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Effect of Acotiamide on Detrusor Underactivity Induced Through Bilateral Pelvic Nerve Crush Injury in Rats

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Purpose: To investigate the effectiveness of acotiamide on lower urinary tract dysfunction by using a rat model of neurogenic underactive bladder induced through pelvic nerve crush (PNC) injury.
Methods: Bilateral PNC injuries were performed on 8-week-old female Sprague-Dawley rats (PNC group); the sham surgery group was used as control (control group). Two weeks after surgery, awake cystometrography (CMG) was performed, and acotiamide (10 or 100 mg/kg) was subcutaneously administered to the control and PNC groups. Subsequently, CMG parameter values obtained before and after treatment were compared.
Results: In baseline CMG, compared to control group, PNC group revealed statistically significant elevations in the intercontraction intervals (ICIs), number of nonvoiding contractions, baseline pressure, threshold pressure, bladder capacity, voided volumes, and postvoid residual. However, contraction amplitudes and voiding efficiency were significantly decreased. In the control group, compared with the baseline values, 10-mg/kg acotiamide resulted in statistically significant elevations in contraction amplitudes. Treatment with 100-mg/kg acotiamide led to statistically significant elevations in contraction amplitudes and decreases in ICI and bladder volume. In the PNC group, there were no statistically significant changes noted in CMG parameters after treatment with 10-mg/kg acotiamide (n = 6). Compared with the baseline values, the administration of 100-mg/kg acotiamide significantly decreased ICI (1,025 ± 186 seconds vs. 578 ± 161 seconds; P = 0.012), bladder capacity (1,841 ± 323 μL vs. 871 ± 174 μL, respectively; P = 0.0059) and postvoid residual (223 ± 46 μL vs. 44 ± 22 μL, respectively; P = 0.023), and increased contraction amplitudes (22.09 ± 1.76 cm H_2O vs. 43.84 ± 6.87 cm H_2O, respectively; P = 0.012) and voiding efficiency (0.87 ± 0.02 vs. 0.94 ± 0.03, respectively; P = 0.029).
Conclusions: Acotiamide showed effectiveness in the treatment of underactive bladder, possibly through activation of bladder afferent and detrusor activities.

Keywords: Underactive bladder; Acotiamide; Animal model

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- **Research Ethics:** The Institutional Animal Care and Use Committee of Jich Medical University approved this study (approval number 22033).
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

- ***HIGHLIGHTS***
  - Treatment with 100-mg/kg acotiamide significantly improved inefficient voiding in PNC rats, a recently established animal model of UAB.
  - Acotiamide appears to exert its effects through activation of bladder afferent and efferent function and it may be used as a therapeutic agent for UAB due to DU.

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INTRODUCTION

Underactive bladder (UAB) is common in elderly individuals. This condition has been associated with an increased risk of institutionalization and poor quality of life [1]. UAB is defined as "the perception of detrusor underactivity (DU), characterized by symptoms of prolonged voiding, hesitancy, slow and/or intermittent stream, and/or sensation of incomplete emptying" [2]. Therefore, DU is the main etiological factor of UAB. Of note, the etiology of DU is multifactorial, involving various abnormalities (neurogenic, myogenic, etc.) [3].

Currently, there is no effective pharmacological treatment for UAB, partly due to the lack of convenient and appropriate animal models of the disease. In a recent study, we demonstrated that rats with pelvic nerve crush (PNC) injury exhibit characteristics of DU, namely significant increases in bladder capacity, voided volumes, postvoid residual (PVR), and decreases in bladder contraction amplitudes and voiding efficiency (VE) [4]. Moreover, we proposed that this animal model may be useful for elucidating the pathophysiology of UAB and developing new therapeutic agents.

Acetylcholine (ACh) is a major neurotransmitter inducing bladder smooth muscle contractions by acting on M3 receptors. As patients with UAB/DU often present with decreased bladder contractility, the application of parasympathetic drugs to enhance bladder contractility may be "theoretically" beneficial [5]. However, in a recent systematic review with meta-analysis does not show the clear evidence-based effectiveness for the use of conventional parasympathomimetics for treating the UAB condition [6].

