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(54) Titre : MEDICAMENT POUR PREVENIR ET TRAITER LA DYSFONCTION SEXUELLE
(54) Title: A MEDICAMENT FOR PREVENTION AND TREATMENT OF SEXUAL DYSFUNCTION

(57) Abrégé/Abstract:
The present invention relates to the medicament for prevention and treatment of sexual dysfunction using potassium channel opener solutions and/or papaverin as a medicament for prevention and treatment of sexual dysfunction. Sexual dysfunction can be treated by increasing blood flow into clitoris or vagina, thereby increasing a secretion from vagina and elevating the sense by means of topically applying a pharmaceutical composition comprising one kind Of K_{ATP} channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim, and/or papaverin to clitoris and vagina immediately before sexual intercourse in female sexual dysfunction patients who have problems in sexual arousal or excitement. Also, since the medicament according to the present invention is directly absorbed to target organ via topical application of the minimum thereof, the effect of the medicament is excellent and the medicament is practically free from systemic or local side effects.

ABSTRACT

The present invention relates to the medicament for prevention and treatment of sexual dysfunction using potassium channel opener solutions and/or papaverin as a medicament for prevention and treatment of sexual dysfunction. Sexual dysfunction can be treated by increasing blood flow into clitoris or vagina, thereby increasing a secretion from vagina and elevating the sense by means of topically applying a pharmaceutical composition comprising one kind of K_{ATP} channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim, and/or papaverin to clitoris and vagina immediately before sexual intercourse in female sexual dysfunction patients who have problems in sexual arousal or excitement. Also, since the medicament according to the present invention is directly absorbed to target organ via topical application of the minimum thereof, the effect of the medicament is excellent and the medicament is practically free from systemic or local side effects.

A medicament for prevention and treatment of sexual dysfunction

FIELD OF THE INVENTION

The present invention relates to a medicament for prevention and treatment of sexual dysfunction, and particularly, to a medicament for prevention and treatment of sexual dysfunction comprising potassium channel openers and/or papaverin.

DESCRIPTION OF THE PRIOR ART

Studies regarding female sexual function are very few compared with studies regarding male sexual function due to social and cultural prejudices in which female sexual expression was traditionally considered as a taboo or disgrace. However, sexual dysfunction exists in women as well as men. In sexual dysfunction of normal couples, erectile dysfunction and dysspermia (i.e., ejaculation disorder) comprise 40% of male sexual dysfunction, and excitement and orgasmic disorders comprise 63% of female sexual dysfunction. (Refer to Frank E, Anderson C, Rubinstein D. Frequency of sexual dysfunction in 'normal'

couples. New Engl J Med 1978: 299: 111- 115). Female sexual response is classified into following phases: sexual desire, sexual arousal, excitement, plateau, orgasm, and resolution. Female sexual dysfunction is classified into following disorders according to female sexual response phases: hypoactive sexual desire disorder, excitement disorder, orgasmic disorder, dyspareunia and vaginismus. (Refer to Leiblum SR. Definition and classification of female sexual disorder. Int J Impot Res 1998: 10: 104-6).

Blood flow into clitoris and vagina increases and a secretion from vagina increases in sexual desire, and blood engorgement in vagina and enlargement of clitoris to sexual stimuli like male penis erection occur in sexual arousal or excitement, although it is difficult to separate clitoris from vagina in female sexual response phase. (Refer to Geer JH. Direct measurement of genital responding. Am Psychol 1975: 30: 415-418). These series of responses in women are very similar to penis erection responses in men. In case of vagina, the relaxation of vascular smooth muscle and increase of blood flow are also important responses in sexual arousal. The blood engorgement in vagina according to the above responses results in increase of length and inner diameter of vagina, and the increase of secreting fluid from vagina makes insertion of the penis into vagina easy. (Refer to Park k, Goldstein I, Andry C, Siroky MB, Krane RJ, Azadzoi KM. Vasculogenic female sexual dysfunction : the hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency. Int J Impot Res 1997: 9: 27-37).

In the past, most of studies regarding causes of female sexual dysfunction were focused on sexual disinclination in terms of psychiatry or temperamental

causes due to female hormone deficiency in post-menopause. Morbidity of female sexual dysfunction increases with age in women like men, and the increase of morbidity of female sexual dysfunction is associated with menopause or the increase of vascular system risk factors. In reality, women with vascular system risk factors or post-menopausal women complained dysfunction of vagina or clitoris more frequently than the control group. (Refer to Sadeghi-Nejad H, Moreland R, Traish A, Azadzoi K, Nehra A, Abobakr RA. et al. Impotence is a couple's disease: studies in female sexual dysfunction. J. Urol 1996: 155: 677A).

Since decrease of female hormone in climacterium or post-menopause results in changes of vascular system, the decrease of female hormone and vasculogenic female sexual dysfunction interact in complex. Practically, the decrease of female hormone in menopause decreases the amount of vaginal secretion by decreasing blood flow into the pelvic region. However, female hormone supplementation therapy restores the blood flow. In addition, while co-administration of progesterone and female hormone inhibits blood improvement effect of estrogen compared with administration of female hormone alone, co-administration of male and female hormones increases sexual drive of women compared with administration of female hormone alone. (Refer to Simon JA. Double-blind comparision of two doses of estrogen and estrogen-androgen in naturally post-menopausal women: neuroendocrine, psychological and psychosomatic effects. Fertil Steril 1996: 66: 871-875). Recently, it was found that this is because the decrease of female hormone acts as vascular system risk factors, and vaginal nitric oxide synthase(NOS) and necrosis of cells such as smooth muscle of vaginal wall, vascular endothelium, nerve, vaginal epithelial cell

or the like are controlled by female hormone.

Hemodynamic studies regarding male erectile dysfunction were developed very well, and attempts to apply the above studies to concepts and studies of vasculogenic sexual dysfunction of female external genitalia which have embryological and anatomical similarity with male external genitalia were tried. As a result of study regarding smooth muscles of clitoris and vagina, it was found that the vaginal engorgement and enlargement of clitoris in sexual arousal resulted from increase of blood flow according to smooth muscle relaxation by neurotransmitters such as nitric oxide(NO) or vasoactive intestinal peptide(VIP) rather than hormones which have systemic and complex actions in case of women like men. Therefore, decrease of blood flow due to various causes in addition to the decrease of female hormone in menopause, or inappropriate response of smooth muscle to neurotransmitters in clitoris or vagina may cause vasculogenic female sexual dysfunction.

To develop a laboratory animal model for study of vasculogenic female sexual dysfunction, arteriosclerosis was induced in the internal organ bone artery of a female rabbit and then blood flow of clitoris and vaginal wall were determined by stimulating pelvic nerves. As a result, blood flow of arteriosclerosis group decreases significantly compared to that of normal control group. This result is associated with decrease in internal pressure of vaginal wall and of corpus cavernosum of clitoris and length of vagina. Therefore, it was suggested that arteriosclerosis acts as an important factor in female sexual dysfunction such as vaginal engorgement insufficiency and clitoral erectile insufficiency. (Refer to Park k, Goldstein I, Andry C, Siroky MB, Krane RJ, Azadzoi KM. Vasculogenic

female sexual dysfunction: the hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency. Int J Impot Res 1997: 9: 27-37). The reason why a concrete approach of vasculogenic female sexual dysfunction is proposed, although decrease of blood flow in clitoris or vagina may occur secondarily by decrease of female hormone as described above, is that vaginal blood flow increased in sexual desire or sexual arousal causes secreting fluid in vagina to increase, thereby reducing pain in sexual intercourse and increasing orgasm and sexual drive according to elevation of sense of clitoris. Therefore, like treatment of male erectile dysfunction, treatment efficiency of a method of directly relaxing smooth muscle in clitoris or vaginal wall which is a target organ may be much higher than that of female hormone therapy which exhibits indirect and secondary effects.

