(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 474 143 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
03.09.2008 Bulletin 2008/36

(21) Application number: **03707504.1**

(22) Date of filing: **24.01.2003**

(51) Int Cl.:
A61K 31/5575 *(2006.01)* ***A61K 31/472*** *(2006.01)*
A61K 31/417 *(2006.01)* ***A61K 31/46*** *(2006.01)*
A61P 15/10 *(2006.01)*

(86) International application number:
PCT/US2003/002082

(87) International publication number:
WO 2003/063776 (07.08.2003 Gazette 2003/32)

(54) **METHODS AND COMPOSITIONS FOR TREATING MALE ERECTILE DYSFUNCTION**

VERFAHREN UND ZUSAMMENSETZUNGEN ZUR BEHANDLUNG DER MÄNNLICHEN EREKTIONSSTÖRUNG

METHODES ET COMPOSITIONS DE TRAITEMENT DE DYSFONCTIONNEMENT ERECTILE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT SE SI SK TR

(30) Priority: **25.01.2002 US 351634 P**

(43) Date of publication of application:
10.11.2004 Bulletin 2004/46

(60) Divisional application:
08001673.6 / 1 930 009

(73) Proprietor: **Modular Properties Ltd**
Altamonte Springs, FL 32701 (US)

(72) Inventors:
- **SALLIS, Ramsey**
  St. Peters SA 5069 (AU)
- **HA, Quoc, Huan**
  Irvine, CA 92614 (US)

(74) Representative: **Zambardino, Umberto**
Botti & Ferrari S.r.l.
Via Locatelli, 5
20124 Milano (IT)

(56) References cited:
US-A- 5 145 852

- **MONTORSI F, GUAZZONI G, BERGAMASCHI F, ZUCCONI M, RIGATTI P, PIZZINI G, MIANI A, POZZA G: "Clinical reliability of multi-drug intracavernous vasoactive pharmacotherapy for diabetic impotence" ACTA DIABETOLOGICA, vol. 31, no. 1, 1994, pages 1-5, XP008044479**
- **SHMUELI J, ISRAILOV S, SEGENREICH E, BANIEL J, LIVNE P: "Progressive treatment of erectile dysfunction with intracorporeal injections of different combinations of vasoactive agents" INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, vol. 11, no. 1, February 1999 (1999-02), pages 15-19, XP008044486**
- **BANIEL J, ISRAILOV S, ENGELSTEIN D, SHMUELI J, SEGENREICH E, LIVNE P M: "Three-year outcome of a progressive treatment program for erectile dysfunction with intracavernous injections of vasoactive drugs" UROLOGY, vol. 56, no. 4, October 2000 (2000-10), pages 647-652, XP008044478**
- **MONTORSI F, GUAZZONI G, BERGAMASCHI F, DODESINI A, RIGATTI P, PIZZINI G, MIANI A: "Effectiveness and safety of multidrug intracavernous therapy for vasculogenic impotence" UROLOGY, vol. 42, no. 5, November 1993 (1993-11), pages 554-558, XP002321590**
- **DATABASE EMBASE [Online] LUE ET AL.: 'Functional evaluation of penile arteries with duplex ultrasound in vasodilator-induced erection', XP002967516 Retrieved from STN Database accession no. 89277323 & UROLOGICAL CLINICS OF NORTH AMERICA 1989,**

Printed by Jouve, 75001 PARIS (FR)

(Cont. next page)

- DATABASE BIOSIS [Online] TRUSS ET AL.: 'Intracavernous pharmacotherapy', XP002967517 Retrieved from STN Database accession no. 1997:170905 & WORLD JOURNAL OF UROLOGY 1997,

Description

FIELD OF THE INVENTION

[0001] This invention relates generally to the fields of medicine and urology. More particularly, the invention relates to the use of compositions for the manufacture of a medicament for treatment of male erectile dysfunction. the use of for the manufacture of a medicament

BACKGROUND OF THE INVENTION

[0002] Sexual dysfunction in both males and females has received a significant amount of popular attention with the greater concerns directed to the particular male problems of erectile capacity and penetration ability. Male sexual dysfunction associated with impotence is generally defined as the inability to attain or sustain an erection satisfactory for normal coitus. Prevalence of erectile problems, including premature ejaculation, has been estimated to be surprisingly high, perhaps as much as 45% worldwide. This is a particular concern among the over-50 male population in the United States, where estimates of impotency range from 18 to 75% for this age group.

[0003] Medical intervention for treatment of erectile dysfunction is becoming increasingly common. Surgical procedures, penile implants and pharmacological agents have been developed for treatment of male erectile dysfunction in recent years.

[0004] Surgical interventions employing penile implants and various patient-controlled mechanical devices are not uniformly successful nor are they appropriate in most situations. A serious disadvantage of treating erectile dysfunction with a surgical implant is the necessity to irreversibly damage the erectile tissues of the penis.

[0005] Pharmacological methods have been developed to treat male erectile dysfunction. The mechanism of erection is dependent on adequate blood flow to the spongy cavernous tissue of the penis, in paired spaces known as the corpora cavernosa. Control of blood flow to the corpora cavernosa involves the process of vasodilation of the cavernosal arteries.

[0006] It is now recognized that vasodilators acting on the penile arteries can be beneficial to achieving an erection. Orally administered vasodilators are currently the most widely accepted treatments for male erectile dysfunction. Such vasodilators include sildenafil. This compound is taken orally about one hour prior to intercourse because instant erection is not achieved with this drug. Unfortunately, this delay may lead to overdosing by patients seeking a more rapid response. While effective, this product may cause undesirable side effects such as headache, flushing, dyspepsia and in some cases abnormal vision such as increased sensitivity to light. Of greater concern, this drug may exacerbate pre-existing heart conditions. Furthermore, sildenafil must be taken on an empty stomach and must not be taken with alcohol.

