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A METHOD OF TREATMENT AND PROPHYLAXIS

FIELD OF THE INVENTION

The present invention relates generally to the treatment and prophylaxis of penile dysfunction. More particularly, the present invention contemplates the treatment and prophylaxis of persistent penile erection resulting from, for example, physiological dysfunction, trauma, surgical intervention or chemical induction. The method of the present invention is practice by the administration of an agent capable of inducing, promoting or otherwise facilitating contraction of the cavernosum. Accordingly, another aspect of the present invention provides a composition comprising a cavernosum contraction -inducing, -promoting or -facilitating agent. In one embodiment, the agents of the present invention are prostaglandins or functional derivatives, homologues, analogues, agonists, mimetics or metabolites thereof. This provides a means for diagnosing the physiological basis behind penile dysfunction.

BACKGROUND OF THE INVENTION

Priapism is defined as a prolonged, usually painful, penile erection generally not directly initiated by sexual stimulus. It results from a disturbance or other dysfunction in the normal regulatory mechanisms which initiate and maintain penile flaccidity. The treatment of this condition ranges from predominately surgical management to less invasive pharmacological therapies. Despite recent advances in the understanding of erectile mechanisms, the pathophysiology of priapism remains obscure in up to 50% of cases (Steers and Selby, 1991). Thus, in the absence of an identifiable aetiology, treatment has been essentially symptomatic. In at least 5% of patients treated for impotence, injection of vasoactive substances such as papaverine, prostaglandin E and phenoxybenzamine or phentolamine, an alpha adrenergic blocking drug, into the corpora cavernosa muscle, is the most likely cause of priapism. Furthermore, the availability of sildenafil citrate (sold under the trademark "Viagra") as an anti-impotence drug, has resulted in its misuse as an aphrodisiac to improve male



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sexual performance. Reports indicate that sildenafil also has caused priapism. If left unattended, the abuse and misuse of erection-producing vasoactive agents is likely to lead to priapism and irreversible muscle damage. Other situations in which priapism is seen include disease states such as sickle cell anaemia and use
5 of unrelated drugs such as antidepressants (ie trazodone).

Current antidotes for priapism are alpha adrenoceptor agonists such as metaraminol, adrenaline, phenylephrine, noradrenaline and ethylephrine. These alpha-mimetics are known to produce systemic side effects including a rise in systemic blood pressure. Hence, such agents are contraindicated for
10 cardiovascular patients. Hence, there is a need to identify reliable, safe and efficacious pharmacological agents for the treatment and prophylaxis of penile dysfunction characterized by prolonged penile erection.

SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word
15 "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

The present invention is predicated in part on the identification of a group of
20 compounds which induce, promote or otherwise facilitate contraction of the cavernosum associated with penile tissue. The agents identified by the present invention do not cause a rise in systemic blood pressure. Particularly preferred agents include the prostaglandins such as but not limited to prostaglandin A2, prostaglandin A1, prostaglandin B1 and prostaglandin B2 as well as functional
25 derivatives, homologues, analogues, agonists, mimetics and metabolites thereof.

Accordingly, one aspect of the present invention contemplates a method for the treatment or prophylaxis of priapism in a male subject said method comprising administering to said subject an effective amount of an agent which induces,

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promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum, without a concomitant rise in systemic blood pressure, the administration of which agent leads to partial or complete penile flaccidity.

Another aspect of the present invention is directed to a method for the treatment or prophylaxis of priapism in a male subject said method comprising administering to said subject an effective amount of a prostaglandin or a functional derivative, homologue, analogue, agonist, mimetic or metabolite thereof which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum, without a concomitant rise in systemic blood pressure, for a time and under conditions sufficient to lead to partial or complete penile flaccidity or to prevent or reduce the likelihood of an erection.

Yet another aspect of the present invention provides a composition for pharmaceutical use comprising an agent which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum in penile tissue said composition further comprising one or more pharmaceutically acceptable carriers and/or diluents.

The preferred agents of the present invention are prostaglandins such as but not limited to prostaglandin A2, A1, B1 and B2. The most preferred agent is prostaglandin A2 or functional derivatives, homologues, analogues, agonists, mimetics or metabolites thereof.

The terms "prostaglandin A2", "Adainus" , "AS-8" and "priapres" may be used interchangeably to refer to "prostaglandin A2".

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graphical representation showing effect of intravenous bolus dose of prostaglandin A2 on blood pressure, heart rate and respiratory rate in anaesthetised baboons.

