996)** : *Risperidone Overdose. Am J Em- ergency Med 14* : 95-96
- Roose K, Gelders Y, Heylen S(1988)** : *Risperidone (R 64 766) in psychotic ; A first clinical therapeutic exploration. Acta Psychiat Belg 88* : 233-241
- Schatzberg AF, Cole JO, DeBattista C(1997)** : *Manual of clinical psychopharmacology. 3rd ed. Washington DC, American Psy- chiatric Press, pp113-116*
- Titusville NJ(1994)** : *Package insert. Risperdal(risperidone) ; Janssen*
- Van Putten(1974)** : *Why do schizophrenic patients refuse to take their drugs? Arch Gen Psychiatry 31* : 67-72