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PHARMACOLOGIC OPTIONS FOR THE OVERACTIVE BLADDER

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ABSTRACT

Objectives. To review the current pharmacologic options for treatment of the overactive bladder and to describe potential therapies on the horizon.

Methods. The literature on the clinical efficacy and safety of the currently available agents is described.

Results. According to the guidelines issued by the Agency for Health Care Policy and Research (AHCPR), anticholinergic agents should be the first-line pharmacologic therapy for patients with detrusor instability. Oxybutynin is the anticholinergic of choice for this indication, whereas propantheline is the second-line therapy. Although calcium antagonists have been investigated, the one such drug introduced for the treatment of overactive bladder (terodiline) was withdrawn from the market because of a risk of cardiac arrhythmia. Studies of potassium channel openers have found either a lack of clinical efficacy or an unacceptable level of side effects. Alpha-adrenergic antagonists may be useful for decreasing bladder overactivity in patients who have autonomous bladders as the result of conditions such as spinal cord injury. Tricyclic antidepressants (particularly imipramine) may be effective in decreasing bladder contractility, although the AHCPR guidelines caution that these drugs should be reserved for use in carefully evaluated patients. Future developments in the treatment of detrusor overactivity are likely to occur in 3 categories: drugs that affect peripheral excitatory mechanisms, drugs that inhibit afferent mechanisms, and drugs that affect more central actions at either the ganglionic, spinal cord, or supraspinal level.

Conclusions. Although pharmacologic management of the overactive bladder has progressed little in the past 10 years, the future may hold the promise of more effective therapies.

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Despite disagreements regarding the details of neurophysiology, neuropharmacology, and neuromorphology, all observers would agree that bladder filling and urine storage require the following: 1) accommodation of increasing volumes of urine at a low intravesical pressure and with appropriate sensation; 2) a bladder outlet that is closed at rest and remains so during increases in intra-abdominal pressure; and 3) an absence of involuntary bladder contractions.[1] All types of therapy for urine storage disorders, whether neuropathic or nonneuropathic in etiology, can be classified within a functional scheme derived from this simple concept. Therapy to improve urine storage may be directed toward inhibiting bladder contractility, decreasing sensory (afferent) input, or increasing bladder capacity.

ANTICHOLINERGIC AGENTS

Most of the neurohumoral stimulus for bladder contraction consists of acetylcholine-induced stimulation of postganglionic parasympathetic cholinergic receptors on bladder smooth muscle. Atropine and atropine-like anticholinergic agents inhibit the binding of acetylcholine to the cholinergic receptor, thereby suppressing involuntary bladder contractions of any etiology.[2,3] These drugs increase the volume of the first involuntary bladder contraction, decrease the amplitude of the involuntary bladder contraction, and may increase total bladder capacity.[4,5] However, involuntary contractions are not entirely inhibited. In several animal models, atropine only partially antagonizes the response of the whole bladder to pelvic nerve stimulation and the response of bladder muscle strips to field stimulation. This so-called atropine

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resistance may be caused by the release of a noncholinergic excitatory neurotransmitter.[3] The existence of atropine resistance in normal human bladder muscle has not been confirmed and may exist only in abnormal states. This hypothesis may explain why it is difficult to abolish involuntary bladder contractions with anticholinergic therapy alone. Anticholinergic agents do not increase the warning time (the time between the perception that an involuntary contraction is about to occur and its actual occurrence). Therefore, urgency and incontinence will continue to occur unless such treatment is used in combination with a timed voiding or toileting regimen.

According to the 1996 practice guidelines issued by the Agency for Health Care Policy and Research (AHCPR), anticholinergic agents should be considered first-line pharmacologic therapy for patients with detrusor instability.[6] Propantheline bromide is the traditional oral agent used to produce an antimuscarinic effect in the lower urinary tract (LUT). The AHCPR guidelines state that propantheline should be the second-line anticholinergic agent for the treatment of detrusor instability in patients who can tolerate the full dosage (the first-line agent being oxybutynin, as discussed under musculotropic relaxants below). The recommended dosage of propantheline is 7.5 to 30 mg administered 3 to 5 times per day, although higher dosages (15 to 60 mg 4 times daily) may be required. There appear to be few differences between the antimuscarinic effects of propantheline on bladder smooth muscle and those of other antimuscarinic agents (for instance, glycopyrrolate, isopropamide, hyoscyamine, anisotropine, and methylbromide).

