

우울 장애의 치료에 있어서 dothiepin-sertraline 병합과 dothiepin 단독 요법의 비교

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Comparison between Dothiepin-Sertraline Combination and Dothiepin Alone Therapy in the Treatment of Depressive Disorder

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ABSTRACT

The dysfunction of either or both noradrenaline and serotonin system are important in the pathophysiology of depression. Previous reports have suggested that there may be an important interaction between these two systems. Recently, some investigators have suggested that the combination of tricyclic antidepressants(TCAs) and selective serotonin reuptake inhibitors(SSRIs) would produce a rapid synergistic effect on down-regulation of either or both of these two systems and that this combination may produce a more rapid and absolute antidepressant effect.

We compared the treatment efficacy, treatment associated side effects, treatment satisfaction, and the quality of life between the combination therapy of dothiepin-sertraline as well as the therapy of dothiepin alone in the treatment of major depressive disorder and dysthymic disorder.

In our study, the combination therapy of dothiepin and sertraline produced a more rapid and absolute antidepressant effect than dothiepin alone. And the patients with combination therapy experienced relatively high treatment satisfaction than the patients with dothiepin therapy. The patients' quality of life improved more rapidly in the combination therapy, especially, in the health perception, social behavior, and life satisfaction, than dothiepin alone. These results support the hypothesis that the combination of TCA and SSRI may produce a rapid synergistic effect on either or both norepinephrine and serotonin system, and more rapid antidepressant effect and high treatment satisfaction.

KEY WORDS : Depressive disorders · Combination therapy · Dothiepin · Sertraline.

서 론

가 (Burn 1995)

(tricyclic antidepressant ; TCA)

(selective serotonin reuptake inhibitor ; SSRI),

(noradrenaline reuptake inhibitor ; NARI)

가

(Banerjee 1977 ; Sulser 1978 ; Vetulani 1976)

가 (Ca-rlsson 1969 ; Mass 1975),

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† : , 136 - 705 5가 126 - 1) (02) 920 - 5354,) (02) 927 - 3507

(Br - unello 1982 ; Drumbrille - Ross Tang 1983 ; Shopsin 1975 ; Stockmeier 1985) 가 on (1988) 가 TCA SSRI 가 Bar - TCA SSRI

Potter (1981) TCA desipramine SSRI zimelidine 3 TCA desipramine SSRI fluoxetine desipramine desipramine fluoxetine des - ipramine Nelson (1991) 가 Baron (1988) 가 Fuller(1987) 가 가 가 Baron (1988) TCA SSRI TCA desipramine SSRI fluoxetine 가 가 가 dothiepin SSRI sertraline dothiepin 가 가 가 가 TCA SS- TCA 가 가 가 Weilberg (1989) TCA flu - 86.7% Seth (1992) 1. 연구 대상 1997 3 1997 9 18 65 DSM - IV(American Psychiatric Association 1994) 17 가 14 18 65 가 가 가 가 TCA SSRI 가 가 가 Nelson (1991)

연구대상 및 방법

1. 연구 대상

1997 3 1997 9

18 65

DSM - IV(American Psychiatric Association 1994)

17

가 14

1

18

65

2. 연구 방법

1) 약물 치료

dothiepin 150mg, sertraline 75mg 가 dothiepin sertraline 가

2) 치료 효능, 부작용, 삶의 질의 평가

(Hamilton 1960), Clinical Global Impression Scale(Guy 1976 ; CGI) Efficacy Index - The-rapeutic Effect(Cohn Wilcox 1985 ; EITE) 가 . 17

17 50% EITE 가 4 가 가 1 4 , Cohn Wilcox(1985)가 fluoxetine, imipramine, placebo

Efficacy Index - Side Effects(Cohn Wilcox 1985 ; EISE) 가 . EISE Co-hn Wilcox(1985)

4 가 가 1 4 TCA SSRI (Cohn Wilcox 1985 ; Nystrom Hallstrom 1987 ; Reimherr 1990) 1 3% 20 가 4

