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DYKSTRA D D ET AL: "TREATMENT OF DETRUSOR-SPHINCTER DYSSYNERGIA WITH BOTULINUM A TOXIN:A DOUBLE-BLIND STUDY" ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION, PHILADELPHIA, PA, US, vol. 71, January 1990 (1990-01), pages 24-26, XP002913911
CARLO ALBERTO MAGGI ET AL: "CYSTOMETRIC EVIDENCE THAT CAPSAICIN-SENSITIVE NERVES MODULATE THE AFFERENT BRANCH OF MICTURITION REFLEX IN HUMANS" JOURNAL OF UROLOGY, BALTIMORE, MD, US, vol. 142, July 1989 (1989-07), pages 150-154, XP002913910 ISSN: 0022-5347

Description

FIELD OF THE INVENTION

[0001] The present invention provides a botulinum toxin for use in a method of treating a urological dysfunction which is an urge type dysfunction in a patient. This is accomplished by administering the botulinum toxin to a lateral bladder wall by injection.

BACKGROUND OF THE INVENTION

[0002] Many medical conditions in urology are rooted in a spastic dysfunction of the sacral reflex arcs. Examples of such conditions include pelvic pain (e.g., interstitial cystitis, endometriosis, prostatodynia, urethral instability syndromes), pelvic myofascial elements (e.g., levator sphincter, dysmenorrhea, anal fistula, hemorrhoid), urinary incontinence (e.g., unstable bladder, unstable sphincter), prostate disorders (e.g., BPH, prostatitis, prostate cancer), recurrent infection (secondary to sphincter spasticity), and urinary retention (secondary to spastic sphincter, hypertrophied bladder neck) and neurogenic bladder dysfunction (e.g., Parkinson's Disease, spinal cord injury, stroke, multiple sclerosis, spasm reflex).

[0003] The prostate is a partially glandular and partially fibromuscular gland of the male reproductive system. During aging, the prostate tends to enlarge (hypertrophy). This prostatic enlargement can lead to urethral obstruction and voiding dysfunction.

[0004] Prostatic enlargement is a common occurrence in older men. Lytton et al. (Lytton, B., Emery, J.M. and Harvard, B.M. [1973] 99: 639-645) estimated that a 45 year old male had a 10% risk of prostate surgery by age 70. The U.S. Census Report estimates that there are 30 million people today over age 65. This segment of the population is projected to rise to 50 million over the next 30 years. Therefore, the number of men with prostatic enlargement also will increase. According to draft reports of the National Kidney and Urologic Disease Advisory Board, 425,000 prostatectomies were performed in the United States in 1989.

[0005] Based on population growth estimates, the number of prostatectomies performed annually will rise to 800,000/year by the year 2020.

[0006] The urethra passes through the prostate (prostatic urethra) as it courses to the external urethral orifice. The prostate has five distinct lobes that are apparent at 12 weeks in the human fetus (Lowsley, O.S. Am. J. Anat. [1912] 13: 299-349.). Although the lobular branching found in the fetus is not visible in the prepubescent prostate, the lateral middle anterior and posterior lobes are used to describe the enlarged prostate.

[0007] A more recent viewpoint is that the prostate also is comprised of several

morphologically distinct zones (McNeal, J. Urol. Clin. North Am. [1990] 17(3): 477-486). The majority of the glandular volume is composed of the peripheral zone (-70-75%). The remainder of glandular volume is divided into the central zone (~20-25%), the transition zone(~5-10%) and the periurethral glandular zone (- 1%).

[0008] McNeal (1990) reported that BPH develops in the transition zone and the periurethral glandular zone. BPH nodules develop either within or immediately adjacent to the preprostatic sphincteric zone. The transition zone is a small region close to the urethra intimately related to the proximal urethral sphincter. The stroma of the transition zone is dense and compact, and is unusually susceptible to neurologically-induced disturbances of growth control. Its glands penetrate the sphincter, while sphincter muscle fibers penetrate the transition stroma. The periurethral glandular zone has a similar urogenic sinus origin as the transition zone.

