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(54) Titre : METHODES ET COMPOSITIONS POUR DES TRAITEMENTS ADMINISTRES AU PENIS
(54) Title: METHODS AND COMPOSITIONS FOR TREATMENTS FOR ADMINISTRATION TO THE PENIS

(57) Abrégé/Abstract:
The invention relates to methods and compositions for increasing growth of the penis; enhancing male erectile function; treatment of Peyronie's disease and other disorders of the penis associated with fibrosis and increased collagen comprising an erectile function-enhancing amount of a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutically acceptable diluent or carrier.

ABSTRACT OF THE DISCLOSURE

The invention relates to methods and compositions for increasing growth of the penis; enhancing male erectile function; treatment of Peyronie's disease and other disorders of the penis associated with fibrosis and increased collagen comprising an erectile function-enhancing amount of a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutically acceptable diluent or carrier.

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METHODS AND COMPOSITIONS FOR TREATMENTS FOR ADMINISTRATION TO THE PENIS

FIELD OF THE INVENTION

The invention relates to methods and compositions for increasing growth of the penis; enhancing male erectile function; treatment of Peyronie's disease and other disorders of the penis associated with fibrosis and increased collagen comprising an erectile function-enhancing amount of a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutically acceptable diluent or carrier.

SUMMARY OF THE INVENTION

The inventor has discovered that males stimulating growth in their penis by any form of biomechanical stimulation will also stimulate a build up of collagen in the penis. The inventor has discovered that certain doses of Calcium Channel Blockers and Calmodulin Blockers and Prostaglandins and IGF1 receptor agonists can increase the rate of penis growth and increase the effectiveness of all forms of penis enlargement.

Penis enlargement refers to any method that stimulates cellular and molecular activities in the penis to cause tissue remodeling that results in changes in the molecular and cellular elements of the penis that will effect a true dimensional increase in the penis, which will result in a true increase in the size of the penis from maximally vasoconstricted, to flaccid, to semi-erect through to a maximally expanded and fully erect size. Any method of penis enlargement to cause this true hypertrophy or growth will have to induce remodeling of the connective tissues of which the major structural component is collagen. This means that penis growth can only occur with remodeling of these structural collagen fibres.

The inventor has observed by direct manual examination that patients who develop thickening of these structural collagen elements in their penis will have a deceleration of their growth rate, and if thickening and strengthening of these penile structures continues it will result in a permanent arrest of the enlargement process. The inventor has observed this to happen in all patients whose growth rate slows and stops. The inventor hypothesizes that an important reason why penis growth slows and stops after several months in all patients he has observed who have enlarged their penises is because the rate of new collagen formed is faster

than the rate that it is being removed and that this hypertrophy of the structural collagen fibers which the inventor has observed in all patients whose growth has slowed, must reduce the effectiveness of any further biomechanical stimulation.

The inventor found that when he was following the medical literature and trying many of the previously described treatments for fibrosis he did not observe any changes in the patients receiving these treatments. The inventor treated several patients' Peyronies's Disease and penis enlargement patients whose penis growth had arrested with the recommended dosing at the recommended frequency for direct Verapamil injections into the penis and into plaque with no observable effect. The inventor tried the recommended topical doses of Calcium Channel and Calmodulin Blockers on patients with Peyronie's Disease and arrested penile growth using the previously described and recommended doses, rates and methods for topical method using Calcium Channel Blockers recommended for Peyronie's Disease and the inventor could not detect any clinical response. The inventor found they were ineffective in increasing penile growth or reducing penile fibrosis, plaque or treating Peyronie's Disease.

But the inventor has discovered that certain doses of Calcium Channel Blockers and Calmodulin Blockers when applied topically or infused continuously or applied intermittently at a higher frequency than was recommended in the medical literature improved their clinical efficacy. When used in a way to constantly maintain and replenish these agents within the penis by either topical or parenteral administration the inventor has discovered that there was a significant reduction in fibrosis. That inventor observed that with increased frequency of small topical applications of Calcium Channel Blockers and Calmodulin Blockers the patients with Peyronie's Disease would within days a experience a noticeable softening and shrinkage of the plaques which over the course of weeks and months, in most cases, resulted in complete clearance of their plaque and fibrosis, and when incomplete, there would only be some small nodules remaining. Additionally, upon careful history taking, the inventor observed a clinical improvement in their erectile function.