In female sexual arousal, responses of female external genitalia may be separated into response of clitoris and vagina. Among them, clitoris has a pair of erectile tissues similar to corpus cavernosum penis. Acetylcholine by cholinergic nerve and nitric oxide by non-adrenergic, non-cholinergic nerve system act as neurotransmitters in sexual arousal, and relaxation of smooth muscle and increase of blood flow due to the neurotransmitters cause enlargement of clitoris. (Refer to Semmens JP, Semmens EC. Sexual function and the menopause. Clin Obstet Gynecol 1984: 27: 717-723).

Azadzoi et al reported that unlike neurotransmitters in clitoris, primary neurotransmitter involved in relaxation of vaginal smooth muscle is VIP, rather than nitric oxide (NO). (Refer to Azadzoi KM, Tarcan T, Siroky MB, Krane RJ, Goldstein I., Characterization of elitoral cavernosal and vaginal smooth muscle contractility in

the rabbit. Int J Impot Res 1998: 10 Suppl 2: S58). However, Hoyle et al reported that all nerves utilizing NO(nitric oxide), NPY(neuropeptide Y), VIP, CGRP(calcitonin gene related peptide) and substance P as neurotransmitters can control blood flow of human vaginal wall and permeability of blood capillary as a result of study regarding neurotransmitters which control blood vessels of human vaginal wall. (Refer to Hoyle CHV, Stones RW, Robson T, Whitley K, Burnstock G. Innervation of vasculature and microvasculature of the human vagina by NOS and neuropeptide-containing nerves. J Anal 1996: 188: 633-644). That is, it is assumed that various neurotransmitters act in complex according to the kind and location of nerve, tissue managed by nerve or the like.

Ion channels of cell membrane are involved in contraction and relaxation of smooth muscle of all organs, and opening and shutting of these ion channels respond diversely according to membrane voltage and ion concentration in cells, etc. Generally, if cell membrane voltage is depolarized by nerve stimulation, membrane voltage-dependent calcium channel opens and increased calcium concentration due to intracellular Ca influx contracts smooth muscle. If potassium channel opens by membrane voltage or increased intracellular calcium concentration, intracellular potassium which maintains higher concentration than outside the cell efflux into outside the cell, and cell membrane voltage becomes re-polarized and membrane voltage-dependent calcium channel becomes closed. These cause intracellular calcium concentration to decrease and smooth muscle to be relaxed.

There are various kinds of potassium channels in cell membrane. Membrane voltage-dependent potassium channels(Kv) which open by membrane

voltage are inhibited by 4-aminopyridine. Also, calcium-dependent potassium channels(Kca) which open and shut by intracellular calcium concentration exist. Most of the calcium-dependent potassium channels are maxi-K channels having large conductance which are inhibited by TEA(tetraethylammonium) or kaliotoxin and charybdotoxin. And the calcium-dependent potassium channels having small conductance are inhibited by apamin. Further, ATP-dependent potassium channels(K_{ATP}) which open by decrease of intracellular ATP concentration in metabolic inhibition or severe hypoxia can be inhibited by tolbutamide or glibenclamide and TEA. However, ATP-dependent potassium channels are rarely open in normal condition. Therefore, there are much different opinions regarding physiological mechanism thereof. (Refer to Leiblum SR. Definition and classification of female sexual disorder. Int J Impot Res 1998: 10: 104-6).

Among various potassium channels, K_{ATP} and maxi-K channels are considered as being physiologically most appropriate in smooth muscle of corpus cavernosum. Maxi-K channels are most common subtype of potassium channels which exist in smooth muscle of corpus cavernosum penis. Maxi-K channels comprise approximately 90% of outward K current in smooth muscle cell of human corpus cavernosum penis which was cultivated in vitro. Also, maxi-K channels control membrane voltage.

Relaxation mechanisms of smooth muscle through opening of potassium channels may be classified into three mechanisms. The first mechanism comprises increase of cGMP production by NO or the like, and accordingly, activation of protein kinase G (PKG). Activated PKG is involved in opening of maxi-K channels and acts on calcium channel to make smooth muscle relaxed by

inhibiting calcium transfer of channel. Although activated PKG is considered as being involved in opening of K_{ATP} channels, there are contradictory opinions regarding the above theory. The second mechanism comprises increase of cAMP by PGE_1 or the like, and accordingly, activation of protein kinase A (PKA). Activated PKA also causes opening of maxi-K channels and closing of calcium channels, thereby inducing relaxation of smooth muscle. Most neurotransmitters causing relaxation of smooth muscle induce relaxation of smooth muscle directly or indirectly by means of these two mechanisms(i.e., the first and second mechanisms). Therefore, that acetylcholine, L-arginine and PGE_1 make slices relaxed in proportion to concentration may be explained in two aspects of calcium channels and potassium channels. That is, it is presumed that cGMP is accumulated via pathway of NO, and then PKG is activated and activity of maxi-K channels increases, and accordingly, calcium channels are inhibited and transfer of calcium ions is inhibited, and then amount of intracellular calcium ions decreases, and the above phenomina make smooth muscle relaxed.

The last mechanism utilizes potassium channel openers such as pinacidil which act directly on potassium channel to make smooth muscle relaxed. Such method may provide excellent relaxation effect and decrease systemic side effects because it acts directly on potassium channel without complex processes using neurotransmitters. Further, such method has clinical value because it may provide complementary effect to relaxation effect of other medicaments. Therefore, study regarding roles of potassium channels in relaxation of vaginal smooth muscle makes direct approach possible and is much simpler than study regarding various neurotransmitters.

Papaverin was first discovered by Meck in 1948, and is an alkaloid extracted from a poppy similar to opium. Papaverin is a direct smooth muscle relaxant. Firstly, papaverin increases concentrations of cAMP and cGMP by inhibiting actions of cyclic mononucleotide phosphodiesterase. Secondly, papaverin controls myosin light chain and inhibits contraction by blocking calcium channels and inhibiting calcium influx. When papaverin was injected to penis of the erectile dysfunction patient, it is difficult to find out what mechanism it mainly works through. However, papaverin relaxes all elements of penis erection tissue, that is, artery of penis, smooth muscle of corpus cavernosum and vein of penis. Therefore, papaverin is a potent smooth muscle relaxant and it is known that a complication of continued penis erection developed very often when papaverin was administered to the male erectile dysfunction patient.

