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Comparison of the synergistic effects of tamsulosin versus phentolamine on penile erection: in vitro and in vivo studies

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Abstract In vitro and in vivo studies were performed to determine the potential use of tamsulosin (TAM) versus phentolamine (PHE) for intracavernosal injection (ICI) therapy when mixed with papaverine (PAP) and/or prostagladin E_1 (PGE_1) or with vasoactive intestinal polypeptide (VIP) for the treatment of erectile dysfunction. We performed isometric tension studies on rabbit ($n = 15$), dog ($n = 5$), and human ($n = 10$) cavernous smooth muscle strips with TAM, PAP, PHE, VIP, PGE_1, and the combinations of PAP and PHE; PAP and TAM; VIP and PHE; VIP and TAM; PAP, PGE_1 and PHE; and PAP, PGE_1 and TAM. TAM-containing trimix (PAP 18.75 mg, PGE_1 6.25 μmg, and TAM 0.875 mg per ml) or PHE-containing trimix (PAP, PGE_1, and PHE 0.625 mg per ml) were also injected into the cavernous bodies of ten mongrel dogs. Among the single agents, TAM and PGE_1 (only in human) had the strongest effect on the relaxation of cavernous muscles in rabbit, dog, and human strips ($P < 0.05$). Relaxation responses to 2- or 3-drug mixtures containing tamsulosin were also significantly better ($P < 0.05$) than PHE-containing ones in rabbit, dog, and human strips. The increase in intracavernosal pressure with a TAM-containing trimix was higher than with a PHE-containing one (0.03 ml; 81.2 vs 75.8 mmHg, 0.04 ml; 103.2 vs 94.3 mmHg), although not statistically different. The drop in systemic blood pressure was lower after injection of a TAM-containing trimix than a PHE-containing one, although not statistically different. In conclusion, tamsulosin might be a more efficacious and safer agent to use for ICI therapy than phentolamine.

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Introduction

Intracavernosal injection (ICI) therapy has been commonly used in the management of erectile dysfunction. Papaverine, phentolamine, and alprostadil (PGE_1) are now frequently used in this therapy either alone or in combinations. The most popular combinations include papaverine and phentolamine, PGE_1 and phentolamine, and papaverine, PGE_1 and phentolamine (trimix) [4, 11]. Recently, it has been reported that Invicorp (vasoactive intestinal peptide [VIP] and phentolamine; Senetek PLC, Nasdaq, SNTKY) induced penile erection sufficient for sexual intercourse in 67% of patients with erectile dysfunction who had failed with ICI therapy and trimix [10, 12].

Recently, both pharmacologic and molecular cloning techniques in human prostatic tissues have revealed the existence of at least three subtypes (α_{1A}, $_{1B}$, and $_{1D}$) of α_1-adrenoceptor (AR) [3, 23, 29]. Moreover, RNase protection studies have shown that the α_{1a}-subtype represented more than 70% of the total mRNA in the human prostate [22]. Among the selective α_1-AR antagonists commonly used for the medical management of benign prostatic hyperplasia (BPH), doxazosin, terazosin, and prazosin have identical activities with all subtypes of α_1-AR but tamsulosin has a modest selectivity for α_{1A}- over -$_{1B}$- but not over α_{1D}-AR [3, 6, 16]. It has also been reported that tamsulosin was more than ten times more potent than doxazosin, terazosin, and alfuzosin in blocking phenylephrine-induced prostatic contraction in dogs [16].

It is known that contractions of the cavernous smooth muscle in response to norepinephrine are mediated predominantly by the activation of α_1-ARs, as in the prostate, although both αA_1- and α_2-ARs have been

identified in corpus cavernosum tissue [2, 13, 28]. Traish et al. [27] demonstrated that α_{1A}- and α_{1D}-AR were more abundant than α_{1B}-AR in human cavernous smooth muscles.

We previously observed that all of the clinically-available We_1-AR antagonists caused concentration-dependent relaxation of rabbit cavernous smooth muscle strips, and that tamsulosin had greater potency than prazosin (more than 100-fold), doxazosin (more than 1000-fold), and terazosin (more than 1000-fold) [25]. Therefore, we postulated that tamsulosin in combination with vasoactive agents might be more effective for induction of penile erection than phentolamine-containing solutions.

To determine tamsulosin's potential as an alternative to phentolamine in ICI therapy for erectile dysfunction when mixed with papaverine, VIP, and/or prostagladin E_1, isometric tension studies on rabbit, dog and human cavernous smooth muscle strips, and in vivo studies in dogs were performed.

Materials and methods

In vitro studies

Chemicals and solutions

Norepinephrine (NE), papaverine hydrochloride, phentolamine hydrochloride, VIP, PG E_1, HEPES, sodium chloride (NaCl), calcium chloride ($CaCl_2$), and magnesium chloride ($MgCl_2$) were purchased from Sigma Chemical Co. (USA), and tamsulosin from Yamanouchi Pharmaceutical Company (Japan).

