

Acotiamide hydrochloride hydrate added to combination treatment with an α -blocker and a cholinergic drug improved the QOL of women with acute urinary retention: case series

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Abstract: Acute urinary retention is the most common urological emergency. To resolve this emergency, urethral catheterization is performed. If the procedure fails and permanent transurethral catheterization is required, the patient's quality of life is significantly affected. Therefore, catheter-free treatment is the ideal goal of therapy for patients with acute urinary retention. Especially, for women, placement of a catheter poses a cosmetic problem. Therefore, the aim of this study was to treat female patients who had already received urapidil/distigmine bromide with acotiamide. Acotiamide was administered at a dose of 100 mg three times daily for 2 weeks, and the outcome of trial without catheter was evaluated. Only female patients were enrolled for this study. Treatment proved successful and all patients become catheter free.

Keywords: female, acute urinary retention, acotiamide hydrochloride hydrate

Introduction

An incidence of acute urinary retention (AUR) in women occurred in 7 per 100,000 population per year, and the male-to-female ratio was 13:1 in one Scandinavian study.¹ Patients may require permanent transurethral catheterization (PTC); however, if PTC lasts too long, catheter-associated urinary tract infections (CAUTIs) will develop at a reported incidence of about 1 million/year.² In addition, in such cases, patients complain of pain, catheter discomfort, and fever. Finally, CAUTIs can lead, for example, to bladder stone, cystitis, and pyelonephritis. Thus, patients suffer a significant loss of their quality of life (QOL).

In this study, we added acotiamide hydrochloride hydrate to the combination treatment with an α -blocker and a cholinergic drug for AUR, aiming at a decrease of the prevalence of CAUTIs.

Case presentation

The aim of this prospective single-arm study was to treat first-episode AUR female patients who had already received urapidil/distigmine bromide with acotiamide. Acotiamide was administered at a dose of 100 mg three times daily for 2 weeks, and the outcome of trial without catheter (TWOC) after treatment was evaluated (Figure 1). The protocol was approved by the Ethics Committee of Sakai-Onshinkai Hospital. Informed consent was obtained from patients before the start of the study. All patients were recruited in this hospital between January 2014 and December 2016.

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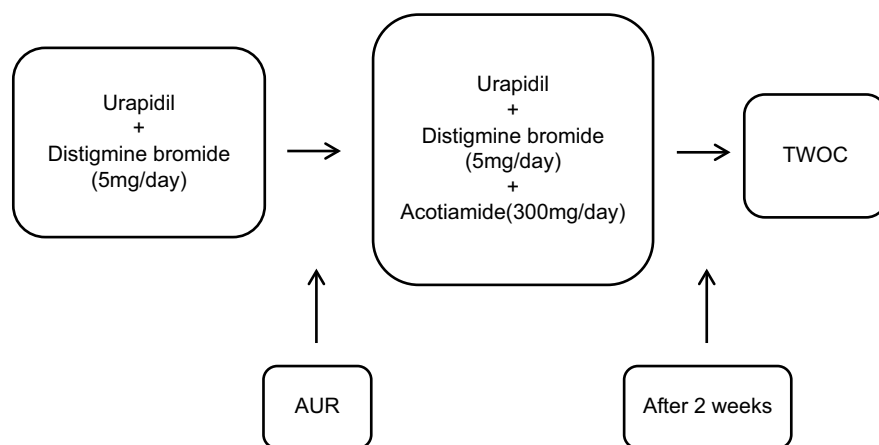


Figure 1 Study design.

Abbreviation: AUR, acute urinary retention; TWOC, trial without catheter.

We enrolled five female patients aged 67–89 years (mean 78.2 years). Two patients have diabetes, two patients have cerebral infarct, and one has lumbar canal stenosis. These diseases led to the development of neurogenic bladder (NGB) manifesting AUR. The dose of distigmine bromide was 5 mg/day for all patients, and the dose of urapidil was 30 mg/day for two patients and 60 mg/day for the other three patients. All the patients were 400 mL over of urinary retention volume. The clinical characteristics of the patients are listed in Table 1. The success rate for a TWOC was 100% at 2 weeks. The mean voiding volume at 2 weeks was 176 mL. The mean postvoid residual urine (PVR) at 2 weeks was 71 mL. The mean rate of PVR at 2 weeks was 27.1%. After 2 months, the mean PVR was 43.4 ± 52.5 mL.

