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Preliminary Results on the Off-Label Use of Duloxetine for the Treatment of Stress Incontinence after Radical Prostatectomy or Cystectomy

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Abstract

Objectives: Stress urinary incontinence (SUI) is a common complaint of patients after pelvic surgery. To date, no pharmacotherapy for men is available, but duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, has been successfully introduced and tested for SUI in women. The aim of our study was to evaluate if duloxetine is safe and effective for men with stress incontinence after radical prostatectomy or cystectomy.

Methods: Twenty patients were included in our study, 15 after radical prostatectomy and 5 after radical cystectomy and orthotopic ileal neobladder reconstruction. Each patient reported at least 3 wk of SUI despite doing consequent pelvic floor exercises. After exclusion of a urinary tract infection, we administered 40 mg duloxetine twice daily for a mean of 9.4 wk (range: 1–35 wk).

Results: After duloxetine, the average daily use of incontinence pads was lowered significantly ($p < 0.001$) from 8.0 (± 6.5) to 4.2 (± 5.9). Seven patients were completely dry or used one pad daily at most. Most patients reported mild side effects such as fatigue or a dry mouth, but these symptoms vanished after a short time. Six patients, however, had severe side effects, mainly massive fatigue or insomnia, and discontinued using duloxetine.

Conclusions: Our preliminary results suggest that duloxetine is effective in men with SUI after prostatectomy or cystectomy. Further prospective studies with more patients included and a longer follow-up are recommended.

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1. Introduction

A frequently observed complication of pelvic surgery is the presence of lesions on the autonomic parasympathetic nerves or the sphincter itself. These lesions can result in urinary incontinence. Thus, after radical prostatectomy, up to 33% of all patients suffer from different degrees of incontinence [1–3]. The results vary depending on the surgery technique, the experience of the surgeon, the age of the patient, and the continence before surgery. The reported rate of incontinence after radical cystectomy and orthotopic ileal neobladder reconstruction is comparable or slightly higher [4,5]. The therapy for incontinence includes pelvic floor exercises [6], the use of incontinence devices such as pads or condom urinals, the endourethral injection of bulking agents or, finally, the implantation of an artificial sphincter [3] or a male sling [7,8]. To date, pharmacotherapy has not been available to support these therapeutic options.

Duloxetine was successfully tested for women with stress and mixed urinary incontinence [9–12] in recent months. Despite of the good results for female patients, there are no published reports about the effect of duloxetine on incontinence after radical prostatectomy or cystectomy.

In our clinic we administered duloxetine as an off-label prescription to patients who presented with urinary incontinence after radical prostatectomy or cystectomy. We now report our preliminary results.

2. Patients and methods

Between October 1998 and July 2005, 20 men (average age, 65.8 yr; range: 47–78 yr) underwent radical prostatectomy ($n = 15$) or cystoprostatectomy with orthotopic ileal neobladder reconstruction ($n = 5$) and suffered from incontinence for a period of >3 wk after the removal of the catheter. Most of the patients had surgery in our hospital by the retropubic approach; two patients were operated in an outside hospital by a perineal approach, one patient received external-beam radiotherapy before surgery (salvage prostatectomy), and one patient received external-beam radiotherapy after surgery (salvage radiotherapy).

In the context of a possible use of duloxetine, we clinically defined incontinence as the use of at least three incontinence pads per day despite vigorous pelvic floor exercises. The average number of incontinence pads used was 8.0/d (range: 3–30/d) before medication. We prescribed the same type of incontinence pads for all patients to make the data comparable.

Patients presenting with this definition of incontinence underwent a comprehensive approach to exclude urinary tract infection or urge incontinence. If a stress urinary incontinence (SUI) was substantiated, pelvic floor exercise by biofeedback was intensified. If continence status did not

improve significantly, patients were informed about the duloxetine study at the next ambulatory visit. After consent and exclusion of contraindications, patients were included in the study and informed about the off-label use of duloxetine and possible side effects. The daily number of pads was fixed and 40 mg duloxetine was administered twice a day beginning 3 wk after catheter removal in the prostatectomy group (average: 90.1 wk; range: 3–356 wk). We included cystoprostatectomy patients 10 wk after surgery at the earliest (average: 22.3 weeks; range: 10–38 wk) to avoid overlapping incontinence effects (eg, due to low filling volume of the neobladder). The dose of duloxetine was chosen according to studies about a good response to duloxetine as therapy for SUI in women [13,14]; furthermore, it can be considered as safe for the patient [15,16]. For the follow-up, the continence status was surveyed by telephone interviews.