The composition of HEPES-buffered physiological salt solution (PSS) was as follows: 140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 5 mM HEPES, 11 mM glucose, pH titrated to 7.4 with 1 N NaOH.

Preparation of cavernous smooth muscle strips

The cavernous strips were obtained from New Zealand White rabbits (2.5–3.0 kg; $n = 15$), mongrel dogs (18–22 kg; $n = 5$), and patients with erectile dysfunction (51–62 years; $n = 10$) during penile prosthetic surgeries. Informed consent was obtained from the patients before surgery. This protocol was approved by the ethics committee for the protection of persons and animals in biochemical research of the Institute of Medical Science, Chung-Ang University, Seoul, Korea.

The rabbits were killed with a blow to the head and exsanguinated. The entire penis was then surgically removed. The penile crura of the dogs were excised after general anesthesia with ketamine (15 mg/kg) and xylazine (0.15 mg/kg). The corpus cavernosum was carefully dissected, freeing it from the tunica albuginea, and surrounding connective tissue. The excised cavernous smooth muscles from rabbits, dogs and men were immediately placed in 100% oxygen-saturated PSS and studied within 1 hour. The muscle strips were trimmed to a size of $2 \times 2 \times 8$ mm and mounted. To record isometric tension, the strips were attached by a silk tie to a fixed support at one end and to a wire-connected force transducer (52–9545, Harvard, UK) and polygraph (50–8630, Harvard, UK) at the other end. The tissue was placed in a 25 ml organ chamber containing PSS which was bubbled with 100% O_2 and maintained at 37°C, pH 7.4. The resting tension for each strip was adjusted to an optimal tension at which contraction by NE was maximal and the developed tension was recorded.

Pharmacological responsiveness

To determine effective concentration $(EC)_{50}$ values for NE, concentration-response curves to NE (10^{-9}–10^{-4} M) were obtained from cavernous smooth muscle. Relaxation responses induced by various vasodilators (tamsulosin, phentolamine, VIP [only in human and rabbit], PGE_1 [only in human and dog], and papaverine) were then studied in the cavernous strips in which tone had been elicited with an EC_{50} of NE. Relaxation studies with combinations of papaverine and phentolamine, papaverine and tamsulosin, VIP and phentolamine (only in human and rabbit), VIP and tamsulosin (only in human and rabbit), papaverine, PGE_1 and phentolamine (only in human and dog), and papaverine, PGE_1 and tamsulosin (only in human and dog) were also performed. Concentration-response curves were determined by adding successive logarithmic increments of the agents from 10^{-9} to 10^{-4} M (PGE_1:10^{-10} to 10^{-5} M; VIP: 10^{-10} to 10^{-6} M) to the chamber.

After a concentration-response curve to each agent or combination was constructed, the strip was washed with fresh physiologic salt solution more than twice during an hour and the tension was allowed to relax to the baseline level. Contractile tension was expressed in grams. The study results were expressed as the percent relaxation of the contraction induced by NE.

In vivo study

Ten male mongrel dogs (15–20 kg) were used for the in vivo study according to a protocol approved by the ethics committee. Anesthesia was induced with an intramuscular injection of ketamine (15 mg/kg) and xylazine (0.15 mg/kg), and boosted every 30 min to 1 h. The femoral artery was cannulated for monitoring systemic blood pressure. Through ''inverted Y-shaped'' perineal incision, the cavernous corpora were dissected and a 21-gauge butterfly needle was inserted into the corpus cavernosum. The needle was connected to a pressure transducer (52–9545, Harvard, UK) and polygraph (50–8630, Harvard, UK) via a three-way valve. Measurement of intracavernosal pressure (ICP) and injection of vasoactive agents were accomplished via these same lines. The lines were flushed with a dilute heparin solution (500 U/100 ml normal saline).

We have used trimix containing papaverine 18.75 mg/ml, PGE_1 6.25 μg/ml, and phentolamine 0.625 mg/ml in ICI therapy for patients with erectile dysfunction. The same regimen was used in this study. The concentration of tamsulosin in the trimix was determined according to the ratio of the molecular weights of tamsulosin and phentolamine (444.98 versus 317.8). Therefore, the concentration of tamsulosin used in this study was 0.875 mg/ml. Preliminary experiments on two dogs showed that 0.03 ml and 0.04 ml of tamsulosin- or phentolamine-containing trimix induced significant penile erection.

Tamsulosin-containing trimix (0.03 ml or 0.04 ml) was administered into the right side of the corpus cavernosum of the dogs. The phentolamine-containing one was injected into the left side of the corporal body 30 minutes after the ICP had returned to the baseline level. After full recovery of the corporal body (2 weeks), the phentolamine-containing trimix was administered into the right side of the corpus cavernosum and then the tamsulosin-containing one into the left side. The following variations were recorded: (a) change in the ICP defined as the peak amplitude of the observed increase in the ICP over baseline (ΔICP) (b) duration of plateau pressure, defined as an ICP more than 80% of the maximal ICP (ΔDP), and (c) systemic blood pressure (ΔBP).

