

## Haloperidol과 bethanechol 병합사용시 혈장 haloperidol 및 reduced haloperidol 농도에 미치는 영향\*

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### The Effects of Coadministration of Haloperidol and Bethanechol on Plasma Haloperidol and Reduced Haloperidol Concentrations\*

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#### ABSTRACT

Bethanechol, a cholinergic agonist, has been recommended for the management of peripheral anticholinergic side effects during the treatment of antipsychotic medications. But there have been few studies which have evaluated the drug interactions of antipsychotics and bethanechol, even the treatment effects of bethanechol on anticholinergic side effects. So the authors have evaluated whether psychopathology and plasma haloperidol and reduced haloperidol concentrations are significantly changed or not when bethanechol was administrated with maintained doses of haloperidol and other coadministered drugs (such as benztrapine). Also we have evaluated the abating effects of bethanechol on anticholinergic side effects during the treatment with haloperidol.

Fifteen schizophrenics with higher than 5 of total score of anticholinergic side effects of 'Rating scale for side effect' were assigned to two groups, and bethanechol 30mg/day and 60mg/day were applied on each group for 4 weeks. The daily haloperidol dosages were fixed before 2 weeks of study. We assessed anticholinergic side effects by 'Rating scale for side effect' and psychopathology by BPRS, and plasma haloperidol and reduced haloperidol concentrations by HPLC at baseline, 2nd week and 4th week.

The results were as followed, 1) there was no significant change of plasma haloperidol and reduced haloperidol concentration, 2) at baseline, the dosage of haloperidol showed significant correlation with the total score of anticholinergic side effect, but not at 2nd week and 4th week, 3) in 60mg/day group, dry mouth and the total score of anticholinergic side effects were significantly improved, but not in 30mg/day group, 4) there was no significant change of BPRS except withdrawal at 2nd week.

These results suggest that coadministration of bethanechol influenced neither on psychopathology nor on plasma haloperidol and reduced haloperidol concentrations and that improved dry mouth and total score of anticholinergic side effects at 60mg/day.

**KEY WORDS** : Schizophrenia · Anticholinergic side effects · Haloperidol · Plasma haloperidol and Reduced haloperidol concentrations.

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4

) (0331) 288 - 0206,

) (0331) 288 - 0184

# 서론

가  
가

(Christensen 1978 ; Madden 1973).

가  
(Wirshing 1995),

bethanechol (Grebb 1995).

, Evertt(1975)

bethanechol

Schubert(1975) phenothiazine

(blurred vision) bethanechol

Pollack Rosenbaum(1987)

clinical trials

bethanechol

sen (1993)

nortriptyline

bethanechol

bethanechol

bethanechol

thanechol 가

, 'dopamine - cholinergic interaction theory'

bethanechol

haloperidol

thanechol , 가 (BPRS)(Ove - rall Gorhan 1962)

, haloperidol bethanechol

haloperidol, reduced haloperidol

## 연구대상 및 방법

### 1. 연구대상

1997 3 5

1) DSM - IV(American Psychiatric Association 1994)

, 2) 'Rating scale for side effect'(Asberg 1970)

가

0 , 가 3

5

haloperidol , 4) 25

informed consent

1)

, 2)

3)

### 2. 연구방법

#### 1) 인구사회학적 자료

haloperidol benztropine

#### 2) Haloperidol, benztropine, bethanechol 및 기타 약물 투여

haloperidol

trial , open bethanechol 30mg/day

60mg/day

2 , haloperidol

ent(

benztropine 1 2mg/day

(laxatives)

PRN lorazepam

, 가 30

4mg

ha - 4 1 2 ( 7 7 ) . Bethanechol

haloperidol  
Bethanechol 가  
( , , ) ,  
가  
가

Millenium TM 2010 chromatography Manger software가 IBM PC column  
Shiseido (Tokyo, Japan) 250 x 4.6mm I.D., 5 µm particle size, reversed phase C<sub>18</sub> column temperature 37

3) 항콜린성 부작용 및 정신병리의 임상적 평가

(1) Rating scale for side effect  
24  
, , , 4 4  
0 3 가 ,  
가  
가 bethanechol , 2 4 ( 3 )

potassium phosphate(monobasic), triethylamine, phosphoric acid, heptane sulfonic acid Sigma (St. Louis, Mo, U.S.A)  
, isoamylalcohol hydrochloric acid E. Merk (Darmstadt, Germany), acetonitrile hexane Burdick & Jackson (Muskegon, MI, U.S.A.) TRh, Milli-Q water system(Millipore Corp, Bedford, MA, U.S.A.)

