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(54) Title: METHOD AND COMPOSITIONS FOR TREATMENT OF SEXUAL IMPOTENCE

(57) Abstract

A method and compositions are described for treating sexual impotence with an oral drug regimen amenable to once a day therapy. The preferred and most effective embodiment utilizes the administration of a long acting, selective alpha-1 blocking agent, such as doxazosin or terazosin, given together with a particular beta adrenergic blocking agent which possesses intrinsic sympathomimetic activity, such as acebutolol or celiprolol. The drug regimen is simple and it is continuously effective throughout the day and over the long term for maintaining a state of normal responsiveness to sexual arousal. It involves the co-administration of two well-characterized, safe and explicitly defined pharmacologic species given orally either as a capsule or tablet. This regimen could provide other metabolic advantages related to its explicit curtailment of putative excessive or inappropriate sympathetic nervous system traffic.

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METHOD AND COMPOSITIONS FOR TREATMENT OF SEXUAL IMPOTENCE

Background of the Invention

This invention generally relates to pharmaceuticals and more specifically to a method and compositions for treating patients with sexual impotence.

Sexual impotence in males may be defined as a failure of penile erection accompanied at times by a failure of ejaculation and orgasm. The known causes for this disability are related to conditions involving failure of male hormone production and are rare. For the majority of cases no hormonal or primary structural defects are clinically demonstrable. Such instances have been considered by exclusion to be on a "vasculogenic" basis, or due to a failure or abnormality of neural control of the genital vasculature, possibly arising from central nervous system dysfunction and possibly involving psychogenic factors. This common type of impotence usually increases in frequency with advancing age.

It is generally agreed that there is no satisfactory oral drug treatment for the correction or improvement of impaired sexual performance (see USA Today, Report on the World Congress on Orgasm, New Delhi, February 7, 1991). In this regard while the whole range of available vasodilator drugs have been tried, and sometimes claimed to be useful for treatment of impotence, worldwide sales of such vasodilator drugs (e.g., nitrates, papaverine, hydralazine) for this use is negligible and some of these drugs (e.g., oral phentolamine or papaverine), drugs have actually been removed from the market for lack of demand. Similarly, the local topical

application to the skin of the penis of such vasodilator drugs also has been extensively tried but is usually ineffective, and consequently is not widely used.

Presently, the only effective drug therapy for male sexual impotence involves the direct injection into the corpora of the penis of either phentolamine, papaverine or prostaglandin. However, this type of injection therapy is inconvenient, only of short-term value, has certain structural risks involving tissue scarring and can cause priapism requiring surgical intervention.

It is therefore the object of the present invention to provide a method and composition fortreating impotence in patients who have no demonstrable organic or hormonal cause for the disorder.

Summary of the Invention

A new oral drug treatment regimen is described involving the oral co-administration of explicitly defined types of alpha and beta blockers to correct impaired sexual function. The discovery is surprising because, when given alone, both alpha and beta blocking drugs have often been reported to impair sexual function and cause impotence. The new treatment is especially relevant for treatment of sexual impotence in the male but it could improve sexual performance in females. The method is particularly suited for patients taking or needing antihypertensive drugs because both of its components have antihypertensive effects. The fact that this

new treatment regimen involves defined alpha and beta blockade to modulate synpathetic nerve activity, supports neural theories of causation of impaired sexual function and suggests that this treatment plan might improve or modify other metabolic functions related to sympathetic imbalance.

In the preferred embodiment, a drug producing selective alpha blockade, such as dibenzyline, doxazosin or terazosin, preferably one of the latter two, alone or in combination with a beta-blocking drug which also possesses vasodilator activity, such as acebutolol, celiprolol, labetolol, or carvedilol, preferably one of the first two, is administered once or twice daily to a patient suffering from impotence. The most preferred embodiment is the co-administration once or twice daily of either doxazosin or terazosin with either acebutolol or celiprolol. This preferred combination produces a reciprocally balanced autonomic blockade of alpha and beta receptors which restores sexual function.

The present method is simpler than previous treatments, since the medication is administered orally and it is consistently effective. It can achieve long-term restoration with maintained readiness of function in response to appropriate stimuli, using once a day oral drug therapy for as long as the correction is desired. Moreover, it is unique in design in presumably attacking directly, simultaneously, and selectively, two nervous pathways using the co-administration of two particular drug types.