That is, patients using these Calcium Channel Blockers and Calmodulin Blockers when applied in this modified way so as to reduce fibrosis, that those Peyronie's patients who were experiencing mild erectile dysfunction prior to beginning the treatment would start getting functional erections without having to rely on PDE5's or intracavernosal injections, and if they had severe erectile dysfunction to begin with, and could not get or maintain functional erections with PDE5's or intracavernosal injections that they would start getting

better spontaneous erections and that with PDE5's or intracavernosal injections they could now successfully maintain a usable erection.

The inventor also observed that if these same protocols for the use of Calcium Channel Blockers and Calmodulin Blockers were used by men with erectile dysfunction who did not have Peyronie's Disease that their erectile function would also improve. In younger men, simply adding some Calcium Channel Blockers and Calmodulin Blockers directly to their intracavernosal injection medication would immediately result in a harder and longer lasting erection indicating direct potentiation of vasodilation of the erectile tissue with a single dose. This immediate improvement in erectile function was also observed even in men without erectile dysfunction with topical use of Calcium Channel Blockers and Calmodulin Blockers. But men with significant fibrotic changes in their penis would also have continued improvement in their erectile function as the fibrosis in their penis was reduced and eliminated.

As well, it was observed that in men who had been unsafely injecting intracavernosal medications and who had induced fibrotic changes within their penis as a result, that using Calcium Channel Blockers and Calmodulin Blockers would reduce and eliminate the fibrosis from their penis and this usually would be accompanied by an improvement in erectile function. As well, two patients who had developed severe erectile dysfunction from extensive fibrosis in their penis, one who had injected acetic acid into his penis and had extensive destruction and fibrosis of his cavernosal tissue, and a second patient who had almost complete obliteration and fibrosis of the carvernosal tissue from recurrent spontaneous priapisms; both of these patients had dramatic reduction in the cavernosal fibrosis and a restoration of functional spontaneous erections after receiving a course of Calcium Channel Blockers treatment by the inventor.

In addition, the inventor has observed that the use of Calcium Channel Blockers and Calmodulin Blockers on men enlarging their penises with any form of biomechanical stimulation would benefit by a prolongation in the period of active penile growth and experience an acceleration of the rate of penile growth; there seems to be an overall synergist effect of Calcium Channel Blockers and Calmodulin Blockers on all observable and measurable parameters of penile growth and enlargement. And this effect is not limited to the connective tissue growth and structural collagen elongation within the penis, but could potentiate collagen elongation and remodeling outside of the penis.

The inventor has observed that Calcium Channel Blockers and Calmodulin Blockers will potentate biomechanical growth in other tissues when they are combined with any of the multitude of methods that produce biomechanical stimulation.

The inventor has also discovered several other pharmacological agents that can increase penile and connective tissue growth when combined with any form of biomechanical stimulation. For example the inventor has found that the local application of small doses of IGF1 receptor agonists, relaxin receptor agonists, and certain prostinoid receptor agonists when combined with biomechanical stimulation can also potentiate, accelerate and generally increase the rate of penis growth.

When referring or using the term, "biomechanical stimulation' the inventor is specifically indicating methods of producing mechanical forces that will increase or accelerate the natural remodeling that occurs in all biological tissues. Biomechanical stimulation for penis enlargement would include the use of intracavernosal vasodilators and mechanical traction to the penis. In summary, the inventor has found that all known methods of penis elongation and penis enlargement can be accelerated and potentiated by Calcium Channel Blockers and Calmodulin Blockers.

The inventor had previously discovered that penis growth with vasodilators alone was potentiated by Relaxin receptor agonists.

The inventor has also discovered the Relaxin receptor agonists will accelerate and potentiate the penile growth experienced by men using effective traction devices.

The inventor also discovered that the prostinoid receptor agonists PGF2alpha, Dinoprost, Bitamoprost, PGE2, and Dinoprostone when applied in very low doses locally to the penis would accelerate penis growth rates from biomechanical stimulation, such as a man using a traction device. And even men whose growth had stopped in some cases could be induced to start growing again with the prostinoid receptor agonists, PGF2alpha and PGE2, listed above.