(2) Brief psychiatric rating scale(BPRS)  
Bethanechol Ov -  
erall Gorham(1962) 가 (BPRS)  
가 가  
가  
가 bethanechol , 2 4  
( 3 )

haloperidol Sigma , reduced haloperidol internal standard Ami-triptyline(Sigma) 0.1 N HCl 1mg/mL  
-70 가

4) 혈장 haloperidol 및 reduced haloperidol 농도 측정

(1)  
12 ,  
7 , 30  
(antecubital vein) 10cc lit -  
hium heparin tube 30 3000rpm 20  
cryogenic vial 1cc  
-70  
bethanechol , 2 4  
( 3 )

1mL 4 15mL pol-  
ypropylene tube 50ng internal standard  
vortex mixing , 200 µL 2N NaOH 가  
vortex mixing (hexane/isoamyl alcohol, 98/  
2, v/v) 5mL tube 90  
1000g 10

(2) haloperidol reduced haloperidol  
haloperidol reduced haloperidol McBurney  
George(1984)가 high performance liquid chromatography(HPLC)

30 µL HPLC system  
Mobile phase 0.05M KH<sub>2</sub>PO<sub>4</sub> acetonitrile sodium heptan sulfonic acid 5 mM, triethylamine 0.01M phosphoric acid pH 4.2가 0.5 µM pore size membrane filter ultrasonicator 30  
PDA detector 214nm mobile phase 1.0mL/min  
haloperidol reduced haloperidol internal standard가  
가 drug free serum (ratio)

High performance liquid chromatography(HPLC)  
Shiseido (Tokyo Japan) model 2009 degasser, Waters Model 510 pump, Model 717 plus autosampler, Waters model 441 UV detector, temperature control system (TCM), Bus LAC/E card

5) 자료분석  
Bethanechol , , , haloperidol

benztropine Mann - Whitney U test , Fisher's Exact test . Haloperidol Spearman's rank correlation coefficient . ' Rating scale for side effect ' , BPRS haloperidol reduced haloperidol Mann - Whitney U test , Wilcoxon signed ranks test

SPSS WIN 7.0

0.05 (2 - tailed)

### 결 과

#### 1. 인구사회학적 특성

가 13 ( 3 , 10 ) , 30mg 6 ( 1 , 5 ) , 60mg 7 ( 2 , 5 ) . 30mg 60mg 35.00 ± 8.72 , 33.29 ± 5.50 , 24.17 ± 7.17 , 23.00 ± 5.29 . 129.50 ± 77.82 , 123.29 ± 66.99 , 54.17 ± 49.46 , 35.00 ± 39.75 . Haloperidol 29.33 ± 17.18mg/day , 32.29 ± 6.97mg/day , benztropine 1.67 ± 0.52mg/day , 1.57 ± 0.53mg/day

**Table 1.** Demographic data and baseline dosage of haloperidol and benztropine

	30mg group (N=6) M(SD)	60mg group (N=7) M(SD)	p
Age(years)	35.00( 8.72)	33.29( 5.50)	NS*
Sex male	1	2	NS**
female	5	5	NS**
Onset age(years)	24.17( 7.17)	23.00( 5.29)	NS*
Duration of illness(months)	129.50(77.82)	123.29(66.99)	NS*
Duration of admission(months)	54.17(49.46)	35.00(39.75)	NS*
Dosage of haloperidol(mg/day)	29.33(17.18)	32.29( 6.97)	NS*
Dosage of benztropine(mg/day)	1.67( 0.52)	1.57( 0.53)	NS*

M : mean, SD : standard deviation

NS : non significant

\* : Mann-Whitney U test

\*\* : Fisher's Exact test

**Table 2.** Correlations between haloperidol dose and anticholinergic side effects( = )

	Base					2nd week total	4th week total
	Micturition disturbance	Constipation	Dry mouth	Blurred vision	Total		
Haloperidol dose	0.038	0.537	0.308	0.143	0.578*	0.299	0.243

\* : p<.05 (by Spearman's rank correlation coefficients)

haloperidol benztropine 가 ( 1).

