

(pharmacokinetic) (pharmacodynamic) (pharmacodynamic)
 (absorption), (distribution), (metabolism), (excretion)
 ADME
 가 (Stockley 1994).
 가 가 (synergistic interaction)
 (combined toxicity) 가

가 가 (Stockley 1994).

(pH), (motility) (antagonistic interaction)
 Cimetidine H2 가
 (tricyclic antidepressant : TCA) L-dopa
 chelating agent L-dopa 가
 (drug transport mechanism) TCA
 가 clonidine clonidine

(free form) lithium thiazide
 가 Valproate(VTA) lithium
 in vitro in Thiazide lithium
 in vivo lithium

(biotransformation) 간 P₄₅₀ 산화효소계와 약물유전학

(endoplasmic reticulum) P₄₅₀ 10
 chromosome mi-steroid, bioacid, cholesterol, prostaglandin steroidogenic
 liver microsomal enzyme (oxidation) 가 , NA- , carcinogen,
 DPH cytochrome P₄₅₀ 가 xenobiotic
 (oxidative metabolism)
 xenobiotic

(induction) (inhibition)
 가 (sequence homology) family, sub-family, gene
 family 40% ,
 subfamily 55%
 , gut flora

(Daly 1996). CYP2D6 wild type CYP2D6*1A allele

가 1, 2, 3, 4, 5, 7, 8, 11, 2D6*1A

17, 19, 21, 24, 27, 51 14 family가 debri - soquine PM CYP2D6*3

5 steroidogenic, 1~4 (CYP2D6A), CYP2D6*4A, B(CYP2D6B)

가 xenobiotic, 1~3 family 가 (Joha -

1A2, 2C9, 19, 2D6, 3A3,4 nsson 1991)(1). Haloperidol

(Daly 1996, 1995). CYP2D6 ha -

가, 20~200 loperidol 가 (Lin Fi -

가 (Daly 1996). ndler 1983 ; Potkin 1984), CYP2D6

가 debri -

soquine EM EM CYP2D6 가

(Bertilsson 1992). 가 CYP

2D6*10B(CYP2D6Ch)가 50% (Johansson 1994 ; Yokota 1993)

(phenotype) (polymorphism) (1). CYP2D6*10B allele

가 가, debrisoquine

가 가 (Johan - (1995). S - mephenytoin

sson 1991). debrisoquine (Wilkinson 1992).

sparteine cytochrome P₄₅₀ 2D6(CYP2D6) CYP2C19 (Goldstein 1994),

가 (PM : poor me - 3%가 S - mephenytoin PM(Bertilsson 1992)

tabolizer) 가 (EM : extensive metabolizer) S - mephenytoin PM 13~23% (Bertilsson

PM 1992 ; Nakamura 1985 ; Horai 1989 ; Jurima

debrisoquine PM 7%(Al - type CYP2C19*1 가 CYP2C19

van 1990), 1%(Bertilsson 1992) allele CYP2C19*2(CYP2C19m1) CYP2

가 PM CYP2D6 allele C19*3(CYP2C19m2) 가 가 . CYP2C19*2

가 PM

(1). allele CYP2D6*1A, CYP2D6*1B, CYP 75% 가 (De Morais 1994a).

2D6*2, CYP2D6*3, CYP2D6*4A, CYP2D6*4B..... CYP2D6 CYP2C19*3 allel ,

*10A, CYP2D6*10B.... PM (De Morais 1994b ;

* allele가

Table 1. Genetic polymorphism of CYP2C19 and CYP2D6

	Caucassian	Orientals	Chinese Japanese	Korean
Debrisoquine poor metabolizer(PM)	7%		1%	
CYP2D6 allele frequency				
PM genotype				
CYP2D6*3	21%		Low than caucassians	
CYP2D6*4A,B	1%		Low than caucassians	
Low function EM genotype				
CYP2D6*10B			50% higher than caucassians	
S-mephenyftion poor metabolizer(PM)	3%	15 - 17%	18 - 23%	13%, 16%
CYP2C19 mutation				
CYP2C19*2/PM mutation		about 75%		
CYP2C19*3 allele frequency	0%		23%	

가 (1). CYP3A family CYP 3A3 CYP3A4 가 midazolam, alprazolam, triazolam 가 BZ verapamil, diltiazem, ni-fedipine (Taylor Lader 1996).