Detailed Description of the Invention

The two stages of the male sexual act are erection and ejaculation, both of which are neurally governed. The first stage, erection, has been thought to be mediated by the parasympathetic nervous system whose activity may be inhibited by alpha adrenergic tone. Cholinergic impulses from the spinal cord cause arterial dilatation and venous constriction in the penis. The arterial blood in the erectile tissue of the penis builds up under high pressure due to the venous constriction which blocks the outflow of blood from the penis. The second stage, ejaculation, is thought to be mediated by the sympathetic nervous system. Sensory nerves in the penis respond to sexual stimulation by sending sensory impulses to the spinal cord. After processing these impulses, the spinal cord sends sympathetic impulses to the male reproductive organs. These sympathetic impulses stimulate alpha-1 adrenergic receptors in these reproductive organs, causing them to contract. This contraction results in the filling of the internal urethra with sperm and prostatic fluid. The corresponding pressure increase in the internal urethra stimulates pressure receptors which send impulses to the spinal cord. Cholinergic impulses are then sent from the spinal cord to the penis where the skeletal muscle surrounding the erectile tissue is stimulated to contract, causing ejaculation of the sperm from the internal urethra.

The method and compositions described herein are based on a system of enteral drug therapy to correct impotence

in patients having no demonstrable organic cause for the disorder. The method employs antihypertensive drugs of the same type often used in normotensive states wherein they have little or no effect on blood pressure. Accordingly, the method is basically applicable to normotensive people. However, it is also useful for treating impotence in hypertensive individuals, particularly when the problem may actually have been caused by their prior hypertensive drug regimen.

The method exploits the seemingly paradoxical observations which have established that sexual function can be impaired by either alpha or beta blocking drugs as well as by the selective administration of either alpha or beta agonists. Surprisingly, it has been found that using certain anti-adrenergic, antihypertensive agents in combination to block both the alpha and beta receptors restores or sustains the normal sexual process.

In the preferred embodiment, a drug producing selective alpha blockade of alpha-1 receptors such as doxazosin and terazosin, or blocking both alpha-1 and alpha-2 receptors, such as dibenzyline, is administered once or twice daily in combination with a beta-blocking drug which also possesses vasodilator activity, such as acebutolol, celiprolol, labetolol, or carvedilol, to a patient suffering from impotence. The combination produces a reciprocally balanced autonomic blockade of alpha and beta receptors which restores sexual function.

The Alpha Blockers

The preferred alpha blocker is a long-acting and selective alpha-1 blocking drug, either doxazosin, 2 to 8 mg/daily, or terazosin, 5-20 mg/day. Other alpha blockers that can be used in combination with beta blockers are the non-selective blockers of alpha-1 and alpha-2 receptors such as dibenzyline, 10 mg administered once or twice daily, phentolamine, 50 mg daily, tolazoline, 50 mg daily (between 25 and 100 mg per day). Doxazosin and terazosin are equally or more effective than the latter group. Moreover, the non-selective alpha blockers can express side effects such as postural hypotension, nausea and vomiting, tachycardia, and hypertension, not usually encountered with either doxazosin or terazosin.

Dibenzyline, administered alone, has little beneficial effect on sexual performance, possibly because its use is associated with some fall in blood pressure, venous pooling, and reactive tachycardia from reflex activation of the unblocked beta sympathetic nervous system. In fact, dibenzyline given by itself has been reported to actually cause either impotence or impaired ejaculation in patients. Gilman, A., et al., The Pharmacological Basis of Therapeutics 183 (1980).

The Beta Blockers

In the preferred embodiment, one of the two preferred selective alpha blockers is administered in combination with a particular type of beta-blocker that also possesses intrinsic vasodilating activity, such as acebutolol,

labetalol, celiprolol, or carvedilol. The vasodilator activity of the preferred effective types of beta blocking agents may involve either alpha-1 blockade, beta-2 agonism, calcium channel blockade, or some other type of non-specific vasodilation, or a combination thereof.

Effectiveness in combination with doxazosin, terazosin, or dibenzyline has been shown for labetolol, 200 to 400 mg, administered twice to three times daily; celiprolol, 200 to 400 mg, administered daily; acebutolol, 200 to 600 mg, administered daily; and carvedilol, 25 mg, administered once or twice daily. Use of well-known types of beta blockers such as non-selective (e.g. propranolol) or cardioselective (e.g., atenolol, pindolol, or metoprolol) beta blockers, alone or in combination with the alpha blockade induced by the first drug, produce either no correction or a worsening of impotence, possibly because these beta blockers lack intrinsic sympathomimetic (beta-2) agonism, or other vasodilator action.

Administration to Patients

The drugs are preferably administered enterally, most preferably in combination in a pharmaceutically acceptable vehicle, such as a tablet. Other methods and forms of administration will be obvious to those skilled in the art. The effective dosages can be determined by one of ordinary skill in the art, based on the dosages approved for other uses combined with empirical observations.