[0009] BPH may be associated with increased amounts of stroma relative to epithelium (Bartsch, G., Muller, H. R., Oberholzer, M., Rohr, H., P., J. Urol. [1979] 122: 487-491).

[0010] A significant portion of the stroma is smooth muscle (McNeal, 1990) which is under sympathetic nervous control. The contractile properties of this smooth muscle could account for the dynamic component of obstruction in BPH (Bruschini, H. et al. [1978] Invest. Urol. 15(4): 288-90; Lepor, H. [1990] Urol. Clin. North Am. 17(3): 651-658).

[0011] In addition to sympathetic control of prostatic stroma, the prostate is highly innervated. The prostate nerve fibers enter the prostate from the posterior lateral aspect, with a concentration of ganglia near the junction between the prostate and the seminal vesicles (Maggi, C.A., ed. [1993] Nervous Control of the Urogenital System, Harwood Academic Publishers; Higgins, J.R.A. and Gosling, J.A. [1989] Prostate SuppL 2: 5-16).

[0012] Acetylcholine (ACH), neuropeptide Y (NPY), vasoactive intestinal peptide (VIP) and noradrenaline fibers have been described in this gland. A rich plexus of ACH-positive nerve cell bodies is associated with secretory acini in all parts of the gland. Some of the ACH fibers also contain NPY neurons. VIP-containing neurons have been found associated with ACH-containing nerve cell bodies. Occasional neurons have been found between the ACH-staining nerve fibers, suggesting that both NPY and noradrenergic neurons supply smooth muscle (Higgins, J.R.A. and Gosling, J.A. [1989] Prostate Suppl. 2: 5-16).

[0013] Autonomic nerves are distributed evenly between the central and peripheral zones of the prostate (Higgins, J.R.A. and Gosling, J.A. [1989] Prostate Suppl. 2: 5-16). Peripheral neuronal control is similar. In addition, there is no difference in the type of nerve fibers found associated with either epithelial or stromal elements of the gland.

[0014] The anatomical studies of nerve fiber types in the prostate, coupled with other studies of innervation of prostatic stroma (Brushing H., Schmidt,R.A, Tanagho, E.A., [1978] Invest. Urol. 15(4): 288-290; Watanabe, H., Shima, M., Kojima, M., Ohe, H.L. [1989] Pharmacol. Res. 21(Suppl 2): 85-94) suggest that cholinergic innervation

influences epithelial behavior, while adrenergic innervation influences stromal tonus (excitability).

[0015] These observations have provided a rationale for the use of, for example, alpha blockers in the treatment of BPH. The effects of alpha blockers (Downie, J.W. and Bialik, G.J. [1988] J. Pharmacol. Exp. Ther. 246(1): 352-358) can also account for improvements in symptoms of BPH as a result of dampening of dysfunctional striated sphincter behavior by the alpha blockers.

[0016] Studies have also shown that there are several tachykinins (for example, substance P [SP], calcitonin gene related peptide [CGRP], neurokinin A, bradykinin, and nerve growth factor [NGF]) that can influence the tonus of smooth muscle (Hakanson, etal., [1987] Neuroscience 21(3): 943-950). Neurotransmitter receptors have been quantified throughout the prostate (e.g., NPY, VIP, SP, leu-enkephalin (L-enk), metenkephalin, 5-HT, somatostatin, acetylcholinesterase positive fibers (ACTH), and dopamine beta-hydroxylase (DBH) (Crowe, R., Chapple, C.R., Burnstock, G. The Human Prostate Gland: A Histochemical and Immunohistochemical Study of Neuropeptides, Serotonins, Dopamine beta-Hydroxylase and Acetylcholinesterase in Autonomic Nerves and Ganglia). There is some variation in receptor density at different prostatic sites in benign prostatic hyperplasia. changes in electrophysiologically recorded cellular behavior and in concentration of neuropeptides within the spinal cord have been shown to be a secondary consequence of mechanical pinch to the tail muscles of a rat, catheter stimulation of the posterior urethra, and electrostimulation of a peripheral nerve. Dyssynergia between the detrusor and the urethral sphincter is a significant finding in prostatodynia patients. Denervation of the prostate has been shown to produce dramatic changes within the prostatic epithelium. Thus there is evidence that experimentally induced alterations in neurological influences can be produced in the sacral, spinal cord, bladder or urethra through mechano-, electro-, chemical or thermal (microwave, laser) methods to change irritative behavior. However, there have been no known attempts to use neurotoxins for therapeutic applications.

