Int Urogynecol J (2011) 22:971–974
DOI 10.1007/s00192-011-1410-7

ORIGINAL ARTICLE

The effect of solifenacin on urethral sphincter morphology

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Received: 17 November 2010 / Accepted: 10 March 2011 / Published online: 6 April 2011

Abstract
Introduction and hypothesis The aim of the study was to determine whether a 6-week course of 5 mg of solifenacin succinate used to treat mixed incontinence, produces measurable changes in the appearance of the urethral sphincter.
Methods Twenty-six women undergoing treatment for mixed incontinence were recruited from a urogynaecology unit after failing to improve with conservative treatments and bladder drill. All underwent dual channel subtracted cystometry, which showed mixed urodynamic stress incontinence and detrusor overactivity. All patients underwent a 3D transperineal ultrasound before solifenacin therapy was started and after 6 weeks of treatment. The urethral length, width and volume of the smooth muscle and total sphincter volume were compared before and after the treatment.
Results Clinically, 13 reported no improvement in either stress or urge incontinence. Eight women reported improvement in their urgency symptoms but no benefit in their stress leakage. Four women reported resolution of both stress and urge incontinence. One woman reported worsening of her bladder symptoms. There was no significant change in the urethral length (p=0.27), width (p=0.50), volume of smooth muscle (p=0.87) or total sphincter volume (p=0.60) before and after treatment with solifenacin.
Conclusions A 6-week course of solifenacin resulted in no measurable changes in the appearance of the urethral sphincter.

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Keywords Solifenacin · Ultrasound · Urethra · Urinary incontinence · 3D

Introduction

Urinary incontinence is an important health problem which affects 14% of the adult female population in the UK [1] and significantly affects quality of life. Mixed urinary incontinence (MUI) is the complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on coughing or sneezing [2]. MUI is very common. Ninety percent of women undergoing surgery for urodynamic stress incontinence (USI) will have urinary urgency incontinence (UUI) in addition to stress incontinence (SI) [3]. The ideal treatment of MUI is unknown, but therapies include anticholinergic medications, bladder drill and pelvic floor exercises. Anticholinergic drugs have beneficial effects on UUI and also in MUI when compared to placebo [4, 5]. A reduction in incontinence episodes has been demonstrated with a variety of different drugs when used for MUI [6, 7]. Solifenacin is equally effective in MUI and UUI and reduces incontinent episodes [6].

In patients with MUI, involuntary urinary leakage is a complex pathological process involving both a detrusor contraction and insufficient resistance at the level of the urethral sphincter to stop leakage. Cholinergic receptors are widely distributed throughtout the lower urogenital tract and might be expected to exert actions at both the level of the detrusor muscle and urethral sphincter. Improvements in continence might be due to changes in the urethral sphincter, but to date, no attempt has been made to image the sphincter after anticholinergic therapy.

Anticholinergic medication reduces overactive bladder symptoms and causes measurable changes in the detrusor

muscle thickness [8]. Transperineal ultrasound can be used to image the urethral sphincter in women [9]. Imaging cadaveric tissue in a water bath and then comparing the histological sections to those seen with ultrasound, has been used to confirm that the ultrasound appearance relate to specific muscle layers [10, 11].

The primary aim of this study was to image the urethral sphincter to identify if there are any measurable effects on urethral sphincter morphology in women treated with the anticholinergic drug solifenacin succinate 5 mg. A secondary aim was to compare any changes in sphincter morphology in responders versus non-responders.

