Investigative Urology

Urodynamic Effects of Propiverine on Detrusor Overactivity and Abdominal Straining during Voiding in Awake Rats with Intravesical Prostaglandin E_2 Instillation

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Purpose: We investigated the effect of propiverine on cystometric parameters based on intraabdominal pressure (IAP) in awake rats in an overactive bladder (OAB) model induced by intravesical instillation of prostaglandin E_2 (PGE_2).

Materials and Methods: Twenty-two female Sprague-Dawley rats were used. Polyethylene catheters were implanted into the bladder to record the intravesical pressure (IVP) and into the femoral artery to administer medication. A balloon-fitted catheter was positioned in the abdominal cavity to record the IAP. Awake cystometries were performed before and after intraarterial administration of propiverine 1 mg/kg (n=6), intravesical administration of 50 μM PGE_2 only (n=6), or intravesical PGE_2 plus 1 mg/kg (n=4) or 3 mg/kg (n=6) of intraarterial propiverine. Cystometric pressure and volume parameters and variables related to detrusor overactivity (DO) were investigated.

Results: Rats administered intravesical PGE_2 showed increased pressure parameters and decreased volume parameters comparable to the DO model, which was effectively prevented by propiverine (1 or 3 mg/kg). Typical DO shown during the filling phase was decreased by intraarterial propiverine (3 mg/kg) injection. After propiverine (3 mg/kg) injection, IAP was increased at the time of micturition pressure with or without threshold pressure ($p < 0.05$, $p < 0.01$) depending on the dose administered.

Conclusions: Propiverine improved pressure- and volume-related parameters in an OAB model. Furthermore, it also decreased the frequency of DO. However, higher concentrations of propiverine induced straining voiding.

Key Words: Propiverine, Sprague-Dawley rats, Prostaglandins

INTRODUCTION

Overactive bladder (OAB) is a highly prevalent disease that increases with age [1]. Its impact on the quality of life is similar to that of hypertension and diabetes and is more serious than that of depression [2]. For these reasons, OAB has an important position in the international drug industry. Although OAB patients show many variable symptoms, the central symptom of OAB is urgency [3,4], which is closely related to detrusor overactivity (DO) during the filling phase in cystometry [5-7]. It was reported that 83% of patients with DO showed urgency, and 64% of patient with urgency showed DO [7]. Thus, it is important to observe DO objectively in clinical and research studies

of OAB. Recently, we investigated nonvoiding contractions in awake animal models by simultaneous registrations of intravesical pressure (IVP) and intraabdominal pressure (IAP) [8].

Anticholinergic therapy is the first-line treatment option for patients with OAB, owing to the parasympathetic activation of the detrusor contractions [5]. Anticholinergic drugs suppress the involuntary detrusor contractions through competition with acetylcholine for the muscarinic receptors during both the storage and the voiding phase [3,9,10]. However, it is known experimentally that these drugs have no effects on voiding contraction and residual volume, because the amount of acetylcholine released during the voiding phase is much more than those of anti-

cholinergic drugs [10]. However, in clinical studies, some patients complained of straining voiding, increased residual volume, and sometimes acute urinary retention. This suggests that anticholinergics may have an influence on detrusor contractions during the voiding phase [11]. Up to now, there has been no experimental evaluation of the effect of anticholinergics during the voiding phase in awake rats by simultaneous registrations of IVP and IAP.

The objective of this study was therefore to perform simultaneous registrations of IVP and IAP to evaluate the effects of propiverine 1 and 3 mg/kg on DO during the filling phase and on abdominal straining during the voiding phase in awake rats with intravesical prostaglandin E_2 (PGE_2) instillation.

MATERIALS AND METHODS

1. Animals
A total of 22 Sprague-Dawley (SD) female rats weighing between 200 and 250 g were used in this study. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and were approved by the Inha-University Animal Ethics Committee. The rats were maintained under standard laboratory conditions with a 12:12 h light: dark cycle and with free access to food pellets and tap water. Simultaneous IVP and IAP were continuously recorded during bladder filing and emptying as described previously [12].