Considering the direction of study regarding female sexual dysfunction hitherto, there is a tendency that for diagnosis of vasculogenic female sexual dysfunction, determination of blood flow of clitoris or vagina using color Doppler ultrasonography waves is mainly carried out and then patients with lowered blood flow are treated with administration of smooth muscle relaxants. As therapeutic agents of female sexual dysfunction which have been developed by many pharmaceutical companies, oral administration of viagra, apomorphine, topical application of PGE_1 cream and the like are known. Also, as effective therapeutic agents of erectile dysfunction, injection therapy of erection inducers into corpus cavernosum is known. Although injection formulations are more effective in erection inducing effect than oral drugs such as viagra, injection formulations have

defects such as pain, a fear to injection, continued penis erection, etc.

SUMMARY OF THE INVENTION

The inventors of the present invention have conducted intensive researches and experiments to develop medicaments which can effectively prevent and treat sexual dysfunction. The present inventors have developed medicaments of the present invention by confirming that when a medicament comprising a potassium channel opener(e.g., nicorandil, cromakalim, pinacidil and minoxidil) and/or papaverin was used, it has an excellent effect of relaxing smooth muscles of corpus cavernosum penis and smooth muscles of vaginal wall through various animal experiments, and finding that the medicament can increase blood flow in penis and clitoris, during researches and experiments.

An object of the present invention is to provide a medicament for prevention and treatment of female sexual dysfunction comprising one kind of potassium channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim, and/or papaverin.

Another object of the present invention is to provide a medicament for prevention and treatment of male sexual dysfunction comprising one kind of potassium channel opener selected from the group consisting of nicorandil and cromakalim, and optional papaverin.

In accordance with the present invention, there are provided a medicament for prevention and treatment of female sexual dysfunction comprising

one kind of K_{ATP} channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim, and/or papaverin.

Also, there are provided a medicament for prevention and treatment of male sexual dysfunction comprising one kind of K_{ATP} channel opener selected from the group consisting of nicorandil and cromakalim, and optional papaverin.

The present invention has many advantages, including providing a medicament for prevention and treatment of sexual dysfunction which can treat sexual dysfunction, and providing a medicament for prevention and treatment of sexual dysfunction which has excellent treatment effects of sexual dysfunction and no side effect. These and other features, aspects, and advantages of the present invention will become better understood with reference to the following description and appended claims.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1a is a graph showing the relaxation of precontracted clitoral strips to the administration of minoxidil, nicorandil, papaverin and PGE_1. Each drug induced a dose-dependent increase of relaxation.

Figure 1b is a graph showing the relaxation of precontracted vaginal strips to the administration of minoxidil, nicorandil, papaverin and PGE_1. Each drug induced a dose-dependent increase of relaxation.

Figure 2a is a graph showing the relaxation of precontracted clitoral strips to the administration of papaverin and PGE_1 after pretreatment of minoxidil or nicorandil. Each drug mixture induced a dose-dependent increase of relaxation. Pretreatment of minoxidil or nicorandil significantly enhanced relaxation induced by papaverin or PGE_1, alone, respectively.

M: minoxidil ; N: nicorandil ; PA: papaverin ; and PG : prostaglandin E_1.

Figure 2b is a graph showing the relaxation of precontracted vaginal strips to the administration of papaverin and PGE_1 after pretreatment of minoxidil or nicorandil. Each drug mixture induced a dose-dependent increase of relaxation. Pretreatment of minoxidil or nicorandil significantly enhanced relaxation induced by papaverin or PGE_1, alone, respectively.

M: minoxidil ; N: nicorandil ; PA: papaverin ; and PG : prostaglandin E_1.

DETAILED DESCRIPTION

The present invention provides a medicament for prevention and treatment of female sexual dysfunction comprising one kind of K_{ATP} channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim as active ingredient, and a pharmaceutically acceptable carrier. Also, the present invention provides a medicament for prevention and treatment of female sexual dysfunction comprising papaverin as active ingredient, and a pharmaceutically acceptable carrier. Further, the present invention provides a medicament for prevention and treatment of female sexual dysfunction comprising papaverin and one kind of K_{ATP}

channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim as active ingredients, and a pharmaceutically acceptable carrier.

The present invention provides a medicament for prevention and treatment of male sexual dysfunction comprising one kind of K_{ATP} channel opener selected from the group consisting of of nicorandil and cromakalim as active ingredient, and a pharmaceutically acceptable carrier. Also, the present invention provides a medicament for prevention and treatment of male sexual dysfunction comprising papaverin and one kind of K_{ATP} channel opener selected from the group consisting of nicorandil and cromakalim as active ingredients, and a pharmaceutically acceptable carrier.

Most of potassium channel openers known to date are K_{ATP} channel openers. For example, nicorandil, cromakalim, pinacidil, minoxidil or the like are known as potassium channel openers, and they are used as anti-hypertensive drugs, hair production-promoting agents and therapeutic agents for angina pectoris (Refer to USP Nos. 4,446,113 and 4,200,640). However, articles in which they are studied as agents for preventing and treating sexual dysfunction are very rare. Only, minoxidil was patented as a therapeutic agent for male erectile impotence in U.S. (Refer to USP No. 5,336,678). While pinacidil has been frequently used for treatment of male sexual dysfunction, it has never been used for treatment of female sexual dysfunction. Although it was reported that there was a possibility that minoxidil can be used for treatment of female sexual dysfunction, it has not been produced as a commercial product. However, among potassium channel openers, nicorandil and cromakalim have not been used for treatment of male or female sexual dysfunction. Papaverin which is used for

treatment of male erectile dysfunction has not been used for treatment of female sexual dysfunction. Particularly, it has been not reported that a medicament comprising potassium channel opener and papaverin in combination has synergistic effect in treatment of female sexual dysfunction.

In the present invention, effects of nicorandil and minoxidil which is used as an hair production-promoting agent for topical application were compared. Both nicorandil and minoxidil when administered alone, have more effective in relaxing effect than PGE_1 does, but have less effective in relaxing effect than papaverin does. This may be because there are differences in mechanisms of action of receptors, innervational structure or the like of clitoral or vaginal smooth muscle, unlike smooth muscle of corpus cavernosum penis. Also, the relaxing effect when minoxidil or nicorandil was pre-treated was greater than the relaxing effect when PGE_1 or papaverin was administered alone.

Based on the results of the present invention, effective medicaments in developing therapeutic agents for female sexual dysfunction comprise suitably nicorandil or papaverin as a single drug, and mixed drugs of nicorandil and papaverin as mixed drugs. This is because these medicaments have an excellent relaxing effect of smooth muscle when used as a single drug, and have an excellent relaxing effect even at low concentrations when used as mixed drugs.

When effects of potassium channel openers were tested and compared, pinacidil has the shortest duration of action, cromakalim has the strongest effect in relaxing smooth muscle, and nicorandil has more effective in relaxing effect of smooth muscle slices than papaverine does because nicorandil has an effect of

accumulating cGMP. When pinacidil was administered at high concentration of 10^{-6} M or more, even completely depolarized corpus cavernosum became relaxed in experiments using smooth muscle slices of corpus cavernosum of a rabbit.