Acotiamide hydrochloride (acotiamide; Z-338), a novel selective acetylcholinesterase (AChE) inhibitor (gastroprokinetic drug). Currently, acotiamide is used in the treatment of functional dyspepsia [7]. In addition, an open-label clinical study revealed that acotiamide is effective in the treatment of UAB, and demonstrated the positive clinical efficacy of acotiamide in 19 patients with UAB [8]. However, the investigators did not perform urodynamic evaluation (e.g., CMG or uroflowmetry) in that study; hence, the detailed urodynamic effect of acotiamide in UAB patients remains unknown.

Nevertheless, there is no physiological evidence regarding the effectiveness of this agent in animal models of UAB. Consequently, the precise functional effect of acotiamide on UAB remains unknown. Therefore, in the present investigation, the effects of acotiamide in PNC rats were examined. The objective was to evaluate the potential of acotiamide as a pharmacological treatment for UAB.

MATERIALS AND METHODS

Animals

The protocol for the handling of Sprague-Dawley rats (females; weight: 180–220 g) in this study was approved by the institutional committee for animal care and use. The animals were maintained in plastic cages with a 12/12-hour light/dark cycle and free access to food and water. The rates were anesthetized using isoflurane. Subsequently, we identified the visceral branches of both pelvic nerves proximal to the major pelvic ganglion near the internal iliac vessels. Thereafter, the nerve was crushed twice (20 seconds each time) using sharp forceps to perform bilateral nerve crush [4]. To prevent infection, the rats were treated twice daily with 100-mg/kg ampicillin through subcutaneous administration for 5 days. Rats in the control group underwent sham operation, which comprised an incision of the lower abdominal and identification of bilateral pelvic nerves, without performing nerve crushing.

Awake Continuous Cystometrography

Cystometrography (CMG) analysis was conducted 14 days after PNC. Anesthesia using isoflurane was followed by exposure of the bladder through an incision of the lower abdominal. Next, insertion of a polyethylene catheter (PE-50; Clay-Adams, Parsippany, NJ, USA) through the bladder dome was carried out, followed by suturing around the catheter. Thereafter, the rats were maintained in cages (width: 80 mm × length: 300 mm × height: 150 mm; Yamanaka Chemical Ind., Ltd., Osaka, Japan). Following full recovery from anesthesia, we measured the intravesical pressure. For this purpose, we connected the catheter to a pressure transducer and a pump for the infusion of physiological saline (rate: 0.08 mL/min).

The evaluation of CMG parameters included the following: (1) intercontraction intervals (ICIs) (i.e., average time between reflex bladder contractions); (2) contraction amplitude (i.e., peak bladder pressure minus basal bladder pressure during each contraction); (3) pressure baseline (i.e., bladder pressure immediately after reflex contraction); and (4) pressure threshold (i.e., bladder pressure immediately before reflex contraction). Moreover, contractions that occurred without voiding and accompanied by an increase in pressure >8 cm H_2O from the baseline values were termed nonvoiding contractions dur-

ing the storage phase. We also determined the average number of nonvoiding contractions/min between voiding contractions. These parameters were calculated in each rat following the initial stabilization period (i.e., 60 minutes) using the average values of 3 to 5 bladder contractions.

Furthermore, we collected voided fluid to determine the voided volume. The PVR was measured by immediately emptying the bladder after voiding through the catheter using gravity. The sum of the voided and residual urine volumes indicated the bladder capacity. The ratio of voided volume over the bladder capacity revealed the VE. We sought to examine the effects of different doses of acotiamide on bladder function in the control group. Thus, we subcutaneously administered acotiamide at doses of 1, 10, and 100 mg/kg, and compared the CMG parameters after treatment with those obtained at baseline. In the PNC group, we administered vehicle or acotiamide (10 and 100 mg/kg), and evaluated the CMG parameters to determine the effect of acotiamide on DU. We selected the dose of acotiamide based on a previous paper examining the effect of acotiamide on gastrointestinal motility using a rat model [9].

