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HOW DOES DRUG TREATMENT IMPROVE URGE INCONTINENCE?

Aims of Study

Among the elderly, urge incontinence is common and severe. Treatment, by conservative measures or by drugs, remains unsatisfactory because of side-effects, limited efficacy, or need for continuing therapy. Urge incontinence is usually ascribed to detrusor overactivity causing leakage, and pharmacotherapy is aimed at reducing detrusor activity. However, detrusor overactivity occurs even in symptom-free subjects, while many other factors, inside and outside the lower urinary tract (LUT), influence continence. Thus the *specific* mechanism of drug action is unclear. Elucidation might point the way to more effective therapies.

Variables corresponding to the physiological mechanisms through which therapy achieves its effects should change in those in whom treatment is successful, and remain unchanged if it is unsuccessful; i.e., should mediate therapeutic response. They might also be expected to differ in these 2 groups prior to treatment; i.e., to predict success. We aimed to use detailed urodynamic testing to identify physiological predictors and mediators of successful pharmacological therapy, and hence determine likely mechanisms of action.

Methods

We conducted an 8-week, placebo-controlled RCT using immediate-release oxybutynin, in cognitively intact subjects age 55 or older, with urge-associated incontinence on voiding diary, but without significant stress incontinence or outlet obstruction on videourodynamics. After titration, the optimal dose was maintained for a month, and evaluations were repeated. The main outcome measures were percentage reduction in frequency of incontinence episodes and complete dryness, based on 4-day voiding diaries at baseline and completion.

Videourodynamic evaluation included uroflowmetry; PVR; provocative cystometry (30 ml/min) with simultaneous monitoring of intravesical, abdominal, and detrusor pressures; voiding cystourethrography; isovolumetric testing; and pressure-flow studies. Urethral pressure profilometry was performed pre-treatment; the presence of functioning striated muscle at the bladder neck was determined by a local pressure rise on voluntary or reflex muscle contraction.

Potential determinants of continence were classified in 5 physiological domains intrinsic to the LUT, as well as 3 clinical (external) domains whose effect was minimized by patient selection and statistical adjustment. The 5 physiological domains encompass possible therapeutic mechanisms: overactive contraction characteristics, bladder capacity, bladder proprioception, detrusor contractility, and adequacy of urethral sphincter function.

To identify potential *predictors* of therapeutic response, we analysed bivariate correlations of *baseline values* with percent improvement. We then developed multivariable models (logistic regressions on dryness), including only one representative of each domain to avoid multiple comparisons. We used the best domain representatives postulated *a priori*, and also those that emerged from bivariate analyses. To identify *mediators* of therapeutic success, we conducted similar analyses for intervention-induced *changes* in the variables. We did all this for both oxybutynin and placebo.

Results

Of 110 subjects randomized, 95 completed the study (84 women and 11 men, mean age 70 years). Fifty-four received oxybutynin, with a median final dose of 2.5 mg tid. Incontinence frequency decreased by 81% on oxybutynin, approximately twice the reduction on placebo. Thirty-four subjects (63%) became dry on oxybutynin and 17% on placebo.

Bivariate analysis revealed significant urodynamic *predictors* of improvement on oxybutynin in the domains of contraction characteristics, sphincter adequacy, detrusor contractility, and possibly bladder proprioception. From multivariable analysis the variables that clearly emerged as predictors were higher overactive contraction "velocity" (dp_{det}/dt) and presence of functioning striated muscle at the bladder neck ($P \leq 0.01$). Smaller post-void residual urine and less warning of impending detrusor overactivity also had predictive value ($P < 0.05$). Few variables were associated with the modest improvement on placebo.

Potential *mediators* of improvement on oxybutynin from bivariate analyses included contraction velocity and possibly PVR. Multivariable analyses confirmed that contraction velocity was a mediator ($P < 0.10$), becoming smaller in those who improved on oxybutynin, but neither PVR nor other contractility variables appeared to be significant. As a proxy for sphincter adequacy we studied urethra-related voiding variables. Both peak flow rate and urethral resistance variables mediated dryness: surprisingly, urethral resistance decreased in those who became dry ($P < 0.05$).

Conclusions

Oxybutynin IR produces marked improvement in incontinence in many but not all elderly subjects. We were unable to show clearly, however, that the mechanisms usually assumed – decreased detrusor contractility or increased (functional) bladder capacity – were the primary mediators of improvement. Our results suggest rather that oxybutynin may produce improvement through subtle changes in the characteristics of the overactive detrusor contractions and perhaps in sphincter control.

Good response is associated with higher overactive contraction “velocity” pre-intervention, and improvement is accompanied by a velocity decrease. Contraction velocity is the result of several factors, but one possibility is that high and low velocities represent contractions with different underlying mechanisms, only the first of which responds to oxybutynin. If so, there may be a place for a new drug that acts on low-velocity contractions.

This study has shown again the importance of the urethral sphincter in the control of urge incontinence, reinforcing the basis of conservative therapy by exercises and biofeedback.