[0017] There is poor correlation between the degree of prostatic enlargement and the severity of symptoms. While 80% of men age 70 show BPH on transrectal ultrasound scans, only 20% seek surgery (Coffey, D.S. and Walsh, P.C. [1990] Urol. Clin. North Am. 17(3): 461-475), the treatment of choice for BPH (Fowler, F.J. Jr., Wennberg, J.E., Timothy, R.P.

[0018] [1988] J. Amer. Med. Assoc., 259(20): 3022-3028). Symptoms of irritation may far exceed symptoms expected based on the size of the prostate. Symptoms may improve after surgical treatment of BPH by procedures such as transurethral resection of the prostate (TURP) (Christensen, Aagaard, M.M. J., Madsen, P.O. [1990] Urol. Clin. North Am. 17(3): 621629), balloon dilation (Dowd, J.B. and Smith, J.J. III [1990] UroL Clin. North Am. 17(3): 671-677), or prostatic hyperthermia (Baert, L., Ameye, F., Willemen, P., et al.,[1990] J. Uro1.144:1383-1386). However, symptoms persist in as many as 15% of all BPH patients (Baert, L., Ameye, F., Willemen, P., et al., [1990] J. Urol. 144: 1383-1386; Wennberg, J.E., Mullly, A.G., Hanley, D., Timothy, R.P., Fowler, F. J., Roos, RP.,Barmy, M.J. et al., [1988] J. Amer. Med. Assoc. 259: 3027-3030). Up to 25% of BPH patients have secondary procedures in long term follow-up studies,

suggesting that surgical approaches do not address the fundamental mechanisms that produce BPH, i.e., the faulty neurological influence (control mechanism) on the integrity of the lower urinary tract.

[0019] The need for repeated surgeries, the morbidity and mortality associated with TURP and the cost of surgery have led to the development of some non-surgical approaches such as androgen ablation (McConnell, J.D., [1990] Urol. Clin. North Am. 17(3): 661-670) and the use of alpha blockers discussed above, but few medical or surgical treatments to date have produced a restoration of void behavior to normal state (flow rate of about 25cc/sec and void volume of about 400cc).

[0020] The present invention uses botulinum toxin to treat a urological dysfunction which is an urge type dysfunction, as recited in the appended claims.

OBJECTS AND SUMMARY OF THE PRESENT INVENTION

[0021] It is an object of the instant invention to provide safe, inexpensive, out patient methods for the prevention and treatment of a urological dysfunction which is an urge type dysfunction.

[0022] It is a further object of the present invention to provide compositions for this therapeutic goal. It is a still further object of the present invention to provide dosages and methods of administration for compositions useful for such use.

[0023] Other objects of the present invention will be readily apparent to those of ordinary skill in the art.

[0024] The present invention provides a botulinum neurotoxin for use in a method of treating a urological dysfunction which is an urge type dysfunction in a patient.

[0025] It is preferred that the botulinum toxin inhibits synaptic function. Such inhibition produces selective denervation, and, for example, atrophy of the prostate and reversal of irritative symptoms associated with prostatic enlargement. In one embodiment of the instant invention, the botulinum neurotoxin induces dysfunction of the presynaptic neuronal terminal by specific binding and blockade of acetylcholine release at myoneural junctions. Such a botulinum neurotoxin can be, for example, botulinum toxin type A (Botox, Allergen).

[0026] Preferably, the botulinum neurotoxin is safe, highly selective and easy to deliver, including when combined with other therapies. Delivery of the botulinum neurotoxin is by injection to the lateral bladder wall.