2. Bladder, intraabdominal, and intraarterial catheter implantation
In brief, SD rats were anesthetized with ketamine (Ketamine; Yuhan Corp, Seoul, Korea; 75 mg/kg intraperitoneally) and xylazine (Rompun; Bayer Korea Corp, Korea; 15 mg/kg intraperitoneally). Through a low abdominal incision, a polyethylene catheter (PE-50; Becton Dickinson, Parsippany, USA) with a cuff was inserted into the dome of the bladder and was held in place with a purse-string suture. To record IAP, an abdominal balloon (Latex; Daewoo Medical, Incheon, Korea) around the cuff of a catheter tip was placed 1 cm proximal to the bladder along the catheter to the bladder and was attached with a silk tie to the catheter. A catheter (PE-10; Becton Dickinson) was inserted into the femoral artery. These catheters were tunneled subcutaneously and anchored to the skin of the back with a silk ligature.

3. Cystometric investigations
Cystometry was performed 3 days after implantation of the catheters in unanesthetized, unrestrained rats in metabolic cages. The indwelling catheter to the bladder was connected to a two-way valve that was connected via a T-tube to a pressure transducer (Research Grade Blood Pressure Transducer; Harvard Apparatus, Holliston, USA) and a microinjection pump (PHD22/2,000 pump; Harvard Apparatus). Another catheter connected to an air-free abdominal balloon was connected to another pressure transducer to record the IAP. Micturition volumes were recorded by means of a fluid collector connected to a force displacement transducer (Research Grade Isometric Transducer; Harvard Apparatus). Room-temperature saline was infused into the bladder continuously at a rate of 10 ml/h. IVP, IAP, and micturition volumes were recorded continuously with Acq Knowledge 3.8.1 software and an MP150 data acquisition system (BIOPAC Systems, Goleta, USA) at a sampling rate of 100 Hz. The mean values from three reproducible micturition cycles were used for evaluation. IAP was defined as the recorded balloon pressure corrected by subtracting the lowest balloon pressure in each voiding cycle, which is comparable to zeroing in human cystometry. Detrusor pressure (DP) was defined as IVP minus IAP. The IVP rises during the filling phase (IVPRs) were defined as increments of IVP that exceeded 2 cmH_2O from baseline, which was interpreted as abdominal straining if occurring with simultaneous similar changes in IAP, or as DO if occurring without simultaneous similar changes in IAP [12].

The following conventional urodynamic pressure-volume parameters were investigated: micturition pressure (MP, maximum bladder pressure during micturition), basal pressure (BP, the lowest bladder pressure during filling), threshold pressure (TP, bladder pressure immediately before micturition), bladder capacity (BC, residual volume at the most recent previous micturition plus the volume of infused saline at micturition), micturition volume (MV, volume of expelled urine), residual volume (RV, bladder capacity minus micturition volume), and micturition interval (MI, time between micturition events). Pressure parameters were respectively measured in IVP, IAP, and DP.

The following DO-related parameters during the filling phase were observed: time of filling phase (interval between the end of a micturition and the point immediately before the next micturition), total number of DO, frequency of DO per minute, and increased amplitude of DO as IVP. In all groups, a period of about 30-60-min micturition cycles was observed and the values from reproducible micturition cycles were used for evaluation.

4. Administration of drug
Stock solutions (0.01 M) of PGE_2 (Sigma Chemical Co., St Louis, USA) were made in absolute ethanol and were then diluted to 50 μM in saline just before use. PGE_2 was infused intravesically at a rate of 10 ml/h. Propiverine 1 or 3 mg/kg was infused into the femoral artery after the baseline cystometry.

The rats were randomly allocated to the following four treatment groups after control cystometries with saline: 1) intraarterial propiverine 1 mg/kg only (n=6), 2) intravesical PGE_2 only (n=6), 3) intravesical PGE_2 and intraarterial propiverine 1 mg/kg (n=4), or 4) intravesical PGE_2 and intraarterial propiverine 3 mg/kg (n=6).

5. Statistical analysis
The results are given as mean values±standard errors of

TABLE 1. Effects of intraarterial administration of propiverine on cystometric parameters in conscious, normal Sprague-Dawley rats

	BP (cmH$_2$O)	TP (cmH$_2$O)	MP (cmH$_2$O)	BC (ml)	VV (ml)	RV (ml)	MI (min)
Baseline (n=6)							
IVP	9.6±1.3	25.1±2.1	52.7±4.0				
DP	8.5±1.2	16.2±2.0	49.2±3.7	1.12±0.12	1.10±0.12	0.02±0.01	6.41±0.47
IAP	1.4±0.2	9.0±1.4	3.5±0.7				
Propiverine 1 mg/kg (n=6)							
IVP	9.8±1.1	25.1±1.8	57.0±5.8				
DP	8.7±1.1	15.7±1.5	52.3±5.7	1.11±0.12	1.09±0.12	0.01±0.01	6.52±0.60
IAP	1.1±0.2	9.4±0.8	4.7±0.7				

