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(54) **L'UTILISATION D'AGENTS DOPAMINERGIQUE DANS LE GESTION DE DYSFONCTIONNEMENT SEXUEL**

(54) **THE USE OF DOPAMINERGIC AGENTS IN THE MANAGEMENT OF SEXUAL DYSFUNCTION**

TITLE OF THE INVENTION

The use of dopaminergic agents in the management of sexual dysfunction.

FIELD OF THE INVENTION

The invention relates to the use of dopaminergic agents, namely pramipexol, for improving or obtaining sexual function, particularly in males.

BACKGROUND OF THE INVENTION

The effects of dopamine agonists on sexual function are known to the practitioners. In most cases, a decrease of the libido is reported when dopamine agonists are administered alone, although some mild and inconsistent enhancement of sexual function has been noted during the treatment of Parkinson's disease with agonists such as amantadine, parlodel, bromocriptine and bupropion. Paradoxically, it is also known that dopaminergic agents enhance libido when co-administered with antidepressives, which themselves decrease libido.

Amantadine, parlodel, bromocriptine and bupropion are examples of dopaminergic agents having a weak activity with severe side effects. Pramipexol (1 to 5 mg / daily dose divided in 3 doses) and ropirinol (3 to 24 mg / daily dose in 2 or 3 subdivided doses) are two promising agonists for the treatment of Parkinson's disease, these drugs having much less undesirable side effects than other dopaminergic agents.

Ropirinol is a selective D_2- agonist while pramipexol is a selective D_3- agonist with a D_2- presynaptic activity.

A rare incidence of decreased libido or impotence is reported for pramipexol and ropirinol when administered to Parkinson's patients not concomitantly treated with levodopa. To the inventors' surprise, patients treated with pramipexol has noticed, on the contrary, an increase of the libido and penile rigidity (that should not be confused with priapism which is an undesirable, uncontrollable and painful penile

rigidity). It was further observed that penile rigidity can be enhanced by the *ad hoc* administration of seldanofil which further improved capacity for full and sustained penetration during sexual intercourse.

STATEMENT OF THE INVENTION

These observations open a new avenue for potential uses of pramipexol and pharmacologically equivalent drugs, namely ropirinol, alone or in combination with vasodilating drugs maintaining a high nitric oxide level, such as sildenofil.

It is worthwhile noting that about 35% of the patients do not respond to sildenofil. Those patients may respond to a combination of sildenofil and pramipexol.

DESCRIPTION OF THE INVENTION

Without being bound to any theory, the inventors have made a comprehensive review of the mechanisms involved in sexual function and tried to draw a *rationale* for the effect of pramipexol on sexual function.

For practical reasons, the discussion is directed to male sexual function. Measurable parameters and visual observations can be more objectively obtained in male subjects for obvious reasons. It is however not excluded that women may benefit from the present invention.

PHYSIOLOGICAL AND PHARMACOLOGICAL BACKGROUND OF THE MALE SEXUAL REFLEXES

There are 4 principal male sexual reflexes: libido, erection, ejaculation and orgasm. The anatomical substrate, the neural pathways and the neurochemical transmitter profile for each of these reflexes are understood to a variable degree.

The libido, or sexual drive is primarily determined by male hormones via their action on central nervous system structures in the hypothalamus and limbic system.

The erection reflex has a segmental and suprasegmental component. The segmental or spinal reflex is influenced by both sympathetic and parasympathetic nerves. The sympathetic nerves originate from the T11-L2 cord levels and reach the target tissues via the hypogastric nerves, pelvic plexus, cavernous nerves and pudendal nerves as postganglionic fibers. The parasympathetic innervation originates from the S2-4 spinal segments and reach the target tissue as nervi erigentes and the pelvic plexus mixed with sympathetic nerves. Descending suprasegmental tracts both facilitate and inhibit the erection reflex. These pathways originate in the hypothalamus and limbic system, the hypothalamic medial preoptic area being the principal integrating center. The tracts descend through the median forebrain bundle, ventrolateral pons and medulla and the lateral columns of the spinal cord. The neurochemical transmitters for the sympathetic nerves is norepinephrine while acetylcholine is for the parasympathetic nerves. **The facilitatory central pathways are dopaminergic**. The erection reflex is facilitated at the segmental level by parasympathetic fibers and inhibited by sympathic nerves.

The erection reflex can be initiated by mechanical stimulation of the peripheral erogenic zones which sets up a primary spinal reflex or by psychogenic stimuli which, through the central facilitatory pathways, sets up a secondary spinal reflex. Synergistic action of both systems are the most efficient. The facilitatory neural impulses for the erection reflex causes massive vasodilation of the penile arteries, maximum filling of the expandable caverns of the corpora vavernosa, and passive compression of the effluent veins. As a result, a marked increase of the penile tumescence occurs. The marked penile arterial vasodilation, which is the ultimate final effector mechanism bringing about erection, is predicated upon relaxation of the arterial smooth muscle. This, in turn, is activated by the rapid synthesis of NO and possibly other vasoactive peptides. NO synthesis is facilitated by cyclic GMP which is degraded by a specific phosphodiasterase. Therefore, the erection reflex can be stimulated by inhibiting this enzyme which would maintain a high NO level. Sildenofil (Viagra) is such a compound.

