

Risperidone이 혈청 Prolactin 농도에 미치는 영향*

전진숙**† · 조 옹** · 오병훈***

The Effect of Risperidone on Serum Prolactin Concentrations*

Jin-Sook Cheon, M.D.,**† Woong Cho, M.D.** , Byoung-Hoon Oh, M.D.***

ABSTRACT

Objectives : Risperidone, an atypical antipsychotics which blocks both dopaminergic and serotonergic receptors, have a good response to the negative symptoms as well as positive symptoms, and improve cognitive dysfunction of schizophrenic patients. Furthermore, it has few extrapyramidal side effects and tardive dyskinesia. Although it had been reported that the atypical antipsychotics have less effect on prolactin(PRL) than the classical antipsychotics, we could experience PRL-associated symptoms such as amenorrhea, galactorrhea and hyperprolactinemia in practice. Therefore, we tried to identify the sex differences of risperidone-induced hyperprolactinemia, to evaluate factors affecting PRL levels, and to know the association between cognitive disorders and PRL.

Methods : The baseline levels of PRL and TSH prior to risperidone administration were measured by enzyme immunoassay method for 50 patients(25 males and 25 females) admitted with schizophrenia, schizoaffective disorder or schizophreniform disorder according to the DSM-IV classification, and the measurements of PRL were repeated on the 2nd and the 4th wks of risperidone administration. Concomitantly, the severity of psychotic symptoms using CGI, BPRS and PANSS, and the cognitive dysfunction using PANSS-CF were assessed prior to, on the 2nd and the 4th wks of risperidone administration. The PRL and TSH levels of 54 healthy controls(29 males and 25 females) who had no medical, neurological and psychiatric illnesses were also evaluated. Furthermore, the correlation with the psychiatric diagnosis, education, age, sex, duration of illnesses, risperidone dosage, duration of risperidone administration, TSH concentration, cognitive function, severity of psychotic symptoms were also identified.

Results :

1) The baseline PRL levels of female schizophrenics(74.3 ± 49.6 ng/ml) were significantly($p < 0.005$) higher than those of males(36.3 ± 24.6 ng/ml), which were significantly($p < 0.0001$ respectively) higher than those of controls(females 16.9 ± 6.1 ng/ml, males 13.3 ± 4.9 ng/ml). The PRL levels measured on the 2nd wks(females 133.7 ± 47.8 ng/ml, males 56.9 ± 23.6 ng/ml) and on the 4th wks(females 146.1 ± 45.9 ng/ml, males 70.0 ± 31.5 ng/ml) after risperidone administration were significantly($p < 0.0001$ respectively) higher in females. The mean dosages of risperidone on the 2nd wks were 3.8 ± 1.7 mg(2 - 6mg) for the females and 4.0 ± 1.6 mg(2 - 6mg) for the males, and on the 4th wks were 4.5 ± 2.1 mg(2 - 8mg) for the females and 5.4 ± 2.2 mg(2 - 8mg) for the males.

2) The rise of PRL levels were positively correlated with increased risperidone dosage in males($r = 0.307$ on the 2nd wks and $r = 0.280$ on the 4th wks), while they were not correlated with dosages in females. For the females, the PRL levels were negatively correlated($r = -0.320$) with decrease of TSH concentration. The baseline PRL levels were not correlated with age, education, duration of illnesses, psychopathology, cognitive disorders in both males and females, while it was negatively correlated with TSH levels only in females($r = -0.320$).

3) The cognitive dysfunction was not correlated with PRL levels in males, while PANSS-CF scores were negatively correlated with PRL levels($r = -0.220$ on the 2nd wks and $r = -0.366$ on the 4th wks) in females. The psychopathology was positively correlated with cognitive dysfunction in both males and

41

1998 10 22

* The essential point of this paper was orally presented at the Annual Meeting of Korean Neuropsychiatric Association on October 22nd in 1998.

** Department of Neuropsychiatry, Kosin University, School of Medicine, Pusan, Korea

*** Department of Neuropsychiatry, Yonsei University, College of Medicine, Seoul, Korea

† : , 602 - 702

34

) (051) 250 - 5070 / 240 - 6245,) (051) 241 - 5069 / 241 - 5832

females. Therefore, the risperidone-induced cognitive improvement seemed to be correlated with improvement of psychopathology in both males and females, and with increase in PRL levels only in females.