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) with n representing the number of animals and patients. For the in vitro study, the concentration-response curves to various vasodilators and combinations of these were analyzed comparatively using a Student's t test and a one way analysis of variance (ANOVA) test. The ΔICP, ΔDP, and ΔBP values induced in vivo by tamsulosin-

and phentolamine-containing trimix were compared using a paired t test. The probability, $P < 0.05$, was considered to be statistically significant for all tests.

Results

In vitro investigations

All vasoactive agents (except PGE_1 in dog) caused the concentration-dependent relaxation of rabbit, dog and human cavernous smooth muscle strips ($n = 5$ for each), which had been pre-contracted with norepinephrine (Fig. 1). Tamsulosin and PGE_1 (only in human) had the strongest such effect, among all the agents, in rabbit, dog, and human tissue, followed in descending order by VIP (human), phentolamine, and papaverine ($P < 0.05$ by ANOVA).

The concentration-response curve of papaverine and tamsulosin showed a leftward shift ($P < 0.05$) compared with that of papaverine and phentolamine, in rabbit, dog, and human cavernous muscle strips ($n = 5$ in each; Fig. 2).

Figure 3 shows a comparison of the relaxation response of cavernous smooth muscle to VIP and phentolamine versus VIP and tamsulosin in cavernous muscle strips from rabbit and patients with erectile dysfunction. The response to VIP and tamsulosin was significantly better ($P < 0.05$) than VIP and phentolamine both in rabbit and human tissue ($n = 5$ in each).