The inventor has also discovered that penis enlargement can be accelerated and potentiated with IGF1 receptor agonists such as IGF1 and LR3 IGF1.

So, to summarize, the presence of Calcium Channel Blockers, Calmodulin Blockers, specific Prostaglandins, and IGF1 receptor agonists at therapeutic levels for sufficient duration of time can cause penis growth if combined with penile traction devices or other forms of biomechanical stimulation to enlarge the penis. Because of the penises location and

the large ratio between the size of the body relative to the penis, the preferred embodiment for these agents would be topical creams, gels, patches or local injections in combination with some form of mechanical mechanism also applied to the penis.

Erectile dysfunction (ED) is defined as the inability to achieve and maintain a penile erection adequate for sexual intercourse. This may be a relative term wherein the frequency of occurrences in which a patient is able to achieve and maintain a penile erection adequate for sexual intercourse has decreased over time as a part of natural aging which is superimposed with other internal and external factors that impact negatively upon the natural sexual responses of males. It is a male health problem which in its most severe form has been estimated to affect about 150 million men worldwide. But in North America it is estimated that by the age of 40 years, approximately 25% of men are having problems with achieving and sustaining an erection, and this probably increases to over 50% for men over 60 years of age.

Impotence generally refers to a severe form of male erectile dysfunction and is defined as the general inability to achieve and sustain an erection sufficient for intercourse. Erectile function naturally declines with age and like the aging process, the decline in erectile function experienced by men as they age is a complex biological phenomenon that results from complicated interactions between psychological, emotional, spiritual and physical factors. Some of the physical factors include genetics, diet, nutrition, environmental exposures to toxins, radiation, hormonal factors such as thyroid, adrenal, gonadal, and growth hormones among others; as well as effects from medications and other iatrogenic effects of medical treatments. These are only some of the various factors that may contribute to natural diseases that combine with aging to cause declining sexual function in men and women.

The complexity of the body makes the diagnosis and treatment of ED imprecise. The hormonal issues are rarely considered in diagnostic workups. For example, the assessment of thyroid, adrenal and growth hormones are not part of the usual diagnostic workup. Even though physicians and the medical literature are now starting to acknowledge testosterone in practical terms, it is rarely considered when a man is being treated for erectile dysfunction. Even though disturbances in these hormonal systems will significantly impact erectile function, they are generally ignored when erectile dysfunction is assessed and treated. In summary, the understanding of erectile dysfunction is very imprecise in modern medical practice.

There is currently no standardized method of diagnosis or treatment that begins to address the many normal causes of ED. The diagnosis of erectile dysfunction generally relies on self-reporting by patients. Since the majority of men experiencing significant erectile dysfunction will not be aware that they are having erectile dysfunction they will not report any concerns to their physician. Even when they are given medical therapies that worsen their erectile function, for example, many common prescription medications, such as anti-hypertensives will worsen erectile function while other medications may improve their erectile function, they will be unaware of these changes. It is the experience of the inventor that patients and physicians tend to recognize only more profound levels of erectile dysfunction and most cases of declining or improving erectile function go unrecognized.

Histologically there are specific changes that have been well documented in the penis of men with erectile dysfunction that tend to increase with age. Men who experience declining erectile function have actual physical changes within their penis. Some of these changes include reduced smooth muscle, reduced diameter and size of the cavernosal nerves, reduced levels of elastin and increased levels of collagen all of which result in impaired vascular response, reduced relaxation of the cavernosal sinuses and impairment of the veno-occlusive mechanism to properly pressurize the cavernosal system. None of the current therapies for erectile function address or are known to treat or improve these physical changes.