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Figure 2 is a graphical representation showing contractile response of prostaglandin A2 on human corpus cavernosum smooth muscle.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, the inventors have identified agents which are useful in the treatment of priapism. The agents of the present invention differ from known priapism-treating agents, such as alpha adrenoceptor agonists, in that the subject agents do not cause systemic side effects such as tachycardia or raised blood pressure and which render these known therapeutic contraindicated for cardiovascular patients.

Accordingly, one aspect of the present invention contemplates a method for the treatment or prophylaxis of priapism in a male subject said method comprising administering to said subject an effective amount of an agent which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum, without a concomitant rise in systemic blood pressure, the administration of which agent leads to partial or complete penile flaccidity.

Reference herein to "priapism" includes and encompasses prolonged or sustained penile erection. Generally, priapism does not result from sexual stimulation. However, the present invention includes the treatment of prolonged penile erection following sexual stimulation. Priapism may also result from surgical intervention, trauma, physiological dysfunction or pharmacological intervention such as following the ingestion or administration of drugs (e.g. sildenafil citrate, papaverine, or phenoxybenzamine) or disease states, due to use of some drugs not related to erectile function/dysfunction or spontaneous unexplained priapism.

The present invention extends to treating a subject having an erection or preventing or at least reducing the likelihood of a subject obtaining an erection. Accordingly, the present invention extends beyond priapism to the treatment of hypersexual stimulation. This may be useful in treating certain cases of habitual sex offenders.

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Although the present invention is directed mainly at the treatment in human males, it also has an application in the veterinary field. For example, difficulties may arise for male stud animals such as stud bulls, horses, sheep and pigs. Such animals may need to be chemically sexually aroused in order to produce semen or to service female animals. To induce a non-aroused state after service, the agents of the present invention may be administered to the male animal.

The preferred agents of the present invention are prostaglandins including functional derivatives, homologues, analogues, agonists, mimetics or metabolites stored thereof.

Accordingly, another aspect of the present invention is directed to a method for the treatment or prophylaxis of priapism in a male subject said method comprising administering to said subject an effective amount of a prostaglandin or a functional derivative, homologue, analogue, agonist, mimetic or metabolite thereof which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum, without a concomitant rise in systemic blood pressure, for a time and under conditions sufficient to lead to partial or complete penile flaccidity or to prevent or reduce the likelihood of an erection.

The preferred prostaglandins of the present invention are prostaglandin A₂, prostaglandin A₁, prostaglandin B₁ and prostaglandin B₂. The most preferred prostaglandin is prostaglandin A₂.

Reference herein to "prostaglandin" and in particular prostaglandin A₂, A₁, B₁ and/or B₂ includes reference to functional derivatives, homologues, analogues, agonists, mimetics or metabolites thereof. The term "functional" means that the molecule behaves in the same therapeutic manner as the "parent" prostaglandin, i.e., the prostaglandin prior to modification.

Derivatives of the prostaglandins of the present invention include alterations to glycosylation, acylation and alkylation patterns as well as hydrophobicity, hydrophilicity, hydrophobic moment, charge and antigenicity.

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The prostaglandin or other compound useful in the practice of the present invention is usefully formulated in a composition or agent form.

Accordingly, another aspect of the present invention provides a composition for pharmaceutical use comprising an agent which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum in penile tissue said composition further comprising one or more pharmaceutically acceptable carriers and/or diluents.

The preferred agent is a prostaglandin such as prostaglandin A2, A1, B1 or B2.

The most preferred agent is prostaglandin A2 or its functional derivative, homologue, analogue, agonist, mimetic or metabolite.

Reference herein to a "composition" includes reference to an "agent".

The composition may comprise the prostaglandin alone or it may be in combination with other therapeutic agents.

The composition of the present invention may be administered in any convenient manner such as but not limited to intravenous, intramuscular, intrarectal, intranasal, subcutaneous, transdermal, transurethral, intraperitoneal or oral administration. Administration may also be *via* patch, i.v. drip, spray or during surgery or other invasive procedure. The most effective administration is *via* injection into the corpus cavernosa. This is referred to as intracavernous drug delivery.

The identification of prostaglandins as an effective treatment of priapism provides a means for identifying physiological causes for conditions such as impotence, hypersexuality and priapism. For example, impotent males may produce excessive amounts of particular prostaglandins. Alternatively, reduced prostaglandin production or local levels may be indicated in priapism patients. The identification of levels of particular prostaglandins provides one level of diagnosis

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for penile dysfunction. Such methods of diagnosis are contemplated by the present invention.