Drug Administration

A 5% weight/volume glucose solution, including 5% volume dimethyl sulfoxide, was used to dissolve acotiamide (Zeria Pharmaceutical Co., Ltd., Tokyo, Japan) [9].

Statistical Analysis

Data are presented as the mean ± standard error of the mean. The JMP software (ver. 9; SAS Institute, Cary, NC, USA) was utilized to perform statistical analyses. CMG parameters were analyzed by nonparametric paired t-test (Wilcoxon signed-rank test). The P-values <0.05 denoted statistically significant differences.

RESULTS

Animals

This study involved 28 rats (12 and 16 in the control and PNC groups, respectively). Among them, 24 rats (12 per group) were subjected to awake CMG.

Body and Bladder Weights

There were no differences observed in body weight between the PNC and control groups (213 ± 3.40 g vs. 208 ± 2.40 g, respectively; P = 0.31). In contrast, statistically significant increases in bladder weight were noted in the PNC group versus the control group (0.14 ± 0.015 g vs. 0.057 ± 0.010 g, respectively; P = 0.0008).

Awake Continuous CMG

Compared with the control group, the PNC group exhibited statistically significant increases in ICI (440 ± 35 seconds vs. 1,100 ± 91 seconds, respectively; P < 0.0001), threshold pressure (8.20 ± 0.43 cm H_2O vs. 12 ± 0.90 cm H_2O, respectively; P = 0.0038), voided volume (590 ± 46 μL vs. 1,700 ± 160 μL, respectively; P < 0.00010), PVR (0 ± 0 μL vs. 688 ± 210 μL, respectively; P = 0.0045), and bladder capacity (590 ± 46 μL vs. 2,400 ± 320 μL, respectively; P > 0.00010). However, it showed statistically significant decreases in bladder contraction amplitudes during voiding (32 ± 2.1 cm H_2O vs. 21 ± 0.99 cm H_2O, respectively; P = 0.0005) and VE (100% ± 0% vs. 78% ± 5.0%, respectively; P = 0.0006).

Administration of Acotiamide in the Control Group

Fig. 1 and Table 1 show representative CMG traces and parameters before and after the administration of acotiamide, respectively. In the control group, there were no statistically significant changes recorded following treatment with in 1-mg/kg acotiamide (n = 4) compared with baseline. However, compared with baseline, treatment with 10-mg/kg acotiamide led to statistically significant elevations in contraction amplitudes (28.10 ± 3.60 cm H_2O vs. 42 ± 4.40 cm H_2O, respectively; P = 0.0074) (n = 4). Compared with baseline, treatment with 100-mg/kg acotiamide 100-mg/kg resulted in statistically significant elevations in contraction amplitudes (33.80 ± 4.40 cm H_2O vs. 57.60 ± 4.10 cm H_2O, respectively; P = 0.01). However, it also induced statistically significant reductions in ICI (444 ± 49 seconds vs. 148 ± 24 seconds, respectively; P = 0.014) and bladder volume (592 ± 66 μL vs. 206 ± 38 μL, respectively; P = 0.013) (n = 4).

Administration of Vehicle or Acotiamide in the PNC Group

Fig. 2 and Table 2 show representative CMG traces and parameters before and after the administration of acotiamide, respectively. In the PNC group, there were no statistically significant changes recorded in CMG parameters after treatment with vehicle (n = 4) or 10-mg/kg acotiamide (n = 6) compared with baseline. Compared with baseline, treatment with 100-mg/kg acotiamide induced statistically significant decreases in ICI (1,025 ± 186 seconds vs. 578 ± 161 seconds, respectively; P = 0.012), bladder capacity (1,841 ± 323 μL vs. 871 ± 174 μL, respectively; P = 0.0059) and PVR (223 ± 46 μL vs. 44 ± 22 μL, respec-