In another alternative embodiment, the present method and compositions could be used to restore sexual function in females and to treat sexual dysfunction associated

with a range of disturbances of the cardiovascular system, including the aging process. It can also be used to design improved antihypertensive drug regimens to maintain sexual function and avoid drug-induced impotence.

The present invention will be further understood by reference to the following non-limiting examples.

The method and compositions emerged from the critical serial testing of prototypical anti-adrenergic, antihypertensive agents over an extended period of time. The agents were first administered and evaluated when given alone and then in various possible combinations to search for a means for allowing or enhancing potency (measured by erection) or the time of a sexual encounter.

Potency was graded on a scale of 0 to 4, with a 3 or 4 grade requiring capacity for penetration and completion of the sexual act. The strategy employed involved a modification of the well-known "N of 1" design, described by Guyatt, et al., N.E. J. Med. 314, 889-892 (1986), the teachings of which are incorporated herein. In this strategy, any positive result is systematically verified by repeated comparison with what happens in the control states, as well as when an alternative treatment is applied with a known effect or lack of one.

All agents tested using this strategy showed extremely high internal consistency as to either a positive effect or lack thereof. Routinely, the agents were given once or twice daily, at least two hours before an anticipated sexual encounter. All drug types were evaluated for their

short term effects, i.e., from 2 to 24 hours after oral administration. However, such acutely positive actions, when demonstrable, did not disappear when longer term usage was evaluated for up to three to six months.

Example 1: Administration of anti-adrenergic or other hypertensive agents alone.

Typical beta-blockers were administered in full daily dosages for a week or longer. Propranolol, 40 mg, was administered t.i.d.; atenolol, 25 or 50 mg, was administered once daily; metoprolol, 100 mg, was administered twice daily; pindolol, 10 mg, was administered once daily.

No positive effects were observed.

Similar uniformly negative results were obtained using other types of agents administered alone, including the alpha-1 blocker, prazosin, in doses up to 5 mg three times daily, and the calcium antagonists, verapamil, 250 mg, twice daily; diltiazem, 90 mg, three times daily; and nifedipine, 20 mg, three times daily.

Non-selective alpha blockade administered alone was similarly evaluated, using phentolamine, 50 mg, once daily; priscoline, 25 to 50 mg, twice daily; and dibenzyline, 10 mg, once or twice daily. Phentolamine can produce partially positive results, but its usage in the two individuals studied consistently caused marked nausea and vomiting within two hours of taking the medications, well known side effects of the drug. Priscoline, 50 mg, twice daily, produced only questionable benefit at best (score = 1), as did dibenzyline. This was also true for the alpha-2 blocker yohimbine, 30 mg,

once daily. Moreover, these agents, when administered alone, all tended to cause reactive tachycardia, nasal stuffiness, and, at times, other evidence of central nervous stimulation of sympathetic outflow, including hypertension.

By contrast, given alone, the longer acting selective alpha blocking agents doxazosin (2-8 mg daily) or terazosin (5-20 mg daily) produced fewer or no side effects and no impairment or, at times, possible slight enhancement of sexual function.

Example 2: Administration of Beta-blocker having vasodilating activity.

Certain beta-blockers also have vasodilating activity, resulting from alpha-1 blockade, from beta-2 agonism arising from a degree of calcium entry antagonism or from non-specific vasodilation. These drugs were tested when administered alone. Acebutolol, 200 to 600 mg, was administered once daily; labetolol, up to 400 mg, was administered three times daily; celiprolol, 200 mg, was administered once or twice daily; and carvedilol, 25 mg, administered once or twice daily, were tested.

All four agents, when administered alone, gave a weakly positive benefit to sexual performance. (score = 1 or 2) These responses are different than the negative effects observed with beta blockers that do not possess vasodilator activity.

Example 3: Administration of Doxazosin, Terazosin, or Dibenzyline in Combination with the Vasodilatory Beta Blockers Labetalol, Celiprolol, and Carvedilol.

The vasodilatory beta-blockers acebutolol, labetalol, celiprolol, and carvedilol, were retested in combination with either selective alpha-1 or non-selective alpha-1 and alpha-2 blockade, produced by administration of doxazosin, 2-8 mg, or terazosin, 10-20 mg, or dibenzyline, 10 mg, once or twice daily. As demonstrated by Example 1, these alpha blockers given alone produce little or no beneficial effects on potency and dibenzyline can impair ejaculation. The lack of benefit may be related to side effects, usually minor in degree, that involve postural hypotension and tachycardia from reactive activation of the beta adrenergic system. Dibenzyline is normally used in much larger dosages to control the blood pressure of a pheochromocytoma (adrenaline or noradrenaline secreting tumors) and to promote urine flow in benign prostatic hypertrophy, usually in dosages of 10 to 40 mg daily. In the present study, the drug caused no untoward side effects and no impairment of vigor or exercise capacity at the dosages used.