Duloxetine was given 9.4 wk on average (range: 1–35 wk). The median time until initiation of duloxetine was 69.1 wk (range: 3–354 wk).

The statistical evaluation was performed by the paired t test and p significance test; all data are expressed as mean \pm standard deviation (SD).

3. Results

Eighteen of 20 patients with a prescription of duloxetine took the medication regularly. After duloxetine, the average daily use of incontinence pads was lowered significantly ($p < 0.001$) from 8.0 (± 6.5) to 4.2 (± 5.9). Fifteen of 18 patients (83.33%) reported an improvement of SUI after use of duloxetine and 7 of 20 patients (35%) were completely dry or used one pad per day at most for safety reasons (mean pad use in these patients before duloxetine: 3.9 ± 1.7).

Six patients reported no side effects at all; the majority reported mild side effects such as fatigue (4), dry mouth (3), nausea (1), or insomnia (1). Most of the side effects vanished at the latest within 4 wk. However, 6 of 20 patients (30%) discontinued the medication because of adverse events. Two patients did not use duloxetine at all because they were afraid of the described side effects and were therefore excluded from further follow-up.

In a subgroup of patients, we analyzed the effect of duloxetine on SUI after an extended period after surgery (at least 8 mo; average: 31.8 mo) despite pelvic floor training ($n = 9$). Again, the mean daily pad use was lowered significantly ($p = 0.007$) from 6.6 (± 4.3) to 2.4 (± 2.3).

4. Discussion

Duloxetine is a combined serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) reuptake

inhibitor [17,18]. At the presynaptic neuron in the Onuf nucleus in the sacral spinal cord, the reuptake of these two neurotransmitters is inhibited, resulting in an increased neural input to the urethral sphincter [10]. As a consequence, the activity of the striated sphincter muscles increases. In different double-blind, randomized, placebo-controlled clinical trials, a significant reduction of urinary incontinence and significantly improved incontinence quality of life (I-QOL) for women could be demonstrated [13,14,19,20].

SUI after pelvic surgery is due to lesions of autonomic parasympathetic nerves or the urethral sphincter itself. Considering the proven effect on the striated sphincter muscles in incontinent women, it is plausible that a similar effect can be reached in men if the nervous structure or the sphincteric apparatus is not totally destroyed. By increasing the neural input the sphincteric activity, and therefore continence, is increased as well.

In our study patients after prostatectomy and patients after cystoprostatectomy reported a comparable reduction of the daily pad use. One limitation of our study is that the questionnaire is not validated. The positive effect could be attributed to the pelvic floor training alone or the combination of duloxetine and pelvic floor training. We therefore looked at patients suffering from incontinence for more than 10 mo after surgery despite pelvic floor training ($n = 9$). Even those patients were able to reduce the daily number of pads significantly by taking duloxetine. Thus, it can be assumed that the positive effect is due to the additional use of duloxetine.

5. Conclusions

According to our preliminary results, duloxetine is a favorable drug to lower the degree of incontinence in patients after radical prostatectomy or cystectomy. Duloxetine was able to promote the recovery of urinary continence in patients who previously practiced pelvic floor exercise without satisfactory results.

The drug is well tolerated by most of the patients; side effects (eg, nausea) vanished often after a short time. However, one third of our patients reported intolerable side effects and discontinued duloxetine therapy.

To clarify which patients benefit the most from duloxetine, further investigations and a long-term follow-up with a larger number of patients should be done. In those subsequent studies, further objective tests such as the incontinence pad test

and questionnaires to assess the I-QOL should be included.

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