#### 2. Haloperidol 투여량과 항콜린성 부작용 정도와의 상관관계

Haloperidol bethanechol ( =0.578, p=.038) , haloperidol bethanechol , 2 4 가 ( 2).

#### 3. Bethanechol 투여에 따른 항콜린성 부작용의 변화

Bethanechol 30mg/day 60mg/day bethanechol , 2 4 가 . 30mg/day 가 . 60mg/day , bethanechol 2 4 ( Z = -2.251, p=.024 Z = -2.264, p=.024) ( Z = -2.379, p=.017 Z = -2.023, p=.043) , 2 4 가 . ( Z = -1.890, p=.059 Z = -1.890, p=.059)

#### 4. Bethanechol 투여에 따른 BPRS의 변화

Bethanechol BPRS 30mg/day 가 60mg/day 가 30mg/day withdrawal (Z = -2.121, p=.034), 2 , 2 4 가 . , thought, paranoid, anxiety - depression 60mg BPRS 가 ( 4).

#### 5. Bethanechol 투여에 따른 혈장 haloperidol 및 reduced haloperidol 농도의 변화

haloperidol reduced haloperidol 30mg/day

**Table 3.** Changes of anticholinergic symptoms scores

	Baseline M(SD)	2nd week M(SD)	4th week M(SD)
Micturition disturbance			
30mg group(N=6)	1.00(0.89)	0.50(0.84)	0.67(0.82)
60mg group(N=7)	1.29(0.76)	0.71(1.25)	0.86(1.21)
Constipation			
30mg group(N=6)	1.83(1.17)	1.50(1.38)	1.50(1.05)
60mg group(N=7)	1.86(0.90)	1.14(0.90)	0.86(1.21)
Dry mouth			
30mg group(N=6)	1.50(0.84)	1.33(0.82)	1.00(0.89)
60mg group(N=7)	2.29(0.49)	1.00(0.82)*	1.00(0.82)*
Blurred vision			
30mg group(N=6)	1.50(0.55)	1.33(0.82)	1.17(0.75)
60mg group(N=7)	1.71(0.95)	1.43(1.13)	1.57(0.79)
Total score			
30mg group(N=6)	5.83(1.17)	4.67(1.75)	4.33(1.75)
60mg group(N=7)	7.14(1.35)	4.29(1.60)*	4.29(1.89)*

M : mean, SD : standard deviation

\* : Vs baseline, p<0.05 (by Wilcoxon signed ranks test)

**Table 4.** Changes of BPRS()

	Baseline M(SD)	2nd week M(SD)	4th week M(SD)
Total			
30mg group(N=6)	48.17(13.99)	44.83(14.05)	44.83(15.21)
60mg group(N=7)	48.57(12.79)	47.71(12.70)	47.57(12.00)
Thought			
30mg group(N=6)	12.50( 4.51)	11.83( 4.71)	11.67( 4.97)
60mg group(N=7)	12.43( 4.56)	12.29( 4.57)	12.43( 4.79)
Paranoid			
30mg group(N=6)	8.50( 3.83)	7.50( 4.32)	7.66( 4.13)
60mg group(N=7)	9.00( 3.96)	8.43( 3.55)	8.71( 3.35)
Withdrawal			
30mg group(N=6)	8.33( 2.06)	7.33( 2.16)*	7.50( 2.43)
60mg group(N=7)	7.43( 2.70)	7.29( 2.69)	7.29( 2.69)
Anxiety-depression			
30mg group(N=6)	6.67( 2.80)	6.33( 2.25)	6.33( 2.94)
60mg group(N=7)	5.29( 2.21)	5.28( 2.21)	5.14( 1.86)

M : mean, SD : standard deviation

\* : Vs baseline, p<0.05 (by Wilcoxon signed ranks test)

**Table 5.** Changes of plasma haloperidol and reduced haloperidol concentrations

	Baseline M(SD)	2nd week M(SD)	4th week M(SD)
Reduced haloperidol(ng/mL)			
30mg group(N=6)	20.61(13.00)	22.76(16.04)	17.59(13.33)
60mg group(N=7)	20.19( 9.90)	17.62(11.58)	15.16( 7.13)
Haloperidol(ng/mL)			
30mg group(N=6)	26.90(10.78)	18.19(10.11)	18.84( 6.19)
60mg group(N=7)	17.49( 7.59)	21.90(10.88)	17.74( 8.32)