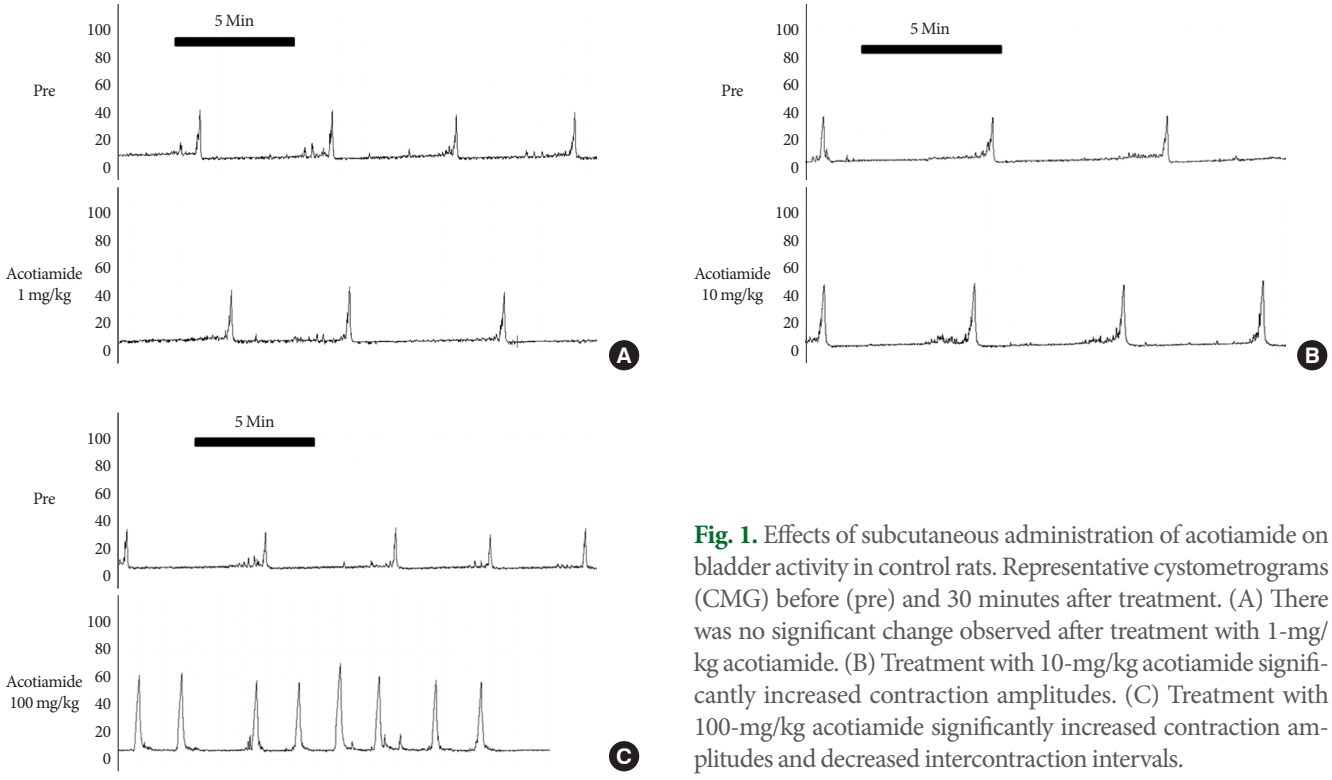

Fig. 1. Effects of subcutaneous administration of acotiamide on bladder activity in control rats. Representative cystometrograms (CMG) before (pre) and 30 minutes after treatment. (A) There was no significant change observed after treatment with 1-mg/kg acotiamide. (B) Treatment with 10-mg/kg acotiamide significantly increased contraction amplitudes. (C) Treatment with 100-mg/kg acotiamide significantly increased contraction amplitudes and decreased intercontraction intervals.

Table 1. Cystometrography (CMG) parameters prior to and following the administration of acotiamide in the control group