Also, when acetylcholine, L-arginine and PGE_1 were *in vivo* administered to corpus cavernosum penis of a living cat which was pretreated with pinacidil, 35 ~ 115 % of internal pressure of corpus cavernosum increased additionally depending on kinds of drugs than when the erection inducer was alone administered. Further, *in vitro* experiments using vaginal wall slices of a rabbit showed that pinacidil was effective in relaxing vaginal smooth wall. A medicament comprising one kind of potassium channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim, and/or papaverin has been used in the present invention for prevention and treatment of female sexual dysfunction for the first time, and it was confirmed that the medicament was effective in prevention and treatment of female sexual dysfunction. Also, in the present invention, when a medicament comprising one kind of potassium channel opener selected from the group consisting of nicorandil and cromakalim, and optional papaverin was topically applied to penis, it was reported that erection inducing effects was great in male sexual dysfunction patients.

In a medicament for prevention and treatment of sexual dysfunction according to the present invention, a medicament comprising one kind of K_{ATP} channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim, and/or papaverin as active ingredient(s) can be used for prevention and treatment of female sexual dysfunction, and a medicament comprising one kind of K_{ATP} channel opener selected from the group consisting of nicorandil and

cromakalim, and optional papaverin as active ingredient(s) can be used for prevention and treatment of male sexual dysfunction. In the medicament for prevention and treatment of sexual dysfunction according to the present invention, the active ingredient(s) is(are) preferably contained in amount of 0.1 ~ 20 % by weight based on total weights of the medicament, and more preferably, in amount of 1 ~ 10 % by weight based on total weights of the medicament.

The daily dose of K_{ATP} channel opener compound of the present invention for prevention and treatment of female sexual dysfunction is generally in the range of from about 10 to 30 mg/day for the average adult woman patient (60 kg), and may be administered in single or divided doses.

The daily dose of K_{ATP} channel opener compound of the present invention for prevention and treatment of male sexual dysfunction is generally in the range of from about 20 to 50 mg/day for the average adult man patient(70 Kg), and may be administered in single or divided doses.

The daily dose of papaverin of the present invention for prevention and treatment of female sexual dysfunction is generally in the range of from about 10 to 30 mg/day for the average adult woman patient (60 kg), and may be administered in single or divided doses.

The daily doses of papaverin and K_{ATP} channel opener compound in the medicament of the present invention as mixed drugs for prevention and treatment of female sexual dysfunction are generally in the range of from about 10 to 30 mg/day and about 10 to 30 mg/day, respectively, for the average adult woman patient (60 kg), and may be administered in single or divided doses.

The daily doses of papaverin and K_{ATP} channel opener compound in the

medicament of the present invention as mixed drugs for prevention and treatment of male sexual dysfunction are generally in the range of from about 20 to 50 mg/day and about 20 to 50 mg/day, respectively, for the average adult man patient (70 kg), and may be administered in single or divided doses.

The concrete dosage will be determined depending on the age and body weight of the subject being treated, response, administration route, duration of treatment and the like. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

The active compounds of the present invention can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

The medicament for prevention and treatment of sexual dysfunction according to the present invention may comprise a pharmaceutically acceptable base in addition to the above-described active ingredient(drug). Bases which can be used in the present invention include for example, alcohols, esters of fatty acids, biocompatible fats, fatty oils, wax, lanolin, paraffin, vaseline, glycerin, starch, cellulose derivatives, polyethylene glycol, silicone oils, bentonite, and mixtures thereof.

Also, one kind of K_{ATP} channel opener selected from the group consisting of nicorandil, minoxidil, pinacidil and cromakalim, and/or papaverin, and a pharmaceutically acceptable skin absorption enhancer can be mixed in various amounts and formulated. Skin absorption enhancers were added in order to pass the active ingredient through clitoris, vaginal tissue or albuginea of penis surrounding corpus cavernosum penis and penis skin to facilitate sexual excitement or erection inducing effects when the active ingredient(drug) was topically applied to clitoris, vagina or penis. Skin absorption enhancers which can be used in the present invention may include for example, fatty alcohols, fatty acids, esters of fatty acids, surfactants, fatty alcohol ethers, propylene glycol or mixtures thereof.

The medicament according to the present invention may comprise additives such as pharmaceutically acceptable solvents, propellants, anti-septives, preservatives, aromatic agents, stabilizers, suspending agents, colorants, emulsifiers, consistency agent or the like, if necessary.

The medicament for prevention and treatment of sexual dysfunction according to the present invention may be used in dosage forms of spray, solution, cream, gel, ointment, lotion, powder, suppository, patch, implant or the like using conventional preparation methods of dosage forms following mixing the above-described K_{ATP} channel opener and/or papaverin, pharmaceutically acceptable base, skin absorption enhancer and additives with specific ratios. The medicament according to the present invention may be administered via the oral, parenteral or topical routes. Preferably, the medicament according to the present invention may be a medicament for topical application.

Preferably, the medicament for prevention and treatment of female sexual dysfunction according to the present invention may be directly administered to clitoris, vagina or vicinity thereof. Also, the medicament for prevention and treatment of male sexual dysfunction according to the present invention may be preferably directly administered to penis or vicinity thereof.

A dosage form of the medicament for prevention and treatment of female sexual dysfunction according to the present invention may be spray, solution, cream, gel, ointment, lotion, powder, patch, suppository or implant. A dosage form of the medicament for prevention and treatment of male sexual dysfunction according to the present invention may be spray, solution, cream, gel, ointment, lotion, powder or patch.

The medicament according to the present invention may be preferably for prevention and treatment of vasculogenic female or male sexual dysfunction.

Although correct mechanism for pharmacological action of the medicament for treatment of sexual dysfunction according to the present invention is not established, when the medicament for treatment of sexual dysfunction according to the present invention was used, potassium channels became open, blood flow into clitoris and vagina increased and both smooth muscle of vaginal wall and smooth muscle of corpus cavernosum penis became relaxed. Therefore, the medicament according to the present invention make diagnosis and treatment of male and female patients having sexual dysfunction possible. For example, it is effective to directly apply the medicament to clitoris or vagina in case of treating female sexual dysfunction, and it is effective to directly apply the medicament to

the penis or vicinity thereof in case of treating male sexual dysfunction.

The previously described versions of the present invention have many advantages including providing a medicament for prevention and treatment of sexual dysfunction which can treat sexual dysfunction, and providing a medicament for prevention and treatment of sexual dysfunction which has excellent treatment effects of sexual dysfunction and no side effect.

In case of female sexual dysfunction patients who have problems in sexual arousal or excitement, sexual dysfunction can be treated by increasing blood flow into clitoris or vagina, thereby increasing a secretion from vagina and elevating the sense by means of applying the medicament for prevention and treatment of sexual dysfunction according to the present invention is applied to clitoris and vagina immediately before sexual intercourse. Also, the medicament for prevention and treatment of sexual dysfunction according to the present invention are applicable to male sexual dysfunction patients. Further, since preferably, the medicament according to the present invention is directly absorbed to target organ via topical application of the minimum thereof, the effect of the medicament according to the present invention is excellent and the medicament according to the present invention is practically free from systemic or local side effects.

Since the medicaments according to the present invention have prevention and treatment effects of sexual dysfunction and no side effect, they are thought to be suitable in maintaining satisfactory sex life between man and wife.

The present invention will now be described in more detail in connection with the following examples, which should be considered as being exemplary only and not limiting the present invention.