Conclusions : The fact that the serum PRL levels of schizophrenics were higher than those of controls, especially in females suggested that it could be related with risperidone dosage in males and with primary pathological process in females. The risperidone-associated cognitive improvement seemed to be related with general improvement of psychopathology as well as the rise of PRL levels especially in females. The facts that the effect of risperidone-induced hyperprolactinemia and the cognitive function were more in females suggested that somewhat different mechanisms could be exerted on them.

KEY WORDS : Schizophrenia · Risperidone · Prolactin · Sex differences · Cognitive dysfunction.

서 론

(Ga-llhofer 1996 ; Kopala 1996) .

PRL) 가 , prolactin(가 PRL 가 30% (Jackson 1994). 가 (Beerpoot 1996 ; Bondolfi 1996), PRL (Sanger Pe-ult 1995 ; Copolov 1997) . risperidone PRL 가 risperidone (Weiden 1996). dopamine(DA) , D₁ (1994) risperidone 10mg 4 Bøgesø (1995) 1 , Peuskens(1995) risperidone razi 1997), Klemm (1996) PRL 가 가 , Dickson (dorsolateral) neurotensin (1995) risperidone 5 (Merchant Dorsa 1993), Liu Alr-3 5 . Bre-eja(1997) 가 serotonin(5-HT) cher Davis(1997) risperidone 14%가 , , , risperidone GABA risperidone D₂ 5-HT₂ (Janssen 1988 ; Ereshefsky Lacombe 1993 ; Kerwin 1994 ; Ames 1996), ₁-adrenergic H₁-histaminergic . Bowden (1992) , D₁ risperidone 1 D₂ , cholinergic haloperidol 3 5 PRL , (Chouinard Arnott 1993). risperidone risperidone D₂/5-HT₂

risperidone 9-hydroxy-risperidone
 가 haloperidol ,
 PRL (hypogonadism) , 54
 luteal() 가 , (29 , 25) .
 1 . ,
 testosterone , , 17 (68%) 10
 (Findling Tyrrell 1986). (40%), 5 (20%), 1 (4%), 1 (4%)
 PRL , 5 (20%), 3 (12%)
 , es- . 12 (48%)
 trogen PRL (Aragona Friesen 1979). 10 (40%), 1 (4%), 1 (4%)
 Estrogen PRL lacto- , 9 (36%), 4 (16%) .
 trophs 가 (Rubin 1987). Adams 가
 (1992) PRL dehydroepiandrosterone ,
 sulfate , PRL es- 가 .
 trogen 2 .
 PRL 가 27.4±7.7 (18 41) , 33.8±
 estrogen (Dic- 7.7 (18 45) 28.2±
 kson 1995), PRL 3.5 (25 40) , 25.2±5.4 (19 41)
 PRL 가 (Reber 1993). (p<0.0001).
 risperidone PRL 11.3±2.4 (6 14) , 10.5±
 , PRL 3.0 (6 18) , 17.0±1.3 (12
 PRL 19) , 14.5±1.7 (2 17)
 (p<0.0001).
 대상 및 방법 148.9±37.1 , 170.4±42.5
 가 .

1. 연구 대상

1997 8 1 1998 7 31 , 50
 DSM - IV(American Psychiatric Associ- 2 가 19 (9
 ation 1994) , 10) , 31 (16 , 15)
 50 (.
 25 , 25) 가 29±14 , 가 82±40
 1) 가 .
 risperidone 2 4.0
 2) 2
 3) ,
 4) 18 45 .
 5) , 2 PRL .
 6) , ,
 , 3 .

Table 1. Psychiatric diagnosis of the patients

Diagnosis	Males (N=25)	Females (N=25)	p-value*
Schizophrenia	17(68%)	12(48%)	N.S.
Paranoid type	10(40%)	10(40%)	N.S.
Undifferentiated type	5(20%)	1(4%)	N.S.
Residual type	1(4%)	1(4%)	N.S.
Disorganized type	1(4%)	0(0%)	N.S.
Schizoaffective disorder	5(20%)	9(36%)	N.S.
Schizophreniform disorder	3(12%)	4(16%)	N.S.