Variable	ICI (sec)	BP	PT	Amp.	NVC/min	Comp.	VV (μL)	PVR (μL)	Cap. (μL)	VE
Pre (n = 4)	441 ± 84	4.97 ± 0.38	8.79 ± 1.04	33.40 ± 3.27	0.13 ± 0.07	0.16 ± 0.01	588 ± 111	0 ± 0	588 ± 111	1 ± 0
Acotiamide 1 mg/kg (n = 4)	515 ± 135	4.54 ± 0.31	9.11 ± 1.26	36.20 ± 3.66	0.11 ± 0.05	0.15 ± 0.01	688 ± 179	0 ± 0	688 ± 179	1 ± 0
P-value	0.29	0.23	0.60	0.10	0.60	0.73	0.29	NA	0.29	NA
Pre (n = 4)	441 ± 61	3.93 ± 0.42	8.16 ± 0.64	28.10 ± 3.60	0.11 ± 0.04	0.15 ± 0.02	588 ± 81	0 ± 0	588 ± 81	1 ± 0
Acotiamide 10 mg/kg (n = 4)	288 ± 30	4.33 ± 0.52	6.61 ± 0.31	42.00 ± 4.40	0.18 ± 0.11	0.19 ± 0.01	380 ± 42	0 ± 0	380 ± 42	1 ± 0
P-value	0.11	0.071	0.068	0.007	0.45	0.38	0.10	NA	0.10	NA
Pre (n = 4)	444 ± 49	4.68 ± 0.42	7.85 ± 0.61	33.80 ± 4.40	0.10 ± 0.038	0.19 ± 0.03	592 ± 66	0 ± 0	592 ± 66	1 ± 0
Acotiamide 100 mg/kg (n = 4)	148 ± 24	5.23 ± 0.21	6.84 ± 0.59	57.60 ± 4.10	0.28 ± 0.21	0.16 ± 0.05	206 ± 38	0 ± 0	206 ± 38	1 ± 0
P-value	0.014*	0.17	0.0005*	0.01*	0.38	0.64	0.013*	NA	0.013*	NA

Values are presented as mean ± standard deviation.
ICI, intercontraction interval; BP, baseline pressure; PT, pressure threshold; Amp., amplitude; NVC, nonvoiding contraction; Comp., bladder compliance; VV, voided volume; PVR, postvoid residual; Cap., bladder capacity; VE, voiding efficiency; NA, not available.
CMG parameters were analyzed by Wilcoxon signed-rank test.
*P < 0.05, statistically significant differences.

tively; P = 0.0023). However, it also resulted in statistically significant increases in contraction amplitudes (22.09 ± 1.76 cm H_2O vs. 43.84 ± 6.87 cm H_2O, respectively; P = 0.012), and VE (0.87 ± 0.023 vs. 0.94 ± 0.031, respectively; P = 0.029). Furthermore, there was no significant difference between bladder capacity (592 ± 66 μL vs. 871 ± 174 μL; P = 0.122, Wilcoxon-Mann-Whitney test) or ICI values (444 ± 49 seconds vs. 578 ± 161 seconds; P = 0.67, Wilcoxon-Mann-Whitney test) of acotiamide-untreated control and 100-mg/kg acotiamide-treated PNC rats.