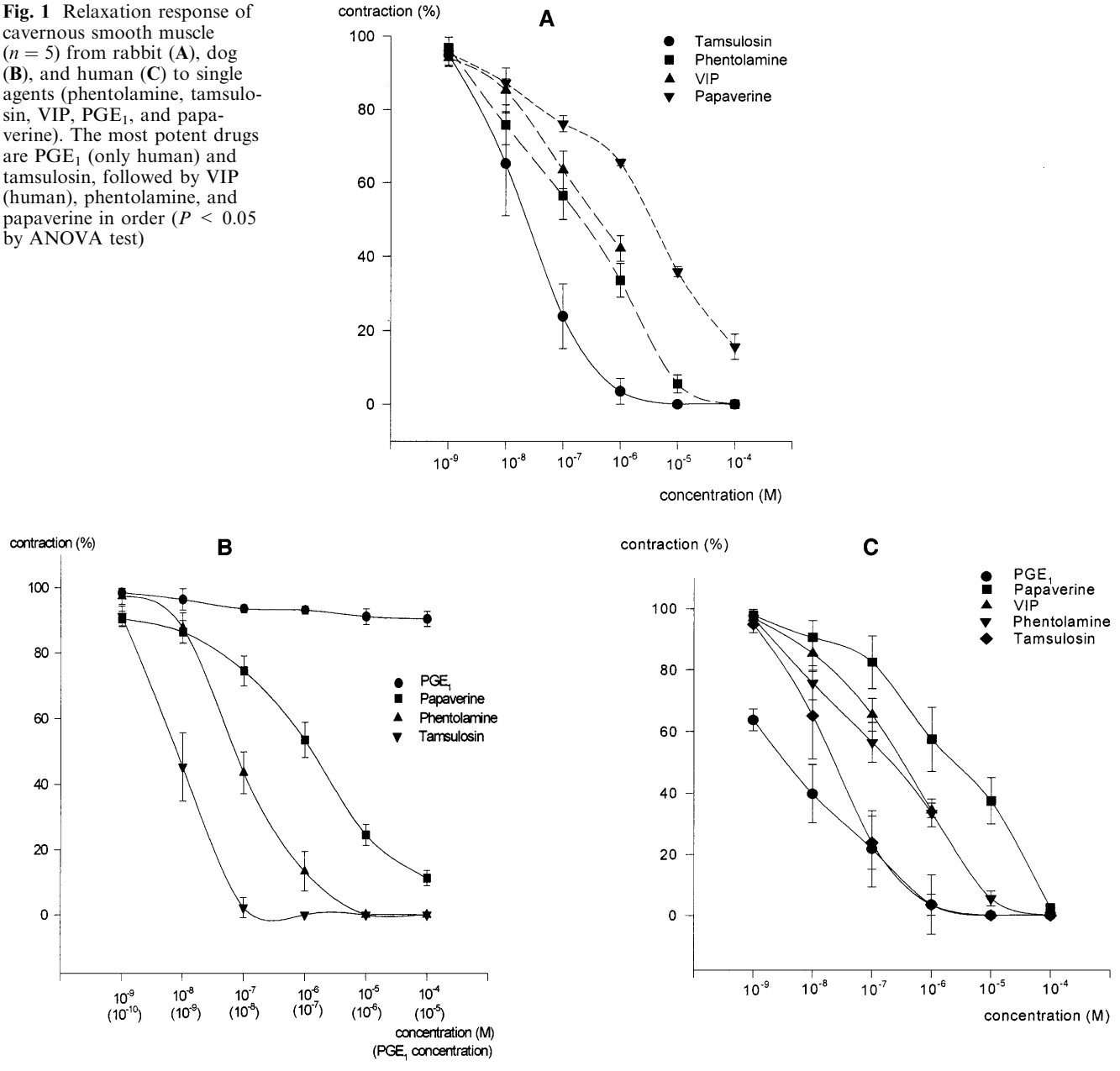

Fig. 1 Relaxation response of cavernous smooth muscle ($n = 5$) from rabbit (**A**), dog (**B**), and human (**C**) to single agents (phentolamine, tamsulosin, VIP, PGE_1, and papaverine). The most potent drugs are PGE_1 (only human) and tamsulosin, followed by VIP (human), phentolamine, and papaverine in order ($P < 0.05$ by ANOVA test)

The relaxation response to the tamsulosin-containing trimix was also significantly better ($P < 0.05$) than the phentolamine-containing one in dog and human tissue ($n = 5$ in each; Fig. 4).

In vivo investigations

Intracavernosal injection of 0.03 ml and 0.04 ml, respectively, of tamsulosin- or phentolamine-containing trimix resulted in an increase in ICP ($n = 10$ in each). In response to the tamsulosin-containing trimix the ΔICP was higher (0.03 ml; 81.2 ± 5.74, 0.04 ml; 103.2 ± 8.61 mmHg) than with the phentolamine-containing trimix (75.8 ± 2.99 and 94.3 ± 13.29 mmHg). However, this was not statistically significant ($P > 0.05$; Fig. 5).

The drop in systemic blood pressure was 3.2 ± 1.51 mmHg and 4.1 ± 1.21 mmHg after injection of 0.03 ml tamsulosin- and phentolamine-containing trimix, respectively; after a 0.04 ml injection, the fall was 5.6 ± 2.35 mmHg and 13.6 ± 6.25 mmHg, respectively, (Fig. 6). These differences in ΔBP induced by these two solutions were not statistically significant ($P > 0.05$).