[0007] A more rapid response in producing an erection has been found for sildenafil applied intranasally. The response is often within five minutes, and the drug is asserted to have fewer side effects than when administered orally. While reducing side effects, the drug nevertheless enters the circulatory system and is able to exert vasodilatory effects in areas other than the penis. Following the nasal route of administration, undesirable side effects can still be produced, some of which may be of medical concern.

[0008] Recognition of the problems associated with systemic administration of vasodilators has led to development of methods for local delivery of vasodilators to the tissues of the penis. For example, a semi-solid vehicle containing a vasodilator for insertion into the urethra has been formulated and shown to be effective in stimulating erection. Disadvantages of this method are the requirement for administration into the urethra, contributing to transient burning or tingling effects reported in some cases, and raising the possibility of urethral infection and scarring. This product is ineffective in up to 60% of patients.

[0009] An alternative and more direct route for delivery of vasodilators is injection into the corpus cavernosum of the penis. This "intracavernosal" route has been successfully used to deliver one or more vasodilators to achieve erections, and has led to the development of a treatment regimen known as intracavernosal pharmacotherapy (ICP).

[0010] Studies have led to the discovery of several vasodilators capable of provoking an erection. The use of papaverine for male erectile dysfunction has been reported. Papaverine is a vascular intracellular smooth muscle relaxant acting by its inhibitory effect on cyclic mononucleotide phosphodiesterases. However papaverine as monotherapy had an unpredictable response, and the drug must be administered in large volumes. Additionally, significant side effects associated with papaverine include the potential for prolonged erection and fibrosis of the corpus cavernosum.

[0011] Another vasodilator that has been used to achieve erection is phentolamine. Phentolamine alone does not reliably produce an erection sufficient for intercourse.

[0012] Prostaglandin E1 (PGE1) is a yet another vasodilator that effects an erection through its action as an alpha-adrenergic blocker. PGE1 has been formulated into suppositories for insertion into the urethra of men suffering from erectile dysfunction. As described above, this method of administration is disadvantageous due to risk of urethral infection and fibrosis. PGE1 has a short half life compared with papaverine and phentolamine. Intracavernosal injection of PGE1 can cause an erection of dose-dependent duration but, in a trial of this method, was associated with significant pain in a large percentage (up to 40%) of the subjects.

[0013] Several combinations of vasodilators have been used for treatment of impotence by the intracaver-

nosal route. Success has been reported in a clinical study using a combination of papaverine and phentolamine in patients having vascular causes of impotence mostly associated with diabetes or atherosclerosis. Clinical success has also been reported in men with erectile dysfunction of neurogenic origin using a combination of papaverine, phentolamine and PGE1. The three-drug mixture has been regarded as more effective than PGE1 alone in inducing an erectile response, with a decreased incidence of pain. This drug combination also decreases the latency between injection and erection and allows a reduction in the total papaverine dose, reducing the risk of prolonged erection and potential incidence of fibrosis.

[0014] Such clinical studies comprise the following:

Montorsi et al. (Adult Urology, 42, 5, 554-558, 1993) used a four-drug vasoactive mixture comprising papaverine hydrochloride, prostaglandin E1, phentolamine mesylate and atropine sulfate for intracavernous therapy of patients with vasculogenic impotence.

Montorsi et al. (Acta Diabetologica 31:1-5, 1994) carried out a study to assess the effectiveness and safety of intracavernous injections of a four-drug vasoactive mixture in diabetic patients with organic impotence. The patients were treated with a combination of 12.1 mg/ml papaverine hydrochloride, 1.01 mg/ml phentolamine mesylate, 10.1 μg/ml prostaglandin E1 and 0.15 mg/ml atropine sulfate.

Shmueli et al. (Int. J. Impotence Res., 11, 15-19, 1999) carried out a study on 452 patients suffering with erectile dysfunction to assess the efficacy of a progressive treatment technique using four protocols of drug injections. Sufficient rigidity was achieved as follows: Protocol I (papaverine and Regitine): 67.4% of the overall patients; Protocol II (prostin VR): 41.5% of the failures from Protocol I; Protocol III (papaverine, Regitine and prostin VR): 63.9% of the failures of Protocol II; Protocol IV (papaverine, Regitine, prostin VR and atrophine sulfate): 64.5% of the failures of Protocol III.

Baniel et al. (Adult Urology, 56, 4, 647-652, 2000) performed a comparative evaluation and follow-up of patients with erectile dysfunction who were treated with vasoactive drugs by intracavernous injection by drug protocol progression according to response. Of 625 patients, 64% responded well to protocol 1 (papaverine and phentolamine); 36% of the remaining patients from protocol 1 responded well to protocol 2 (prostaglandin E); 72.5% of the remaining patients from protocol 2 responded well to protocol 3 (papaverine, phentolamine and prostaglandin E); and finally, 59.5% of the remaining patients from protocol 3 responded well to protocol 4 (papaverine, phentolamine, prostaglandin E and atropine sulfate).

[0015] The collective experience of urologists reviewing clinical trials and treating patients with erectile dysfunction has led to an appreciation that despite impressive successes with some patients, no one therapy or composition can be applied across-the-board to treat all erectile problems.

SUMMARY

[0016] The invention relates to the use of a composition in the manufacture of a medicament for treating sexual dysfunction in a male mammal according to claim 1.

[0017] Assessment of the physical condition can include measuring blood flow to the arteries of the penis. The physical assessment can also include determining the sensitivity and condition of the nerves of the penis.