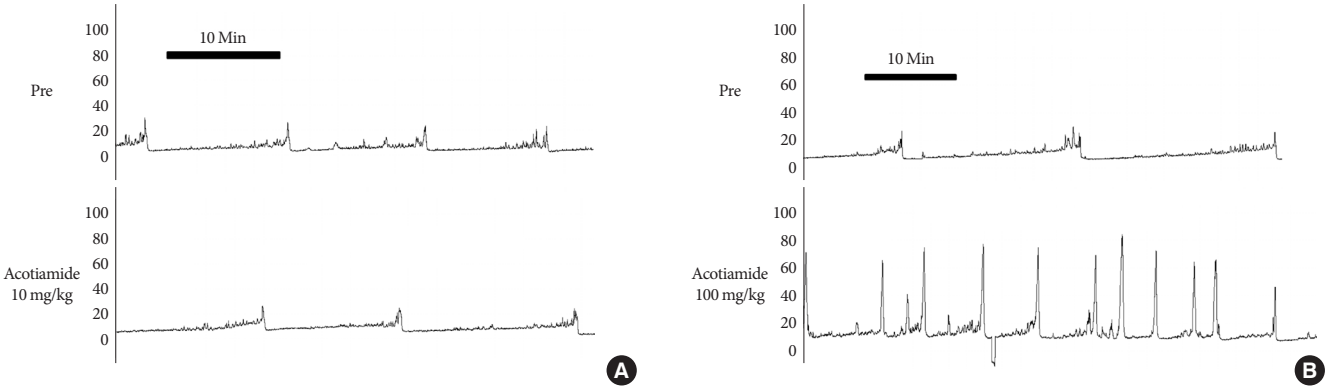

Fig. 2. Effects of subcutaneous (S.C.) administration of acotiamide on bladder activity in pelvic nerve crush rats. Representative cystometrography before (pre) and 30 minutes after treatment. (A) There was no significant change after treatment with 10-mg/kg acotiamide. (B) Treatment with 100-mg/kg acotiamide significantly increased contraction amplitudes and decreased intercontraction intervals.

Table 2. Cystometrography (CMG) parameters prior to and following the administration of acotiamide in the pelvic nerve crush (PNC) group

Variable	ICI (sec)	BP	PT	Amp.	NVC/min	Comp.	VV (μL)	PVR (μL)	Cap. (μL)	VE
Saline (n=4)	1,359±179	5.30±0.78	14.30±2.59	22.80±1.70	0.19±0.05	0.43±0.10	1,783±377	1,811±994	3,594±966	0.50±0.22
Vehicle (n=4)	1,552±392	4.75±0.60	10.00±1.52	21.50±1.65	0.13±0.04	0.78±0.23	1,953±1,315	2,128±966	4,082±1396	0.60±0.17
P-value	0.58	0.076	0.13	0.15	0.48	0.087	0.87	0.13	0.69	0.21
Saline (n=6)	998±80	4.20±0.37	10.05±0.75	20.10±1.71	0.12±0.02	0.39±0.07	1,775±255	406±112	2,113±298	0.82±0.04
Acotiamide 10 mg/kg (n=6)	1,242±246	3.96±0.52	8.30±0.63	20.87±1.28	0.17±0.07	0.48±0.05	1,726±258	386±110	2,181±310	0.82±0.04
P-value	0.38	0.31	0.13	0.67	0.52	0.24	0.81	0.83	0.81	0.99
Saline (n=6)	1,025±186	5.31±0.63	11.31±1.47	22.09±1.76	0.02±0.01	0.33±0.04	1,619±288	223±46	1,841±323	0.87±0.02
Acotiamide 100 mg/kg (n=6)	578±161	5.99±0.38	9.82±1.20	43.84±6.87	0.013±0.01	0.29±0.07	827±176	44±22	871±174	0.94±0.03
P-value	0.012*	0.15	0.034*	0.012*	0.8	0.33	0.005*	0.023*	0.006*	0.029*

ICI, intercontraction interval; BP, baseline pressure; PT, pressure threshold; Amp., amplitude; NVC, nonvoiding contraction; Comp., bladder compliance; VV, voided volume; PVR, postvoid residual; Cap., bladder capacity; VE, voiding efficiency.
CMG parameters were analyzed by Wilcoxon signed-rank test.
*$P<0.05$, statistically significant differences.

DISCUSSION

The major results of this study are as follows. In the control group, treatment with 10-mg/kg acotiamide significantly increased contraction amplitudes, while treatment with 100-mg/kg acotiamide significantly increased contraction amplitudes and decreased ICI. In the PNC group, treatment with 100-mg/kg acotiamide significantly decreased ICI, bladder capacity, and PVR, whereas it increased contraction amplitudes and VE. The clinical features and pathophysiology of UAB/DU have been previously elucidated. Nevertheless, thus far, randomized clinical trials have not identified effective drugs for the treatment of UAB/DU [10]. For instance, ASP8302 (a new positive allosteric modulator for the muscarinic M3 receptor) failed to demonstrate efficacy in patients with UAB [11]. Thus, there are unmet medical needs in this setting.

In vivo studies revealed that acotiamide improves gastric motility through the inhibition of AChE activity in dogs [12, 13] and rats [9]. In a previous organ bath study using rat and human bladder strips, Singh et al. [14] showed that acotiamide di-

rectly induced nerve-mediated contractions of the bladder through antagonism with prejunctional muscarinic receptors. Nevertheless, thus far, studies have not used animal models of UAB with lower urinary tract dysfunction to examine bladder activity *in vivo* after treatment with acotiamide. Therefore, the present investigation is the first to demonstrate the therapeutic efficacy of acotiamide on bladder function using an *in vivo* animal model of UAB.