Accordingly, another aspect of the present invention contemplates a method for diagnosing the physiological basis behind priapism in a male subject, said method
5 comprising determining the level in said subject of prostaglandin A2, A1, B1 and/or B2 or derivatives and/or metabolites thereof wherein low levels of one or more of said prostaglandin is indicative of a causative effect for priapism.

Yet another aspect of the present invention is directed to the use of a prostaglandin or a functional derivative, homologue, analogue, agonist, mimetic or
10 metabolite thereof in the treatment of priapism in a male subject.

Preferably, the prostaglandin is prostaglandin A2.

The present invention is further described by the following non-limiting Examples.

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EXAMPLE 1
EFFECTS OF ADAINUS PHARMACOLOGICALLY INDUCED
PROLONGED ERECTION (PIPE)

Six male baboons weighing between 8 kg and 12 kg were used for the experiment.

5 The animals were sedated with ketamine and anaesthetised with intravenous pentobarbitone injected through an indwelling venous catheter. Drugs were injected into the right corpora cavernosa at the mid-third of the shaft using a 29G needle and 1 ml syringe. Blood pressure was monitored through a cannulated femoral artery connected to the transducer. A measuring tape was used to
10 measure penile length visually from a marked point at the base of the penis to the tip of urethral orifice. Changes in penile length were recorded for a period of 100 min after injection.

Intracavernous injection of papaverine (40 mg) or phenoxybenzamine (3 mg) which produced maximal penile length within 20 and 40 min were repeated one
15 week later and prostaglandin A2 was given at the peak time of the turgidity.

In human patients and human volunteers, intracavernous injection of prostaglandin A2 (150 µg) was tested on prolonged erection (lasting more than 4 hours) induced by 60 mg of papaverine.

EXAMPLE 2
RESPONSE TO ADAINUS (PROSTAGLANDIN A2)

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In baboons, intracavernous injection of papaverine (40 mg) or phenoxybenzamine (3 mg) produced a 130% increase in penile length within 10 min after administration (Table 1). This increase in penile length lasted for more than 100 min. This was repeated one week later and when prostaglandin A2 was injected
25 intracavernosally at the maximum rigidity at 20 min, the latter produced a marked reduction in penile length and within 40 min of injection, the penile size reduced to the original state of rugosity (Table 1). The fall in systemic blood pressure produced by prostaglandin A2 ranged from 8 to 16 mmHg.

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Intracavernous injection of prostaglandin A2 (150 µg) readily reduced the penile length in patients and volunteers who were having prolonged erection induced by 60 mg of papaverine for 4 hours or more. Maximal reduction in rigidity and penile length to the rugose state was achieved within 30 min after injection of prostaglandin A2 in four out of five subjects. In one volunteer, there was a relapse of tumescence within 60 min after the first injection of prostaglandin A2 (150 µg). This was corrected by an additional injection of prostaglandin A2 (100 µg). The fall in mean systemic blood pressure ranged from 7 to 10 mmHg (Table 2).

EXAMPLE 3

OUTCOME

The present study indicates that administration of prostaglandin A2 is an efficient alternative to metaraminol or adrenaline in correcting pharmacologically induced prolonged erection in man. Unlike the sympathomimetic compounds that raise the systemic blood pressure (Figure 1), intracavernous injection of 100 to 150 µg of prostaglandin A2 produced a pressure fall of 7 to 16 mmHg in the baboon and man.

This mild fall in blood pressure produced by the administration of prostaglandin A2 may suggest a dilatation of vasculature facilitating penile engorgement. Subjective observation in the present study, both in the baboon and man indicates that the marked contractile property of prostaglandin A2 on the corpora cavernosa muscle probably dominates this effect in reversal to PIPE. Prostaglandin A2 is 8.2 times stronger than noradrenaline in contracting human corpora cavernosa muscle *in vitro* and 500, 2.5 and 50 times stronger than dopamine, adrenaline and amine, respectively (Figure 2). The results also suggest that if prostaglandin A2 exists physiologically (especially in excessive amounts) then this might contribute to detumescence or non-erectile state of the penis more readily than noradrenaline.