[0018] The nature of the sexual dysfunction treatable by the method can be erectile dysfunction. Premature ejaculation can also be treated.

[0019] The respective amounts of PGE1, papaverine, phentolamine, and atropine range from 8-35 μM, 14-45 mM, 2-15 mM and 0.05-0.15 mM.

[0020] The relative amounts of the vasodilators can be varied in different formulations of the compositions. This is advantageous for preparation of customized formulations tailored to individual patient needs, e.g., in a clinical setting. In one embodiment, the composition can include respective amounts of PGE1, papaverine, phentolamine and atropine of about 3 μg, 13.5 mg, 2.5 mg, and 0.15 mg in a volume of 1 ml. In other embodiments, the respective amounts can be about 6 μg, 10.5 mg, 2 mg, and 0.15 mg. In yet other embodiments, the respective amounts can be about 12 μg, 6 mg, 2.5 mg and 0.05 mg; 12 μg, 21 mg, 4 mg, and 0.3 mg; or 3 μg, 5 mg, 1 mg and 0.8 mg in a volume of 1 ml. In general, preferred embodiments of the compositions can range in amounts from about 3-12 μg/ml PGE1, 5-15 mg/ml papaverine, 1-5 mg/ml phentolamine, and 0.5-0.15 mg/ml. In yet a further embodiment, the composition can include papaverine, phentolamine, and atropine in amounts of about 12 μg, 4 mg and 0.2 mg in a volume of 1 ml.

[0021] The composition used in the method can be in a pharmaceutically acceptable vehicle. The vehicle can further include a stabilizer.

[0022] The effective amount of a composition used in the method of treatment can be contained in a volume from about 0.1 ml to about 2 ml.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] The invention is pointed out with particularity in the appended claims. The above and further advantages of this invention may be better understood by referring to the following description, taken in conjunction with the accompanying drawings, in which:

FIG. 1 is graphic showing criteria used to determine a test dosage.

FIG. 2 is a graphic showing criteria used to determine a prescribed dosage.

DETAILED DESCRIPTION

[0024] The invention provides the use of a composition for the manufature of a medicament for treating sexual dysfunction in a male mammal By a method as defined in claim 1 . A pharmaceutical composition of one or more agents is administered by ICP in an amount effective to cause the male to sustain an erection. The method includes an assessment of the general, physical and psychological condition of the male. A test dose of a pharamaceutical composition is formulated, guided by information obtained in the assessment step. A test dose of the formulated composition is administered to the subject by ICP. The erection characteristics of the male are observed following administration of the test dose. The composition may be subsequently adjusted to provide an effective erection.

[0025] The method is suitable for use in any male mammal capable of sustaining an erection. The sexual dysfunction can include erectile dysfunction (ED) and premature ejaculation (PE). The sexual dysfunction can be of physical or psychological origin. The origin of the physical component can be either neurogenic, i.e., caused by nerve damage, or vasculogenic, i.e., caused by arterial damage. It is contemplated that subjects having sexual dysfunction of psychogenic origin may be benefited by the treatment because the confidence built up in having a satisfactory erection will eliminate future performance fears.

Pharmaceutical Compositions

[0026] The method includes administration of a pharmaceutical composition effective to cause a male to sustain an erection. The compositions of the invention are be admixtures of more agents as recited in claim 1 known to produce an erection in a male subject. Any Phentolamine is known as an antihypertensive agent It is a competitive, non-specific alpha-adrenoceptor antagonist that works by direct action on smooth muscle to cause relaxation. Atropine is an anti-muscarinic anti-cholinergic drug believed to stimulate the release of nitrous oxide from the sinusoidal endothelium of corporal tissue. The prostaglandins are a family of important regulatory hormone-like compounds found mainly in the genital organs. PGE1 is a vasodilator that acts as a potent smooth muscle relaxant by functioning as an alpha adrenergic blocker, as well as by elevating intracellular levels of cGMP. Papaverine acts as a smooth muscle relaxant by inhibiting cyclic mononucleotide phosphodiesterases, leading to increased cAMP and cGMP concentrations. It is known to block voltage dependent calcium channels.

[0027] The compositions used in the invention can be provided, e.g., to a clinic, in several base formulations that are further tailored to the individual needs of the patient by the methods described herein.

[0028] As an example of the method, six base formulations can be provided, designated by identifier codes such as F0, F1, F2, F3, F4, F5 and F6. Formulation F0 which is not porit of this invention can be, for example, a one-drug formulation, containing, e.g., PGE1 alone. Formulations F1-F6 all contain combinations of vasodilators PGE1, phentolamine, atropine and papaverine. The formulations can include combinations containing all four of these drugs, or only three, i.e., phentolamine, atropine and papaverine.

[0029] Each combination drug formulation can further be provided in multiple formulations that vary according to the relative proportions of the drugs within them. Availability of such premixed formulations provides a convenient means of prescribing amounts of the combined agents tailored in proportion to the particular needs of the patient. As an example, F1 can contain a mixture of stock solutions of PGE1, papaverine, phentolamine and atropine, combined by volume in the ratios of 15: 45: 25: 15, respectively. F2 can contain the same four drugs, combined in the ratios of 30: 35: 20: 15. F3 can contain these drugs in the ratios of 60: 20: 25: 5. F5 can contain the four vasodilators in the same ratios as F2, but at double their concentrations. F6 can be a diluted version of F2, containing the same four vasodilators, e.g., at half strength. A three-drug formulation can be included, designated, e.g., F4, that contains a combination of three vasodilators, e.g., papaverine, phentolamine and atropine. In preferred embodiments, these three drugs can be combined in the ratios of 40:40:20 by volume. Further details of methods of preparing three- and four-drug formulations found to be effective in the practice of the invention are provided in the examples below.

