# Urodynamics

## PRINCIPLES, PRACTICE AND APPLICATION

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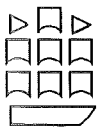

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# 4. Pharmacologic treatment of voiding dysfunction

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## INTRODUCTION

Most drugs which affect lower urinary tract function do so by initially combining with specialized functional components of cells known as receptors. The drug–receptor interaction alters the function of a cell component and initiates the series of biochemical, physiologic and urodynamic changes that we associate with the use of that agent. Many such drugs affect accepted neurotransmitter mechanisms: by affecting the synthesis, transport, storage or release of neurotransmitter, the combination of the neurotransmitter with postjunctional receptors, or the inactivation, degradation or reuptake of neurotransmitter. Other drugs affect receptor mechanisms that are not universally accepted as a part of the normal physiology of bladder filling/urine storage or lower urinary tract emptying. In any case, the complex physiologic and biochemical changes which occur after receptor activation are what are ultimately responsible for the contraction, relaxation, facilitation or inhibition which occurs. These mechanisms, 'metabolically distal' to receptor stimulation and blockade, are also potential sites of pharmacologic stimulation, inhibition or modulation. The basics of lower urinary tract pharmacology have been covered in Chapter 3. This chapter will include the relevant pharmacologic principles on which drug therapy for voiding dysfunction is based, making liberal reference to Chapter 3, and summarize current data and opinion on the efficacy of various drugs for voiding dysfunction.

Despite disagreements on some details, all 'experts' would doubtless agree that, for the purposes of description and teaching, two phases of micturition exist from a conceptual point of view and can be succinctly summarized as follows (Wein 1981, Wein et al 1991).

Bladder filling and urine storage require:

1. accommodation of increasing volumes of urine at a low intravesical pressure and with appropriate sensation
2. a bladder outlet which is closed at rest and remains so during increases in intraabdominal pressure
3. absence of involuntary bladder contractions (detrusor instability or detrusor hyperreflexia).

Lower urinary tract emptying requires:

1. a coordinated contraction by the bladder smooth musculature of adequate magnitude and duration
2. concomitant lowering of resistance at the level of the smooth sphincter (the smooth muscle of the bladder neck and proximal urethra) and of the striated sphincter (the periurethral and intramural urethral striated musculature)
3. absence of anatomic obstruction.

This very simple overview implies that any type of voiding dysfunction must result from an abnormality of one or more of the factors listed above. This description, with its implied subdivisions under each category, provides a logical framework for the discussion and classification of all types of voiding dysfunction. There are indeed some types of voiding dysfunction which represent combinations of filling/storage and emptying abnormalities. Within this scheme, however, these become readily understandable and their detection and treatment can be logically described. All aspects of urodynamic, radiologic and videourodynamic evaluation can be conceptualized as to exactly what they evaluate in terms of either bladder or outlet activity during filling/storage or emptying within this scheme. Likewise, one can easily classify all known treatments for voiding dysfunction under the broad categories of whether they facilitate filling/storage or emptying and whether they do so by an action that is primarily on the bladder or on one or more of the components of the bladder outlet. We will use this classification (Tables 4.1 and 4.2) as the framework for discussion. As an apology to others in the field whose works have not been specifically cited, it should be noted that references have generally been chosen because of their review or informational content and are not meant to imply originality or initial publication on a particular subject.

**Table 4.1** Therapy to facilitate bladder emptying

A. Increasing intravesical pressure/bladder contractility
   1. External compression, Valsalva
   2. Promotion or initiation of reflex contractions
      a. Trigger zones or manoeuvres
      b. Bladder training, tidal drainage
   3. Pharmacologic therapy
      a. Parasympathomimetic agents
      b. Prostaglandins
      c. Blockers of inhibition
         (1) alpha-adrenergic antagonists
         (2) Opioid antagonists
   4. Electrical stimulation
      a. Directly to the bladder or spinal cord
      b. To the nerve roots
      c. Transurethral intravesical electrotherapy
   5. Reduction cystoplasty