가 가 4 가 가 (4 - Point Index Side Effect Self Rating Scale ; 4 - PISSS) 20

4 Efficacy Index Ratio(Cohn Wilcox 1985 ; EIR) 가 , Cohn Wilcox(1985) EITE/EISE 0.25 , 4

health related quality of life battery(Revicki 1992 ; HRQOL) , 2 , 4 , 6 가 (health perception), (cognitive function), 가 (home management), (social behavior), (life satisfaction) 5 가 가 2 가

3) 통계분석방법

independent samples T - test 1 , 2 , 4 , 6 paired T - test SP - SS for windows release 7.0 , p<.05

결 과

1. 대상군의 특성

6 14 , 14 6 4 6 , 2 36 , 20 , 16 (50.5±12.0 ; 50.1±11.1) (: =1 : 19 ; : =2 : 14) 가 . (: =15 : 5 ; =9 : 7), (5.8±4.9 ; 4.2±7.8), (22.9±5.9 ; 21.0±4.8) (Table 1). 4 sertraline 87.5mg, dothiepin 81.9mg , dothiepin 138.4 mg . 6 sertraline 95.8mg, dothiepin 79.2mg dothiepin 152.1mg (Table 2).

Table 1. Demography and patient characteristics

Charateristic	Combination group (n=20)	Dothiepin group (n=16)
Age(year)	50.5 ± 12.0	50.1 ± 11.1
Sex(Male : Female)	1 : 19	2 : 14
Diagnosis		
Major depression	15	9
Dysthymic disorder	5	7
Duration of illness(year)	5.8 ± 4.9	4.2 ± 7.8
Baseline HAM-D-17 total score	22.9 ± 6.0	21.0 ± 4.8

2. 두 군 간의 치료효과 비교

1
 ,
 , 4 (11.1 ; 14.2, p<.05)
 (Table 3, Fig. 1).
 %
 ,
 4 (49.7% ; 30.4%, p<.05)
 (Table 3, Fig. 2).
 50%
 2
 , 20 7

Table 2. Mean daily dosage of medication during the treatment

	Combination group (n=20)		Dothiepin group (n=16)
	dothiepin(mg)	sertraline(mg)	dothiepin(mg)
Baseline	25.0	27.5	46.9
1st week	45.0	48.8	73.4
2nd week	63.8	71.2	101.6
4th week	81.9	87.5	138.4
6th week	79.1	95.8	152.1

Table 3. Comparison between combination group and dothiepin group in HAM-D-17* total score and % change during the treatment

	Combination group (n=20)		Dothiepin group (n=16)	
	total score	% change(%)	total score	% change(%)
Baseline	22.9	0	21.0	0
1st week	18.6	18.4	18.5	10.8
2nd week	15.2	33.4	16.6	19.3
4th week	11.1 ^a	49.7 ^b	14.2	30.4
6th week	9.7	58.1	10.3	50.5

a : significantly lower than dothiepin group p<.05
 b : significantly higher than dothiepin group p<.05
 * : HAM-D-17 = 17-item Hamilton depression rating scale

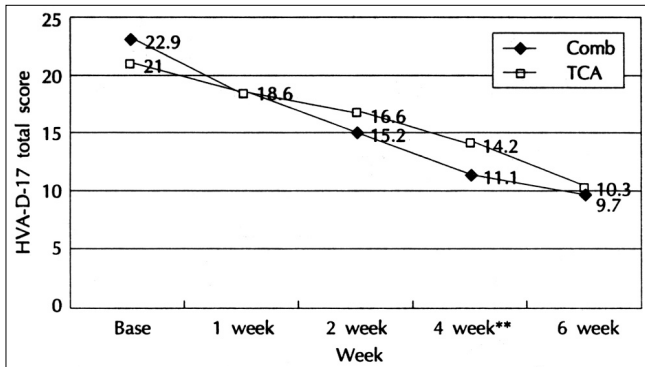


Fig. 1. 17-item Hamilton depression rating scale(HAM-D-17) total score during the treatment.
 ** : Statistically different p<.05

35% (35.0% ; 0.0% ;
 p<.05). 4 20 9
 , 16 3
 (45.0% ; 18.8%, p<.05). 6
 14 11 (78.6%), 14 8
 (57.1%)
 2
 4 (Fig. 3).
 EITE
 , 1 (2.40 ; 1.75, p<.05) 4
 (2.78 ; 2.25, p<.05)
 가
 (Ta-
 ble 4). , CGI 가