[0030] All formulations can be provided in a suitable pharmaceutical vehicle. The components of the composition will preferably be in a vehicle that is physiologically compatible and that will allow the dissolution or suspension of the composition components. The components are preferably in an aqueous based pharmaceutically acceptable solution.

[0031] Suitable pharmaceutical vehicles are well known to those skilled in the art and are described in several manuals, including Remington's Pharmaceutical Sciences, 15th edition. is not stable in water at room temperature although for practical purposes it may be at room temperature for short periods of time. Formulations containing PGE1, papaverine, phentolamine and atropine, should be kept under refrigeration. A combination of papaverine, phentolamine and atropine can be stored without refrigeration.

Assessment Of Sexual Dysfunction

[0032] The invention includes the use of a composition for the manufacture of a medicament for treating sexual dysfunction in a male mammal by a method that includes ICP administration of a pharmaceutical composition of

more agents as defined in claim 1 in an amount effective to cause the male to sustain an erection. It has been shown that the most effective combinations of agents can be determined with the least number of test doses, and with minimization of unwanted side effects of incorrectly prescribed medication, by the disclosed methods.

[0033] In a first step in the method of treatment, subjects are assessed to determine the nature of their sexual dysfunction. In the practice of the invention with human males, patient health history and the nature of the sexual problem are determined by interviewing the subject. It is important that the medical history be thorough and detailed in order alert the practitioner to any possible medical conditions that should be addressed. Information obtained from the history can include significant medical conditions, e.g. diabetes, medications currently taken, use of tobacco or alcohol and drug abuse if any, as well as age and an overall assessment of health by the patient.

[0034] The subject is further asked to a respond to questions regarding a number of clinical indicators. The clinical indicators can include but are not limited to: the nature of the erection the patient is capable of sustaining during sexual encounters and by masturbation, the duration of the period of erectile dysfunction, the absence or presence and nature of the patient's morning erections, the percentage frequency of erections sufficient for vaginal penetration, the response of the patient to sildenafil, if known, and the occurrence, if any, of premature ejaculation.

Formulation of Test Dose

[0035] The method includes a step of formulating a test dose of a pharamaceutical composition effective to cause the male to sustain an erection. Formulation of a diagnostic test dose of medication is guided by a compilation of clinical indicators. The clinical indicators can be compiled such that patients can be assigned to one of several initial treatment groups. The clinical indicators are displayed in the form of a chart, namely annexed chart 1, that correlates the compiled clinical information with the selection of a test dose formulation.

[0036] Any number of treatment groups can be designated, and any combination of appropriate clinical indicators may be used. Determination of treatment group categories and selection of appropriate formulations is based on clinical experience with a population of subjects who fall into categories having particular combinations of indicators, including age groups. Compilation of such information from a population can be used to predict the appropriate effective combination and dosage of agents to be used in a customized formulation for a patient who falls into a particular treatment group.

[0037] In an example of this invention, it has been determined that the longer the patient has had the erectile problem, the more likely it will be that he will require a stronger formula or a greater dose of formulations described herein. The rigidity and duration of a patient's erections is also informative: the less rigid and the less able to penetrate, the more advanced the problem, indicating the need to provide a stronger formula or a greater dose. If the patient has tried sildenafil, his response to this medication is instructional: failure to respond to sildenafil indicates a greater likelihood of requiring a higher dose or a stronger formula. Conversely, a good response to this drug tends to imply that a weaker dosage will be appropriate. The choice of test dosage can also be guided according to the nature of the patient's problem. For example, a patient seeking help for erectile dysfunction (ED) may require a higher dose or a stronger formula than a patient with a problem of premature ejaculation (PE). The quality of a patient's morning erections can also provide information about the nature of the problem. The stronger a patient's erections are in the mornings, the more likely it is that the problem is of psychological origin and hence can be resolved using a weaker dose. Age has also found to a factor in patient response to a particular formulation: the older the patient, the less responsive he is to the medication. Therefore, a greater dose or stronger formulation is generally required with increasing patient age.

[0038] The method for formulating a test dose is shown in Chart 1 (FIG. 1). In this example, compiled clinical indicators were used to define four categories of male erectile dysfunction (designated Groups 1-4), for purposes of choosing a test dose of medication. The choice of formulation of the test dose was further varied within each of the four groups according to the age of the patient

[0039] Assessment of the subject can include the use of physical diagnostic tests which may further assist in determining the formulation of the test dose. A useful diagnostic test is a measurement of blood flow through the penis. Any method suitable for performing this measurement can be utilized. Preferably, this test is performed using an ecodoppler. This test is used to determine if there has been any reduction in blood flow through the patient's cavernosal arteries. Blood flow can be used as a parameter for categorizing patients into diagnostic test groups. As an example, blood flow values may be divided into four groups, as shown in the chart in FIG. 1, e.g., with ranges of blood flows correlated with groupings, such as Group 1, 20cm/s; Group 2, 15-20cm/s; Group 3, 10-15cm/s; Group 4, <10cm/s.

[0040] A further physical diagnostic test that may be used is measurement of the sensitivity of the nerve system to the head of the penis. Any method suitable for performing this measurement can be used. A preferred method to perform this test is biothesiometry. Biothesiometry is used to determine if there is any neuropathy (nerve damage). Nerve damage can cause ED of neurogenic origin. This test is used to determine the degree if any of peripheral neuropathy or damage to the nerves that cause the cavernosal arteries to dilate and allow blood to flow into the penis provoking an erection. Biothesiometry is also used to determine how strong the phys-

ical component of PE is, by determining the degree of hypersensitivity of the glans or head of the penis. The greater the sensitivity, the more likely it is that the PE is physical in nature (low ejaculatory threshold). As seen in the example shown in FIG. 1, if the results of nerve testing indicate that a patient has a strong neurogenic component, but a weak vascular component to his ED, this information can be helpful in assignment of the patient to a particular group.