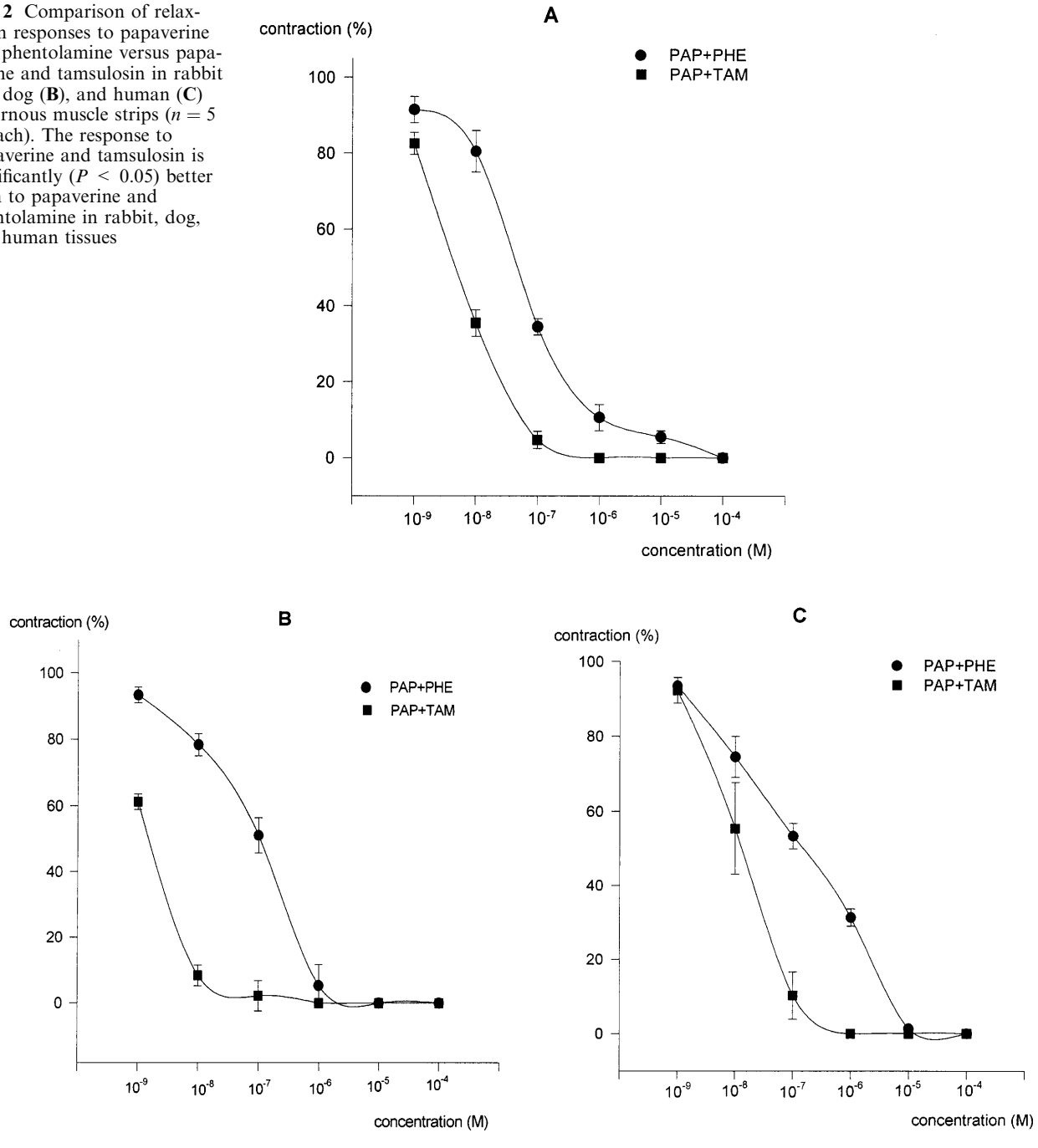

Fig. 2 Comparison of relaxation responses to papaverine and phentolamine versus papaverine and tamsulosin in rabbit (**A**), dog (**B**), and human (**C**) cavernous muscle strips ($n = 5$ in each). The response to papaverine and tamsulosin is significantly ($P < 0.05$) better than to papaverine and phentolamine in rabbit, dog, and human tissues

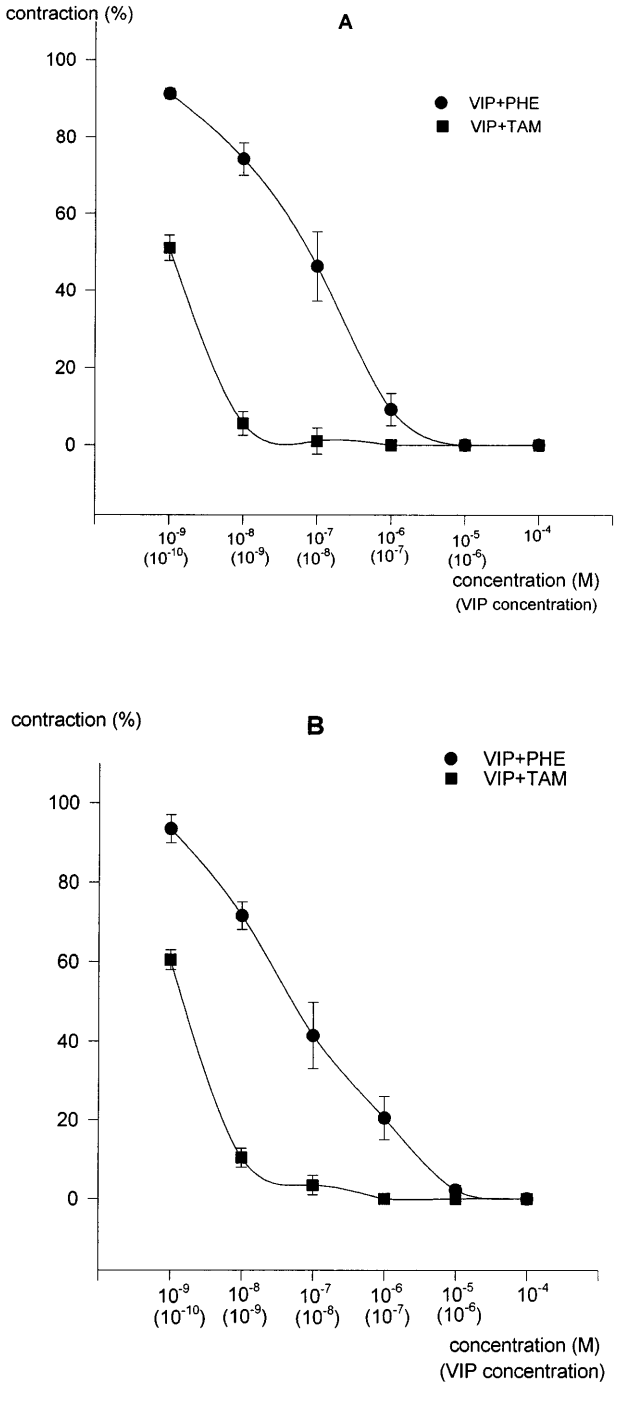

Fig. 3 Comparison of relaxation responses of rabbit (**A**) and human (**B**) cavernous smooth muscle ($n = 5$) to VIP and phentolamine versus VIP and tamsulosin. The response to VIP and tamsulosin is significantly ($P < 0.05$) better than to VIP and phentolamine