*Statistically non-significant by the ²-test

$\pm 1.6\text{mg}(2.6\text{mg})$, $4.5 \pm 2.1\text{mg}(2.8\text{mg})$, $4.5 \pm 2.1\text{mg}(2.8\text{mg})$, $4.5 \pm 2.1\text{mg}(2.8\text{mg})$

(4).

2. 연구 방법

2
risperidone PRL, risperidone
2 4 PRL
9 1.5ml
2 8 24 가 -10
PRL
(Micropartite Enzyme Immunoassay) Abbott AxSYM Pr-
olactin PRL
PRL
, , , , , , , TSH
, ,

Table 2. Comparison of demographic data between controls and patients according to sex

	Males		Females	
	Controls (N=29)	Patients (N=25)	Controls (N=25)	Patients (N=25)
Age(Yrs)	28.2 ± 3.5	27.4 ± 7.7	25.2 ± 5.4	33.8 ± 7.7*
Education(Yrs)	17.0 ± 1.3*	11.3 ± 2.4	14.5 ± 1.7*	10.5 ± 3.0
TSH(μU/ml)	1.7 ± 0.9	1.4 ± 0.7	1.7 ± 1.0	1.5 ± 1.5
PRL(ng/ml)	13.3 ± 4.9	36.3 ± 24.6*	16.9 ± 6.1	74.3 ± 49.6*

· These data represent Mean ± S.D.

*p<0.0001 by the two-tailed t-test

Table 3. Comparison of PRL levels between drug-free and drug-naive patients

	No.	Males	Females	p-value*
		(N=25)	(N=25)	
Drug-free (N=19)	No.	9	10	
	PRL(ng/ml)			
	Mean ± S.D.	27.2 ± 11.3	100.9 ± 62.5	p<0.01
	Normal	3(33.3%)	1(10.0%)	N.S.
	Increase	6(66.7%)	9(90.0%)	N.S.
Drug-naive (N=31)	No.	16	15	
	PRL(ng/ml)			
	Mean ± S.D.	41.4 ± 28.6	56.5 ± 29.5	N.S.
	Normal	5(31.3%)	3(20.0%)	N.S.
	Increase	11(68.7%)	12(80.0%)	N.S.

*Two-tailed t-test or ²-test

· Statistically non-significant(N.S.) between drug-free vs drug-naive females, and between drug-free vs drug-naive males by two-tailed t-test

TSH risperidone
, 9 1.5ml
2 8 7
가 -10
TSH
(Micropartite Enzyme Immunoassay)
Abbott AxSYM Ultrasensitive hTSH II TSH
CGI,
Brief Psychiatric Rating Scale(BPRS)(Thiemann 1987) Kay (1987) The Positive and Negative Syndrome Scale(PANSS) ri-

Table 4. Comparison of PRL levels between male and female patients according to the risperidone administration

	()	Males	Females	p-value*
		(N=25)	(N=25)	
Baseline	Risperidone(mg)	0	0	
	PRL(ng/ml)	36.3 ± 24.6	74.3 ± 49.6	p<0.005
2 Wks	Risperidone(mg)	4.0 ± 1.6	3.8 ± 1.7	N.S.
	PRL(ng/ml)	56.9 ± 23.61	133.7 ± 47.82	p<0.0001
4 Wks	Risperidone(mg)	5.4 ± 2.2	4.5 ± 2.1	N.S.
	PRL(ng/ml)	70.0 ± 31.53	146.1 ± 45.94	p<0.0001

· These data represent Mean ± S.D.