The ideal anticholinergic agent would be one that inhibits only the muscarinic receptor subtype responsible for bladder contraction. However, it has been very difficult, either experimentally or clinically, to identify a compound that would affect only bladder contractility and not the salivary secretory glands. All antimuscarinic agents have the potential to inhibit salivary secretion (causing dry mouth), block the ciliary muscle of the lens to cholinergic stimulation (causing blurred vision for nearby objects), and cause tachycardia, drowsiness, and inhibition of gut motility. Drugs that have some ganglionic blocking activity may also cause orthostatic hypotension and, at high doses, impotence.

MUSCULOTROPIC RELAXANTS

Agents classified as musculotropic relaxants or antispasmodics are all said to have an inhibitory effect on bladder smooth muscle contraction metabolically distal to the attachment of acetylcholine to the cholinergic receptor in the smooth muscle cell membrane. However, they all have an atropine-like effect, and questions remain regarding the degree to which the clinical, as opposed to the laboratory, efficacy of these drugs is attributable to this atropine-like effect. Most have some in vitro local anesthetic properties as well.

Oxybutynin is a moderately potent anticholinergic agent that has strong, independent musculotropic relaxant activity and local anesthetic activity. The 1996 AHCPR guidelines state that oxybutynin is the anticholinergic of choice when pharmacologic therapy is to be used for patients with detrusor instability.[6] The recommended oral adult dosage is 2.5 to 5 mg 3 or 4 times daily. Several studies have found this drug to be effective in the management of various types of bladder overactivity.[7–10] For example, in a randomized, double-blind, placebo-controlled trial, Moisey *et al.* found that 17 of 23 patients with detrusor instability experienced symptomatic improvement with 5 mg oxybutynin 3 times daily and 9 had evidence of urodynamic improvement (primarily an increase in maximal bladder capacity).[7] Thüroff *et al.* compared oxybutynin, propantheline, and placebo in patients with symptoms of instability and either detrusor instability or hyperreflexia.[10] Oxybutynin (5 mg 3 times daily) was most effective, although propantheline was used at a relatively low dose of 15 mg 3 times daily. The authors pointed out that their 67% rate of good or excellent results with oxybutynin compared favorably with the 61% to 86% range calculated from other studies. The potential side effects are antimuscarinic in nature and cause a considerable number of patients to discontinue this medication.

Flavoxate is another drug that has a direct inhibitory action on smooth muscle, as well as having anticholinergic and local analgesic effects.[11] However, this agent has questionable clinical efficacy and is not recommended for the treatment of detrusor instability, according to the AHCPR guidelines.[6]

CALCIUM ANTAGONISTS

The dependence of contractile activity on changes in cytosolic calcium varies from tissue to tissue, as do the characteristics of the calcium channels involved. Nonetheless, interference with the inflow or intracellular release of calcium is a mechanism by which bladder smooth muscle relaxation may be achieved.[12] An agent that combines calcium antagonistic activity with anticholinergic activity may therefore offer improved clinical efficacy. The calcium antagonist terodiline was found effective in several clinical studies conducted during the 1980s and early 1990s.[13–15]

However, this agent was withdrawn from the market following reports of the potential for cardiac arrhythmia (specifically, torsade de pointes).[16,17]

POTASSIUM CHANNEL OPENERS

Potassium channel openers relax various types of smooth muscle by increasing potassium efflux and causing membrane hyperpolarization.[18] Such agents also abolish spontaneous contractile activity in normal and hypertrophied preparations and will inhibit contractions caused by carbachol (an acetylcholine agonist) and electrical stimulation.[19] Theoretically, a potassium channel opener would have the advantage of not affecting the contractile power of a normal micturition. However, assessments of these agents have found a lack of clinical efficacy or an unacceptable level of side effects.[20,21]

ALPHA-ADRENERGIC ANTAGONISTS

Alpha-adrenergic antagonists have been used to decrease bladder overactivity with some success in patients who have so-called decentralized or autonomous bladders as the result of myelodysplasia, spinal cord injury, or radical pelvic surgery.[22]

TRICYCLIC ANTIDEPRESSANTS

The tricyclic antidepressants are a complex group of drugs that have central and peripheral anticholinergic effects, as well as sedative effects, and block the active reuptake of norepinephrine and serotonin. However, the exact mechanisms by which these drugs act in the LUT remain a matter of debate.

