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**Vasomax for the treatment of male erectile dysfunction**

**Abstract** This paper reviews laboratory and clinical data concerning oral phentolamine mesylate, Vasomax, an α-1, α-2 adrenergic receptor antagonist developed specifically for treatment of erectile dysfunction. A contemporary view of the neurovascular mechanisms in penile erection includes the effects of both smooth muscle relaxation and contraction. Contraction of the cavernosal arteries and trabecular smooth muscle appears to be predominantly under the control of α-adrenergic innervation. Conversely, adrenergic blockade of α-1 and α-2 receptors has been shown to facilitate penile erection in both animal and human models. The pharmacokinetic profile of Vasomax appears well suited for an oral erectogenic agent. Vasomax is rapidly absorbed and eliminated in normal males. Peak plasma concentrations are achieved in 30–60 min, and the half-life approximates 5–7 h. Food decreases the rate, but not the extent of bioavailability. Vasomax has low protein binding and is excreted primarily via urine and feces. There is a strong dose-response relationship in maximum plasma concentration (Cmax) and area under the curve (AUC), and there are no clear age-related differences in absorption or elimination rates. Efficacy of Vasomax has been systematically evaluated in two (ZON300, ZON301) large-scale, placebo-controlled trials, in addition to two long-term open-label studies. In both studies, Vasomax was associated with significant improvements in the erectile function domain scores of the International Index of Erectile Function (IIEF). Further improvements were noted as the duration of treatment and dose level were increased. The percentage of successful penetration attempts was also significantly improved with Vasomax compared to placebo. For patients who continued in open-label treatment with Vasomax, efficacy was generally well maintained. Vasomax was well tolerated by the majority of patients. The most common side effects observed were nasal congestion (10%), headache (3%), dizziness (3%), tachycardia (3%) and nausea (1%). Side effects were generally dose-related and in the mild-to-moderate range in all three studies. Furthermore, side effects seldom resulted in treatment discontinuation. Very few serious adverse events were observed in these trials. In summary, Vasomax appears to be effective in the treatment of male erectile dysfunction and well-tolerated by the majority of patients. The drug has a satisfactory side effect profile, without significant risk of cardiovascular effects. Results of clinical trials with Vasomax support the concept of adrenergic-blockade as a clinically relevant mechanism in the control of penile erection.

**Introduction**

Detumescence of the erect penis is controlled by adrenergic innervation. Activation of the adrenergic pathways to the penis results in contraction of the cavernosal arteries, reduced cavernosal arterial inflow, and contraction of the trabecular smooth muscle with associated collapse of the lacunar spaces. The resultant loss of corporal veno-occlusive function leads to detumescence. Intracavernosal administration of adrenergic agonists initiate detumescence and have become a routine treatment for prolonged erection or priapism. There are several adrenergic agonists with varying affinities for the α-adrenergic receptors. Norepinephrine, in particular, is the principal autonomic neurotransmitter that binds to both α-1 and α-2 adrenergic receptors. During sexual activity, there are several physiologic activities associated with norepinephrine or catecholamine release at the adrenergic synapse. As one approaches orgasm during sexual activity, for example, marked increases in heart rate and systolic blood pressure occur secondary to...
catecholamine release. Psychologically-mediated release of catecholamines may occur in stressful situations, such as fear of failure, performance anxiety, anger, shame, and embarrassment. Physiologic and/or psychologically-mediated catecholamine release may also occur secondary to pain associated with Peyronie’s disease, prostatitis, epididymitis, or even non-genital pain such as headache. Such conditions are associated with catecholamine release and a concomitant erectile lytic effect [1].

On the other hand, α-adrenergic receptor antagonists have historically been utilized to facilitate penile erection in men with erectile dysfunction [2, 3, 4, 5]. In particular, antagonizing the α-adrenergic contractile response will delay the onset of detumescence and act to prolong the duration of erection initiated by sexual stimulation. Adrenergic blockade might also potentiate the stimulatory effect of smooth muscle relaxation by removing inhibitory responses mediated by catecholamine release from the sympathetic nervous system.