*two-tailed t-test

· p<0.005 between baseline and 2wks in males¹, and in females²; p<0.005 between baseline and 4wks in males³, and in females⁴; statistically non-significant(N.S.) between 2wks and 4wks in males, and in females by the oneway ANOVA and Scheffe's multiple comparison test

Table 5. Comparison of changes in psychopathology between male and female patients according to the risperidone administration

		Males	Females	p-value*
		(N=25)	(N=25)	
Baseline	CGI	5.9 ± 0.8	5.8 ± 1.0	N.S.
	BPRS	73.2 ± 6.6	76.3 ± 8.5	N.S.
	PANSS	129.3 ± 9.9	130.0 ± 12.4	N.S.
	PANSS-CF	21.1 ± 1.4	21.4 ± 3.4	N.S.
2 Wks	CGI	4.6 ± 0.6	4.6 ± 0.8	N.S.
	BPRS	62.3 ± 4.9	64.1 ± 8.7	N.S.
	PANSS	110.5 ± 9.1	111.0 ± 14.0	N.S.
	PANSS-CF	17.6 ± 1.6	18.1 ± 2.9	N.S.
4 Wks	CGI	3.8 ± 0.6	3.8 ± 0.9	N.S.
	BPRS	54.9 ± 5.1	54.9 ± 8.4	N.S.
	PANSS	96.2 ± 10.6	96.5 ± 13.1	N.S.
	PANSS-CF	15.1 ± 2.2	15.4 ± 2.7	N.S.

· These data represent Mean ± S.D.

*Statistically non-significant by the two-tailed t-test

· p<0.005 respectively of CGI, BPRS, PANSS, PANSS-CF scores between baseline, 2wks and 4wks by the oneway ANOVA and Scheffe's multiple comparison test

speridone , risperidone 2 4 가 PRL 41.4 ± 28.6ng/ml , 15
PRL 56.5 ± 29.5ng/ml
PANSS (P₂), 16 5 (31.3%)
(N₅), (G₁₀), (G₁₁), 11 (68.7%) 가
(G₁₅) 5 (Kopala 1996) PA - , 15 3 (20.0%) 12
NSS - Cognitive Function(PANSS - CF) ri - (80.0%) 가
speridone , risperidone 2 4 가

Minitab Release 6.1.1. - (Minitab
1987) SPSS for Windows Release 5.0.1(SPSS 1989
1992)

결 과

1. Prolactin 농도의 변화

PRL 36.3 ± 24.6ng/ml, 74.3 ±
49.6ng/ml 가 (p<0.005),
(13.3 ± 4.9ng/ml, 16.9 ± 6.1ng/ml)
(p<0.0001)(2).

Risperidone PRL Risperidone
4 . Risperidone 2
PRL 56.9 ± 23.6ng/ml, 133.7 ± 47.8ng/ml
, 4 PRL 70.0 ± 31.5ng/ml,
146.1 ± 45.9ng/ml
가 (p<0.0001). 2

PRL , 4 PRL
가 4 PRL
PRL . Risp -
eridone 2 4.0 ± 1.6mg(2 6mg),
3.8 ± 1.7mg(2 6mg) , 4 5.4 ± 2.2mg(2
8mg), 4.5 ± 2.1mg(2 8mg)
가 .

PRL
3 . ,
2
19 9 PRL 27.2 ± 11.3ng/
ml , 10 PRL 100.9 ± 62.5ng/
ml (p<0.01). 9 3
(33.3%) (0 25ng/ml) 6 (66.7%)
PRL 가 가 , 10 1
(10.0%) 9 (90.0%) 가
, .
31 16

2. Prolactin 농도에 영향미치는 요인

PRL
PRL 가 risperidone 가 (2
= 0.307, 4 = 0.280),
TSH PRL
(= - 0.320)가 . PRL

TSH (= - 0.320).

3. 인지기능과 Prolactin의 연관성

Risperidone 가
Risperidone , risperidone 2 , risperidone
4 가 CGI, BPRS,
PANSS 가 PANSS - CF
5 . CGI risperidone
5.9 ± 0.8 , 5.8 ± 1.0 ,
risperidone 2 4.6 ± 0.6 , 4.6 ±
0.8 , risperidone 4 3.8 ± 0.6
, 3.8 ± 0.9
. BPRS ris -
peridone 73.2 ± 6.6 ,
76.3 ± 8.5 , risperidone 2 62.3 ±
4.9 , 64.1 ± 8.7 , risperidone 4
54.9 ± 5.1 , 54.9 ± 8.4

PANSS risperidone 129.
3 ± 9.9 , 130.0 ± 12.4 , risperidone
2 110.5 ± 9.1 , 110.0 ± 14.0
, risperidone 4 96.2 ± 10.6 ,
96.5 ± 13.1
. PANSS - CF ris -
peridone 21.1 ± 1.4 ,
21.4 ± 3.4 , risperidone 2 17.6 ± 1.6
, 18.1 ± 2.9 , risperidone 4
15.1 ± 2.2 , 15.4 ± 2.7

risperidone 2, 4
가 가 (p<0.005).