[0041] Based upon the combination of information gained from the interview and physical testing, an appropriate formulation is selected to be used in a test dose of medication. As described above, the amount and composition is based on the determined clinical indicators, as well as the age of the patient. In an embodiment using a chart for compilation of clinical indicators and suggested dosages, for example as shown in FIG. 1, the formulation and volume of the composition to be tested can be determined as indicated in the lower portion of the chart.

Administration of Test Dose

[0042] The method includes a step of administering by a test dose of a pharmaceutical composition effective to cause a male to sustain an erection. The test dose of the medication is administered intracavernosally, i.e., by ICP, because this method delivers the medication to its precise site of action (i.e., the corpus cavernosum), minimizing unwanted side effects caused by systemic administration of drugs such as centrally acting vasodilators.

[0043] The method further includes a step of observing one or more characteristics of the erection in order to evaluate the quality of the erection that results from administration of the test dose. Any method suitable for evaluating the quality of the erection can be used. Suitable methods can include visual inspection, measurement of erection angle, palpation, timing of initiation and duration of erection following administration of the agent, ability to penetrate, ability to ejaculate, presence or absence of discomfort, response to erotic stimulus, and time required for return of flaccidity. Yet another suitable test is to measure the change in blood flow to the penis following administration of the test dose. Once the response to the test formulation has been determined, an adjustment can be made depending on this response. The dosage can be either reduced or increased depending on the quality of the erection that the patient has achieved using the diagnostic dose. Directions for adjustment of the dosage are compiled into a table, as well as directions for prescribing a dosage based on the results of the diagnostic test step. Such a table is shown in FIG. 2.

[0044] There is virtually no discomfort when the patient injects the composition because the central part of the penis is relatively insensitive in contrast to the penis head, which is a sensitive area. The central shaft is composed of spongy tissue and injection into this area places the solution into the cavernosa. The patient may have some initial trepidation concerning the first self-injection. This is readily overcome by instructions and practice in the physician's office and a complete instruction sheet or videotape accompanying the dosage kits. Fear of pain is dispelled, and in fact some patients need to be warned that a lack of pain is not an indication that the drug did not reach the targeted area.

[0045] In practice, the patient simply injects the proper dose into the dose into the proximal third of the penis. Typically, a rapid response is obtained within 5 minutes. The duration of the erection is, on average, 25 to 45 minutes. The penis remains erect during this period regardless of ejaculation, in contrast to agents such as sildenafil, with which the penis becomes flaccid after ejaculation. Erotic stimulation is not required with this treatment, as it is with sildenafil.

EXAMPLES

Example 1. Preparation of Formulations For Erectile Dysfunction

[0046] This example describes the preparation of agents found to be effective and convenient for use in the invention, with designations corresponding to those indicated in the charts in FIGS. 1 and 2. In this example, six base formulations of the compositions were prepared and designated by code numbers F0, F1, F2, F3, F4, F5 and F6. Formulation F0 which is not part of this invention was prepared to include PGE1 only, at a concentration of 10 μg/ml. Formulations designated F1, F2, F3, F5 and F6 all contained combinations of four vasodilators, i.e., PGE1, phentolamine, atropine and papaverine, but in differing proportions or concentrations. F1 contained a mixture of solutions of PGE1, papaverine, phentolamine and atropine, combined in the respective ratios of 15: 45: 25: 15 by volume. The final formulations were achieved conveniently by combining mixtures of stock solutions in varying volume proportions. For specifically, a solution of PGE1 was prepared in saline at a concentration of 20 μg/ml. A solution of papaverine was prepared in a hydrochloride vehicle at a concentration of 30 mg/ml. Phentolamine was prepared in a hydrochloride solution at a concentration of 10 mg/ml, and atropine was prepared in a sulphate solution at a concentration of 1mg/ml. Using solutions thus prepared, formulation F1, having the ratio of 15:45:25:15, was prepared by mixing 15 mls of the PGE1 (20 μg/ml), 45 mls of papaverine (30 mg/ml), 25 mls of phentolamine(10mg/ml) and 15mls of atropine (1mg/ml), for a total volume of 100 mls. Accordingly, final concentrations of the four vasodilators in formulation F1 were PGE1: 3 μg/ml; papaverine: 13.5 mg/ml; phentolamine: 2.5 mg/ml; and atropine: 0.15 mg/ml.

[0047] Formulation F2 contained the same four drugs, prepared from stock solutions at the concentrations stated above, but combined in the ratios of 30: 35: 20: 15 by volume. Therefore the resulting formulation contained PGE1, papaverine, phentolamine, and atropine at the

respective final concentrations of 6 μg/ml, 10.5 mg/ml, 2.0 mg/ml and 0.15 mg/ml. F3 contained the same four drugs combined in the ratios of 60: 20: 25: 5, to yield a composition containing PGE1, papaverine, phentolamine, and atropine at the respective final concentrations of 12 μg/ml, 6.0 mg/ml, 2.5 mg/ml and 0.05 mg/ml. F5 contained the four vasodilators in the same ratios as F2, but at double their concentrations. F6 was prepared by combining the same four vasodilators in the ratios for F2, but at half strength.

[0048] Formulation F4 contained a combination of only three vasodilators, i.e., papaverine, phentolamine and atropine in the ratios of 40:40:20 by volume, using stock solutions prepared as described above. Final concentrations of papaverine, phentolamine and atropine solutions in formulation F4 were therefore 12.0 mg/ml, 4 mg/ml, and 0.2 mg/ml, respectively. In general, the above described formulations contained amounts of PGE1, papaverine, phentolamine, and atropine, in the range of about 8-35 μM, 14-45 mM, 2-15 mM and 0.05-0.15 mM, respectively.