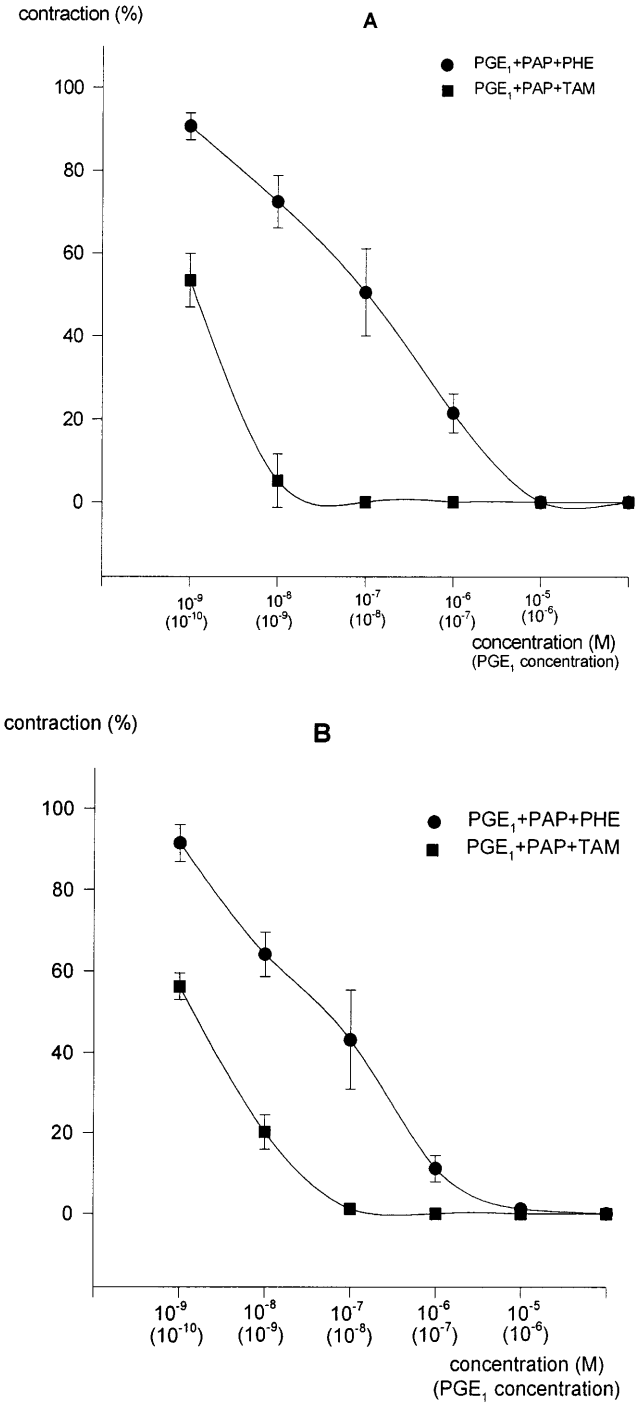

Fig. 4 Comparison of relaxation response of dog (**A**) and human (**B**) cavernous smooth muscle ($n = 5$) to papaverine, phentolamine and PGE_1 vs papaverine, tamsulosin and PGE_1. The response to the tamsulosin-containing trimix is significantly better ($P < 0.05$) than to the phentolamine-containing one

There was also no difference ($P > 0.05$) in the duration of the plateau pressure between the two groups (Fig. 7).

Discussion

Following the approval by the FDA of alprostadil sterile powder (Caverject; Pharmacia & Upjohn, USA) for use in patients with erectile dysfunction, PGE_1 monotherapy has been most commonly used for ICI therapy by physicians treating erectile dysfunction; alprostadil has the advantage of a lower rate of complications such as prolonged erection and fibrous plaque formation, when compared to papaverine alone or to combinations of

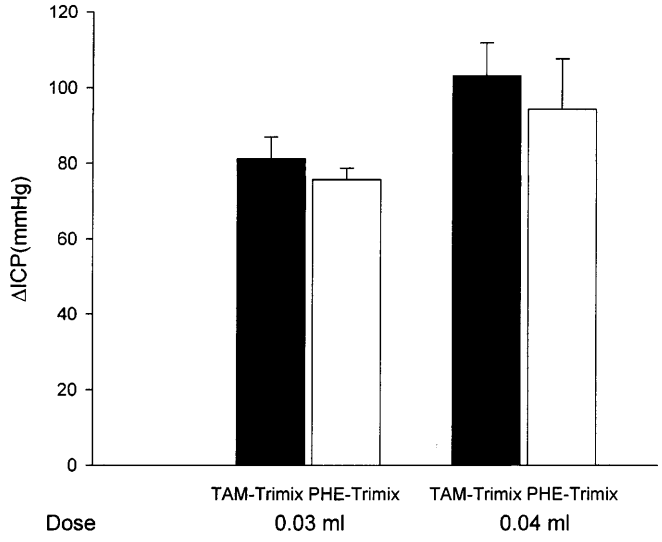

Fig. 5 Intracavernous pressure increase (ICP) in response to tamsulosin (TAM)-containing trimix and phentolamine (PHE)-containing trimix ($n = 10$ in each). There is no difference in ICP between the two groups