3. 부작용 및 안전성

. EISE

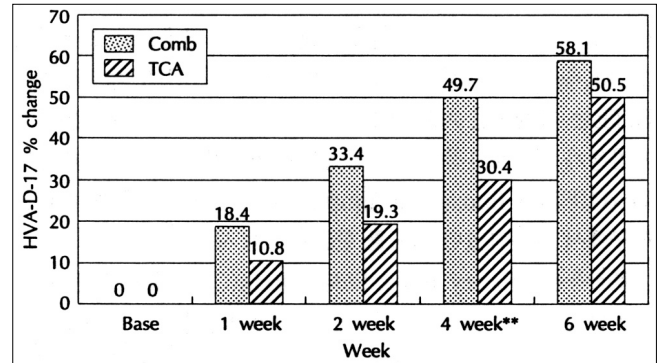


Fig. 2. 17-item Hamilton depression rating scale(HAM-D-17) % change during the treatment.
 ** : Statistically different p<.05

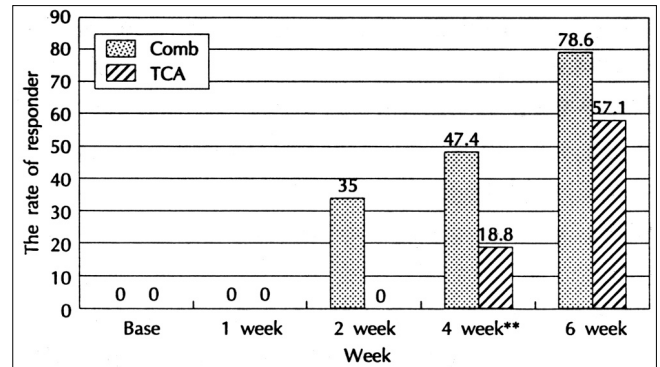


Fig. 3. The rate of responder* during the treatment.
 *responder : improved HAM-D-17 total score >50%
 ** : Statistically different p<.05

(Table 4). 4 가 가 (30%) TCA (20%), (81.3%), (56.3%), (15%), (10%) (37.5%), (37.5%), (25%), (70%), (45%), (40%), (35%), (Table 5).

Table 4. The Efficacy index ratio, Efficacy index therapeutic effect, and Efficacy index side effects during the treatment

	Combination (n=20)			Dothiepin (n=16)		
	EIR**	EITE**	EISE**	EIR**	EITE**	EISE**
Baseline						
1st week	2.11*	2.40*	1.30	1.18	1.75	1.63
2nd week	2.08*	2.53	1.53	1.32	2.06	1.81
4th week	2.03	2.78*	1.50	1.60	2.25	1.63
6th week	2.09	2.85	1.54	1.60	2.47	1.67

* : significantly higher than dothiepin group p<.05
 ** : EIR = Efficacy Index Ratio,
 EITE = Efficacy Index Therapeutic Effect,
 EISE = Efficacy Index Side Effects

Table 5. The incidence of treatment associated side effects of combination therapy and dothiepin alone therapy

	Combination group (n=20)	Dothiepin group (n=16)
Dry mouth	70%(14)	81%(13)
Visual disturbance	45%(9)	56%(9)
Constipation	40%(8)	38%(6)
General fatigue	10%(2)	38%(6)
Anorexia	35%(7)	0%(0)
Dyspepsia	30%(6)	19%(3)
Headache	15%(3)	25%(4)
Nausea	20%(4)	0%(0)
Dizziness	20%(4)	13%(2)
Tremor	15%(3)	19%(3)
Increased sweat	15%(3)	13%(2)
Mictuition disturbance	15%(3)	13%(2)
Agitation	15%(3)	0%(0)
Palpitation	10%(2)	13%(2)
Amnesia	5%(1)	13%(2)
Diarrhea	5%(1)	13%(2)
Taste perversion	10%(2)	6%(1)
Sexual dysfunction	10%(2)	0%(0)
Insomnia	5%(1)	0%(0)
Vomiting	5%(1)	0%(0)

Table 6. Comparison of Health related quality of life battery between combination group and dothiepin group during the treatment