Several receptor sub-types have been identified within the α-adrenergic system, each of which may have discrete effects on male sexual function. Several studies have suggested that pre-synaptic, α-2 receptors are involved in the central control of erection, whereas post-synaptic α-1 and α-2 receptors are involved in peripheral relaxant and contractile effects on corporal smooth muscle [6, 7, 8]. Although the independent effects of α-1 and α-2 stimulation and blockade have been described, relatively little attention has been paid to the combined or interactive effects of α-1 and α-2 blockade. Based on the clinical findings reported with oral phentolamine, it appears that a nonselective combination of α-1 and α-2 blockade may offer certain advantages. Historically, α-blocking agents have been used in the treatment of erectile dysfunction prior to the advent of phosphodiesterase inhibitors. Yohimbine, an α-2 antagonist, has been extensively studied in animals, and has been used clinically for the past half century, despite a lack of well-controlled outcome research [6, 8]. α-1 Antagonists, such as doxazosin, which are commonly used in the treatment of benign prostatic hypertrophy or hypertension, have been associated with mildly positive effects on male sexual function. Oral phentolamine mesylate, a nonselective α-blocker, developed specifically to improve ED, has been used successfully for facilitating erections and treating men with erectile dysfunction [1–5].

**Mechanisms of action of Vasomax**

The mechanism of action of phentolamine in regulating corpus cavernosum smooth muscle tone has been postulated to be via α-adrenergic receptor blockade. Detailed biochemical and physiological studies of the mechanism of action of phentolamine mesylate in human corpus cavernosum tissue have recently been reported [7]. Phentolamine mesylate was found to be an effective α-1 and -2 adrenergic receptor blocker in corpus cavernosum erectile tissue. Phentolamine competitively displaced specific α-1 receptor ligands (2-[beta-(4-hydroxy-3-[125I]iodophenyl)-ethylaminomethyl]-tetralone {HEAT} and prazosin) and specific α-2 receptor ligands (rauwolscine and RX 821002). The affinity of phentolamine for α-1 adrenergic receptors was comparable to the α 1A selective receptor antagonist 5-methylurapidil, but was less than that of prazosin. The affinity of phentolamine for the α-2 adrenergic receptors was greater than that of the α-2 receptor agonist UK 13304 and norepinephrine, but was less than that of the α-2 receptor antagonists delequamine (RS 1385–197) and rauwolscine. The relatively high affinity of phentolamine mesylate for α-1 and α-2 adrenergic receptors suggests that 30 min following oral ingestion of 40 mg of Vasomax, the mean plasma phentolamine concentrations (40–50 nM) will sufficiently occupy the α-adrenergic receptors in corpus cavernosum erectile tissue, and thereby result in inhibition of adrenergic-mediated physiologic activity [7, 8].

In corpus cavernosum erectile tissue, phentolamine mesylate shifted the dose response of phenylephrine (selective α-1-mediated) and UK-14304 (selective α-2-mediated) contraction in a concentration-dependent manner. Phentolamine mesylate also induced concentration dependent relaxation in erectile tissue pre-contracted with the selective α-1 receptor agonists phenylephrine and oxymetazoline, the selective α-2 receptor agonist UK 14,304 and the non-selective agonist norepinephrine. These data indicate that phentolamine α-adrenergic binding activity mediates the physiologic inhibition of adrenergic-induced corpus cavernosum contractile tone and the resulting relaxation response [7, 8].

Contractile responses by 80 mM KCl and endothelin are mediated by non-adrenergic mechanisms. Those mediated by KCl are thought to occur by electromechanical coupling via depolarization of the corpus cavernosum smooth muscle, primarily by activation of L-type calcium channels and calcium influx. Those mediated by endothelin are thought to occur via receptor mediated intracellular calcium release. Phentolamine mesylate, however, induced relaxation of corpus cavernosum strips pre-contracted with 80 mM KCl or endothelin. Such data suggest that phentolamine mediates corpus cavernosum tissue contractility by both adrenergic and non-adrenergic pathways. This relaxation response was attenuated by the competitive nitric oxide synthase inhibitor L-nitroarginine and by the mechanical disruption of the endothelium. One likely possibility to explain phentolamine mesylate-induced relaxation of KCl-contracted tissue was an additional non-adrenergic, endothelial-based, nitric-oxide mechanism [1, 7, 8].

Indirect antagonism is a recognized complementary pharmacologic mechanism of action of many natural and synthetic agonists and antagonists. Phentolamine mesylate is an adrenergic antagonist to the contractile substance norepinephrine. Phentolamine was found to also possess the agonist function of tissue relaxation via