The 1996 AHCPR guidelines caution that tricyclic antidepressants should be reserved for use in carefully evaluated patients.[6] The guidelines state that the usual oral dosage of imipramine is 10 to 25 mg initially administered 1 to 3 times per day, but less-frequent administration is often possible because of the long half-lives of these drugs. The total daily dosage is typically 25 to 100 mg.

Imipramine, in particular, is useful for facilitating urine storage by decreasing bladder contractility and increasing outlet resistance.[23–27] In a study by Castelden *et al.*, elderly patients with detrusor instability began therapy with a single 25 mg nighttime dose of imipramine.[27] The dose was increased by 25 mg every third day until the patient either achieved continence, experienced side effects, or reached a dose of 150 mg. Of 10 patients, 6 became continent. Among those who underwent repeat cystometry, bladder capacity increased by a mean of 105 mL, bladder pressure at capacity decreased by a mean of 18 cm H_2O, and maximum urethral pressure increased by a mean of 30 cm H_2O. In our experience, imipramine and atropine-like agents often have additive effects on the LUT. Therefore, a combination of imipramine and an antimuscarinic or antispasmodic drug may be useful for decreasing bladder contractility. However, the side effects may be additive as well.

Doxepin is another tricyclic antidepressant that has been evaluated for the treatment of UI. In a randomized, double-blind, cross-over study by Lose *et al*, women with involuntary bladder contractions and either frequency, urgency, or urge UI received either a single 50 mg dose of doxepin at bedtime or this dose plus an additional 25 mg in the morning.[28] Doxepin produced a significant decrease in nighttime frequency and nighttime incontinence episodes. This treatment also resulted in a nearly statistically significant decrease in urine loss and in cystometric measurements of first sensation and maximum bladder capacity.

If a tricyclic antidepressant is prescribed for the treatment of voiding dysfunction, the patient must be informed that this is not the usual indication for the drug and that side effects may occur. At the generally larger doses used to achieve antidepressant effects, the most frequent side effects of the tricyclic antidepressants are those attributable to the systemic anticholinergic activity of these drugs.[29,30] Central nervous system (CNS) side effects and postural hypotension may also occur. Imipramine is contraindicated in patients receiving monoamine oxidase inhibitors because severe CNS toxicity may develop. In addition, these agents can produce arrhythmias and should therefore be used with caution in patients with cardiovascular disorders.[29] Side effects such as weakness, fatigue, and orthostatic hypotension may be especially marked in elderly patients.

PROSTAGLANDIN INHIBITORS AND BETA-ADRENERGIC AGONISTS

Some laboratory evidence is available to suggest that prostaglandin inhibitors or beta-adrenergic agonists should be effective in decreasing bladder contractility. However, these lines of investigation have not proved fruitful in the clinical setting.

FUTURE DEVELOPMENTS

Future developments in the treatment of detrusor overactivity are apt to occur in 3 categories. The first category consists of drugs that affect peripheral excitatory mechanisms. Such therapies could take the form of more specific receptor antagonists, drugs that affect membrane phenomena, or drugs that affect excitation contraction coupling. The second category includes drugs that inhibit afferent (sensory) mechanisms. The third category consists of drugs that affect more central

actions at either the ganglionic, spinal cord, or supraspinal level.

At the 1997 meeting of the American Urological Association, the category of agents that affect afferent mechanisms was the most commonly mentioned of the newer treatment strategies. A total of 9 abstracts were presented on capsaicin, an irritant and algogenic compound obtained from hot red peppers.[31–39] One abstract dealt with a new potassium channel opener (YM-934),[40] and one with a phosphodiesterase-1 inhibitor (vinpocetine).[41] Two abstracts described work with tolterodine, a selective muscarinic antagonist that has less of an effect on salivary gland smooth muscle than on detrusor smooth muscle.[42,43]

CONCLUSIONS

At present, anticholinergic agents remain the most common pharmacologic therapy for the overactive bladder. According to the AHCPR guidelines, oxybutynin is the anticholinergic of first choice, followed by propantheline. Alpha-adrenergic antagonists may be useful for the treatment of patients with decentralized bladders. The AHCPR advises that tricyclic antidepressants should be used only in carefully evaluated patients. Imipramine, in particular, can help decrease bladder contractility.

Although the pharmacologic management of overactive bladder has progressed little in the past 10 years, the future may hold the promise of more effective therapies. Among the promising treatments on the horizon are agents designed to affect peripheral excitatory mechanisms, inhibit afferent mechanisms, or affect more central actions at either the ganglionic, spinal cord, or supraspinal level.

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