PRL
PANSS - CF PRL 가
(2 = - 0.220, 4 = - 0.366).

risperidone

PRL 가

ridone

PRL

가
rispe -

고 찰

(Salokangas 1983). homovanillic acid(HVA)

(Sumiyoshi 1997).

Yonkers (1992)
가

(1992)

가

PRL 가가

PRL

. Pohjalainen (1998)

DA

estrogen DA

. Wong (1988)

DA D₂

(follicular)

, D₂

. Crowley (1978)

catecholamine

. Xiao Becker(1994)

us)

trus)

DA 가

(proestrus)

(diestr -

(es -

DA

. Seeman Lang(1990)

가

estrogen

estrogen

PRL

TSH PRL

polypeptide(

adrenergic

PRL

arsall Gold 1986). Estrogen

rotropin

trogen

1980).

PRL

DA

DA

(1984)

PRL

(Pickar

1987).

PRL

, (1986)

,

가

PRL

. Gruen (1978a)

가

,

,

,

risperidone

PRL

가

, risperidone

가

, Gruen (1978a)

PRL 가 가

risperidone PRL

가 가

PRL

, TRH

, vasoactive intestinal

PRL 가

, Ach DA

(Pe -

thy -

es -

가 (Tolis

PRL

(Gruen 1978b). Ferrier

가

calcium channel

HVA

PRL 가

가

(1987)

가

(1986)

BPRS

PRL

(1996)

PRL

가

PRL

가

PRL

Kleinman (1982) 가 PRL , risperidone 가 PRL 가가
 17 가 PRL , TSH DA
 Risperidone PRL estrogen 가 ,
 가 risperidone 가 가 , 가
 PRL 가 TSH
 , risperidone PRL **결론**
 PRL estrogen risperidone
 가 (defect state)
 (Bilder 1985). Davis (1991) 가 PRL
 / (deficit) DA , PRL
 , DA DA , risperidone
 . Klosterkötter (1997) 가 가 가 , PRL
 , Walker Lewine(1988) , PRL
 DSM - IV ,
 (anterior cingulate) 50 (25 , 25)
 DA (Dolan risperidone PRL TSH
 1995). 2 4 PRL , PANSS - CF
 가 CGI, BPRS, PANSS , 2 4 가 ,
 DA , 54 (PRL TSH
 DA D₂ , 29 , 25)
 serotonin - dopamine antagonists(SDAs) , , , ,
 risperidone (Borison , , , TSH , ,
 1996). Stip Lussier(1996) risperidone
 1) PRL 36.3 ± 24.6ng/ml, 74.
 가 Nopoulos (1994) 3 ± 49.6ng/ml 가 (p<0.
 005), (13.3 ± 4.9ng/ml, 16.9 ± 6.1ng/ml)
 (p<0.0001). Risperidone
 2 PRL 56.9 ± 23.6ng/ml, 133.7
 가 PRL ± 47.8ng/ml , 4 PRL 70.0 ± 31.5ng
 /ml, 146.1 ± 45.9ng/ml
 가 (p<0.0001). Risperidone
 risperidone 2 4.0 ± 1.6mg(2 6mg), 3.8 ± 1.7mg
 , PRL 가 (2 6mg) , 4 5.4 ± 2.2mg(2 8mg), 4.5

±2.1mg(2 8mg)

2) PRL

PRL 가 risperidone 가
(2 =0.307, 4 =0.280),
TSH

PRL (= -0.320)

PRL

TSH

(= -0.320).