CYP2C19 CYP2D6

기분안정제

Lithium

lamotrizine CBZ VPA gabapentin Lithium

CBZ CYP3A3/4 VPA 가 , lithium CBZ VPA

Gabapentin

Lamotrizine

felbamate, tiagabine oxcabazepine, vigabatrine, zo-

nisamide

(novel psychotropic action) (Ketter 1999).

lithium lithium (Joseph 1997).

Freeman Stoll 1998).

Lithium

Lithium 가

1995). Lithium Lithium thiazide, nonst-eroidal antiinflammatory drugs(NSAID), angiotensin con-verting enzyme(ACE) inhibitors lithium Li-thium acetazolamide, mannitol, aminophylline, caffeine, theophy-lline lithium

(Ketter 1999)(2).

Lithium VPA CBZ lithium

(Freeman Stoll 1998). CBZ

(Chaudhry Waters 1983).

CBZ , agranulocytosis

VPA가

gabapentin lamotrigine

(Stanton 1997 ; Schaffer Schaffer 1997 ; gabapentin lithium 가

Lamot-

rigine 가

(Carabrese 1996).

가

Table 2. Drugs and physical conditions altering blood lithium levels

	Increased blood lithium level	Decresed blood lithium level
Drugs	Thiazide Nonsteroid antiinflammatory drugs Angiotensin converting enzymes inhibitors	Acetazolamide Mannitol Aminophylline Caffeine Theophylline
Physical conditions	Renal disease Dehydration Old age	Pregnancy

CBZ가 가

lithium CBZ . SSRIs
 fluoxetine(Grimsley 1991) fluvoxamine(Fritze 1991)
 CBZ sertraline(Lane 1994) par-
 . Clozapine lithium
 가 (Calabrese 1996 ;
 McElroy 1991 ; Zarate 1995 ; Kimmel 1994 ; Ba-
 nov 1994 ; Suppes 1994). Risperidone zotepine
 가
 nefazodone CBZ
 (Ashton Wolin 1996). CBZ
 nefazodone CYP3A3/4 nefazodone
 CYP3A3/4 alprazolam, triazolam
 CBZ CYP3A3/4 alprazolam, clon-
 azepam
 verapamil diltiazem CBZ
 dihydropyridine nimidipine nifedipine
 (Price DiMarzio 1988 ; Brodie Ma-
 cPhee 1986).
 . Olanzapine
 lithium 가
 olanzapine clozapine 가 가,
 . Clonazepam, lorazepam
 BZ lithium
 가
 CYP3A3/4 CBZ
 lamotrizine CBZ
 CBZ 45%
 가 가
 (Warner 1992)(3).

Carbamazepine

CBZ 가 (autoinduction)
 가 가
 CBZ CYP3A3/4 CBZ
 epoxide metabolite(10, 11 - epoxide CBZ : CBZ -
 E) , epoxide hydrolase
 diol metabolite . CBZ CYP3A3/4 CBZ - E 가 , CBZ
 (autoinduction) CBZ 가
 (heteroinduction)
 2~4 가 가
 CBZ 24 , 25ml/min
 가 가 가 8 ,
 75ml/min
 가 CBZ - E
 가 (Ketter 1999). CBZ
 가 , CBZ
 가 CBZ
 VPA CBZ
 CBZ VPA CBZ VPA 가
 VPA CBZ
 CBZ VPA 가
 clozapine 가
 (Denbow Fraser 1990).

