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RESEARCH LETTER

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Amezinium metilsulfate, a sympathomimetic agent, may increase the risk of urinary retention in multiple system atrophy

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Abstract In 5 patients with multiple system atrophy, administration of 15 mg/day of amezinium metilsulfate, an adrenergic agent, during 6 months for the treatment of postural hypotension exacerbated post-micturition residuals as compared to that before treatment (178 ml versus 113 ml for a change of 37 %, $p < 0.05$). Amezinium metilsulfate most probably stimulates both α1B-receptors in the vascular wall and α1A/D-receptors in the proximal urethra.

Key words amezinium metilsulfate · sympathetic receptor agonist · multiple system atrophy (MSA) · postural hypotension · urinary retention

Introduction

The most commonly used drugs to treat postural hypotension are direct and indirect sympathomimetic agents [1, 2]. Lower urinary tract dysfunction is a feature of patients with multiple system atrophy (MSA). Both urinary urgency, frequency and voiding difficulty are common [3–5]. We previously reported that voiding difficulty in MSA patients particularly in the early stage of disease may be treated with selective α1A-adrenergic antagonists without marked exacerbation of postural hypotension [6]. We now report that nonselective sympathomimetic drugs may increase post-micturition residuals (PMR) in MSA patents.

Materials and methods

We reviewed our case records of MSA patients who met the clinical diagnostic criteria including MRI findings [1]. Five patients underwent amezinium treatment for their postural hypotension (four men and one woman, mean age 58 years, Table 1). Autonomic tests revealed that all patients had central and peripheral types of cardiovascular and urinary dysfunction [5]. Four of the patients had high urethral closure pressure and two had detrusor-sphincter dyssynergia. PMR was noted in three (cases 2,3,5), who were taught clean, intermittent self-catheterization (CISC) once (case 2) to twice a day (cases 3,5). No abnormality was found in the patients by ECG, chest radiography or by blood chemistry (including blood sugar), urinalysis or abdominal ultra-sonography (including the kidney and prostate). None was under fludrocortisone treatment. Each patient was prescribed 15 mg/day (range 10–20 mg/day) of amezinium metilsulfate for 6 months (range 3–12 months) for the treatment of postural hypotension. PMR and urinary symptoms were evaluated before and again after the treatment. Results were analyzed by the Student's *t* test.

Results

After treatment, the mean volume of PMR was increased as compared to that before treatment (178 ml versus 113 ml for a change of 37 %, $p < 0.05$) (Fig. 1). None of the patients had change of their urinary filling symptoms. Voiding difficulty changed in none of four patients, but it appeared in one patient (case 4) who had no voiding difficulty before the treatment. The increase in the volume of PMR was related to none of the urodynamic parameters including detrusor-sphincter dyssynergia. One patient (case 4) started CISC twice a day, and two patients augmented the number of CISC according to their volume of PMR (case 3, 3 times; case 5, 3 times).

Table 1 Patient characteristics

Patient	1	2	3	4	5
Age (years)	49	51	61	64	67
Sex	M	F	M	M	M
Duration (years)	2	2	6	11	2
Urodynamic study					
Post-micturition residuals (ml) (normal < 30)	–	200	206	–	160
UPmax (cmH2O) (41 < normal < 82)	87	> 100	> 100	> 100	67
First sensation (100 < normal < 300)	150	120	308	140	140
Maximum bladder capacity (200 < normal < 600)	200	220	330	196	180
Detrusor hyperreflexia	+	+	+	+	–
Low compliance bladder	+	+	–	–	+
Detrusor areflexia on voiding	–	+	+	–	+
Bethanechol supersensitivity	+	np	np	np	np
Detrusor-sphincter dyssynergia	+	–	–	–	+
Uninhibited sphincter relaxation	–	+	+	+	–
Neurogenic sphincter EMG	–	+	+	+	+

UPmax maximum urethral closure pressure; *np* not performed

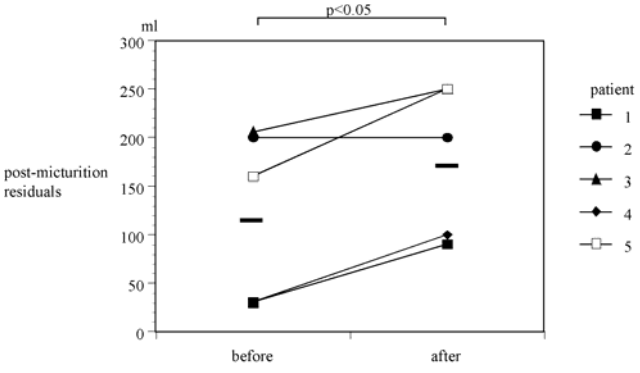

Fig. 1 Post-micturition residuals before and after amezinium treatment (bar: mean volume of residual urine)

Discussion

We showed that amezinium, an indirect vasoconstrictor agent, caused 35 % increase of PMR ($p < 0.05$) in patients with MSA, with a minimum increase in subjective voiding difficulty. Although the number of the patients was small and the effects of the drug in the study reported here were modest, our findings suggest that sympathomimetic agents may increase the risk of urinary retention in patients with MSA.

The proximal urethra has two structures involved in the maintenance of continence; the internal (smooth) and external (striated) sphincters. The proximal urethra has an abundance of α1A/D-adrenergic receptors [7, 8]. In contrast, the vascular wall has an abundance of α-1B receptors particularly in the elderly [9]. The blockade of these receptors by non-selective α-1 antagonist prazosin is widely used in treatment of idiopathic hypertension. Similarly, prazosin is reported to be beneficial in treatment of both bladder neck obstruction and detrusor-sphincter dyssynergia caused by spinal cord injury or other neurological diseases [10], resulting in decreases in EMG activities [11], urethral pressure and PMR [12]. Recently developed α1A/D-selective antagonists (moxisylyte, tamsulosin, etc.) are the choice for ameliorating voiding difficulty because of fewer cardiovascular side effects, particularly in patients with autonomic failure and in the elderly [6].

Non-selective adrenergic drugs are used for a relief of stress urinary incontinence [13], in which low urethral pressure is a contributory mechanism. As we could not make repeated urodynamic studies, the exact mechanism of amezinium on the increase in PMR is not clear. However, the patients in the present study commonly had high urethral closure pressure, which is rather uncommon in MSA patients in our previous report [5]. In our patients with increased PMR, increase in subjective voiding difficulty was only minimum. Therefore, measurement of PMR is necessary for the assessment of evacuating disorder in neurological patients. The lower urinary tract dysfunction is not only troublesome but also a cause of morbidity in patients with MSA [4, 5]. Currently, there is no selective α-1 receptor agonist either for the vascular wall or the urethra. A single drug is unlikely to benefit all MSA patients because of the adverse effects, and non-selective sympathomimetic agents may exacerbate voiding difficulty by stimulating both α1B-receptors in the vascular wall and α1A/D-receptors in the proximal urethra.

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