3)

PRL

PANSS - CF PRL 가
(2 = -0.220, 4 = -0.366).

risperidone

PRL

가

PRL

risperidone

Risperidone

PRL 가가

, risperidone PRL 가

PRL 가

가

중심 단어 : Risperidone · Prolactin

참고문헌

권영재 · 김종은(1987) : 정신분열증 환자의 혈청 Prolactin 값과 임상양태와의 관계. 가톨릭대학의학부논문집 40 : 1139-1148

김명숙 · 연병길(1986) : 정신분열증 남자환자의 혈청 Prolactin 함량의 변화와 임상적 호전과의 연관성에 관한 연구. 신경정신의학 25 : 27-38

김철웅 · 서해숙(1997) : 정신분열병 환자의 혈중 Prolactin 농도와 Haloperidol에 대한 치료 반응도와의 관계. 인하의대학술지 4 : 367-371

주진형 · 김성운 · 우종인(1996) : 급성정신분열장애환자의 Haloperidol 치료시 임상 호전도와 혈중 Prolactin 농도의 관계. 신경정신의학 35 : 433-441

Adams JB(1992) : Human breast cancer : concerted role of diet, prolactin and adrenal C₁₉-△₅-steroids in tumorigenesis. Int J Cancer 50 : 854-858

American Psychiatric Association(1994) : Diagnostic and Statisti-

cal Manual of Mental Disorders. 4th ed, Washington DC, American Psychiatric Association

Ames D, Marder SR, Wirshing WC(1996) : Risperidone : clinical applications. In : The New Pharmacotherapy of Schizophrenia. Ed by Breier A, Washington DC, American Psychiatric Press, pp15-40

Aragona C, Friesen HG(1979) : Lactation and galactorrhea. In : Endocrinology. Vol 3, Ed by DeGroot LJ, Cahill GF Jr, Odell WD, Martini L, Potts JT Jr, Nelson DH, Steinberger E, Winegrad AI, New York, Grune & Stratton, pp1613-1627

Beerpoort LJ, Lipska BK, Weinberger DR(1996) : Neurobiology of treatment-resistant schizophrenia : new insight and new models. Eur Neuropharmacology S 2 27-34

Bilder RM, Mukherjee S, Rieder RO, Pandurangi AK(1985) : Symptomatic and neuropsychological components of defect states. Schizophr Bull 11 : 409-419

Bondolfi G, Baumann P, Dufour H(1996) : Treatment-resistant schizophrenia : clinical experience with new antipsychotics. Eur Neuropharmacology 6 : S 2 21-25

Borison RL(1996) : The role of cognition in the risk-benefit and safety analysis of antipsychotic medication. Acta Psychiatr Scand 94 : 5-11

Bowden CR, Voina SJ, Woestenborghs R, De Coster R, Heykants J(1992) : Stimulation by risperidone of rat prolactin secretion in vivo and in cultured pituitary cells in vitro. J Pharmacol Exp Thera 262 : 699-706

Bøgesø KP, Arnt J, Frederiksen K, Hansen HO, Hyttel J, Pedersen H(1995) : Enhanced D₁ affinity in a series of piperazine ring substituted 1-piperazine-3-arylidans with potential atypical antipsychotic activity. J Med Chem 38 : 4380-4392

Brecher M, Davis JM(1997) : Prolactin levels and adverse events in patients treated with risperidone. Biol Psychiatry 42(1S) : 173S

Chouinard G, Arnott W(1993) : Clinical review of risperidone. Can J Psychiatr 38 (Suppl 3) : S89-S95

Copolov D(1997) : New name for atypical antipsychotics? Am J Psychiatr 154 : 439

Crowley WR, O'Donohue TL, Jacobowitz DM(1978) : Changes in catecholamine content in discrete brain nuclei during the estrous cycle of the rat. Brain Res 147 : 315-326

Davis KL, Kahn RS, Ko G, Davidson M(1991) : Dopamine in schizophrenia : a review and reconceptualization. Am J Psychiatry 148 : 1474-1486

Dickson RA, Dalby JT, Williams R, Edwards A(1995) : Risperidone-induced prolactin elevations in premenopausal women with schizophrenia. Am J Psychiatry 152 : 1102-1103

Dolan RJ, Fletcher P, Frith CD, Friston KJ, Frackowiak RSJ, Grasby PM(1995) : Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. Nature 378 : 180-182