Example 2. Determination of Test and Effective Doses of Formulations

[0049] This example describes how test doses and adjusted doses of formulations designated by identifiers F0-F6, described herein, can be determined by a practitioner, by reference to guidelines provided in chart form. In the charts shown in this example (FIGS. 1 and 2), predictive clinical indicators were compiled into four patient groups having the observed combination of parameters. Correlations were made with dosages found to be effective for each of these groups. Referring to FIG.1, it can be seen that to determine an appropriate test dose for a 30-year-old classified in Group 3, a suggested test dose is 14 units (0.14 ml) of formulation F2. By contrast, a 60-70 year old subject in the same group could initially be administered 36 units (0.36 ml) of formulation F2. In this example, all dosage volumes are shown in units, where 10 units = 0.1 ml.

[0050] Referring now to Chart 2, (FIG. 2), if the resulting erection is 70-80% in response to the test dose, the prescribed dose is increased by 25-50% of the volume used for the test dose (e.g., by 0.09-0.18 ml of F2 for a 60-70 year old subject with erectile dysfunction, ED).

[0051] Chart 2 provides additional guidance for selection of an effective dosage following administration of the test dose. As seen in the notes below the chart, formulations can be modified for the rare patients who experience a priapism or prolonged erection (3-6 hours) following administration of the test dose. If the problem resolves with conservative treatment or with the administration of an antidote such as epinephrine, the test formulation is changed from F2 to F1, then to F0 if necessary. If the patient experiences a priapism that requires draining, the formulation is changed to F0 (containing PGE1 alone), starting at 20 units.

[0052] Also shown in Chart 2 is direction for a practitioner whose patient experiences no response with the maximum dosage (100 units), e.g., of formulation F2. In this case, the patient can be tested with 100 units of F5, which contains the same ingredients as F2 but at double their respective concentrations.

[0053] The prescribed dosage table (Chart 2) also contains columns to separate patients with erectile dysfunction (ED) and those with premature ejaculation (PE). The reason for this separation is that patients with PE tend to require a more conservative adjustment than those with ED.

Claims

1. Use of a composition including papaverine, phentolamine and atropine and optionally also PGE1 for the manufacture of a medicament for treating sexual dysfunction in a male mammal via intracavernosal pharmacotherapy (ICP) administration, such that the male mammal can sustain an erection, by a method comprising the steps of:

   a) assessing the general, physical and psychological condition of the male;
   b) formulating a test dose of said composition guided by step (a) and by annexed chart 1;
   c) administering the test dose;
   d) observing at least one erection characteristic of the male subsequent to administration of the test dose; and
   e) adjusting the composition according to the observations in step (d) and the dosage adjustment table according KS annexed chant 2 to provide an effective erection, wherein the amounts of papaverine, phentolamine and atropine are in the range of 14-45 mM, 2-15 mM and 0.05-0.15 mM and the amount of PGE1, when present, is in the range of 8-35 μM .

2. The use according to claim 1, wherein said composition includes papaverine, phentolamine, atropine and PGE1.

3. The use of claim 1 or 2 wherein assessing the physical condition in step a) further comprises measuring blood flow to the arteries of the penis.

4. The use of claim 1 or 2 wherein assessing the physical condition in step a) further comprises determining the sensitivity and condition of the nerves of the penis.

5. The use of claim 1 or 2 wherein said sexual dysfunction is erectile dysfunction.

6. The use of claim 1 or 2 wherein said sexual dysfunc-

tion is premature ejaculation.

7. The use of claim 2 wherein said composition comprises an amount of PGE1, papaverine, phentolamine, and atropine of about 3 μg, 13.5 mg, 2.5 mg, and 0.15 mg in a volume of 1 ml.

8. The use of claim 2 wherein said composition comprises an amount of PGE1, papaverine, phentolamine, and atropine of about 6 μg, 10.5 mg, 2 mg, and 0.15 mg in a volume of 1 ml.

9. The use of claim 2 wherein said composition comprises an amount of PGE1, papaverine, phentolamine, and atropine of about 12 μg, 6 mg, 2.5 mg and 0.05 mg in a volume of 1 ml.

10. The use of claim 2 wherein said composition comprises an amount of PGE1, papaverine, phentolamine, and atropine of about 12 μg, 21 mg, 4 mg, and 0.3 mg in a volume of 1 ml.

11. The use of claim 2 wherein said composition comprises an amount of PGE1, papaverine, phentolamine, and atropine of about 3 μg, 5 mg, 1 mg and 0.8 mg in a volume of 1 ml.

12. The use of claim 1 wherein said composition comprises an amount of papaverine, phentolamine, and atropine of about 12 μg, 4 mg and 0.2 mg in a volume of 1 ml.

13. The use of claim 1 or 2 wherein said composition is in a pharmaceutically acceptable vehicle.

14. The use of claim 13 wherein said pharmaceutical vehicle further comprises a stabilizer.

15. The use of claim 1 or 2 wherein said effective amount of the composition is contained in a volume from about 0.01 ml to about 2.0 ml.