In summary on the basis of the above facts, the erection reflex can be stimulated at the level of penile smooth muscle (dilation), or stimulation of the parasympathic

nerves and/or inhibiting the sympathetic nerves, or by stimulating the central dopaminergic system or perhaps a judicial combination of more than one factors.

The neural pathways that mediate the ejaculation reflex is similar to those of the erection reflex but the trigger signal is mainly a sympathomimetic one. This indicates the fine tuning of the plasticity and the dynamic equilibrium that must operate to ensure effective sexual function. The ejaculation reflex activates smooth muscles in the seminal vesicles and prostate and mediated by fibers in the pudendal nerve. This action expels the semen and usually is associated with orgasm. While the ejaculation reflex usually occurs while the erection is still in full force, ejaculation and orgasm may still occur without significant erection.

Orgasm is a complex sensory experience mainly localized to the erogenic zones and require the integrity of somatic sensory afferent fibers in the pudendal nerve. Orgasm is also associated with complex autonomic phenomena (breathing, pulse, blood pressure, etc.) and psychological experience all of which require the integrity of still undefined peripheral and central neural pathways.

RATIONALE FOR USING DOPAMINERGIC AGENTS FOR IMPROVING MALE SEXUAL FUNCTIONS

From the foregoing discussions it becomes clear that abnormal or defective sexual reflexes may arise from pathological alterations of the nerves and neuronal centers that mediate and control these reflexes. Abnormalities of the relevant sympathetic or parasympathetic or somatosensory afferent nerves at the periphery can be involved in a great variety of diseases such as peripheral neuropathies (i.e. diabetes) or myelopathies (i.e. trauma, multiple sclerosis, etc.). Another common cause of erectile disfunction is vascular insufficiency with impaired blood flow to the penile arteries or defective smooth muscle dilatation in response to the parasympathetic nerve signal. These peripheral causes of erectile dysfunction can be treated by vasodilatory agents or drugs that increase NO level of arterial smooth muscles (i.e. Sildanofil). However in a substantial number of cases impaired sexual reflexes and erectile dysfunction can be caused mainly by a defect in the facilitatory central

pathways for the segmental reflexes. **These pathways are dopaminergic**. Hypoactive suprasegmental facilitation of the sexual reflexes may occur in psychiatric diseases (i.e. depression) or simply because of anxiety and stress or due to undetermined causes. The administration of vasodilatory treatment modalities for such cases will only be partially useful. However, **dopaminergic drugs can be expected to restore the facilitation of the various sexual reflexes, particularly those subserving erection**. Such an approach may also be effective to supplement peripheral vasodilatory treatment when the main dysfunction is peripheral. Some mild and inconsistent enhancement of sexual function has, indeed, been noted during the administration of dopamine agonists such as amantadine, parlodel, bromocriptine and bupropion. However these were relatively weak dopaminergic agents with severe side effects. With the advent of pramipexol, the situation has dramatically changed.

PRELIMINARY CLINICAL OBSERVATIONS

In 1997, pramipexol hydrochloride or PH (Mirapex) has been introduced into the treatment of Parkinson's disease either to boost the action of levodopa or as a first-line medication. As noted later PH is a potent ligand for all classes of striatal dopamine receptors and produces strong dopaminergic stimulation without significant major side effects. This has been a big improvement over previously available direct dopaminergic agents. In our practice we have encountered 5 idiopathic Parkinson's patients in stages 1-2 of the disease, who were taking therapeutic doses (about 1 mg tid) of Mirapex. These patients noted marked improvement of their bradycardia and rigidity of limbs, but in addition they noted 2 additional features that could not by any means be attributed to the motor effects of Mirapex. This included a conspicuous sustained increase of the caliber and length of the penile shaft as well as a sustained increase of tumescence. However, this did not reach the state of priapism and there was no penile discomfort at all. In addition, the 5 male patients observed that upon normal natural stimulation of the penis during sexual encounters, a much firmer and more sustained erection could be attained and there was a facilitation of the ejaculation and the intensity of orgasm. In 2 patients, the additional use of Viagra further improved these functions and there were no

harmful interactions between PH and Viagra. From these observations and from the above discussed central neurotransmitter pharmacology, there is a real potential of using PH to correct or improve erectile dysfunction not only in patients with central and/or peripheral erectile dysfunction, but also in patients who suffer penile atrophy (affecting the corpora cavernosa) after prostatectomy.

DESCRIPTION OF SALIENT FEATURES OF PRAMIPEXOL HYDROCHLORIDE

Pramipexol is an agonist of all classes of central and peripheral dopamine receptors. It is excreted in the urine. The drug is indicated to treat early and late Parkinson's disease alone or in combination with Levodopa. The average daily dose of 1 mg tid po must be built up gradually over a period of weeks. Side effects, usually with full dose, include orthostatic hypotension, hallucination, dyskinesisas, headache, constipation and somnolence. Side effects are mild and rare. Serious drug interaction may occur with agents that tend to cause hypotension. Therefore, its combined use with Sildanofil hydrochloride should be envisaged cautiously.

OBJECTS OF THE PRESENT INVENTION

Based on the above observations, the present invention provide a therapeutic usefulness of pramipexol for male sexual dysfunction in the following situations:

a) A single-time use for obtaining or improving erection otherwise not possible, without or with Sildanofil, in patients with central or peripheral neurogenic erectile dysfunction;

b) A chronic use of a dose for the purpose of obtaining or improving erection; and

c) A chronic use to prevent or minimize penile atrophy after prostatectomy.

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