All of the current medications being used to treat erectile dysfunction work by directly or indirectly causing smooth muscle relaxation in the erectile tissue. This results in dilation of the arteries bringing blood into the erectile tissue and dilation of the cavernosal sinuses. These effects are transient, from minutes to several hours and they can only be effective while they are present in the penis at therapeutic levels, and this would include oral agents (phosphodiesterase-5 inhibitors, such as LevitraTM, ViagraTM, and CialisTM, dopamine agonists, such as UprimaTM, and alpha-receptor blocking drugs), intracavernosally injected vasodilators (papaverine, phentolamine, prostaglandin E1, vasoactive intestinal peptide), transurethral vasoactive agents (prostaglandin E1, sometimes marketed as MUSETM), vacuum erection devices, and vascular surgery. Rings work by reducing venous out flow relative to inflow. Penile prostheses simply replace the erectile tissue with a rigid or semi-rigid structure. Each of these options has its own disadvantages. However, all of the current medications do not reverse or improve the physical changes causing erectile

dysfunction, hence, they have no ability to cure erectile dysfunction. They can be effective while these medications are present at therapeutic levels in the tissues where they directly exert their effects.

Current pharmacological treatments for erectile function such as phosphodiesterase 5-blockers and intracavernosally administered medications, such as the vasodilator PGE1alpha improve erectile responses by transiently producing elevated levels of blood flow and increased dilation of the cavernosal tissue to allow the arterial inflow to sufficiently pressurize the erectile tissue and activate the veno-occlusive system tissue to produce a usable erection.

It is known that men who consistently under all circumstances fail to respond with functional erections to maximal pharmacotherapy with oral or intracavernosal medications have to resort to using a pump and a very tight penile ring or undergo the surgical insertion of an implant. Frequent prolonged use of pumps and rings will damage the penis, and surgery results in an immediate irreversible destruction of the erectile tissues.

Histologically, there are specific changes that are associated with erectile dysfunction. These histological changes are:

1. increase in the percentage of collagen relative to smooth muscle in the cavernosal tissues;
2. decrease in the percentage of smooth muscle relative to collagen in the cavernosal tissues;
3. reduced elastin;
4. decreased cavernosal arterial inflow;
5. decreased cavernosal expansion during sexual stimulation; and
6. increased level of sexual stimulation needed to achieve and maintain a functional erection.

There is, therefore, a need for a safe, effective treatment that would induce long lasting physical changes in the penis that would allow a man's penis to be functional without the need to take a pill or inject medication into the penis every time he wants to be sexually active, and that could actually induce long lasting physical changes in the penis that would improve erectile function after medication had been discontinued.

The inventor has discovered that pharmaceutical compositions comprising a blocker selected from the group consisting of calcium channel blockers, metabolites thereof,

calmodulin blockers and metabolites thereof that have been used to treat medical conditions unrelated to erectile dysfunction can effectively treat male erectile dysfunction and induce physical changes to improve erectile function.

The invention is of particular value in the treatment of Peyronie's disease.

Accordingly, in one aspect, the invention provides a pharmaceutical composition for enhancing male erectile function comprising an erectile function-enhancing amount of a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier.

Preferably, the calcium channel blocker is verapamil, diltiazem or felodipine; and the calmodulin blocker is trifluoperazine.

Preferably, the composition is in the form of a cream, spray, gel, ointment or patch.

In a further aspect, the invention provides a use of a male erectile function-enhancing amount of a pharmaceutical composition of a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier.

In a yet further aspect, the invention provides a method of enhancing male erectile function comprising administering to a male an erectile function-enhancing amount of a composition comprising a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier, as hereinabove defined.

Preferably, the administration comprises subcutaneous injection, high pressure jet device, intracavernous injection, intravenous injection, intramuscular injection, intradermal injection, intra-nasal or, preferably, topical administration.

In a still yet further aspect, the invention provides a method of manufacturing a medicament intended for the application of enhancing male erectile function characterized in that the medicament is a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof; and admixed with a pharmaceutical acceptable diluent or carrier.

Preferably, the blocker is selected from verapamil, diltiazem, felodipine and trifluoperazine.

As used herein, "enhanced erectile function" refers to the ability to achieve and maintain a penile erection adequate for sexual intercourse more often than the man was able to before the treatment presented in the instant application. Indications that this treatment is effective include the decreased or eliminated reliance on medications and/or improved response to the medications currently used to treat erectile dysfunction or aid in achieving an adequate erection, more frequent spontaneous erections, an improved ability to sustain an erection before and after ejaculation, a reduction in the absolute and relative refractory period after ejaculation before another erection can be achieved, a reduced requirement for stimulation to achieve and maintain an erection and an increase in frequency, firmness and duration of morning erections and an increase in frequency, firmness and duration of spontaneous erections. Any of these indicators, alone or in combination, can be used as a measure of effectiveness.