EXAMPLE 1

To test the medicament for prevention and treatment of sexual dysfunction according to the present invention, among women patients who came to outpatient department of urology in Hospital, 18 patient volunteers, who consented after explanations of objects and test methods of this study were evaluated. The average age of 18 volunteers was 41.3 years old, and they have neither a history of sexual dysfunction nor diseases which cause sexual dysfunction.

First, the size of clitoris in basal state was measured with caliper. The size of clitoris, diameter of clitoral artery and clitoral blood flow of peak systolic velocities(PSV) and end diastolic velocities (EDV) were measured by color Doppler ultrasonography.

Then, 2% minoxidil solution was applied to the 18 volunteers, and changes in the size of clitoris, diameter of clitoral artery and clitoral blood flow of peak systolic velocities(PSV) and end diastolic velocities (EDV) were measured using the same method. Thereafter, 2% minoxidil solution was completely washed out.

After a long time passed, 5% nicorandil solution was applied to the 18 volunteers, and changes in the size of clitoris, diameter of clitoral artery and clitoral blood flow of peak systolic velocities(PSV) and end diastolic velocities (EDV) were measured using the same method.

The size of clitoris and diameter of clitoral artery after application of the drug increased compared with those of the basal state. However, there was no statistically significant difference because of personal differences and deficiency in discriminant ability of measurement apparatus and measurement standard. Mean scores of peak systolic velocities(PSV) and end diastolic velocities (EDV) of

clitoral artery in basal state were 5.40 ± 0.78 cm/s and 1.76 ± 0.44cm/s, respectively.

After application, both 2% minoxidil solution and 5% nicorandil solution significantly increased clitoral blood flow of PSV to 9.88 ± 2.76 cm/s and 16.87 ± 3.53 cm/s, respectively ($p<0.05$). Also, clitoral blood flow of EDV after applying 2% minoxidil solution and 5% nicorandil solution was increased to 3.52 ± 1.26 cm/s and 4.69 ± 2.21 cm/s, respectively. Also, it was found that relaxing effect of 5% nicorandil solution was much superior to that of 2% minoxidil solution. In the meantime, questions regarding changes of sense were given to the volunteers. However, answers to the questions were different and inconsistent due to personal differences and differences in test methods.

From the above results, it can be known that when 2% minoxidil solution was topically applied to clitoris, the blood flow rate of clitoral artery significantly increased, and when 5% nicorandil solution was topically applied to clitoris, the blood flow rates of clitoral artery significantly increased.

Therefore, K_{ATP} channel opener solutions can be used to improve clitoral artery of female sexual dysfunction patients, and they are expected to be effective in male sexual dysfunction patients.

EXAMPLE 2

Using slices(0.1 x 1.2 x 3 mm) obtained from vaginal smooth muscle of New Zealand white rabbits(2.5 ~ 3.5 Kg), isometric contraction was measured. Relaxation responses of the slices contracted with phenylephrine pretreatment against L-arginine, PEG_1 and acetylcholine were compared. In each response,

using apamin, kaliotoxin, glibenclamide, tolbutamide, 4-aminopyridine and TEA which are potassium channel blocker as well as minoxidil and pinacidil which are K_{ATP} channel openers, effects of the above compounds on contraction and relaxation response of vaginal smooth muscle were tested.

As a result, there was no spontaneous contraction of slices in basal state, biphasic response consisting of relaxation following contraction by electrical field stimulation (Grass SD9 stimulator, Frequency: 200 Hz, Delay: 1 msec, duration: 20 msec, 60 volts) was shown. The relaxation following contraction by electrical field stimulation was not inhibited by atropine pretreatment. However, it was inhibited by bretyllium or acetylcholine pretreatment. Slices were contracted proportional to the concentration of phenylephrine. Magnitude order of relaxation of slices contracted with phenylephrine (1 ~ 5 μM) pretreatment was Pinacidil > acetylcholine ≥ minoxidil ≥ PEG_1 ≥ L-arginine. Relaxation effect of L-arginine (1 ~ 100 mM) and PEG_1 (1 ~ 100 mM) even at high concentration were 5 ~ 10 % and 5 ~ 20 %, respectively. Relaxation effect of acetylcholine (5 ~ 50 μM) was approximately 60% and similar to that of minoxidil (10 μM). However, duration of action of acetylcholine was short and strength of relaxation effect of acetylcholine was weak, and therefore, the slices became re-contracted following temporary relaxation when treated with acetylcholine. Pinacidil (10 μM) made the slices completely relax, and some slices was relaxed to values below the basal values. Relaxation response by acetylcholine was partly inhibited by high concentration of K_{ATP} channel blockers or voltage–sensitive potassium channel blockers. Also, relaxation response by acetylcholine was completely inhibited by apamin or kaliotoxin even at a low concentration (1 μM). Relaxation response by pinacidil

(10 μM) was completely inhibited by TEA or 4-aminopyridine pretreatment. However, relaxation response by pinacidil (10 μM) was not inhibited by apamin or kaliotoxin pretreatment

From the above results, it was found that neurotransmitters involved in relaxation response of vaginal smooth muscle of a lapin exhibit relaxation effects via potassium channels like in other smooth muscle, and relaxation response by pinacidil was the greatest.

EXAMPLE 3

After enucleating clitoris, vagina, urethra, cystis and uterus from a matured New Zealand female rabbit (3.0 ~ 4.0 kg), slices consisting of smooth muscle of clitoris (1 x 1 x 5 mm) and distal vaginal wall (2 x 3 x 8 mm) were prepared while removing surrounding tissues under a microscope for microsurgery. Tension of slices were measured through a polygraph (SD9, Grass Instrument, Quincy, MA, USA) connected to a force displacement transducer. Firstly, Tension was applied to each slice using a weight of 1.0 g and each slice was incubated for over 30 minutes. Then, after administering 100 μl of phenylephrine (10^{-6} M), tension of 1.0 g was added repeatedly until isometric tension appears. Time in which difference in maximum contraction tensions of before and behind contraction curves was below 10% was considered as state where isometric tension was accomplished by measuring amplitudes of contraction curve after administering phenylephrine. Relaxing responses of slices to drugs administered were evaluated as follows. After contracting slices by adding 100 μl of phenylephrine (10^{-4} M) to the slices in which isometric tension was accomplished, effective

concentration, maximum relaxation tension and maximum relaxation concentration were significantly measured by administering the drug in from low concentration to high concentration (concentration in bath, 10^{-8} ~ 3 x 10^{-5} M), respectively into contracted slices.

As the drug, nicorandil, minoxidil, papaverin and PGE_1 were cumulatively administered in from low concentration (10^{-8} M) to high concentration (3 x 10^{-5} M). As a result, relaxation ratio increased proportionally to the concentration of the drug, respectively, in both slices of clitoris and vaginal wall. The results were shown in Figure 1a and 1b.

From the above results, it was found that magnitude order of maximum relaxation ratio of slices of clitoral and vaginal smooth muscle by single drug was follows: papaverin, nicorandil, minoxidil, and PEG_1. The results were shown in Table 1 below.