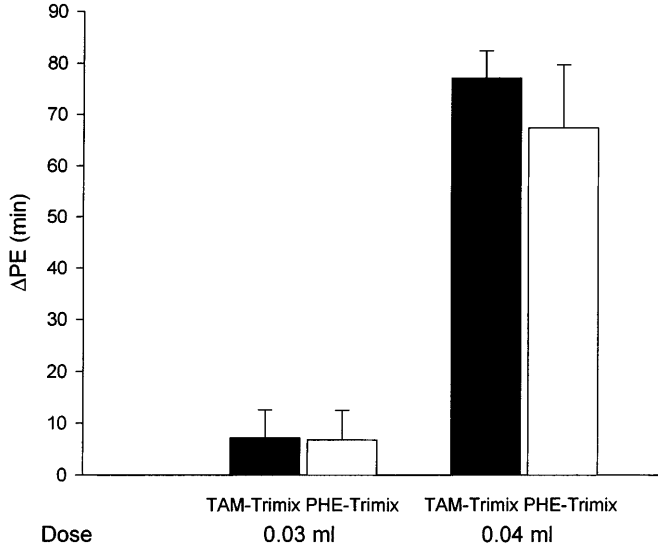

Fig. 6 Duration of plateau pressure (DPE) in response to tamsulosin (TAM)-containing trimix and phentolamine (PHE)-containing trimix. No significant difference in imPE between the two groups is noted

vasoactive agents [4, 11]. Although the results of various regimens of ICI therapy for erectile dysfunction are difficult to compare, it has been suggested that trimix was the most effective regimen in inducing erection sufficient for vaginal penetration, followed by a two-drug solution (bimix), then PGE_1 alone [4, 18]. Thus, in those patients who fail to respond, or who experience significant pain with PGE_1 alone, a bimix may induce a sufficiently rigid erection. Furthermore, patients in whom a bimix fails, may have functional erections with a trimix. However, the patients who have unsuccessful results with high dose of trimix should be treated with more cumbersome or more invasive treatment modalities, including the combination of a vacuum erection device and ICI or implantation of a penile prosthesis [8, 21]. Thus, it appears that more effective agents, which can achieve functional erections in patients with erectile dysfunction refractory to trimix are needed. These potential agents may include Invicorp (Senetek PLC, Nasdaq, SNTKY) and a four-drug mixture containing forskolin [7, 10, 12, 20]. To evaluate the applicability of tamsulosin in combination with papaverine and/or PGE_1 or VIP as a novel intracavernosal vasoactive agent, we performed the in vitro and in vivo studies described.

In the present study, relaxation responses of cavernous smooth muscles to tamsulosin-containing solutions (papaverine and tamsulosin, VIP and tamsulosin, and papaverine, PGE_1 and tamsulosin) were significantly better than those to phentolamine-containing solutions in the rabbit, dog, and human tissues. These pronounced effects of tamsulosin-containing solutions on muscle relaxation may be explained by the fact that contraction of the cavernous smooth muscle is mediated predominantly via α_1-ARs rather than α_2-ARs. It has been reported that α_1-ARs predominate functionally in human and rabbit cavernous tissues, although both α_1- and α_2-ARs are expressed [2, 13, 28]. Traish et al. [27] demonstrated that α_{1A}- and α_{1D}-AR were more abundant than th_{1B}-AR in human cavernous smooth muscles. It is known that phentolamine is a competitive inhibitor of α_1- and α_2-ARs while tamsulosin is a selective α_1-AR antagonist with a selectivity of $\alpha_{1D} \geq \alpha_{1A} \gg \alpha_{1B}$) [3, 6, 11, 16].