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EXAMPLE 4**TESTING OTHER PROSTAGLANDINS**

Prostaglandins A1, B1 and B2 are also tested using the above protocol. Results indicate that these prostaglandins are also effective in inducing, promoting or
5 otherwise facilitating contraction of the cavernosum but were not as active as prostaglandin A2.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and
10 modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

TABLE 1

EFFECT OF AS-8 ON PAPAVERINE AND PHENOXYBENZAMINE INDUCED PROLONGED ERECTION (PIPE) IN BABOONS

MEAN CHANGE IN PENILE LENGTH (% OF CONTROL)

(MINUTES AFTER INJECTION)	1	2	5	10	20	40	60	80	100
PAPAVERINE (40 mg)	30	40	52	130	130	130	130	130	130
<u>1 WEEK LATER</u>									
PAPAVERINE (40 mg) followed by AS-8 (100 µg) 20 mins later	32	38	65	130	142	15	0	0	0
PHENOXYBENZAMINE (3 mg)	10	15	15	48	80	120	120	120	120
<u>1 WEEK LATER</u>									
PHENOXYBENZAMINE (3 mg) followed by AS-8 (100 µg) 20 mins later	7	15	20	38	85	10	0	0	0

As-8 was given 20 minutes after the drug administration. Each value represents mean of six results.

TABLE 2
MEAN DECREASE IN LENGTH OF TURGID PENIS (%)

MINUTES AFTER AS-8 INJECTION	1	5	10	20	30
PATIENTS (2)-%	10	50	80	90	100
VOLUNTEERS (3)-%	10	30	75	80	95

Intracavernous injection of AS-8 (150 µg) on prolonged erection induced by papaverine (60 mg) for 4 hours or more in human.

BIBLIOGRAPHY

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2. Boyle ET, *et al.* *J. Urol* 143: 933-935, 1990.
3. Brindley GS. *Lancet* 2(8396): 220-221, 1984.

CLAIMS

1. A method for the treatment or prophylaxis of priapism in a male subject said method comprising administering to said subject an effective amount of an agent which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum, without a concomitant rise in systemic blood pressure, the administration of which agent leads to partial or complete penile flaccidity.
2. A method according to claim 1 wherein the agent is a prostaglandin or a functional derivative, homologue, analogue, agonist, mimetic, or metabolite thereof.
3. A method according to claim 2 wherein the prostaglandin is prostaglandin A2.
4. A method according to claim 1 or 2 or 3 wherein the agent is intracavernously administered.
5. A method for the treatment or prophylaxis of priapism in a male subject said method comprising administering to said subject an effective amount of a prostaglandin or a functional derivative, homologue, analogue, agonist, mimetic or metabolite thereof which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum, without a concomitant rise in systemic blood pressure, for a time and under conditions sufficient to lead to partial or complete penile flaccidity or to prevent or reduce the likelihood of an erection.
6. A method according to claim 5 wherein the prostaglandin is prostaglandin A2.
7. Use of a composition comprising a prostaglandin which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the cavernosum in penile tissue, in the manufacture of a medicament for the treatment of priapism in a male subject, wherein said prostaglandin is selected from the group consisting of prostaglandin A1, prostaglandin B1, prostaglandin B2, and prostaglandin A2, and one or more pharmaceutically acceptable carriers and/or diluents.

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8. The use according to claim 7, wherein said prostaglandin is prostaglandin A2.
9. A composition for pharmaceutical use comprising an agent which induces, promotes or otherwise facilitates contraction of corpora cavernosa muscle in the caverosum in penile tissue said composition further comprising one or more pharmaceutically acceptable carriers and/or diluents.
10. A composition according to claim 9 wherein the agent is a prostaglandin or a functional derivative, homologue, analogue, agonist, mimetic or metabolite thereof.
11. A composition according to claim 10 wherein the prostaglandin is prostaglandin A2.
12. An agent for use in treating priapism in a male subject comprising a prostaglandin or a functional derivative, homologue, analogue, agonist or mimetic thereof.
13. An agent according to claim 12 wherein the prostaglandin is prostaglandin A2.
14. Use of a prostaglandin or a functional derivative, homologue, analogue, agonist, mimetic or metabolite thereof in the manufacture of a medicament in the treatment of priapism in a male subject.
15. Use according to claim 14 wherein the prostaglandin is prostaglandin A2.
16. A method for diagnosing the physiological basis behind priapism in a male subject, said method comprising determining the level in said subject of prostaglandin A2, A1, B1 and/or B2 or derivatives or metabolites thereof wherein low levels of one or more of said prostaglandin is indicative of a causative effect for priapism.