CBZ clozapine
neuroleptic malignant syndrome (Muller Becker 1988)
risperidone
(de Leon Bork가 1997 ; Lane Chang 1998).
quetiapine(Seroquel) CYP3A3/
4 가 carbamazepine 가
(Ketter 1999).
CBZ
CYP3A3/4 가
CYP CBZ 가
CYP3A3/4 CBZ
가 VPA CBZ
가 (3).

Valproate

VPA GABA

Table 3. Drug-drug interactions of carbamazepine

Mechanism	Drug	Affected drug	Blood level
CYP3A3/4 inhibition	Diltiazem	Carbamazepine	Increased
	Verapamil		
	Fluoxetine		
	Fluvoxamine		
Induction	Nefazodone	Carbamazepine	Decreased
	Carbamazepine		
	Felbamate		
	Phenobarbital		
Epoxide hydrolase inhibition	Valproate	Epoxide-carbamazepine	Increased
		Free carbamazepine	Increased
Heteroinduction (CYP2D6?)	Carbamazepine	Tricyclic antidepressants	Decreased
		Haloperidol	
		Fluphenazine	
		Thiothixene	
		Olanzapine	
		Risperidone	
CYP3A3/4 induction	Carbamazepine	Quetiapine	Decreased
		Clonazepam	
		Alprazolam	
		Clobazam	

가 . Va-
lproic acid divalproex sodium
80~90%
(Graves 1995). VPA diazepam, carbamazepine,
phenytoin, tiagabine
VPA 1 가
50% conjugation
glucuronide metabolite가 40%
- oxidation , 2-
ene - VPA가
10% 가 cytochrome P₄₅₀
(Ketter 1999). VPA lithium CBZ
가
(Bourgeois 1988).
P₄₅₀ , epoxide hydrolase, glucuronyl trans-
ferase
CBZ - E, lamotrigine, TCAs,
BZ . Cimetidine, phenothiazine, flu-
oxetine VPA 가 , CBZ,
phenytoin, phenobarbital, rifampin VPA
(Ketter 1999)(4).
VPA lithium CBZ
가 가 가
가 , 가
VPA CBZ VPA
CBZ
VPA VPA CBZ - E

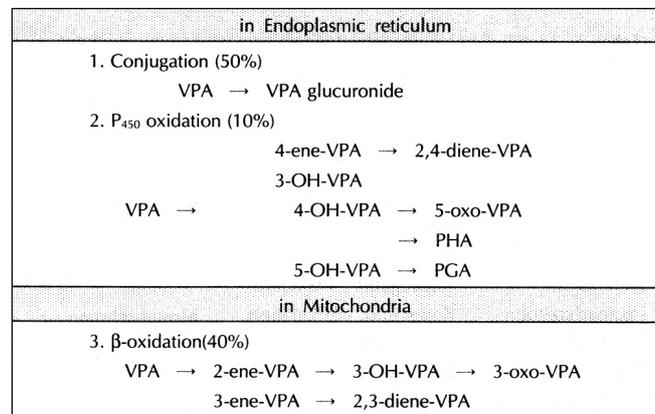


Fig. 1. Metabolism of valproate.

glucuronide
in vitro CYP
 2C19 .
 가 . Gabapentin GABA
 . GABA release
 (Taylor 1995).
 가
 . lithium
 .
 가 (Ketter 1999).
 Lamotrigine 5-HT₃
 glutamate release . Lamotri-
 gine ()
 . CBZ oxcarbazepine glutamate release
 (Calabrese 1999). la-
 motrigine (Sander 1991 ; Ring 1993). 70%가
 . Zo-
 nisamide sulfonamide
 carbonic anhydrase (Peters Sorkin 1993).
 . Lamotrigine 85%가 conjugation
 10%
 . CBZ lamotrigine
 VPA
 .
 glucuronidation
 (Ketter 1999). lamotrigine VPA , 17
 , CBZ . Lamotrigine (Kanba 1994)
 CBZ
 lamotrigine CBZ-E가 가
 가 . Topiramate AMPA/
 . AMPA/kainate NMDA
 kainate glutamate
 .
 5~17% 1998).
 (Shorvon 1996). . Verapamil lithium
 70% . CBZ (Helmuth
 phenytoin 가 1989 ; Wright Jarrett 1991 ; Dubovsky 1987). ve-
 . *In vitro* CYP2C19 , rapamil lithium
 CYP2C19 phe- 가 (Weirauch 1984). CBZ
 nytoin (Bourgeois 1996). Tiagabin CYP3A3
 GABA (Sudak Jansen 1995). /4 , CBZ