BP: basal pressure, TP: threshold pressure, MP: micturition pressure, BC: bladder capacity, VV: voided volume, RV: residual volume, MI: micturition interval, IVP: intravesical pressure, DP: detrusor pressure, IAP: intraabdominal pressure. Results are expressed as mean±standard error of the mean. There was no statistical differences between baseline and propiverine 1 mg group in urodynamic parameters.

TABLE 2. Effects of intraarterial administration of propiverine on intraabdominal pressures in conscious Sprague- Dawley rats with intravesical instillation of PGE$_2$

	BP (cmH$_2$O)	TP (cmH$_2$O)	MP (cmH$_2$O)
Baseline (n=16)	1.31±0.11	5.37±0.39	2.80±0.29
PGE$_2$ 50 μM (n=6)	0.94±0.24	5.48±0.73	3.79±0.76
Propiverine 1 mg/kg + PGE$_2$ 50 μM (n=4)	1.40±0.23	6.52±0.75	4.19±0.43
Propiverine 3 mg/kg + PGE$_2$ 50 μM (n=6)	1.35±0.22	9.20±1.55	4.43±0.38[a]

BP: basal pressure, TP: threshold pressure, MP: micturition pressure. Results are expressed as mean±standard error of the mean. [a]: p < 0.05 (unpaired Student's t-test), versus baseline

TABLE 3. Effects of intraarterial administration of propiverine on cystometric pressure parameters by intravesical and detrusor pressures in conscious Sprague-Dawley rats with intravesical instillation of PGE$_2$

	BP (cmH$_2$O)	TP (cmH$_2$O)	MP (cmH$_2$O)
Baseline (n=16)			
IVP	8.47±0.71	24.19±1.34	58.0±2.55
DP	6.92±0.28	19.93±2.04	55.20±2.52
PGE$_2$ 50 μM (n=6)			
IVP	13.3±1.21[b]	29.8±1.68[a]	108.9±8.62[b]
DP	12.3±1.10[b]	24.3±2.16[a]	100.13±6.06[b]
Propiverine 1 mg/kg + PGE$_2$ 50 μM (n=4)			
IVP	8.65±0.69[c]	28.18±1.34	98.51±4.85[b]
DP	8.25±0.48	25.14±1.84	86.57±7.42[b]
Propiverine 3 mg/kg + PGE$_2$ 50 μM (n=6)			
IVP	8.04±0.71[c]	28.96±1.25	107.7±3.22[b]
DP	7.02±0.76[c]	20.09±2.11	90.27±8.03[b]

BP: basal pressure, TP: threshold pressure, MP: micturition pressure, IVP: intravesical pressure, DP: detrusor pressure. Results are expressed as mean±standard error of the mean. [a]: p < 0.05, [b]: p < 0.01 (unpaired Student's t-test), versus baseline, [c]: p < 0.01 (unpaired Student's t-test), versus PGE$_2$ 50 μM.

the mean (SEMs). Normal distributions were confirmed by use of SigmaStat 2.0 (SPSS Inc, Chicago, USA). Statistical significance was determined by paired or unpaired t-tests. Statistical significance was defined as p < 0.05.

RESULTS

1. Effects of propiverine 1 mg/kg on normal rats
There were no significance differences in pressure- or volume-related parameters before and after the administration of propiverine 1 mg/kg in normal rats. Thus, we showed that propiverine 1 mg/kg had no effect on pressure-volume parameters in normal rats (Table 1).

2. Effects of PGE$_2$ with or without propiverine on IAP recorded at the points of BP, TP, and MP
The rats showed no changes in IAP recorded at the point of BP, TP, or MP after intravesical instillation of PGE$_2$ 50 μM compared with baseline cystometries. The rats administered intravesical PGE$_2$ 50 μM and simultaneous intraarterial propiverine 1 mg/kg also showed no changes in IAP at those three points compared with baseline and PGE$_2$-instilled cystometries. The rats administered intra-

vesical PGE$_2$ 50 μM and simultaneous intraarterial propiverine 3 mg/kg showed increased IAP at MP (p < 0.05) only compared with baseline cystometries (Table 2).