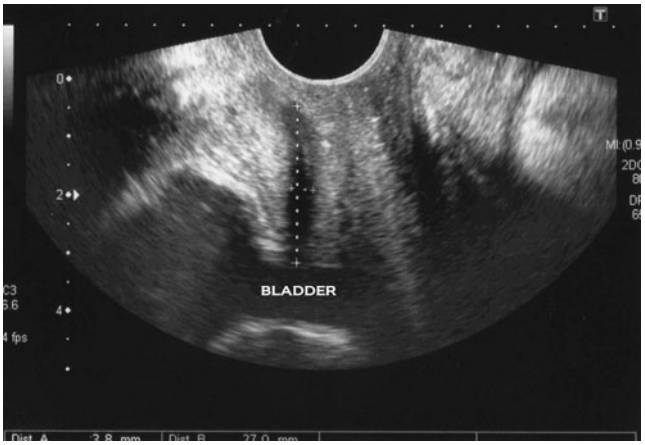

Fig. 1 Calipers measuring urethral length and width

Methods

Women who had failed to respond to bladder drill and conservative therapies, undergoing dual channel subtracted cystometry, were considered for this study. Forty-five consecutive women were identified from a secondary care urogynaecology clinic. Thirty-five women were successfully recruited into the study over an 8-month period. Mixed USI and detrusor overactivity (DO) were the inclusion criteria for this study. Patients underwent a transperineal 3D ultrasound scan using a GE 730 expert ultrasound machine (GE Healthcare, Waukesha, WI, USA) with a transvaginal probe applied to the external urethral meatus. Patients were examined in the dorsal supine position with their legs abducted. A sagittal view was obtained including the urethra and bladder neck. A volume box is then placed around these tissues and the 3D probe activated to take 20 slices through the urethra. This process takes 4–6 s. Any movement during the scanning process results in distortion, making the images uninterpretable. Repeat image acquisition was necessary in this instance. An initial measurement was made of the urethral length and the width of the black, hypoechoic core (which is presumed to be longitudinal smooth muscle) (Fig. 1). Volumes were produced for the hypoechogenic core (Fig. 2.) and for the total sphincter volume (Fig. 3.) by hand-marking the individual slices. The computer software then calculates the volumes. Two operators checked all results. Patients were then prescribed solifenacin 5 mg daily and reviewed clinically and for a repeat transperineal ultrasound 6 weeks later. The ultrasound operators were blinded to the clinical outcomes. The clinical outcomes of the symptoms of SI and urgency were assessed with the Patient Global Impression of Improvement score (PGI-I). Pre and postoperative sphincter measurements were compared with the Wilcoxon signed-rank test as normal distributions could not be confirmed. Women who had any response to therapy (improved stress or urge incontinence at follow-up) were compared to those who derived no benefit or got worse (responders vs. non-responders). All women signed written informed consent. The study was approved by the South East Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency. A study size of more than 25 subjects was used after the recommendations of Machin et al. for this situation, where it is difficult to estimate relevant standard deviations before the study [12]. Research involving the use of drug therapy is tightly regulated in the UK. Sample size quantification has to be justified, and hence, the study size was restricted based on this quantification.

Results

Thirty-five women had pretreatment ultrasound scans. In four women, the image quality was poor and accurate measurements could not be obtained. Four did not continue with the trial medication until the second visit due to unacceptable side effects. They discontinued treatment between 3 days and 2 weeks. One woman decided not to take the medication after the initial visit. These women

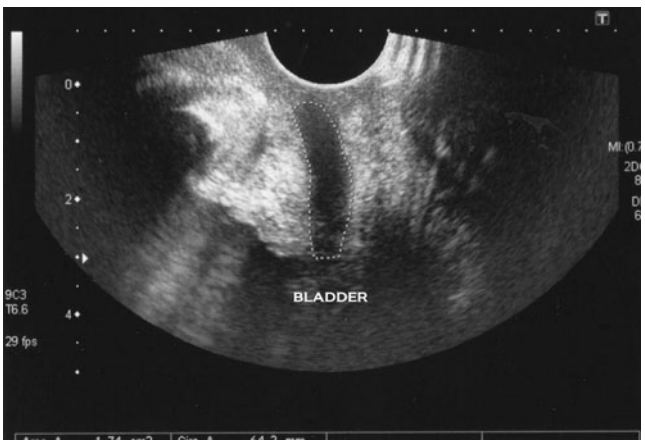

Fig. 2 Calipers measuring area of hypoechogenic core

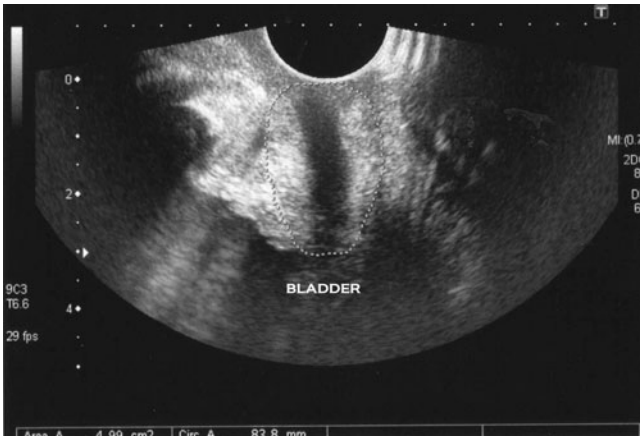

Fig. 3 Calipers measuring 2D area of total sphincter

were excluded from the analysis, and hence, the study group consisted of 26 women. The mean parity was 2. The mean age was 52 years (range 30–84). Sixteen (62%) women were postmenopausal of which two were taking oral hormone replacement therapy.