Table 1. Maximal relaxation (%) of each strip

	Clitoris	Vagina
Single drug		
Mi	34.79± 10.01 (N=9, n=12)	40.83± 9.89 (N=8, n=11)
Ni	65.25± 18.54 (N=9, n=13)	68.01± 17.12 (N=7, n=8)
PG	27.05± 12.18 (N=10, n=10)	27.75± 11.95 (N=8, n=14)
PA	80.81± 7.83 (N=7, n=9)	75.19± 10.39 (N=7, n=11)
Double mixture		
Mi + PG	37.31± 15.42 (N=7, n=12)	42.49± 16.05 (N=9, n=17)
Ni + PG	43.32± 16.16 (N=7, n=8)	46.61± 20.04 (N=8, n=15)
Mi + PA	87.93± 18.83 (N=7, n=11)	73.06± 24.0 (N=7, n=16)
Ni + PA	103.06± 12.75 (N=7, n=9)	91.84± 20.44 (N=7, n=10)
Triple mixture		
Mi+PG+PA	94.31± 10.88 (N=4, n=8)	93.48± 15.96 (N=4, n=6)
Ni+PG+PA	99.01± 15.31 (N=4, n=8)	105.8± 5.58 (N=4, n=5)

Mi; minoxidil, Ni; nicorandil, PG; prostaglandin E1, PA; papaverine,

N; number of animals,

n; number of strips

EXAMPLE 4

Following the procedure as described in Example 3 except that nicorandil and papaverin; minoxidil and papaverin; nicorandil and prostaglandin; and minoxidil and prostaglandin were used as mixed drugs, relaxation ratio of each slice was measured.

After contracting slices of clitoral corpus cavernosum smooth muscle and vaginal smooth muscle with 100 μl of phenylephrine (10^{-4} M) and pre-treating the contracted slices with nicorandil (10^{-5} M), papaverin was cumulatively administered from low concentration (10^{-8} M) to high concentration (3×10^{-5} M). As a result, relaxation ratio increased proportionally to the concentration of the mixed drugs, respectively, in the above two slices. The results were shown in Figure 2a and 2b.

In the mixed drugs, pre-treatment with nicorandil significantly increased maximum relaxation ratio of the drug which followed rather than pre-treatment with minoxidil did. Papaverin exhibited stronger relaxation effect than prostaglandin. Also, the mixed drugs had stronger relaxation effect than the medicament comprising a single drug. Among the mixed drugs, mixture of nicorandil and papaverin exhibited the strongest relaxation effect. The results were shown in Table 1 below.

Table 1. Maximal relaxation (%) of each strip

	Clitoris	Vagina
Single drug		
Mi	34.79± 10.01 (N=9, n=12)	40.83± 9.89 (N=8, n=11)
Ni	65.25± 18.54 (N=9, n=13)	68.01± 17.12 (N=7, n=8)
PG	27.05± 12.18 (N=10, n=10)	27.75± 11.95 (N=8, n=14)
PA	80.81± 7.83 (N=7, n=9)	75.19± 10.39 (N=7, n=11)
Double mixture		
Mi + PG	37.31± 15.42 (N=7, n=12)	42.49± 16.05 (N=9, n=17)
Ni + PG	43.32± 16.16 (N=7, n=8)	46.61± 20.04 (N=8, n=15)
Mi + PA	87.93± 18.83 (N=7, n=11)	73.06± 24.0 (N=7, n=16)
Ni + PA	103.06± 12.75 (N=7, n=9)	91.84± 20.44 (N=7, n=10)
Triple mixture		
Mi+PG+PA	94.31± 10.88 (N=4, n=8)	93.48± 15.96 (N=4, n=6)
Ni+PG+PA	99.01± 15.31 (N=4, n=8)	105.8± 5.58 (N=4, n=5)

Mi; minoxidil, Ni; nicorandil, PG; prostaglandin E1, PA; papaverine,

N; number of animals,

n; number of strips

A medicament comprising nicorandil or papaverin as a single drug, or a medicament comprising mixed drugs of nicorandil and papaverin as mixed drugs exhibited an excellent relaxation effect of clitoral and vaginal smooth muscle. Therefore, these medicaments can be developed as topical therapeutic agents for female sexual dysfunction. Especially, in results of table 1 above, a medicament comprising a potassium channel opener and papaverin in combination exhibited a synergistic effect in treatment of sexual dysfunction.

Although the present invention has been described in detail with reference to the above specific embodiments, other embodiments are possible. Therefore, it should be apparent to those skilled in the art that various modifications and changes thereof can be made without departing from the spirit and scope of the invention and that such modifications and changes be included in the scope of the following claims.

What is claimed is:

1. A medicament for prevention and treatment of female sexual dysfunction comprising one kind of K_{ATP} channel opener selected from the group consisting of nicorandil, pinacidil and cromakalim as active ingredient, and a pharmaceutically acceptable carrier.

2. The medicament for prevention and treatment of female sexual dysfunction according to claim 1, wherein said active ingredient is contained in amount of 0.1 ~ 20 % by weight based on total weights of the medicament.

3. The medicament according to claim 1 for topical application.

4. The medicament for prevention and treatment of female sexual dysfunction according to claim 1, wherein said medicament is directly administered to clitoris, vagina or vicinity thereof.

5. The medicament for prevention and treatment of female sexual dysfunction according to claim 1 or 4, wherein dosage form of said medicament is spray, solution, cream, gel, ointment, lotion, powder, patch, suppository or implant.

6. The medicament according to claim 1 for prevention and treatment of vasculogenic female sexual dysfunction.

7. A medicament for prevention and treatment of female sexual dysfunction comprising papaverin as active ingredient, and a pharmaceutically acceptable carrier.

8. The medicament for prevention and treatment of female sexual dysfunction according to claim 7, wherein said active ingredient is contained in amount of 0.1 ~ 20 % by weight based on total weights of the medicament.

9. The medicament according to claim 7 for topical application.

10. The medicament for prevention and treatment of female sexual dysfunction according to claim 7, wherein said medicament is directly administered to clitoris, vagina or vicinity thereof.

11. The medicament for prevention and treatment of female sexual dysfunction according to claim 7 or 10, wherein dosage form of said medicament is spray, solution, cream, gel, ointment, lotion, powder, patch, suppository or implant.

12. The medicament according to claim 7 for prevention and treatment of vasculogenic female sexual dysfunction.

13. A medicament for prevention and treatment of female sexual dysfunction comprising papaverin and one kind of K_{ATP} channel opener selected from the

group consisting of nicorandil, pinacidil and cromakalim as active ingredients, and a pharmaceutically acceptable carrier.

14. The medicament for prevention and treatment of female sexual dysfunction according to claim 13, wherein said total active ingredients are contained in amount of 0.1 ~ 20 % by weight based on total weights of the medicament.

15. The medicament according to claim 13 for topical application.

16. The medicament for prevention and treatment of female sexual dysfunction according to claim 13, wherein said medicament is directly administered to clitoris, vagina or vicinity thereof.

17. The medicament for prevention and treatment of female sexual dysfunction according to claim 13 or 16, wherein dosage form of said medicament is spray, solution, cream, gel, ointment, lotion, powder, patch, suppository or implant.

18. The medicament according to claim 13 for prevention and treatment of vasculogenic female sexual dysfunction.

19. A medicament for prevention and treatment of male sexual dysfunction comprising one kind of K_{ATP} channel opener selected from the group consisting of nicorandil and cromakalim as active ingredient, and a pharmaceutically acceptable carrier.