	Combination group (n= 20)					Dothiepin group (n= 16)				
	HP**	COG**	HM**	SB**	LS**	HP**	COG**	HM**	SB**	LS**
baseline	4.80	5.10	4.50	31.0	31.0	4.06	4.68	4.00	30.4	5.13
2nd week	4.53*	4.31	3.15*	27.0*	27.0*	4.00	4.94	2.94*	28.3	5.06
4th week	4.16*	3.72	1.83*	26.4*	4.17*	4.19	4.28	2.34*	26.9	4.50*
6th week	4.07*	3.21*	2.83*	26.4*	4.08*	3.71	3.29*	1.86*	24.2*	4.40*

* : significantly improved compared with the baseline score (p<.05)

** : HP=health perception, COG=cognitive fuction, HM=home management, SB=social behavior, LS=life satisfaction

4. 치료 만족도

가 Efficacy Index Ratio 1 (2.11 ; 1.18, p<.05) 2 (2.08 ; 1.32, p<.05) (Table 4).

5. 두 군 간의 삶의 질 비교

가 , 가 , 5 가 , 2 6), (2 ; 4) 가 (Table 6).

고 찰

dothiepin sertraline dothiepin 1 , % , % 1 18.4% ; 2 19.3%, 2 33. 4% ; 4 30.4%, 4 49.7% ; 6 50. 5%). , 2 35.0% 4 18.8% 가 가 EITE . EITE

1 4 가

1 2.40

6 2.47

Nelson (1991) %

fluoxetine desipramine 가

1, 2, 3, 4 desipramine

2, 4

6 가

% , % 4

가 가 EITE, 가 가 , Nelson (1991)

EIR 6 가 . Ba-

ron (1988) Nelson (1991)

3 4

6 가

Nelson (1991) 6

가

Baron (1988) SE 가 가 EI-

fluoxetine desipramine 가 EIR 1, 2

4 , 4, 6

가

가

, TCA SSRI ,

Nelson (1991) fl-

uoxetine desipramine 가 desipramine

2.5 가 , desipramine fluoxe-

tine desipramine 40%

SSRI가 , , ,

cytochrome P450 2D6 가 (Hart-

ter 1995) , , , ,

fluoxetine paroxetine TCA 가 EISE

가 sertraline TCA

(Mitchell Mitchell 1994 ; Warrington

1992) dothiepin ,

dothiepin, sertraline 6

dothiepin 가가 2

dothiepin

가 가 , ,

(Carlsson 1969 ; Maas 1975)

(NARI)

Dubini (1997)
xetine fluoxetine
ine , ,

NARI rebo-
, reboxet-
ine , ,

가

결 론

dothiepin sertraline

dothiepin

TCA SSRI

TCA SSRI

가

TCA SSRI

가

중심 단어 : Dothiepin · Sertraline.

참고문헌

American Psychiatric Association(1994) : *Diagnostic and Statistical Manual of Mental disorders, 4th ed.* Washington DC, American Psychiatric Association

Barnergee SP, Kung LS, Riggi SJ, Chanda SK(1977) : *Develop-*

ment of β -adrenergic receptor subsensitivity by antidepressants. *Nature* 268 : 455-456

Baron BM, Ogden A, Spiegel BW, Stegeman J, Ursillo RC, Dudley MW(1988) : Rapid down regulation of beta adrenoreceptor by co-administration of desipramine and fluoxetine. *Eur J Psychiatry* 154 : 125-134

Brunello N, Baraccia ML, Chuang DM, Costa E(1982) : Down-regulation of β -adrenergic receptors following reated injections of desmethyl-imipramine. *Neuropharmacology* 21 : 1145-1149

Burns RA, Rock T, Edwards DRL, Katona CLE, Harrison DA, Robertson MM, Nairac B, Abou-Saleh MT(1995) : Predictors of response to amine specific antidepressant. *J Affect Disord* 35 : 97-106

Carlsson A, Corrodi H, Fuxe K, Hokfelt T(1969) : Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-ethyl-metathyramine. *Eur J Clin Pharmacol* 5 : 357-366

Cohn JB, Wilcox C(1985) : A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder. *J Clin Psychiatry* 46 : 26-31