Ereshefsky L, Lacombe S(1993) : Pharmacological profile of risperidone. Can J Psychiatr 38 (Supp 3) : S80-S88

Ferrier IN, Johnstone EC, Crow TJ(1984) : Hormonal effects of apomorphine in schizophrenia. Brit J Psychiatr 144 : 349-357

Findling JW, Tyrrell JB(1986) : Anterior pituitary & somatome-

- ns : 1. anterior pituitary. In : *Basic & Clinical Endocrinology*. 2nd ed, Ed by Greenspan FS, Forsham PH, East Norwalk, Lange, pp43-94
- Gruen PH, Sachar EJ, Altman N, Langer G, Tabrizi MA, Halpern FS (1978a)** : Relation of plasma prolactin to clinical response in schizophrenic patients. *Arch Gen Psychiat* 35 : 1222-1227
- Gruen PH, Sachar EJ, Langer G, Altman N, Leifer M, Frantz A, Halpern FS (1978b)** : Prolactin responses to neuroleptics in normal and schizophrenic subjects. *Arch Gen Psychiat* 35 : 108-116
- Jackson DM, Ryan C, Evenden J, Mohell N (1994)** : Preclinical findings with new antipsychotic agents : what makes them atypical? *Acta Psychiat Scand* 89 (Suppl 380) : 41-48
- Janssen PAJ, Niemegeers CJE, Awouters F, Schellekens KHL, Mogens AAHP, Meert TF (1988)** : Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin- S_2 and dopamine- D_2 antagonistic properties. *J Pharmacol Exp Thera* 244 : 685-693
- Kay SR, Fiszbein A, Opler LA (1987)** : The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13 : 261-276
- Kerwin RW (1994)** : The new atypical antipsychotics ; a lack of extrapyramidal side-effects and new routes in schizophrenia research. *Brit J Psychiat* 164 : 141-148
- Kleinman JE, Weinberger DR, Rogol AD, Bigelow LB, Klein ST, Gillin JC, Wyatt RJ (1982)** : Plasma prolactin concentrations and psychopathology in chronic schizophrenia. *Arch Gen Psychiat* 39 : 655-657
- Klemm E, GrEwald F, Kasper S, Menzel C, Broich K, Danos P, Reichmann K, Krappel C, Rieker O, Briele B, Hotze AL, Meller H-J, Biersack H-J (1996)** : [23 I] IBZM SPECT for imaging of striatal D_2 dopamine receptors in 56 schizophrenic patients taking various neuroleptics. *Am J Psychiatry* 153 : 183-190
- Klosterkötter J, Schultze-Lutter F, Gross G, Huber G, Steinmeyer EM (1997)** : Early self-experienced neuropsychological deficits and subsequent schizophrenic diseases : an 8-year average follow-up prospective study. *Acta Psychiat Scand* 95 : 396-404
- Kopala LC, Fredrikson D, Good KP, Honer WG (1996)** : Symptoms in neuroleptic-naïve, first-episode schizophrenia : response to risperidone. *Biol Psychiatry* 39 : 296-298
- Kuruvilla A, Peedicayil J, Srikrishna G, Kuruvilla K, Kanagasabapathy AS (1992)** : A study of serum prolactin levels in schizophrenia : comparison of males and females. *Clin Exp Pharmacol Physiol* 19 : 603-606
- Laughren TP, Brown WA, Williams BW (1979)** : Serum prolactin and clinical state during neuroleptic treatment and withdrawal. *Am J Psychiatry* 136 : 108-110
- Liu W, Alreja M (1997)** : Atypical antipsychotics block the excitatory effects of serotonin in septohippocampal neurons in the rat. *Neuroscience* 79 : 369-382
- Marder SR, Meibach RC (1994)** : Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 151 : 825-835
- McCreadie RG (1996)** : Managing the first episode of schizophrenia : the role of new therapies. *Eur Neuropharmacology* 6 : S 2 3-5
- Merchant KM, Dorsa DM (1993)** : Differential induction of neurotensin and c-fos gene expression by typical versus atypical antipsychotics. *Proc Natl Acad Sci USA* 90 : 3447-3451
