

발기부전 치료의 새로운 PDE₅ (Phosphodiesterase) 억제제들

New PDEs Inhibitors for Erectile Dysfunction

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Abstract

Phosphodiesterases (PDEs) are functionally diverse enzymes with wide organ and tissue distributions. Of these enzymes, PDE₅ has received particular attention largely because of the introduction and widespread use of the selective PDE₅ inhibitor sildenafil citrate (Viagra) as an oral therapy for erectile dysfunction(ED). Within the corpus cavernosum of the penis, PDE₅ influences regulation of vascular and trabecular smooth muscle contractile tone by enzymatically degrading the cyclic 3',5' - guanosine monophosphate(cGMP), the key second messenger. By reversibly inhibiting this enzymatic activity, the competitive inhibitors of PDE₅, including sildenafil and newly introducing tadalafil(Cialis™) and vardenafil(Lebitra™) act as potent 'agonists' of the erectile response. Data from separate 12 - week multicenter, randomized, double - blind, placebo - controlled trials involving sildenafil, as well as tadalafil and vardenafil, have demonstrated that approximately 80% (or more) of men reported improved erections after treatment with each of these PDE₅ inhibitors at the upper end of the dosing range. PDE₅ inhibitors have been well tolerated. In clinical studies, vasodilator effects(e.g. headache and flushing) have generally been mild, transient, and infrequently associated with premature study discontinuation. The present article reviews the characteristics of new PDE₅ inhibitors in experimental and clinical studies.

Keywords : Erectile dysfunction; Sildenafil; Tadalafil; Vardenafil; Phosphodiesterase 5 inhibitors

: ; ; ; ; 5

1970

가 가

가

. 1980

가

가

papave-

가 2

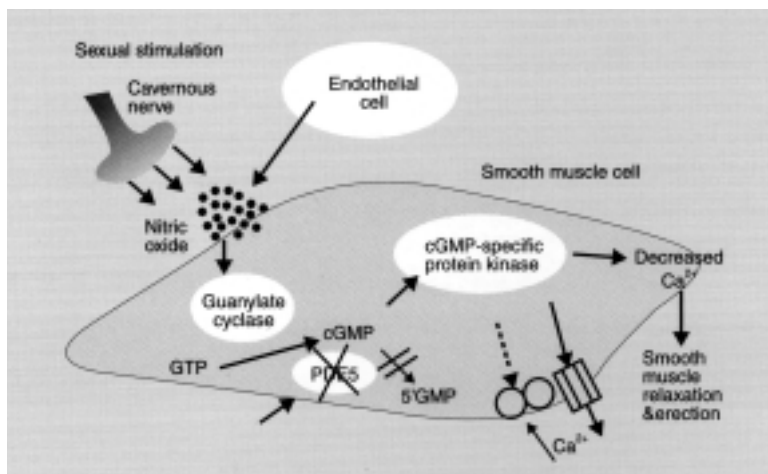
가

rine

가

1998

(Viagra)



1. NO - cGMP - PDE₅

PDE₅ 가

가

5

Sildenafil

Tadalafil, Vardenafil

PDE₅

가

()

PDE₅
monophosphate)

cGMP(cyclic guanosine

NO()가

NO

NO

L - arginine

,

80%

. NO

가

가 guanylyl cyclase

가

GTP cGMP

cGMP

가

가

,

2002

cGMP

Apomorphine

(Uprima)

cGMP guanylyl cyclase

phosphodiesterases(PDEs)

50%

11

PDEs가

Sildenafil

Ta-

PDEs

, PDE₅가

dalafil, Vardenafil

PDE₅

cGMP

PDE₅

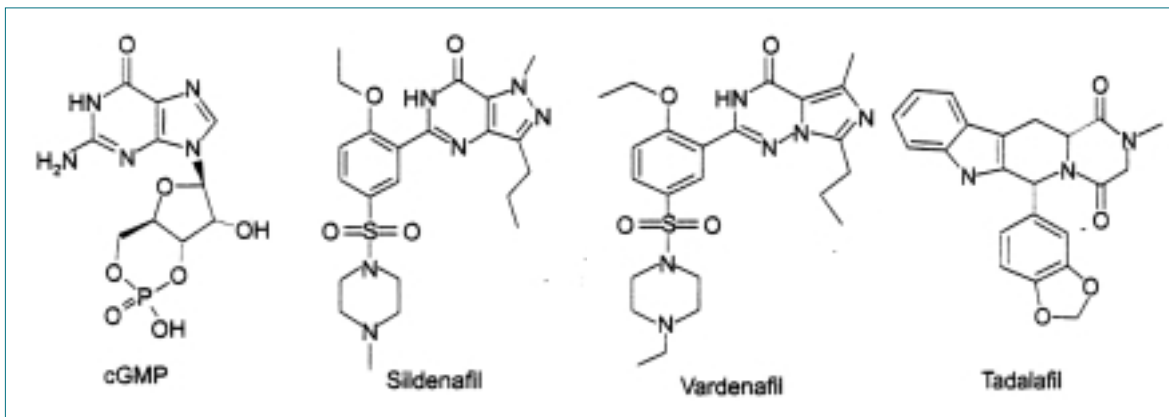
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PDE