Patentansprüche

1. Verwendung einer Zusammensetzung, welche Papaverin, Phentolamin und Atropin und optional auch PGE1 enthält, für die Herstellung eines Medikaments für die Behandlung der sexuellen Dysfunktion in einem männlichen Säugetier, über intracavemosale Pharmakotherapie (ICP) Verabreichung, so dass das männliche Säugetier eine Erektion aufrechterhalten kann, mit einer Methode, die die Schritte umfasst:

   a) Abschätzung der allgemeinen, physischen und psychologischen Kondition des männlichen Säugetiers;

   b) Formulierung einer Testdosis dieser Zusammensetzung, angeleitet durch Schritt (a) und durch das beiliegende Diagramm 1;
   c) Verabreichung der Testdosis;
   d) Beobachtung von mindestens einer Erektion, die charakteristisch für das männliche Säugetier ist, im Anschluss an die Verabreichung der Testdosis; und
   e) Anpassung der Zusammensetzung gemäß den Beobachtungen aus Schritt (d) und der Dosierungsanpassungstabelle, gemäß dem beiliegenden Diagramm 2, um eine effektive Erektion zu bewirken, wobei die Menge von Papaverin, Phentolamin und Atropin im Bereich von 14-45 mM, 2-15 mM und 0,05-0,15 mM liegt und die Menge von PGE1, falls vorhanden, im Bereich von 8-35 μM liegt.

2. Verwendung gemäß Anspruch 1, wobei die Zusammensetzung Papaverin, Phentolamin, Atropin und PGE1 enthält.

3. Verwendung gemäß Anspruch 1 oder 2, wobei die Abschätzung der physischen Kondition im Schritt a) weiterhin das Messen des Blutflusses zu den Arterien des Penis umfasst.

4. Verwendung gemäß Anspruch 1 oder 2, wobei die Abschätzung der physischen Kondition im Schritt a) das Bestimmen der Sensitivität und des Zustandes der Nerven des Penis umfasst.

5. Verwendung gemäß Anspruch 1 oder 2, wobei die sexuelle Dysfunktion eine erektile Dysfunktion ist.

6. Verwendung gemäß Anspruch 1 oder 2, wobei die sexuelle Dysfunktion eine vorzeitige Ejakulation ist.

7. Verwendung gemäß Anspruch 2, wobei die Zusammensetzung PGE1, Papaverin, Phentolamin und Atropin in einer Menge von ungefähr 3 μg; 13,5 mg; 2,5 mg und 0,15 mg in einem Volumen von 1 ml umfasst.

8. Verwendung gemäß Anspruch 2, wobei die Zusammensetzung PGE1, Papaverin, Phentolamin und Atropin in einer Menge von ungefähr 6 μg; 10,5 mg; 2 mg und 0,15 mg in einem Volumen von 1 ml umfasst.

9. Verwendung gemäß Anspruch 2, wobei die Zusammensetzung PGE1, Papaverin, Phentolamin und Atropin in einer Menge von ungefähr 12 μg; 6 mg; 2,5 mg und 0,05 mg in einem Volumen von 1 ml umfasst.

10. Verwendung gemäß Anspruch 2, wobei die Zusammensetzung PGE1, Papaverin, Phentolamin und

Atropin in einer Menge von ungefähr 12 µg; 21 mg; 4 mg und 0,3 mg in einem Volumen von 1 ml umfasst.

11. Verwendung gemäß Anspruch 2, wobei die Zusammensetzung PGE1, Papaverin, Phentolamin und Atropin in einer Menge von ungefähr 3 µg; 5 mg; 1 mg und 0,8 mg in einem Volumen von 1 ml umfasst.

12. Verwendung gemäß Anspruch 2, wobei die Zusammensetzung Papaverin, Phentolamin und Atropin in einer Menge von ungefähr 12 µg, 4 mg und 0,2 mg in einem Volumen von 1 ml umfasst.

13. Verwendung gemäß Anspruch 1 oder 2, wobei die Zusammensetzung in einem pharmazeutisch verträglichen Träger ist.

14. Verwendung gemäß Anspruch 13, wobei der pharmazeutische Träger weiterhin ein Stabilisierungsmittel umfasst.

15. Verwendung gemäß Anspruch 1 oder 2, wobei die effektive Menge der Zusammensetzung in einem Volumen von ungefähr 0,01 ml bis ungefähr 2,0 ml enthalten ist.

Revendications

1. Utilisation d'une composition incluant de la papavérine, de la phentolamine et de l'atropine et, en option, également du PGE1 pour la fabrication d'un médicament pour le traitement d'un dysfonctionnement sexuel chez un mammifère mâle par administration de pharmacothérapie intracavemeuses (ICP), de telle sorte que le mammifère mâle puisse entretenir une érection, par un procédé comprenant les étapes consistant à :

a) évaluer la condition générale, physique et psychologique du mâle ;
b) formuler une dose à tester de ladite composition guidée par l'étape (a) et par le diagramme 1 annexé ;
c) administrer la dose à tester ;
d) observer au moins une érection caractéristique du mâle après administration de la dose à tester ; et
e) ajuster la composition selon les observations de l'étape (d) et le tableau d'ajustement posologique selon le diagramme 2 annexé pour obtenir une érection efficace, dans laquelle les quantités de papavérine, phentolamine et atropine sont dans l'intervalle de 14-45 mM, 2-15 mM et 0,05-0,15 mM et la quantité de PGE1, lorsqu'il est présent, est dans l'intervalle de 8-35 µM.

2. Utilisation selon la revendication 1, dans laquelle ladite composition comprend de la papavérine, de la phentolamine de l'atropine et du PGE1.

3. Utilisation selon la revendication 1 ou 2, dans laquelle l'évaluation de la condition physique dans l'étape a) comprend en outre la mesure du flux sanguin vers les artères du pénis.

4. Utilisation selon la revendication 1 ou 2, dans laquelle l'évaluation de la condition physique dans l'étape a) comprend en outre la détermination de la sensibilité et de la condition des nerfs du pénis.