Administration to the cavernosal tissue encompasses injections directly into the cavernosal tissue, which is preferred for men who have previously been trained on the proper method for intracavernosal injections and are currently using intracavernosal injections. For men who are not skilled with IC injections, the preferred injection would be injections to the connective tissues, which surround the cavernosal tissue from where the active agents of the present invention, in a water-based or oil-based system, will diffuse into the cavernosal tissue. Through this route, generally less of the administered dose would be delivered to the cavernosal tissue than if it were injected directly into the cavernosal tissue. Other routes of administration considered to be administration to the cavernosal tissue include urethral suppositories, implantable sustained-release drugs or devices, and transdermal devices or vehicles which are directly in contact with or adhered to the penis, such as patches, creams, or lotions. Optionally, the transdermal devices or vehicles may be delivered by a condom-like device.

In preferred embodiments of the invention the pharmaceutical compositions are administered to the penile and cavernosal tissue of the penis of a male patient.

The pharmaceutical composition is administered to the patient in a pharmaceutically acceptable sterile dosage form to the tissues of the penis, which includes the cavernosal tissue. The composition may be administered topically by transdermal vehicles or devices, such as creams, lotions, or patches. The composition may be administered by urethral suppository, or parenterally using a needle, auto-injector, slow sustained injection pump, high

pressure jet injection device, microinfusion pump, or implantable sustained release drug or device. Sterile dosage forms include, but are not limited to, syringes and needles, urethral suppositories, or transurethral implants, ampoules or vials, or transdermal vehicles or devices, such as creams, lotions or patches.

The active ingredient can also be delivered to the penile and cavernosal tissue transdermally. A suitable delivery vehicle or device is situated in direct contact with the skin of the penis to effect delivery of the agent to the penile and cavernosal tissue. The vehicle or device may include agents which enhance the transdermal absorption rate or agents which aid in the absorption of the pharmaceutical composition into the cavernosal tissue.

A particularly preferred transdermal device of the present invention is a patch. A patch is designed to adhere to or be brought into contact with the skin of the penis so that the pharmaceutical composition contained by the patch can be absorbed transdermally and into the penile and cavernosal tissue. The patch may also contain agents which enhance, control, or a combination of both, the transdermal absorption of the pharmaceutical composition and/or the absorption of the pharmaceutical composition into the penile and cavernosal tissue. Optionally, these agents can be applied in conjunction with the pharmaceutical composition, at a different time, and/or a different route of administration. The patch may also include adhesives specially designed to adhere to the often sensitive skin of the penis.

Kits comprising pharmaceutical compositions of the invention formulated in sterile unit dosage forms suitable for administration to the penile tissue, including instructions for use in written, oral, videotape, compact disc, other digital electronic form, or other recorded media, are contemplated. Conveniently, a kit wherein the sterile unit dosage forms are for oil based depot injections and instructions for use are provided.

Thus, in a further aspect, the invention provides a kit comprising the above-described compositions and an instruction for using the combination in treating, improving, curing or preventing male erectile dysfunction.

The appropriate dosage and frequency of treatment may vary depending upon desire or need of the degree of enhanced erectile function sought. Other health related factors would also be considered. Men without need of great enhancement of their erectile function may not need maximal treatment.

The frequency of administration may be in the range of two to three times a day for intercavernosal injection, more preferably from 3 to 7 times a week, or as infrequently as

monthly for delayed release formulations or topical administrations. The patient's condition should be monitored and the dosage adjusted, usually titrated upward, if enhanced erectile function is not achieved. Enhancement in erectile function may start immediately, but the major therapeutic effect may be expected to be achieved within 2 weeks to 6 months, more often within 4 weeks to 3 months. This may be followed by a maintenance phase during which there are intermittent or less frequent administrations. This may involve administrations of at least quarterly, bimonthly, biweekly, weekly injections, depending on the route of administration.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In order that the invention may be better understood, preferred embodiments will now be described by way of example only with reference to the following examples.