Priscoline, 25 or 50 mg, administered once or twice daily, was also effective, although slightly less so than the dibenzyline. Prazosin (2 to 6 mg once daily) was not effective.

By contrast, daily administration of either doxazosin or terazosin with either acebutolol or celipolol

produced marked to complete restoration of sexual performance, maintained for as long as the combined treatment is given.

Example 4: Administration of Doxazosin or Dibenzyline in Combination with Beta Blockers propranolol, metoprolol, atenolol, and pindolol.

The older typical beta blockers, propranolol, metoprolol, atenolol, and pindolol (which lack vasodilator activity), were combined with either dibenzyline, doxazosin or terazosin and tested for their effect on impotence. These compounds do not have vasodilator activity.

These combinations produced either no benefit or worsening of impotence, reemphasizing that only beta blockers which also have intrinsic vasodilator activity (attributable to alpha-1 blockade, beta-2 agonism, calcium channel blockade, or non-specific vasodilation) can work in combination with the non-selective alpha-1 and alpha-2 blockade to enable or enhance sexual responsiveness.

Modifications and variations of the present invention, a method and compositions for treating impotence, will be obvious to those skilled in the art from the foregoing detailed description, and are intended to come within the scope of the appended claims.

I claim:

1. A method for treating impotence in patients comprising the administration to a patient suffering from impotence of an effective amount of a blocking agent selected from the group consisting of long-acting and selective alpha-1 blocking agents and non-selective alpha-1 and alpha-2 adrenergic blocking agents given in combination with a beta-adrenergic blocking agent having intrinsic sympathomimetic vasodilating activity.

2. The method of claim 1 wherein a long-acting and selective alpha-1 blocking agent selected from the group consisting doxazosin and terazosin is administered in combination with a beta blocker selected from the group consisting of acebutolol and celiprolol.

3. The method of claim 1 wherein the agents are co-administered orally at least once a day to the patient.

4. The method of claim 2 wherein the alpha blocker is doxazosin administered in an amount of between 2 and 8 mg per day, or terazosin administered in an amount of between 5 and 20 mg per day.

5. The method of claim 1 wherein the alpha adrenergic blocking agents is selected from the group consisting of dibenzyline, priscoline, tolazoline and phentolamine.

6. The method of claim 5 wherein the alpha blocker is dibenzyline administered in an amount between 10 and 20 mg per day, phentolamine administered in an amount between 50 and 100 mg per day, tolazoline administered in an amount between 25 and 100 mg per day.

7. The method of claim 1 wherein the beta adrenergic blocking agent is selected from the group consisting of acebutolol, labetalol, celiprolol, and carvedilol.

8. The method of claim 7 wherein the beta adrenergic blocking agent is labetalol administered in an amount between 400 and 1200 mg per day, celiprolol administered in an amount between 200 and 400 mg per day, acebutolol administered in an amount between 200 and 600 mg per day, or carvedilol administered in an amount between 25 and 50 mg per day.

9. A composition for treating impotence in patients comprising an effective amount of a blocking agent selected from the group consisting of long-acting and selective alpha-1 blocking agents and non-selective alpha-1 and alpha-2 adrenergic blocking agents in combination with a beta-adrenergic blocking agent having intrinsic sympathomimetic vasodilating activity.

10. The composition of claim 9 wherein the agents are in combination with a pharmaceutically acceptable vehicle for oral administration to a patient.

11. The composition of claim 9 wherein the alpha adrenergic blocking agent is selected from the group consisting of doxazosin, terazosin, dibenzyline, priscoline, and phentolamine.

12. The composition of claim 9 wherein the beta adrenergic blocking agent is selected from the group consisting of labetalol, acebutolol, celiprolol, and carvedilol.

13. The composition of claim 9 comprising a long-acting and selective alpha-1 blocking agent selected from the group consisting doxazosin and terazosin in combination with a beta blocker selected from the group consisting of acebutolol and celiprolol.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09672

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 31/415; A61K 31/16
U.S. CL.: 514/401; 514/625

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	514/401, 514/625, 514/651

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US,A, 4,801,587 (VOSS et al.) 31 JANUARY See entire document	1-13
Y	Annals of Internal Medicine, issued 15 JULY 1988 GRANT GWINUP, "Oral Phentolamine in Nonspecific Exectile Insufficiency "pages 162-163, See entire document.	1-13

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IV. CERTIFICATION

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