Our in vitro results suggest that the use of tamsulosin, instead of phentolamine, in combination with other vasoactive agents, might be a more effective regimen for ICI therapy. To test this hypothesis in vivo, we measured ICP and systemic BP (data not shown) after a mixture of papaverine (3 mg) and phentolamine (1 μg) or papaverine and tamsulosin (1.40 μg) was injected into the rabbit corporal body. Because ICI with PGE_1 did not cause full erection in the rabbit [17], we performed an in vivo study using a 2-drug mixture, which did not contain PGE_1. In this experiment, ICI with papaverine (4 mg) induced full erection (nearly 100% of systolic BP) without a fall in systemic BP. However, neither tamsulosin nor phentolamine caused an increase in ICP as compared with a 3 mg dose of papaverine alone (50–60 mmHg). No difference in ICP was noted between tamsulosin- and phentolamine-containing solutions. Furthermore, systolic BP decreased by 25–30% (30–40 mmHg) after injection of a tamsulosin-containing solution while a phentolamine-containing one caused a fall of 10–20 mmHg. The lack of a synergistic effect with either tamsulosin or phentolamine might be due to this marked decrease in systemic BP. Functional predominance of α_1-AR subtypes in the rabbit blood vessel might contribute to the more notable drop in systemic BP after injection of a tamsulosin-containing solution compared to a phentolamine-containing one. It has been reported that contractile responses of the rabbit aorta

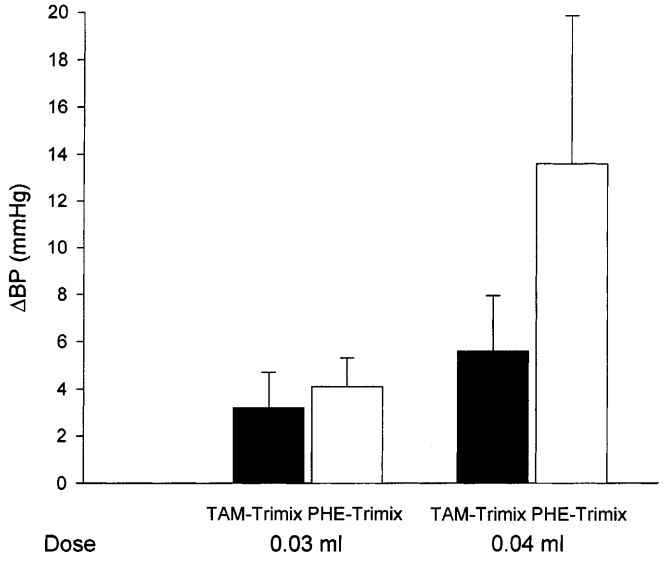

Fig. 7 The drop in systemic blood pressure (TBP) after intracavernous injection of tamsulosin (TAM)-containing trimix and phentolamine (PHE)-containing trimix on BP between the two groups is not significantly different

and internal iliac artery are mediated via α_{1D}-ARs while those of the human artery via α_{1B}-ARs [9, 14, 19, 26].

It is not established whether functional PGE_1 receptors are present in cavernous smooth muscles of the dog. Aboseif et al. [1] reported that PGE_1 receptors were demonstrated in cavernous tissues from men and monkeys but not dogs. Moreover, no relaxation response of dog cavernous muscle to PGE_1 was noted in our in vitro study. However, Cahn et al. [7] demonstrated that PGE_1 (10 μmg) elicited an increase in ICP, up to a maximum of 80 to 90% of mean arterial pressure, and PGE_1 also increased cAMP levels significantly in cultured canine cavernous smooth muscle cells. We also observed that ICI with PGE_1 caused full erection in the dog [24]. Our in vivo study with dogs showed that the increase in ICP and the duration of the plateau pressure induced by the tamsulosin-containing trimix was higher than that obtained with the phentolamine-containing trimix, although not statistically different. The drop in systemic BP was also lower after injection of the tamsulosin-containing trimix than with the phentolamine-containing one, although no statistical difference was noted. The relaxation responses to vasoactive drugs of the precontracted cavernous smooth muscles as used in our in vitro experimental design would be different than erectile responses to them in vivo. Erectile responses induced by vasoactive agents might be different according to animal species. Thus, further study is needed to evaluate the effects of tamsulosin-containing solutions on penile erection in patients with erectile dysfunction.

Intracavernous phentolamine as a single agent seldom produces a satisfactory erection, whereas oral or buccal phentolamine has produced a 30–40% erectile response [5]. This suggests that phentolamine might have an effect on the central nervous system. Kaplan et al. [15] reported that addition of an oral α_1-AR antagonist (doxazosin) might have a beneficial effect in patients with erectile dysfunction for whom ICI therapy alone with PGE_1 failed. To date, oral tamsulosin has not been reported to have a beneficial effect on erection in patients with BPH. Further study will be necessary to investigate a probability of beneficial effect of the oral tamsulosin in combination with intracavernous vasoactive agents as well as the synergistic effect of intracavernous tamsulosin in men with erectile dysfunction.

In summary, our in vivo study with dogs showed that tamsulosin mixed with papaverine and PGE_1 increased the intracavernous pressure more than phentolamine, but not to a statistically significant degree. However, the relaxation effects of tamsulosin on cavernous tissue in the organ chamber were superior to those of phentolamine, and were particularly prominent with human as compared with rabbit and dog cavernous tissue. Therefore, tamsulosin might be a more efficacious and safer agent to use for ICI therapy than phentolamine.

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