B. Decreasing outlet resistance
   1. At a site of anatomic obstruction
      a. Prostatectomy
      b. Balloon dilatation
      c. Intraurethral stent
      d. Decrease prostate size/tone
         (1) LHRH agonists
         (2) Antiandrogens
         (3) 5-α reductase inhibitors
         (4) Alpha-adrenergic antagonists
      e. Urethral stricture repair/dilatation
   2. At the level of the smooth sphincter
      a. Pharmacologic therapy
         (1) Alpha-adrenergic antagonists
         (2) Beta-adrenergic agonists
      b. Transurethral resection or incision of the bladder neck
      c. Y–V plasty of the bladder neck
   3. At the level of the striated sphincter
      a. Pharmacologic therapy
         (1) Skeletal muscle relaxants
            (a) Benzodiazepines
            (b) Baclofen
            (c) Dantrolene
         (2) Alpha-adrenergic antagonists
      b. Surgical sphincterotomy, injection of botulinum A toxin
      c. Urethral overdilatation
      d. Urethral stent
      e. Pudendal nerve interruption
      f. Psychotherapy, biofeedback

C. Circumventing problem
   1. Intermittent catheterization
   2. Continuous catheterization
   3. Urinary diversion

**Table 4.2** Therapy to facilitate bladder filling/urine storage

A. Inhibiting bladder contracility/decreasing sensory input/increasing bladder capacity
   1. Timed bladder emptying; habit training; prompted voiding
   2. Pharmacologic therapy
      a. Anticholinergic agents
      b. Musculotropic relaxants
      c. Calcium antagonists
      d. Potassium channel openers
      e. Prostaglandin inhibitors
      f. Beta-adrenergic agonists
      g. Tricyclic antidepressants
      h. Dimethyl sulphoxide
      i. Polysynaptic inhibitors
   3. Biofeedback, bladder retraining
   4. Bladder overdistension
   5. Electrical stimulation (reflex inhibition)
   6. Acupuncture
   7. Interruption of innervation
      a. Central (subarachnoid block)
      b. Peripheral (sacral rhizotomy, selective sacral rhizotomy)
      c. Perivesical (peripheral bladder denervation)
   8. Augmentation cystoplasty

B. Increasing outlet resistance
   1. Physiotherapy, biofeedback
   2. Electrical stimulation of the pelvic floor
   3. Pharmacologic therapy
      a. Alpha-adrenergic agonists
      b. Tricyclic antidepressants
      c. Beta-adrenergic antagonists
      d. Oestrogens
   4. Vesicourethral suspension (SUI)
   5. Bladder outlet reconstruction
   6. Surgical mechanical compression
      a. Sling procedures
      b. Artificial sphincter
   7. Non-surgical mechanical compression
      a. Periurethral polytef
      b. Periurethral collagen, fat
      c. Occlusive devices

C. Circumventing problem
   1. Antidiuretic hormonelike agents
   2. Intermittent catheterization
   3. Continuous catheterization
   4. Urinary diversion
   5. External collecting devices
   6. Absorbent products

## SPECIFIC METHODS OF PHARMACOLOGICAL THERAPY

### THERAPY TO FACILITATE BLADDER EMPTYING

Absolute or relative failure to empty results from decreased bladder contractility, increased outlet resistance or both (Barrett & Wein 1991). Absolute or relative failure of adequate bladder contractility may result from temporary or permanent alteration in any one of the neuromuscular mechanisms necessary for initiating and maintaining a normal detrusor contraction. Inhibition of the micturition reflex may also occur in a neurologically normal individual secondary to painful stimuli, especially from the pelvic and perineal areas, or may be psychogenic. Drug therapy may also inhibit

bladder contractility, through either neurologic or myogenic mechanisms. Non-neurogenic causes, including intrinsic impairment of bladder smooth muscle function, may result from overdistension, severe infection or fibrosis. Increased outlet resistance is generally secondary to anatomic obstruction, but may be secondary to a failure of coordination of the smooth or striated sphincter during bladder contraction. Treatment for failure to empty generally consists of attempts to increase intravesical pressure or facilitate the micturition reflex, decrease outlet resistance or both.