20. The medicament for prevention and treatment of male sexual dysfunction according to claim 19, wherein said active ingredient is contained in amount of 0.1 ~ 20 % by weight based on total weights of the medicament.

21. The medicament according to claim 19 for topical application.

22. The medicament for prevention and treatment of male sexual dysfunction according to claim 19, wherein said medicament is directly administered to penis or vicinity thereof.

23. The medicament for prevention and treatment of male sexual dysfunction according to claim 19 or 22, wherein dosage form of said medicament is spray, solution, cream, gel, ointment, lotion, powder or patch.

24. The medicament according to claim 19 for prevention and treatment of vasculogenic male sexual dysfunction.

25. A medicament for prevention and treatment of male sexual dysfunction comprising papaverin and one kind of K_{ATP} channel opener selected from the group consisting of nicorandil and cromakalim as active ingredients, and a pharmaceutically acceptable carrier.

26. The medicament for prevention and treatment of male sexual dysfunction

according to claim 25, wherein said total active ingredients are contained in amount of 0.1 ~ 20 % by weight based on total weights of the medicament.

27. The medicament according to claim 25 for topical application.

28. The medicament for prevention and treatment of male sexual dysfunction according to claim 25, wherein said medicament is directly administered to penis or vicinity thereof.

29. The medicament for prevention and treatment of male sexual dysfunction according to claim 25 or 28, wherein dosage form of said medicament is spray, solution, cream, gel, ointment, lotion, powder or patch.

30. The medicament according to claim 25 for prevention and treatment of vasculogenic male sexual dysfunction.

Fig. 1a

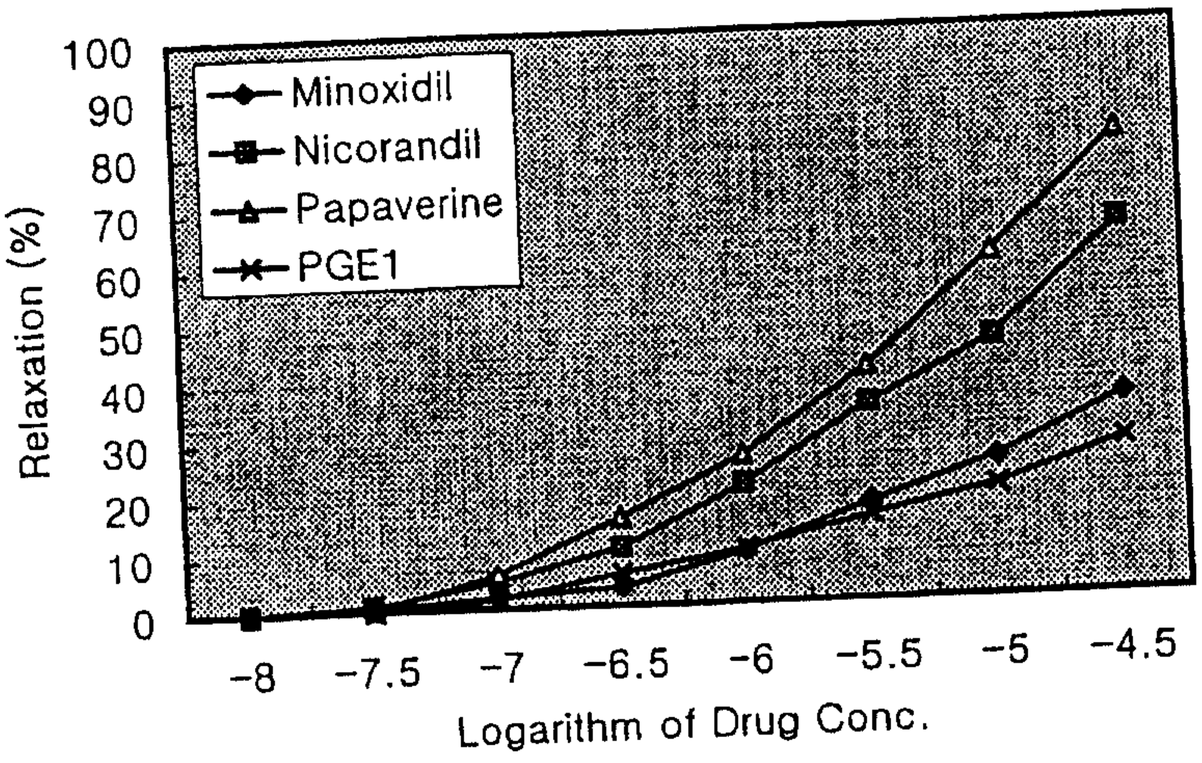

Minoxidil
Nicorandil
Papaverine
PGE1
Relaxation (%)
100
90
80
70
60
50
40
30
20
10
0
-8
-7.5
-7
-6.5
-6
-5.5
-5
-4.5
Logarithm of Drug Conc.