5. Utilisation selon la revendication 1 ou 2, dans laquelle le dysfonctionnement sexuel est un dysfonctionnement érectile.

6. Utilisation selon la revendication 1 ou 2, dans laquelle le dysfonctionnement sexuel est l'éjaculation précoce.

7. Utilisation selon la revendication 2, dans laquelle ladite composition comprend des quantités de PGE1, de papavérine, de phentolamine et d'atropine d'environ 3 µg, 13,5 mg, 2,5 mg et 0,15 mg dans un volume de 1 ml.

8. Utilisation selon la revendication 2, dans laquelle ladite composition comprend des quantités de PGE1, de papavérine, de phentolamine et d'atropine d'environ 6 µg, 10,5 mg, 2 mg et 0,15 mg dans un volume de 1 ml.

9. Utilisation selon la revendication 2, dans laquelle ladite composition comprend des quantités de PGE1, de papavérine, de phentolamine et d'atropine d'environ 12 µg, 6 mg, 2,5 mg et 0,05 mg dans un volume de 1 ml.

10. Utilisation selon la revendication 2, dans laquelle ladite composition comprend des quantités de PGE1, de papavérine, de phentolamine et d'atropine d'environ 12 µg, 21 mg, 4 mg et 0,3 mg dans un volume de 1 ml.

11. Utilisation selon la revendication 2, dans laquelle ladite composition comprend des quantités de PGE1, de papavérine, de phentolamine et d'atropine d'environ 3 µg, 5 mg, 1 mg et 0,8 mg dans un volume de 1 ml.

12. Utilisation selon la revendication 1, dans laquelle ladite composition comprend des quantités de papavérine, de phentolamine et d'atropine d'environ 12 µg, 4 mg et 0,2 mg dans un volume de 1 ml.

13. Utilisation selon la revendication 1 ou 2, dans laquel-

le ladite composition est dans un véhicule pharmaceutiquement acceptable.

14. Utilisation selon la revendication 13, dans laquelle ledit véhicule pharmaceutique comprend en outre un stabilisant.

15. Utilisation selon la revendication 1 ou 2, dans laquelle ladite quantité efficace de la composition est contenue dans un volume d'environ 0,01 ml à environ 2,0 ml.

CHART 2

SUGGESTED PRESCRIPTION FOR ED			SUGGESTED PRESCRIPTION PER PE	
Erection Not Rigid Cannot Penetrate	Erection 50-70% Firm & Rubbery Just Able to Penetrate	Erection 70-80% Reasonably Firm Penetration Reasonably Easy	Erect. <50% Not Firm	Erection 70% Firm & Rubbery
Double	+ 50-75%	+ 25 – 50%	+ 50%	Same Dose
• If patient has a priapism, or 100% response for 3-6 hours which reduces with conservative treatment or epinephrine, change F2 to F1 (2) or F1 to F0. (3)				
• If patient has a priapism that requires draining, start with 20F0.				
• F5 (4) is high potency F2. If 100F2 fails, use 100F5.				
• F4 does not need refrigeration. Start with 75% of the volume appropriate for F2.				
• F6 (5) is diluted F4 (i.e., non-refrigerated), for use with PE patients. Start with 14F6.				

FIG. 2

(1) F2 = PGE1 6 µg/ml; Papaverine 10,5 mg/ml; Phentolamine 2,0 mg/ml; Atropine 0.15 mg/ml

(2) F1 = PGE1 3 µg/ml; Papaverine 13,5 mg/ml; Phentolamine 2,5 mg/ml; Atropine 0,15 mg/ml

(3) F0 = PGE1 10 µg/ml

(4) F5 = PGE1 12 µg/ml; Papaverine 21,0 mg/ml; Phentolamine 4,0 mg/ml; Atropine 0,30 mg/ml

(5) F6 = PGE1 3 µg/ml; Papaverine 5,25 mg/ml; Phentolamine 1,0 mg/ml; Atropine 0,075 mg/ml

CHART 1

SCHEME FOR FIRST TEST DOSE					
	Group 1	**Group 2**		**Group 3**	**Group 4**
	Blood flow >20cm/s Erection 100% PE Neurogenic ED Psychogenic ED	Blood flow 15-20cm/s Erection >70-75% Sustain Poor Morning Erection OK Dysfunction <12 Months Penetration >50% of the time Sildenafil Worked Well		Blood flow 10-15cm/s Erection <65% Sustain Poor Morn. Erect Poor Dysfunction 12-24 Mo. Penetration 50% of time	Blood flow <10cm/s Erection <50% ± Diabetes Sustain Poor Morn. Erect. Poor Dysfunction >24 Months Penetration Not Possible
AGE	F1*	F1	F2**	F2	F2
20-30	10	18	-	14	20
30-40	14	24	-	20	26
40-50	16	34	-	26	30
50-60	18	-	20	30	36
60-70	20	-	24	36	40
70+	22	-	26	40	50

FIG. 1

*F1= PGE1 3 µg/ml; Papaverine 13.5 mg/ml; Phentolamine 2.5 mg/ml; atropine 0.15 mg/ml

**F2= PGE1 6 µg/ml; Papaverine 10.5 mg/ml; Phentolamine 2.0 mg/ml; Atropine 0.15 mg/ml

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **MONTORSI et al.** *Adult Urology,* 1993, vol. 42 (5), 554-558 **[0014]**
- **MONTORSI et al.** *Acta Diabetologica,* 1994, vol. 31, 1-5 **[0014]**
- **SHMUELI et al.** *Int. J. Impotence Res.,* 1999, vol. 11, 15-19 **[0014]**
- **BANIEL et al.** *Adult Urology,* 2000, vol. 56 (4), 647-652 **[0014]**