Drumbrille-Ross A, Tang SW(1983) : Noradrenergic and serotonergic input necessary of imipramine induced changes in betha but not S2 receptor density. *Psychiatry Res* 9 : 207-215

Dubini A, Bosc M, Polin V(1997) : Do noradrenaline and serotonin differentially affect social motivation and behavior?. *European Neuropsychopharmacology* 7 (Suppl) : 49-55

Fuller RW(1987) : Pharmacologic property of serotonergic agents and antidepressant drugs. *J Clin Psychiatry* 48 : 5-11

Guy W(1976) : *ECDEU Assessment Manual for Psychopharmacology.* Rockville, Md, US Department of Health, Education, and Welfare, pp218-222

Hamilton M(1960) : A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23 : 56-62

Hartter S, Arand M, Oesch F, Heimke C(1995) : Non-competitive inhibition of clomipramine, N-methylation by fluvoxamine. *Psychopharmacology* 117 : 149-153

Maas JW(1975) : Biogenic amines and depression. *Arch Gen Psychiatry* 32 : 1357-1361

Mitchell PB, Mitchell MS(1994) : *The mamagement of depression : Part 2 The place of the new antidepressants.* *Austrlian Family Physician* 23 : 1771-1781

Nelson JC, Mazure CM, Bowers MB, Jatlow PI(1991) : A Preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Arch Gen Psychiatry* 48 : 303-307

Nierenberg AA, Cole JO, Glass L(1992) : Possible trazodone potentiation of fluoxetine. *J Clin Psychiatry* 53 : 83-85

Nystrom C, Hallstrom T(1987) : Comparison between a serotonin and a noradrenaline reuptake blocker in the treatment of depressive outpatients. *Acta Psychiatr Scand* 75 : 377-382

Potter WZ, Calil HM, Extein I(1981) : Specific norepinephrine and serotonin uptake inhibitors : a crossover with pharmacokinetic, biochemical, neuroendocrine and behavioral parameters. *Acta Psychiatr Scand* 290 : 152-170

Reimherr FW, Chounard G, Cohn CK, Cole JO, Itil TM, LaPierre YD, Masco HL, Mendels J(1990) : Antidepressant efficacy of

- sertraline : A double blind, placebo and amitriptyline controlled, multicenter study in outpatients with major depression. J Clin Psychiatry 51 : 18-27*
- Revicki DA, Brown TR, Martindale JJ (1992) :** *Reliability and validity of health related quality of life battery for evaluating outpatient antidepressant treatment. Quality of Life Research 1 : 257-266*
- Seth R, Jennings AL, Bindman J (1992) :** *Combination treatment with noradrenaline and serotonin reuptake inhibitors in resistant depression. Br J Psychiatry 161 : 562-565*
- Shopsin B, Gershon S, Goldstein M, Freidman F, Wilk S (1975) :** *Use of synthesis inhibitors in defining a role for biogenic amines during imipramine treatment in depressive patients. Psychopharmacol Commun 1 : 239-249*
- Stochmeier CA, Martino AM, Kellar KJ (1985) :** *A strong influence of serotonergic axons on beta adrenergic receptors in rat brain. Science 230 : 323-325*
- Sulser F, Vetulani J, Mobley PL (1978) :** *Mode of action of antidepressant drugs. Biochemical Pharmacology 27 : 257-261*
- Vetulani J, Stawartz RJ, Dingell JV (1976) :** *A possible common mechanism of action of antidepressant treatment. Arch Pharmacol 293 : 109-114*
- Weilberg JB, Rosenbaum JF, Biedermann J, Sachs GS, Pollack MH, Kelly K (1989) :** *Fluoxetine added to non-MAOI antidepressant converts nonresponder to responder. J Clin Psychiatry 50 : 447-449*
- Warrington SJ (1992) :** *Clinical implication of the pharmacology of serotonin reuptake inhibitors. Int Clin Psychopharmacol 7 Suppl. 2 : 13*
- Zajacka JM, Jefferies H, Fawcett J (1995) :** *The efficacy of fluoxetine combined with a heterocyclic antidepressant in treatment-resistant depression. J Clin Psychiatry 56 : 338-343*