Fig. 1b

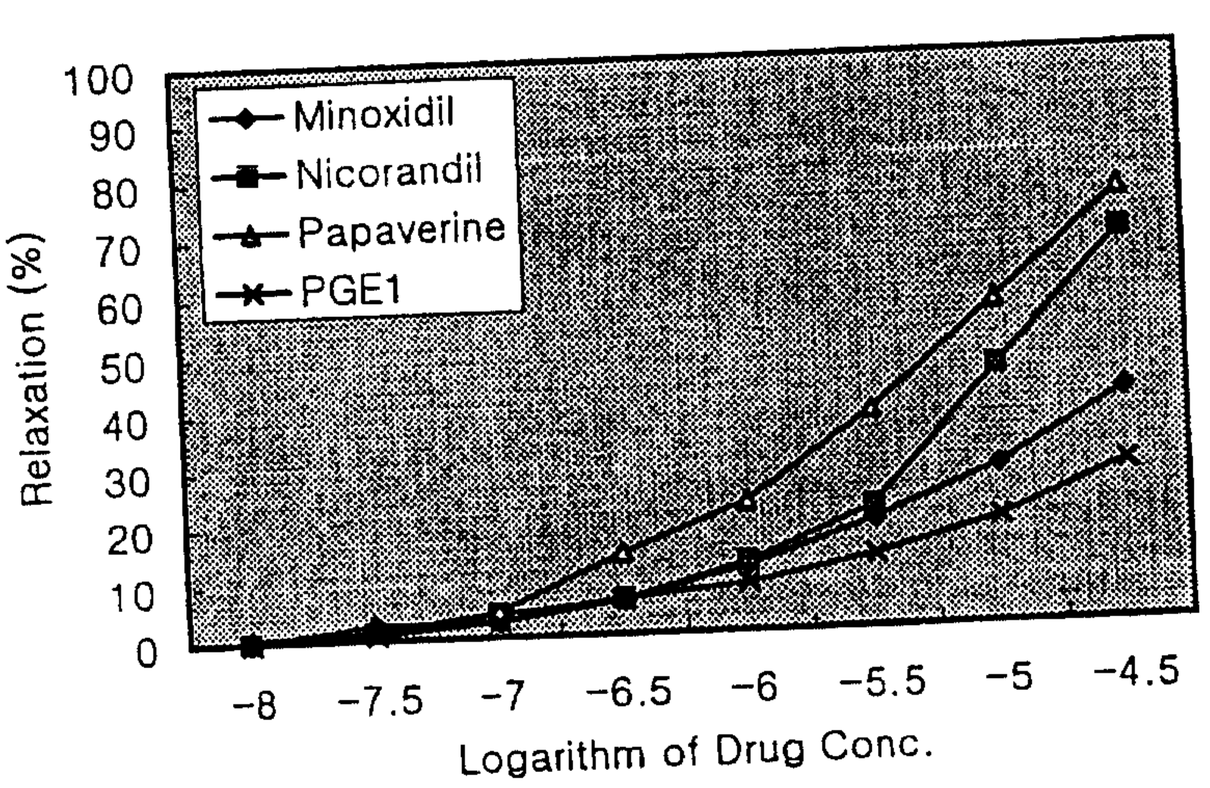

Minoxidil
Nicorandil
Papaverine
PGE1
Relaxation (%)
100
90
80
70
60
50
40
30
20
10
0
-8
-7.5
-7
-6.5
-6
-5.5
-5
-4.5
Logarithm of Drug Conc.

Fig. 2a

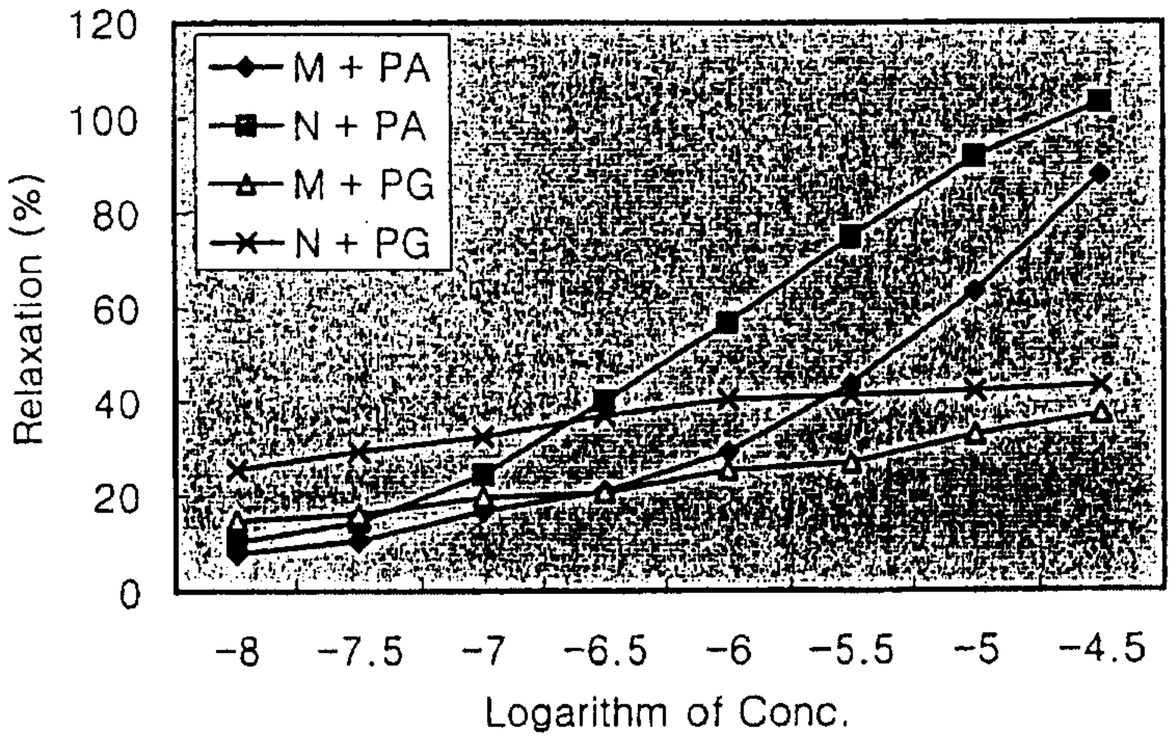
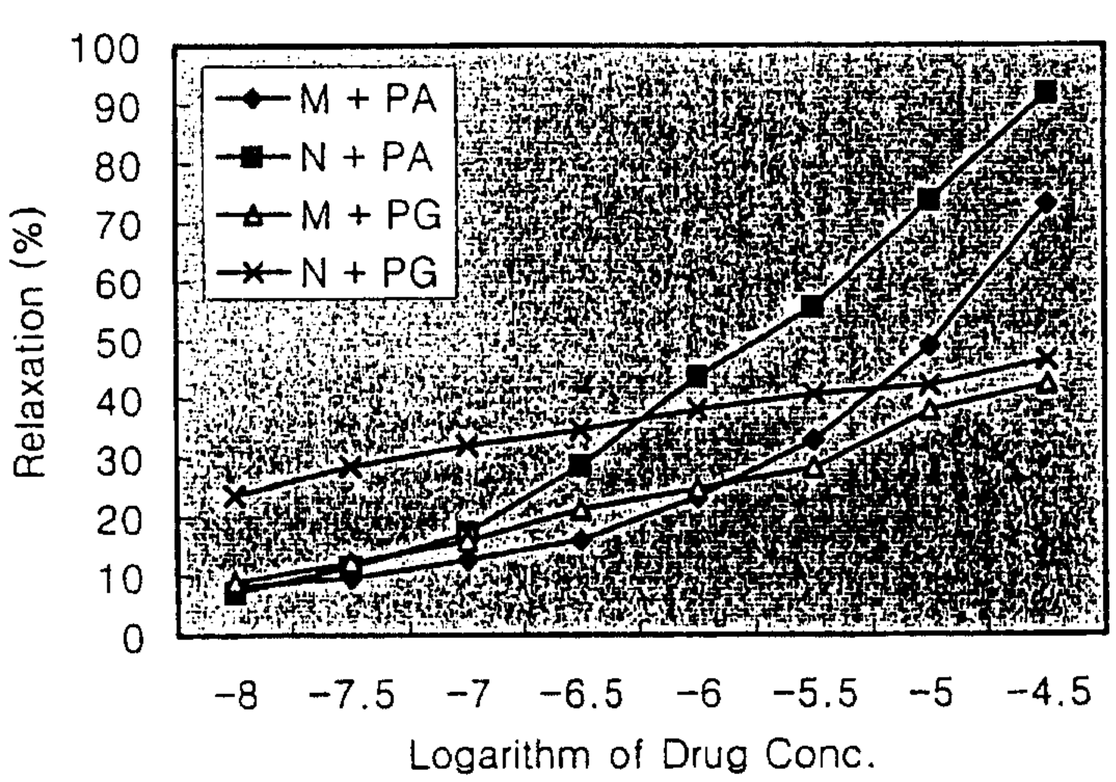

M + PA
N + PA
M + PG
N + PG
Relaxation (%)
120
100
80
60
40
20
0
-8
-7.5
-7
-6.5
-6
-5.5
-5
-4.5
Logarithm of Conc.

Fig. 2b


M + PA
N + PA
M + PG
N + PG
Relaxation (%)
100
90
80
70
60
50
40
30
20
10
0
-8
-7.5
-7
-6.5
-6
-5.5
-5
-4.5
Logarithm of Drug Conc.