Combination Drug Therapy Improves Compliance of the Neurogenic Bladder

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Abbreviations and Acronyms

CCS = continent catheterizable stoma without bladder augmentation

CIC = clean intermittent catheterization

DSD = detrusor sphincter dyssynergia

FUDS = fluoroscopic urodynamic studies

MCC = maximum cystometric capacity

MMC = myelomeningocele

Pdet = detrusor pressure

SCI = spinal cord injury

VUR = vesicoureteral reflux

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For other articles on a related topic see pages 1210 and 1216.

Purpose: Typical management of increased bladder storage pressures and decreased compliance related to neurogenic bladder dysfunction consists of antimuscarinic therapy with or without clean intermittent catheterization. However, these measures are often unsuccessful. In this patient group we commonly use combination therapy consisting of antimuscarinics combined with imipramine and/or an α-blocker.

Materials and Methods: A retrospective chart review was performed identifying all patients with neurogenic bladder dysfunction who were initially on no drug therapy or antimuscarinic therapy alone and were later switched to 2 or 3 drug therapy.

Results: In the group initially on no therapy and subsequently on 2 drugs (22) mean bladder pressure at capacity decreased 52% and mean compliance increased 5.0-fold. Similarly in the group starting without therapy but ending up on 3 drugs (28) bladder pressure decreased 67% and compliance increased 9.7-fold. In the group initially on an antimuscarinic agent alone (27) triple drug therapy decreased bladder pressure 60% and compliance increased 3.0-fold (all $p < 0.01$). There were also improvements in incontinence, vesicoureteral reflux, detrusor overactivity and detrusor sphincter dyssynergia.

Conclusions: In this highly selected group of patients with neurogenic bladder dysfunction and poor bladder compliance combination medical therapy with 2 or 3 drugs improved compliance, decreased bladder pressures at capacity and improved clinical outcomes. Combination therapy requires further study of the side effect profile but these results suggest that it should be considered for patients in whom antimuscarinic agents alone fail.

Key Words: adrenergic alpha-antagonists; cholinergic antagonists; imipramine; urinary bladder, neurogenic; urodynamics

NEUROGENIC bladder is a heterogeneous combination of symptoms and urodynamic findings that are the end result of neurological injury to the bladder. Patients often have incontinence, urgency, frequency and/or impaired bladder emptying. Urodynamically there is often poor compliance, neurogenic detrusor overactivity and/or detrusor sphincter dyssynergia.

The management goals of neurogenic bladder dysfunction are the same regardless of the etiology. The bladder must be emptied efficiently and if voiding is impossible the gold standard method of emptying is clean intermittent catheterization in those who are able.[1] Bladder storage pressures must be kept below 40 cm H_2O because higher pressures have been shown to

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carry a high risk of renal dysfunction and vesicoureteral reflux in children with myelodysplasia.[2]

Medical therapy to reduce detrusor overactivity in the neurogenic bladder has focused on antimuscarinic therapy for several decades. These therapies have been proven to increase bladder capacity, decrease bladder filling pressure and improve compliance.[3,4] Although antimuscarinics combined with CIC is the most commonly recommended medical therapy for the neurogenic bladder the results are sometimes unsatisfactory, and many patients continue to have poor bladder compliance and remain incontinent.[5]

Bladder receptors other than the muscarinic variety have been shown to mediate bladder contraction and relaxation. There are α and β-adrenergic receptors in the bladder neck, prostate and detrusor body, and the tricyclic antidepressant imipramine has been shown to suppress bladder overactivity by various mechanisms.[6]

In 1985 McGuire and Savastano used a spinal cord injured primate model to investigate the effects of α-adrenergic blockade plus anticholinergics on the decentralized bladder.[7] They found that the α-blocker phenoxybenzamine decreased bladder pressure with filling and increased capacity. With the addition of atropine, an anticholinergic, these effects were even more marked, indicating a synergistic effect on detrusor tone. They concluded that medical therapy can improve compliance by affecting neuromuscular processes, and that the poor compliance seen in SCI is not just the effect of collagen increase and fibrosis.

Based on these data and the demonstrated safety of these 3 therapies in this population, we commonly use a combination regimen in the treatment of the neurogenic bladder refractory to antimuscarinic therapy.[3,4,8–13] Initially all patients with neurogenic bladder with detrusor overactivity are placed on optimal dose antimuscarinics. The decision to add a second or third drug depends on the clinical scenario. In cases with milder symptoms and marginal compliance on urodynamics the second and third therapies are instituted one at a time, but in the event of dangerously high bladder filling pressures all 3 are started simultaneously. When choosing between imipramine and α-blockers it is often the disease process that guides the decision. In SCI with detrusor sphincter dyssynergia or autonomic dysreflexia we use an α-blocker since it can decrease maximum urethral closing pressure and decrease the symptoms of autonomic dysreflexia.[9] However, we prefer to add imipramine in cases of MMC since the bladder neck is often already widely open.

MATERIALS AND METHODS

A retrospective chart review was performed of all FUDS performed at the University of Michigan from February 1998 to January 2007. Patients were included in the analysis if they had a neurological diagnosis consistent with neurogenic bladder and symptomatic bladder dysfunction. Patients also had to have undergone 2 urodynamic studies, 1 at the initial consultation and the other while on multidrug therapy. Patients were excluded from analysis if they were treated with bladder surgery or botulinum toxin injections between the 2 FUDS (1) or if urodynamic information was incomplete (5). Patient information collected included age, gender, neurological disease, all subsequent urological surgeries and level of neurological function. At the initial and followup FUDS the bladder management method, medications and urinary symptoms were noted. If multiple FUDS were done on the same patient, typically annually, the studies performed after all medication adjustments were considered the followup FUDS. The treating physician listed all medications and doses actually taken by the patient regardless of what was prescribed. Patients on antimuscarinic therapy alone were not included in this study if they had normal compliance and minimal symptoms since these individuals do not require multidrug therapy.

FUDS were performed using a 7Fr triple lumen urethral catheter after urinary tract infection was excluded. One lumen was used to fill the bladder with radiopaque contrast material at a rate of 50 ml per minute, the second was used to measure bladder pressure and the third was placed in the area of the urethral sphincter to measure urethral pressure. Bladder pressure was measured throughout filling and the bladder was visualized with fluoroscopic observation. Filling was terminated if the patient demonstrated vesicoureteral reflux, experienced symptoms of bladder fullness or autonomic dysreflexia, or if typical catheterized bladder volume was reached. DSD was identified fluoroscopically and/or with an increase in urethral pressure accompanied with a detrusor contraction. Any magnitude of uninhibited detrusor contraction was considered detrusor overactivity.

Compliance was calculated with a pressure-volume curve including up to the end of the initial compliance curve (tonus filling limb) or termination of filling for reasons previously indicated. A best-fit area under the curve was calculated with isolated detrusor contractions excluded. In simplified terms compliance was calculated by dividing the filling volume by the change in Pdet over that volume (fig. 1).

The Wilcoxon matched pairs signed ranks test was used to determine the statistical significance of changes in MCC, compliance and bladder pressure at maximum capacity when comparing the initial to the followup FUDS, and McNemar's test was used for all binomial compliance data.

Based on pharmacotherapy the patients were divided into 3 groups of A—initially on no bladder medication and at followup FUDS on 2 medications (22), B—initially on no medication and at followup on 3 drug therapy (28), and C—initially only on antimuscarinic bladder medication started by the referring physician before urological consultation and at followup on 3 drug therapy (27).