칼슘통로차단제들

Table 6. Interactions of calcium channel blockers with other drugs used in bipolar disorder

Affected drugs	Drug-drug interactions
Lithium	Decreased blood lithium level Potential neurotoxicity(choreoathetosis), severe bradycardia, parkinsonism
Carbamazepine	Increased blood carbamazepine levels Potential neurotoxicity
Antipsychotics	Enhanced parkinsonism

(Gadde Calabrese 1990 ; Price DiMarzio 1988)
(2). 가 (Mac -
Phee 1986).

VPA gabapentin
lithium CBZ, VPA,
gabapentin, lamotrigine
(Joseph 1997).

(1998)(6).

항불안제

BZ 50

BZ

Benzodiazepines

BZ benzene ring 1, 4 diazepine ring
R1, R2, R3, R4, R7, R2'
2 - keto - BZ(chlordiazepoxide,
diazepam, flurazepam, clorazepate, bromazepam), 3 - OH -
BZ(oxazepam, lorazepam, temazepam), 7 - nitro - BZ(cl -
onazepam, nitrazepam), triazolo BZ(alprazolam, triazolam),
imidazo BZ(midazolam) 5가
가
(Chouinard 1999). BZ
glucuronide conjugation
Lorazepam, oxazepam, temazepam 3 - OH BZ
conjugation 2 - keto -

BZ conjugation 가 3 - OH
Triazolo BZ imidazo BZ conjugation
hydroxylated metabolite
conjugation
Clonazepam, nitrazepam 7 - nitro - BZ
(nitroreduction) acetylation
oxidation nitroreduction cytochrome P450
가 CYP2C19가 diazepam
CYP3A3/4가 alprazolam, clonazepam, diazepam, midazepam,
triazolam (Chouinard 1999).
, fluoxetine, cimetidine, isoniazid, pr -
opranolol BZ CYP
BZ
BZ
가
(pharmacodynamic tolerance)
cimetidine BZ

3 - OH BZ
glucuronide
가
BZ
SSRIs, nefazodone
, ketoconazole , erythromycin
, cimetidine

SSRIs fluvoxamine norfluoxetine 가
in vitro CYP3A3/4 fluoxetine, paroxetine, se -
traline (Preskorn
1997). *In vivo* fluoxetine 40mg 10 alp -
razolam 25% , fluvoxamine 100mg
10 alprazolam . Fluvox -
amine alprazolam 가
alprazolam fl -
uvoxamine 가 alprazolam
(Fleishaker Hurst 1994). nefazodone
CYP3A3/4 (Richelson 1997). Nefazodone
triazolam, alprazolam
가
(Barbhaiya 1995 ; Kroboth 1995).
benzodiazepine 가
ketoconazole intracona -

zole . *in vitro* fluvoxamine
(von Molke 1996).
erythromycin triazo-
lam, midazolam 가 (Gonzalez
1992). CYP cimetidine
alprazolam
cimetidine
midazolam 가 가
cimetidine BZ

Buspirone

Buspirone 가
5-HT_{1A} D2 가
(Fulton Brogden 1997). TCAs,
haloperidol, benzodiazepine, cimetidine, ranitidine, NSAIDs

결 어

가
,
phantom drug interaction

가
.
in vitro *in vivo*
가

가
중심 단어 :

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