M : mean, SD : standard deviation

All itemse : non-significant

haloperidol reduced haloperidol

haloperidol , benz - tropine , BPRS

haloperidol reduced haloperidol

Bethanechol haloperidol 가

haloperidol

haloperidol

haloperidol anticholinergics . Betha - nechol 2 , 4 가

haloperidol , bethanechol , 60mg/day

chol 30mg/day . Bethane - 가

haloperidol 가

bethanechol 60mg/day , 2 4

10~30mg ,

10~30mg , 1%

pilocarpine bethanechol 10~30mg (Grebb 1995). , Pollack Rosenbaum(1987)

10~30mg

10~30mg , 10

~30mg

mg/day 4 , BPRS

bethanechol  
 1% pilocarpine  
 BPRS 2 withdrawal BP-  
 RS haloperidol reduced  
 haloperidol  
 haloperidol  
 가 , haloperidol  
 가 (Bigelow 1985 ; Ge-  
 rlach 1985 ; Neborsky 1984),  
 hyperbolic ( 1989 ; Kirch 1985) linear  
 (Debuck 1981 ; Evans 1981 ; Smith 1979)  
 , curvilinear  
 ( 1988 ; 1988 ; Davis 1985 ; Mi-  
 ller 1984 ; Potkin 1985 ; Van Putten 1985)  
 가  
 , haloperidol  
 (Davis 1985 ; Forsman Larsson 1978),  
 2~12ng/mL 가 (Baldess-  
 arini 1988 ; Boer 1996) . reduced ha-  
 loperidol haloperidol piperidine nitro-  
 gen oxidative N - dealkylation hydroxy  
 haloperidol . haloperidol  
 haloperidol 6~300%  
 reduced haloperidol haloperidol  
 가 (Chang 1989 ; Korpi Wyatt  
 1984). cytochrome P450  
 haloperidol (Jann 1992 ; Ty-  
 ndale 1991)가 haloperidol (interc-  
 onversion)  
 (Chang 1989). , reduced haloperidol  
 haloperidol 가  
 haloperidol reduced  
 , ph-  
 enobarbital diphenylhydantoin(Linnoila 1980) car-  
 bamazepine( 1989 ; Arana 1986 ; Jann 1985 ;  
 Kidron 1985) P450  
 haloperidol 가 haloperidol  
 , hepatic cytochrome P450 IID6 iso-  
 enzyme fluoxetine haloperidol re-

duced haloperidol 가 ( 1995 ;  
 Goff Baldessarini 1993, Goff 1990), reduction ratio(re-  
 duced haloperidol : haloperidol ratios) 가 ( 1995)  
 가 . Benztropine mesylate  
 (Mc-  
 Evoy 1983 ; Stanilla Simpson 1995).  
 , bethanechol  
 (Dollery 1991 ; McEvoy  
 가  
 , bethanechol , 2 4  
 haloperidol reduced haloperidol  
 haloperidol bethanechol  
 , 30mg/day 60mg/day bethanechol  
 haloperidol reduced haloperidol  
 bethanechol haloperidol reduced halo-  
 peridol  
 가 ,  
 Tan-  
 don Greden (1989) , bethanechol  
 가  
 BPRS withdrawal , bethanechol  
 be-  
 thanechol 4가 가  
 (Brown Taylor 1996) (Arky 1997 ;  
 Ellenhorn 1997),  
 (Dollery 1991) . , 2  
 withdrawal bethanechol  
 bethanechol cholin-  
 ergic excess (confusion),  
 (seizure), , (myoclonus), neurop-  
 sychiatric signs , , , 가,  
 가, , , , , biliary colic  
 nonob-  
 structive urinary retention bethanechol  
 cholinergic excess

4 5  
30mg/day 60mg/day  
cholinergic excess

mg/day bethanechol , 60  
ridol haloperidol reduced halope -  
cess , cholinergic ex -

가 ,  
bethanechol ,  
가 ,

day bethanechol 60mg/  
가  
가 가

중심 단어 : . Bethanechol .  
haloperidol reduced haloperidol .

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