The results obtained in the control group suggest that low-dose acotiamide affected the bladder efferent and/or detrusor function, while high-dose acotiamide additionally stimulated bladder afferent pathways to decrease bladder capacity. Currently, there is a lack of *in vivo* data regarding the effects of acotiamide on normal rat bladder function. Therefore, such data may be meaningful for the future functional urological study of acotiamide.

According to the results obtained in the PNC group, the sites of action of high-dose acotiamide in PNC rats included both bladder afferent and efferent pathways, similar to the control group. Our previous study using a similar PNC rat model showed that intravesical instillation of a TRPV4 agonist induced activation of bladder afferent activity, as evidenced by a significant decrease in functional bladder capacity without changes in bladder contraction amplitudes [4]. In addition, we found that administration of 100-mg/kg acotiamide in PNC rats improved ICI or bladder capacity to their levels in acotiamide-untreated control rats, suggesting that the acotiamide 100-mg/kg treatment normalized the UAB condition without inducing overactive bladder-like functional changes in PNC rats. Taken together, the findings indicate that acotiamide may be an effective drug therapy for UAB due to DU.

In this study, dosage selection was based on the results of a previous study of rat gastric walls [9]. However, the clinical dose of acotiamide in humans is 300 mg/day [7], which is lower than the dosage used in the present study. Kawachi et al. [9] reported that species difference may be, at least partly, responsible for the variations in the efficacy of acotiamide for gastric contraction observed between rats and humans. AChE inhibitory activity in rats and humans is similar [7]. Nevertheless, the effective dose of acotiamide in rats may be higher than that administered in humans [12, 15]. The gastroprokinetic drug itopride acts in a similar manner to acotiamide, exhibiting AChE inhibitory activity. Notably, a similar difference between the effective doses of itopride in rats and humans has been shown [16]. Thus, additional clinical studies are required to precisely determine the effective dose of acotiamide for the treatment of UAB in humans.

There are a few limitations in this study. First, we used female rats in this study because our PNC model has only been verified in female rats [4]. However, in a previous report, Jeong et al. [17] demonstrated that UAB occurs in both sexes; thus, further studies using male PNC animal models are needed to examine the efficacy of acotiamide for male UAB. Secondly, we did not evaluate the effects of acotiamide on bladder sensory nerves. So far, there has been no report regarding the evaluation of the direct effect of acotiamide on sensory systems in the bladder or other organs. Therefore, a further study will be planned to investigate the effect of acotiamide on bladder afferent function. Thirdly, we did not evaluate other systemic effects, such as those on blood pressure or respiratory function. In clinical practice, the use of AChE inhibitors has been associated with adverse effects on the central and peripheral nervous systems. Nonetheless, severe adverse events (e.g., cholinergic crisis) have not been recorded in clinical trials of acotiamide conducted to date [7]. Thus, we expect that acotiamide will be linked to a relatively favorable safety and tolerability profile in clinical practice. However, further clinical investigations are warranted to comprehensively examine the usefulness of acotiamide in the treatment of patients with UAB.

In conclusion, in PNC rats, a recently established animal model of UAB, treatment with 100-mg/kg acotiamide significantly improved inefficient voiding, as evidenced by decreased ICI, bladder capacity and PVR, and increased contraction amplitudes and VE. According to these findings, acotiamide may be used as a therapeutic agent for UAB due to DU. Acotiamide appears to exert its effects through activation of bladder afferent and efferent function.

AUTHOR CONTRIBUTION STATEMENT

· Conceptualization: *ET, NY*
· Data curation: *ET*
· Formal analysis: *ET*
· Funding acquisition: *ET*
· Methodology: *ET*
· Project administration: *ET*
· Visualization: *ET*
· Writing - original draft: *ET, KN, NY*
· Writing - review & editing: *JK, TS, SA, TF*

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