3. Effects of PGE$_2$ with or without propiverine on pressure-related parameters
Recorded as IVP or DP, OAB was successfully induced in rats by intravesical instillation of PGE$_2$, which resulted in increases in BP, TP, and MP compared with baseline cystometries (p < 0.01, p < 0.05, and p < 0.01, respectively). The rats administered PGE$_2$ and propiverine 1 mg/kg showed decreased BP by IVP (p < 0.01), compared with PGE$_2$-instilled cystometries, and decreased MP by IVP and DP (p < 0.01, p < 0.01), compared with baseline cystometries. The rats administered PGE$_2$ and propiverine 3 mg/kg showed decreased BP by IVP and DP (p < 0.01 and

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p < 0.01, respectively), compared with PGE₂-instilled cystometries, and decreased MP by IVP and DP (p < 0.01 and p < 0.01, respectively), compared with baseline cystometries (Table 3).

4. Effects of PGE₂ with or without propiverine on volume-related parameters

OAB was successfully induced in rats by intravesical instillation of PGE₂, which resulted in decreases in BC, VV, and MI without changes in RV, compared with baseline cystometries (p < 0.05, p < 0.05, and p < 0.05, respectively). The rats administered PGE₂ and propiverine 1 or 3 mg/kg showed no change in volume-related parameters compared with baseline or PGE₂-instilled cystometries (Table 4).

5. Effects of PGE₂ with or without propiverine on DO-related parameters

DO was not observed in baseline cystometries. After intravesical instillations of PGE₂, DO of 2.0±0.42 /min was observed (p < 0.01) compared with baseline cystometries. However, DO was not significantly decreased after propiverine injection in rats with intravesical PGE₂ instillation (Table 5).

DISCUSSION

OAB is known to include various different pathophysiologic mechanisms [13,14]. Recently, among those mechanisms, special attention has been given to the sensory and

afferent mechanisms [10,14]. Research on the new generation of OAB drugs is focused on the inhibition of afferent firing before the generation of a detrusor contraction during the filling phase, whereas the present anticholinergic drugs suppress the afferent firing after the generation of DO [14].

The intravesical PGE₂ instillation method, one of the OAB models, induces DO by the indirect activation of afferent nerves in the bladder as well as the direct activation of detrusor muscle. Prostanoids are endogenous signaling molecules that are distributed in both human and rat bladder. When the bladder is injured or stimulated, the prostanoids activate capsaicin-sensitive afferents. Then, tachykinins are released from the afferents, which lower the threshold for afferent firing, and, finally, stimulate the detrusor to induce overactivity [15-17]. Experimentally, the tachykinins initiate a micturition reflex by stimulating NK1,NK2 receptors, and intravesical prostanoids can induce DO in cystometry in vivo [14,16,17]. In our study, the cystometric features of OAB patients were successfully generated by intravesical prostanoids in rats, which showed increased BP, TP, and MP and decreased BC, MV, and MI.

The detrusor contraction is mainly caused by stimulating muscarinic receptors, and the M3 subtype in particular is believed to have the most major action for detrusor contraction [9,18]. In general, anticholinergic drugs inhibit involuntary detrusor contraction during the storage phase, but they do not significantly affect contractions during the voiding phase, because the quantity of acetylcholine is sev-

TABLE 4. Effects of intraarterial administration of propiverine on cystometric volume parameters in conscious Sprague-Dawley rats with intravesical instillation of PGE₂

	BC (ml)	VV (ml)	RV (ml)	MI (min)
Baseline (n=16)	1.25±0.08	1.25±0.08	0	7.34±0.46
PGE₂ 50 μM (n=6)	0.84±0.19ᵃ	0.84±0.19ᵃ	0	5.18±0.83ᵃ
Propiverine 1 mg/kg+PGE₂ 50 μM (n=4)	0.98±0.13	0.98±0.12	0	5.73±0.82
Propiverine 3 mg/kg+PGE₂ 50 μM (n=6)	0.91±0.05	0.91±0.05	0	5.50±0.11

BC: bladder capacity, VV: voided volume, RV: residual volume, MI: micturition interval. Results are expressed as mean±standard error of the mean. ᵃ: p < 0.05 (unpaired Student's t-test), versus baseline

TABLE 5. Effects of intraarterial administration of propiverine on the cystometric parameters related to detrusor overactivity in conscious Sprague-Dawley rats with intravesical instillation of PGE₂