PDE₅

PDE₅

Pharmacotherapeutics



2. cGMP, sildenafil, vardenafil and tadalafil

PDE		PDE ₅		cGMP가 PDE ₅	
				cGMP가 PDE ₅	
				(2).	
11		PDE		가	
PDE ₁	PDE ₆			가	
PDE ₇		PDE ₁₁		PDE ₅	
				PDE ₅ inhibitor	
PDE 2, 3, 4, 5				PDE ₅	PDE 11
		PDE 2, 3, 4 cAMP			
PDE ₅ cGMP		PDE ₅		50%	
		가		IC ₅₀	Sildenafil IC ₅₀
		PDE ₅ 가		3.5~8.5 nM, Vardenafil	0.1~0.7 nM, Tadalafil
				0.9~6.7 nM	cGMP ,
		PDE ₅ Sildenafil,		,	IC ₅₀
Vardenafil	Tadalafil	cGMP	가	PDE ₅	
		cGMP	IC ₅₀	가	
PDE ₅		Sildenafil	Vardenafil		
		가 cGMP	guanine	PDE ₅ inhibitor	Vardenafil PDE ₅ 가
		, Tadalafil	가	가	Sildenafil
cGMP	guanine		cone	PDE ₆	6~8

(PDE₅), Vardenafil 2~9
- ()
PDE₆
(phototransduction)
tadalafil PDE₆ 780

Tadalafil Sildenafil, Vardenafil PDE_{11a}

PDE_{11a}
(1).

PDE₅

1. Sildenafil

100 mg
(C_{max}) (t_{max}) 30~120 (60)
30
1~1.5
t_{max}가 60
29% Sildenafil
가 1/2 (t_{1/2}) 3~5
Sildenafil cytochrome P450 3A4 2C9
Cimetidine Erythromycin, Ketokonazole
Sildenafil
Sildenafil 24
Sildenafil
2~8
Sildenafil 80% , 13%

1. PDE₅

Family	Sildenafil	Tadalafil	Vardenafil
PDE5	1	1	1
PDE6	6~8(7*)	780	2~9(16*)
PDE11a	1,500(203*)	14(7*)	640(346*)

1) Cialis monograph 2003
2) (*) Vardenafil monograph

2. Vardenafil

PDE₅ 50%
IC₅₀ Sildenafil 10
t_{max} 0.7~0.9 , t_{1/2} 4~5
92.5% , 4.9%
96

3. Tadalafil

2
가 17.5 가
cytochrome P450 3A4 61%
, 36% Sildenafil,
Vardenafil 가 CYP3A4
Tadalafil

1. Sildenafil Citrate(Viagra™, Pfizer)

1998

Pharmacotherapeutics

Sildenafil 3 가
25% 25 mg, 50 mg, 100 mg
56%, 77%, 84% 가
75% 100 mg, 23%
50 mg, 2% 25 mg
133 65% 가
가 100 mg, 33%가 50 mg PDE₆
25 ~ 100 mg
(blue haze)가
가
가
70%, 56%, 가
42.5%, 80% 5
Sildenafil 가 SS -
penogram 104 76% 가
가 , 가
가
Sildenafil citrate
cytochrome p - 450 isoenzyme
7 ~ 25%, 가 , 65
7 ~ 34%, 4 ~ 19%, 1 ~ 11%, Ci-
2 ~ 9%, 가 1 ~ 6% metidine, Ketoconazole, Erythromycin
가 31.8% 가
25.8%, 4.5%, 6.1%,
4.5%, 4.5%가 가
가 5
2. Tadalafil(Cialis™, Eli Lilly)
PDE₅ inhibitor
IC₅₀ 0.9 nM Sildenafil citrate 3.5 nM
가 17.5
Tadalafil 가 16

		24 ~ 36		. Vardenafil hydro-						
		chloride 40		(Tmax)						
가	PDE ₆	Sildenafil 70	Tadalafil 2							
PDE		가	3.94	Sildenafil 3.82						
	Tadalafil	Tadalafil 17.5								
	PDE _{11a}	Porst	39.5%, Vardena-							
Sildenafil	Vardenafil	fil 20 mg 74.6%	6	20 mg						
		83%	가							
		Goldstein 18								
		PDE _{11a} 452	10 mg, 20 mg							
		3	가							
		32%, Ta-	가?							
dalafil 20 mg 75%	30 59%,	23%, 10 mg 49%, 20 mg 54%								
4 ~ 24 80%, 24 ~ 36 79%										
121	가	20 mg 11%,	가 10%,							
67%, Tadalafil 85.4%	가	10%	Goldstein	20 mg 6						
		73%								
		31%, Tadalafil 71%	가							
		80%								
16%,	5%, 5%	Brock								
		440								
		vardenafil 10 mg, 20 mg								
		21.8%, 46.6%, 47.5%								
3. Vardenafil (Levitra™, Bayer/Glaxosmithkline)		9.9%, 37.2%, 34.2%								
Sildenafil	가 Vardenafil	13%, 59%, 65%								
IC ₅₀ (50%)	가	Donatucci	81%,							
0.7 nM 가	PDE ₅ 가	66%								
		15								
		Sildenafil citrate	PDE ₅							
cGMP		11%,	10%,	10%						

Pharmacotherapeutics

		5	가	Via-
		gra	Cialis	Levitra
	PDE ₅	80% 가		
Sildenafil			가가	,
	2	가		
Tadalafil, Vardenafil				
PDE ₅				
80%				
Tadalafil	24 ~ 36			
	, Vardenafil	PDE ₅		
가	15			
가	PDE ₅			
	Sildenafil	Vardenafil		
PDE ₆				
가		Tadalafil		
PDE _{11a}	PDE ₅			
	PDE _{11a}			

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