[0027] A therapeutically effective amount of the botulinum neurotoxin is the dosage sufficient to inhibit neuronal activity for at least one week, more preferably one month, most preferably for approximately 6 to 8 months or longer. Dosing can be single dosage or cumulative (serial dosing), and can be readily determined by one skilled in the art.

Neurotoxin can be delivered serially (i.e., one time per month, one time per every six months) so that the therapeutic effect can be optimized. Such a dosage schedule is readily determined by one skilled in the art based on, e.g., patient size and the condition to be treated, and will depend on many factors, including the neurotoxin selected, the condition to be treated, the degree of irritation, and other variables.

[0028] The aforementioned methods of treatment should be particularly useful for the long term control of urge type disfunction, without the need for surgical intervention. Furthermore, the instant invention provides for control of a urological disorder which is an urge type dysfunction in a highly selective manner, without the potential side effects and treatment failures associated with current treatment modalities.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0029] Without being bound by theory, the basis for the treatment of a urological dysfunction which is an urge type dysfunction is the removal or modulation of the neural basis for the dysfunctional regulation of the affected tissue. It is preferred that the neurotoxin cause long-lasting inhibition of synaptic function, preferably greater than one week, more preferably greater than one month, most preferably six to eight months or longer. Botulinum toxin is the neurotoxin according to the instant invention, botulinum toxin A is preferred and Botox (Allergen) is more preferred.

[0030] The toxin can be formulated in any pharmaceutically acceptable formulation in any pharmaceutically acceptable form. Such forms and formulations include liquids, emulsions, suspensions, solutions, and the like. The toxin can also be used in any pharmaceutically acceptable form supplied by any manufacturer.

[0031] In a preferred embodiment in accordance with the method of the instant invention, the botulinum neurotoxin is botulinum toxin type A. Therapeutically effective amounts of botulinum toxin can be any amounts or doses that are less than a toxic dose, for example, less than about 3000 IU/70 kg male, preferably between 100 IU/70 kg male to 1200 IU/70 kg. The dosages can be given as a single dose, or as divided doses, for example, divided over the course of four weeks.

[0032] The botulinum neurotoxins for use in the instant invention are administered by injection. Such injection is administered to the lateral bladder wall.

[0033] Preferably, the neurotoxin is injected every three days until a therapeutic effect is achieved or up to about 2500 units.

[0034] The following examples are provided by way of describing specific embodiments without intending to limit the scope of the invention in any way.

Example 1

Effect of Neurotoxin Injection on Urological Dysfunctions: Human Data

[0035] Patient 1 was a 55 year old T12 paraparetic female secondary to traumatic injury 14 years previous. The patient presented with urge incontinence, and had been on self catheterization every 2 hours during the day and two times at night. The patient received injections into the lateral bladder wall in two weekly injections of 200 IU each for a total of 4001U of botulinum toxin. The patient's voiding diary data revealed pre-injection capacities of between 150-200 cc. Post injection, diary data indicated bladder capacity increased to 300-400 cc. In addition, the patient no longer had annoying constant urge type dysfunction, slept through the night and was continent on self-catheterization every 4 hours.

Anvendelse af botulinum-toksinterapi til behandling af dysfunktion af urge-typen

Patentkrav

1. Botulinum-neurotoksin til anvendelse i en fremgangsmåde til behandling af en urologisk dysfunktion, der er en dysfunktion af urge-typen, hos en patient, hvor botulinum-neurotoksinet administreres til en lateral væg af blæren ved injektion.

2. Botulinum-neurotoksin til anvendelse ifølge krav 1, hvor botulinum-toksinet er botulinum-toksin type A.

3. Botulinum-neurotoksin til anvendelse ifølge krav 2, hvor botulinum-toksinet type A er 400 IU af botulinum-toksin type A.

4. Farmaceutisk acceptabel formulering omfattende botulinum-toksin til anvendelse i en fremgangsmåde til behandling af en urologisk dysfunktion, der er en dysfunktion af urge-typen, hos en patient, hvor formuleringen administreres til en lateral væg af blæren ved injektion.