- Nopoulos P, Flashman L, Flaum M, Arndt S, Andreasen N (1994)** : Stability of cognitive functioning early in the course of schizophrenia. *Schizophr Bull* 14 : 29-37
- Pearsall HR, Gold MS (1986)** : Other neuroendocrine tests. In : *Diagnostic and Laboratory Testing in Psychiatry*. Ed by Gold MS, Pottash ALC, New York, Plenum, pp59-75
- Peuskens J (1995)** : Risperidone in the treatment of patients with chronic schizophrenia : a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Brit J Psychiat* 166 : 712-726
- Pickar D, Wolkowitz OM, Doran AR, Labarca R, Roy A, Breier A, Narang PK (1987)** : Clinical and biochemical effects of verapamil administration to schizophrenic patients. *Arch Gen Psychiat* 44 : 113-118
- Pohjalainen T, Rinne JO, Nägren K, Syvälahti E, Hietala J (1998)** : Sex differences in the striatal dopamine D_2 receptor binding characteristics in vivo. *Am J Psychiatry* 155 : 768-773
- Reber PM (1993)** : Prolactin and immunomodulation. *Am J Med* 95 : 637-644
- Rubin RT (1987)** : Prolactin and schizophrenia. In : *Psychopharmacology : The Third Generation of Progress*. Ed by Meltzer HY, New York, Raven Press, pp803-808
- Salokangas RKR (1983)** : Prognostic implications of the sex of schizophrenic patients. *Brit J Psychiat* 142 : 145-151
- Sanger DJ, Perrault G (1995)** : Effects of typical and atypical antipsychotic drugs on response decrement patterns in rats. *J Pharmacol Exp Thera* 272 : 708-713
- Shiwach RS, Carmody TJ (1998)** : Prolactogenic effects of risperidone in male patients- a preliminary study. *Acta Psychiat Scand* 98 : 81-83
- Seeman MV, Lang M (1990)** : The role of estrogens in schizophrenia gender differences. *Schizophr Bull* 16 : 185-194
- Stip E, Lussier I (1996)** : The effect of risperidone on cognition in patients with schizophrenia. *Can J Psychiat* 41 (Supp 2) : 35S-40S
- Sumiyoshi T, Hasegawa M, Jayathilake K, Meltzer HY (1997)** : Sex differences in plasma homovanillic acid levels in schizophrenia and normal controls : relation to neuroleptic resistance. *Biol Psychiatry* 41 : 560-566
- Tarazi FI, Florijn WJ, Creese I (1997)** : Differential regulation of dopamine receptors after chronic typical and atypical antipsychotic drug treatment. *Neuroscience* 78 : 985-996
- Thiemann S, Csernansky JG, Berger PA (1987)** : Rating scales in research : the case of negative symptoms. *Psychiat Res* 20 : 47-55
- Tolis G (1980)** : Prolactin : physiology and pathology. In : *Neuroendocrinology*. Ed by Krieger DT, Hughes JC, New York, Sinauer, pp321-328
- Walker E, Lewine RJ (1988)** : The positive/negative symptom distinction in schizophrenia ; validity and etiological relevance. *Schizophr Res* 1 : 315-328
- Weiden P, Aquila R, Standard J (1996)** : Atypical antipsychotic drugs and long-term outcome in schizophrenia. *J Clin Psychiatry* 57 (Supp 11) : 53-60
- Wong DF, Broussolle EP, Wand G, Villemagne V, Dannals RF,**

- Links JM, Zacur HA, Harris J, Naidu S, Braestrup C, Wagner HN Jr, Gjedde A(1988)** : *In vivo measurement of dopamine receptors in human brain by positron emission tomography ; age and sex differences. Ann N Y Acad Sci 515 : 203-214*
- Xiao L, Becker JB(1994)** : *Quantitative microdialysis determination of extracellular striatal dopamine concentration in male and female rats : effects of estrous cycle and gonadectomy. Neuroscience Lett 180 : 155-158*
- Yonkers KA, Kando JC, Cole JO, Blumenthal S(1992)** : *Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. Am J Psychiatry 149 : 587-595*