EXAMPLE 1

55 year old male on penis enlargement using traction combined with intracavernosal injections for 7 months. After 1 inch of growth in length of erect penis, growth rate had slowed and stopped and had been static for over 4 months.

After 3 months without any new additional growth, the patient was started on topical Verapamil 200mg/ml resulting in new additional penile growth of 1-1.5/16th of an inch growth of the fully erect penis length in the first month on Verapamil and a total of 6/16 inches of new growth over the first 3 months on topical Verapamil.

EXAMPLE 2

49 year old male with severe ED. Patient had previously experienced ongoing spontaneous priapisms and had continuous erections for 3 months. But when seen, patient was totally impotent and unable to erect. The penis was a solid fibrotic mass with extensive fibrosis of the cavernosal system. No response to PDE5's or IC test doses. During several attempted IC injections by the inventor with extensive experience and skill in the intracavernosal injection technique, the physician was unsuccessful to achieve an aspiration which indicated that the needle had entered the cavernosal system. The skilled physician was unable to locate erectile tissues on several attempts prior to initiating Verapamil and the patient had profound erectile dysfunction with no response to maximal dose PDE5's and maximal dose intracavernosal injections. Patient started applying Verapamil 200mg/ml 0.1 ml 5-8 times a day to the penis. After one month, the patient was re-examined and a dramatic softening of the patient's fibrotic penis was noted, and the patient reported his first

spontaneous erection in months. After 3 months of topical Verapamil, the patient's spontaneous erections were now sometimes penetrable, and he was consistently developing penetrable erections with Viagra® and Levitra® with maximum firmness of 70-75%. As well, test doses of intracavernosal medication by the physician were now frequently aspiration positive, which means that the physician was now able to find soft cavernosal tissue and now the patient was experiencing erections lasting for 15-20 minutes. But the patient's clinical improvement plateaued, and after six months with continued softening there was no significant improvement in erectile function until the topical Verapamil was combined with 2.5% testosterone. This gave a dramatic improvement in spontaneous erections and a dramatic improvement in the firmness of the spontaneous erections now exceeding > 80% as well as a dramatic increase in the firmness and duration of erections achieved when the patient used PDE5's. There was also an increased response to IC medications when the erections of topical Verapamil were compared to the erections with topical Verapamil combined with Testosterone.

EXAMPLE 3

46 year old male on penis enlargement using IC injections; initial growth rate without topical Verapamil was 1-2/16" per month for the first 4 months. Patient started Verapamil 0.1 ml 5-6 times/day in the fifth month of treatment and growth rate increased to 3-4/16" per month and the active growth rate of the patient did not decelerate at 4-6 months. The patient maintained an active growth rate over $2/16^{th}$ of an inch for over 9 months before significant deceleration in the growth rate occurred.

EXAMPLE 4

Patient with severe ED secondary to Peyronie's disease started on Verapamil 0.1 ml of 200mg/ml applied to penis 5-6 times per day. The inventor/physician noted a dramatic reduction in fibrosis and plaque such that the plaque was not palpable after 3-4 months. As well, following the daily use of topical Verapamil the patient began to get functional spontaneous erections. Prior to starting the Verapamil treatment there was no response to PDE5's, and within weeks of starting Verapamil there was a dramatic improvement in the erections in response to PDE5's.

EXAMPLE 5

62 year old male had extensive Peyronie's disease following several years of IC medications. The patient had developed these extensive masses of fibrotic nodular plaques throughout the entire penile shaft from 2001 through to 2008. During this time that these fibrotic changes were developing, the patients erectile dysfunction worsened, and PDE5's were no longer giving usable erections. The strength=dose of intracavernosal medication had increased over 2,000 percent and now instead of erections lasting over 2 hours to just prior to starting topical Verapamil therapy, a dose 2,000 percent stronger was only causing a soft semi-erection for 5-10 minutes. The patient started on Verapamil 2mg/ml 0.5 ml added to each IC dose and topical Verapamil 200mg/ml applied 5-6 times per day. Within one month there was dramatic shrinkage of multiple plaques in the penis. After 3 months there were only three small plaques of 1-3mm diameter left and an estimated reduction of plaque volume by 95- 98% after 4 months of active treatment which remained stable for several months after stopping the topical Verapamil. As well, the patient experienced a dramatic improvement in erectile function such that the volume of intracavernosal medications were reduced by 40 percent and now instead of a brief semi-erection, the erectile response to this reduced dose was now staying hard and usable for 1 to 1 ½ hours.