### Increasing intravesical pressure

*Parasympathomimetic agents*

Since at least a major portion of the final common pathway in physiologic bladder contraction is stimulation of parasympathetic postganglionic muscarinic cholinergic receptor sites (see Chapter 3, Wein et al 1991), agents that imitate the actions of acetylcholine (ACh) might be expected to be useful to treat patients who cannot empty because of inadequate bladder contractility. ACh itself cannot be used for therapeutic purposes because of actions at central and ganglionic levels and because of its rapid hydrolysis by acetylcholinesterase and by butyrylcholinesterase (Taylor 1990). Many acetylcholine-like drugs exist. Bethanechol chloride (BC) exhibits a relatively selective action on the urinary bladder and gut with little or no nicotinic action (Taylor 1990). It is cholinesterase-resistant and causes an in vitro contraction of smooth muscle from all areas of the bladder (Raezer et al 1973, Barrett & Wein 1991). Agents similar to BC have long been recommended (Starr & Ferguson 1940) for the treatment of postoperative or postpartum urinary retention. In this instance, BC should be used only if the patient is awake and alert and if there is no outlet obstruction. The dose is 5–10 mg subcutaneously. For over 30 years BC has been used in the treatment of the atonic or hypotonic bladder (Lee 1949) and has been reported as effective in achieving 'rehabilitation' of the chronically atonic or hypotonic detrusor (Sonda et al 1979). Bethanechol has also been used to stimulate or facilitate the development of reflex bladder contractions in patients with suprasacral spinal cord injury (Perkash 1975).

Although BC has been reported to increase gastrointestinal motility and has been used in the treatment of gastrooesophageal reflux, and although anecdotal success in specific patients with voiding dysfunction seems to occur, attempts to facilitate bladder emptying in series of patients where BC was the only variable have been disappointing (Finkbeiner 1985). A pharmacologically active subcutaneous dose (5 mg) did not demonstrate significant changes in flow parameters or residual urine volume in a group of women with a residual urine volume equal to or greater than 20% of bladder capacity, but no evidence of neurologic disease or outlet obstruction in a group of 27 'normal' women of approximately the same age or in a group of patients with a positive bethanechol supersensitivity test (Wein et al 1980). This dose did increase intravesical pressure at all points along the filling cystometrogram and also decreased bladder capacity threshold, findings previously described by others (Sonda et al 1979). Although BC is capable of eliciting an increase in bladder smooth muscle tension, as would be expected from in vitro studies, its ability to stimulate or facilitate a physiologiclike bladder contraction in patients with voiding dysfunction has been unimpressive (Finkbeiner 1985). Similar sentiments have been expressed by Andersson (1988) and others (see Barrett & Wein 1991).

It is difficult to find reproducible urodynamic data that support recommendations for the usage of BC in any specific category of patients. Most, if not all, 'long term' reports in such patients are neither prospective nor double blind and do not exclude the effects of other simultaneous regimens (such as treatment of urinary infection, bladder decompression or timed emptying and other types of treatment affecting the bladder or outlet), an important observation to consider when designing such drug studies. Short term studies in which the drug was the only variable have generally failed to demonstrate significant efficacy in terms of flow and residual urine volume data (Barrett 1981). Whether repeated doses of BC or any cholinergic agonist can achieve a clinical effect that a single dose cannot is speculative, as are suggestions that BC has a different mode of action or effect on atonic or decompensated bladder muscle than on normal tissue. BC, administered subcutaneously, does cause an increased awareness of a distended bladder (Downie 1984). In the laboratory, a functioning micturition reflex is an absolute requirement for the production of a sustained bladder contraction by a subcutaneous injection of drug (Downie 1984). Clinically, there is little logic for its use in patients with detrusor hyperreflexia, who already have bladder contractions, though the contractions are uncontrollable. Patients with incomplete lower motor neuron lesions seem to constitute the most reasonable group for a trial of BC (Awad 1985), although subcutaneous administration may be required. It is generally agreed that, at least in a 'denervated' bladder, an oral dose of 200 mg is required to produce the same urodynamic effects as a subcutaneous dose of 5 mg (Diokno & Lapides 1977).

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