Clinically, 13 (50%) reported no improvement in either stress or urge incontinence. Eight women (31%) reported improvement in their urgency symptoms but no benefit in their stress leakage. Four women (15%) reported resolution of both stress and urge incontinence. One woman reported worsening of her bladder symptoms. Twelve women (46%) were subsequently treated with a suburethral sling for persistent SI. One woman underwent a cystoscopy for urge predominant symptoms with microscopic haematuria. No significant pathology was discovered.

There was no significant change in any of the urethral sphincter morphological parameters in women treated with solifenacin. There was no significant difference in the urethral length (p=0.27), width (p=0.50) and volume of smooth muscle (p=0.87) and total sphincter volume (p=0.60) before and after treatment. When comparing responders to non-responders, there was no significant difference in the change in the urethral length (p=0.27), width (p=0.50) and volume of smooth muscle (p=0.87) and total sphincter volume (p=0.60).

Discussion

This study was designed to test the concept that the treatment of urinary incontinence with anticholinergic therapy might produce measurable changes in the urethral sphincter. Unfortunately, we were unable to demonstrate any morphological changes in the urethral sphincter caused by a course of solifenacin therapy.

Ultrasound has been used to assess bladder and urethral morphology in a number of different clinical scenarios. The assessment of bladder wall thickness in women and its association with DO was originally described in 1994 [13]. Current trials are studying the effect of drug therapy on bladder wall thickness. Subsequently, the urethral sphincter has been imaged with both 2D [14] and 3D [15] ultrasound. Several studies have documented changes in the appearance of the urethral sphincter caused by drugs such as duloxetine [14, 16]. Transperineal ultrasound is cheaper and more readily accessible than other technologies such as MRI [17]. Despite widespread availability, there are relatively few studies assessing the urethral sphincter with ultrasound. This seems an anomalous situation as urethral function must be important in the maintenance of continence.

The study was designed to look for any changes in the urethral sphincter. Women with mixed incontinence were chosen as these are a common group treated with anticholinergic therapy, and therefore, the drug was to be used within its license. Solifenacin is not indicated for SI alone. Women with DO were not included as these patients were less likely to show beneficial effects on the sphincter, as this is presumed to be normally functional in the absence of the symptoms of SI. One limitation with the study is that there were a small number of responders. It is possible that changes in the urethral sphincter are only seen in women who respond to drug therapy. However, the sample size of the study was limited in the ethical approval. The study might be too small to identify small changes in sphincter morphology in women who responded to treatment. However, there were no obvious trends in any of the measurements, making this unlikely. This issue was partially addressed by comparing responders with non-responders but the groups were small, making statistical assumptions uncertain. A higher dose of drug therapy might have resulted in measurable changes in the sphincter morphology. It is difficult to power a study when no previous work in area has been performed and there is no knowledge of expected mean and standard deviations of any likely change. This study could act as a pilot for further studies, although this is less likely as there were no measurable differences.

The reliability of 3D ultrasound measurements of the urethral sphincter has been demonstrated with good interobserver error in pregnancy [18]. The tissue planes may be better demarcated in younger women or those who are pregnant. In our population, the majority were post-menopausal. We did not repeat the test–retest reliability measures in our population, but this is a potential source of error.

At the time that this project was conceived, there seemed to be good evidence that drug therapy affected the morphological characteristics of the urethral sphincter. This study was designed to identify if this finding could be confirmed in other clinical settings with different drug

therapies. Ultrasound failed to demonstrate morphological changes caused by solifenacin. Combining ultrasound with assessments of urethral function may help to address whether alterations in structure relate to function [15]. Tests such as urethral pressure profiles or measures of resistance could be used, but all have limitations in their reproducibility and clinical applicability [19].

This study has failed to show any changes in the urethral sphincter caused by solifenacin. It would seem likely that any benefits derived from solifenacin are not due to affects seen in the urethral sphincter. The reduction in incontinence episodes seen with anticholinergic therapy is most likely related to the effect of drug therapy relaxing the detrusor, rather than any benefit in the strength of the sphincter.

Conflicts of interest J. Duckett received industry support from Astellas (£15,000) to complete this study but wrote the paper and analysed the results independently.

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