EXAMPLE 6

39 year old male on penis enlargement using traction combined with intracavernosal injections stopped growing. For three months there was no further increase in his penis length measurements despite adequate biomechanical stimulation. The patient added on drop of a 0.01 percent by weight PGF2alpha aqueous solution applied topically to the skin of the penis at mid shaft 2-6 times per day. When the patient returned in four weeks he experienced 1.5-2/16ths of an inch growth. After three months there had been 6.5-7/16th of an inch of new growth in the erect length of the penis.

Although this disclosure has described and illustrated certain preferred embodiments of the invention, it is to be understood that the invention is not restricted to those particular embodiments. Rather, the invention includes all embodiments which are functional or mechanical equivalence of the specific embodiments and features that have been described and illustrated.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A pharmaceutical composition for enhancing male erectile function comprising an erectile function-enhancing amount of a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier.

2. A pharmaceutical composition for treatment of Peyronies disease and other disorders of the penis associated with fibrosis and increased collage comprising a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier.

3. A pharmaceutical composition for penis enlargement comprising a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, relaxin receptor agonist, and a pharmaceutical acceptable diluent or carrier.

4. A composition as claimed in any one of claims 1 to 3 wherein said calcium channel blocker is verapamil.

5. A composition as claimed in any one of claims 1 to 3 wherein said calcium channel blocker is diltiazem.

6. A composition as claimed in any one of claims 1 to 3 wherein said calcium channel blocker is felodipine.

7. A composition as claimed in any one of claims 1 to 3 wherein said calmodulin blocker is trifluoperazine.

8. A composition as claimed in any one of claims 1 to 7 wherein said composition is in the form of a cream, spray, gel, ointment or patch.

9. A use of a male erectile function-enhancing amount of a pharmaceutical composition comprising a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier.

10. A use of a composition for the treatment of Peyronies disease comprising a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier.

12. A use as claimed in any one of claims 9 to 11 wherein said calcium channel blocker is verapamil.

13. A use as claimed in any one of claims 9 to 11 wherein said calcium channel blocker is diltiazem.

14. A use as claimed in any one of claims 9 to 11 wherein said calcium channel blocker is felodipine.

15. A use as claimed in any one of claims 9 to 11 wherein said calmodulin is trifluoperazine.

16. A use as claimed in any one of claims 9 to 15 wherein said composition is in the form of a cream, spray, gel, ointment or patch.

17. A method of enhancing male erectile function comprising administering to a male an erectile function-enhancing amount of a composition comprising a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier.

18. A method for the treatment of Peyronies disease comprising administering to a male a composition comprising a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof, and a pharmaceutical acceptable diluent or carrier.

20. A method as claimed in any one of claims 17 to 19 wherein said calcium channel blocker is verapamil.

21. A method as claimed in any one of claims 17 to 19 wherein said calcium channel blocker is diltiazem.

22. A method as claimed in any one of claims 17 to 19 wherein said calcium channel blocker is felodipine.

23. A method as claimed in any one of claims 17 to 19 wherein said calmodulin blocker is trifluoperazine.

24. A method as claimed in any one of claims 13 to 17 wherein said administration comprises subcutaneous injection, high pressure jet device, intracavernous injection, intravenous injection, intramuscular injection, intradermal injection, intra-nasal or topical administration.

25. A method as claimed in claim 18 wherein said administration is topical administration.

26. A method of manufacturing a medicament intended for the application of enhancing male erectile function characterized in that said medicament comprises a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof; and admixed with a pharmaceutical acceptable diluent or carrier.

27. A method of manufacturing a medicament intended for the application of treating Peyronies disease characterized in that said medicament comprises a blocker selected from the group consisting of a calcium channel blocker, a metabolite thereof, a calmodulin blocker and a metabolite thereof; and admixed with a pharmaceutical acceptable diluent or carrier.

29. A method as claimed in any one of claims 26 to 28 wherein said blocker is selected from verapamil, diltiazem, felodipine and trifluoperazine.