Group	Filling phase (min)	Total No. of DO	Freq. DO. /min	Increased Pr of DO Peak from baseline (IVP. cmH₂O)
Baseline (n=16)	5.61±0.10	0	0	0
PGE₂ 50 μM (n=6)	3.80±0.32ᵃ	7.50±1.82ᵃ	2.0±0.42ᵃ	3.5±0.23ᵃ
Propiverine 1 mg/kg+PGE₂ 50 μM (n=4)	5.21±0.78	6.91±7.41ᵃ	1.33±1.13ᵃ	4.9±0.82ᵃ
Propiverine 3 mg/kg+PGE₂ 50 μM (n=6)	4.80±0.34	5.0±0.72ᵃ	1.2±0.21ᵃ	3.6±0.62ᵃ

No.: number, DO: detrusor overactivity, Freq.: frequency, Pr: pressure, IVP: intravesical pressure. Results are expressed as Mean±standard error of the mean. ᵃ: p < 0.01, versus baseline. There was no significant differences among the groups of intravesical PGE₂ instillation with or without propiverine injection.

eral dozen times higher than that during the storage phase [10]. In the present study, propiverine significantly decreased BP only, the basal tension of the bladder, in the intravesical PGE_2 group and showed no effect on MP, BC, VV, or MI. This might be partly related to the accumulation of continuously infused intravesical prostanoids in this rat model. However, we know that there were some effects of the propiverine, because this group showed no differences in pressure or volume parameters compared with the control group, unlike the intravesical PGE_2 only instillation group.

If we look at the effects by different concentrations of propiverine on the PGE_2-instilled state of rat bladder, propiverine 3 mg/kg decreased BP by DP but not by IVP, whereas propiverine 1 mg/kg showed no decrease in BP by either IVP or DP. This suggests that the higher dose of propiverine decreased the basal tension of the detrusor. This is not in accordance with previously reported studies, in which the investigators did not observe any difference in BP, but only in MP. We suspect that the reason for this is the difference in animal models. Our study is the first observation of propiverine effects in the animal model of prostanoid-induced OAB [5,11]. The volume parameters were significantly decreased after PGE_2 instillation and increased to the levels of control rats after propiverine injection. This suggests that propiverine inhibits the effects of PGE_2, regardless of concentrations of propiverine. Also, DO was not seen in control rats, but was shown in PGE_2-instilled animals. The propiverine showed no effects on the frequency or pressure of DO, which is in contrast with the conventional concept for anticholinergic drugs. We conclude that the propiverine did not have any effect on the DO in animal models of prostanoid-induced OAB. This is supported by the fact that some anticholinergic drugs for OAB show no effects in some patients [5,18,19].

The side effects of anticholinergic drugs are well known and described through clinical and basic research. However, straining voiding, which is a complaint from some people taking anticholinergic medication, has not been well investigated in previous reports [19,20]. This symptom is a straining of the abdomen to void because of feeling difficulty in voiding or a sense of residual urine and could be related to urinary retention [21]. In the present study, we checked the grade of straining during the voiding phase by using our models. There were no differences in abdominal straining on MP between the control rats and the PGE_2-induced OAB model. Straining was not increased after infusion of propiverine 1 mg/kg but was significantly increased after infusion of propiverine 3 mg/kg. This suggests that in the OAB model, taking a higher dose of anticholinergic drugs showed more straining during voiding. This finding may be associated with acute urinary retention and dysuria, which are among the complications of anticholinergic drugs. According to the study by Elisa et al, which was based on patient information collected by general practitioners in the United Kingdom [21], increased risk of voiding difficulty and acute urinary retention were observed in patients administered anticholinergic drugs, and these patients should be closely monitored during the first 30 days of treatment for signs or symptoms of urinary retention. Therefore, the presence and significance of these symptoms need to be taken into consideration when elucidating the side effects of anticholinergic drugs in future research.

CONCLUSIONS

Propiverine improved pressure and volume-related parameters in an OAB model induced by intravesical PGE_2, showing that propiverine can inhibit the activation of bladder contractions and possibly providing experimental evidence for decreased urgency symptoms after administration of propiverine in patients. Furthermore, propiverine also decreased the DO frequency. However, a higher concentration of propiverine induced straining voiding, suggesting the need for clinical studies of the side effects of anticholinergic drugs, which are still unknown.

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