Discussion

AUR is the most common emergency urological disease in the world and is characterized by sudden and painful inability to urinate. However, due to these symptoms, it is easily diagnosed. In most male patients with AUR, development of benign prostatic hyperplasia, severe lower urinary tract symptoms, increased PVR, aging, and NGB increase AUR. A TWOC is the standard care for AUR³ in which the inserted catheter is typically removed after 1–3 days. This procedure

will typically allow patients to void in 23%–40% of the cases. Moreover, a TWOC followed by an α -blocker improves the success rate in men.^{4,5} In women, AUR often develops after surgery, cystitis, detrusor underactivity (DU), gynecological disease, hysteria, and so on.⁶ Moreover, surgery to remove obstructions is not performed in female patients and must, therefore, endure permanent catheter placement. Thus, there is a significant loss of QOL for these patients. In female DU patients, Yamanishi et al showed that combination therapy of urapidil plus distigmine bromide improved outcomes compared to urapidil monotherapy.⁷ Despite improvements in therapy, symptoms in patients persist and they continue to suffer; thus, new treatment needs to be developed.

It remains largely unknown whether the administration of other compounds to patients already treated with an α -blocker plus distigmine bromide will improve outcomes and further reduce symptoms. To our knowledge, the utility of combination therapy using three drugs (urapidil/distigmine bromide plus acotiamide) in a TWOC after AUR has not been studied to date. However, despite the success achieved in the present study population, it might be argued that patients were overtreated; this should be evaluated in future investigations.

Despite the positive outcome, there are several limitations of the study in terms of study design: “obviously, controlled,

Table 1 Patients' characteristics of five cases

	Age	Initial illness	Preliminary medication	PVR volume (mL) after 2 weeks	PVR volume (mL) after 2 months
Case 1	67	Cerebral infarct	Urapidil (30 mg) + distigmine bromide (5 mg)	70	14
Case 2	85	Lumbar canal stenosis	Urapidil (30 mg) + distigmine bromide (5 mg)	80	10
Case 3	79	Diabetes	Urapidil (60 mg) + distigmine bromide (5 mg)	140	124
Case 4	89	Cerebral infarct	Urapidil (60 mg) + distigmine bromide (5 mg)	0	0
Case 5	71	Diabetes	Urapidil (60 mg) + distigmine bromide (5 mg)	56	69

Abbreviation: PVR, postvoid residual urine.

randomized, double-blind clinical trials have to be planned and performed to confirm our preliminary results.” However, our study is the first to report the use of acotiamide in female patients with AUR. This drug is effective in patients with functional dyspepsia and appears to exert an antagonistic effect on muscarinic M1, M2, and M3 receptors, thereby inhibiting the negative feedback system by blocking muscarinic auto receptors that regulate acetylcholine release.⁸ Especially, Doi et al think that this drug is a potent antagonist not for muscarinic M3 receptor but for both muscarinic M1 and M2 receptors.⁹ Our previous study showed that substituting acotiamide for distigmine bromide decreased PVR by ~45 mL after 2 weeks of treatment. In female patients, a decrease in PVR of about 33 mL was observed after a treatment period of 2 weeks in which distigmine bromide changed from acotiamide.¹⁰ In this study, despite combination treatment with an α -blocker and a cholinergic drug, AUR was induced in female patients with NGB. Therefore, we surmise that this protocol improved the voiding function for AUR in female patients by improved regulation of detrusor function. Remarkably, our results demonstrated a success rate for TWOC of 100% at 2 weeks. This result suggests that combination therapy of urapidil/distigmine bromide and acotiamide could have the potential to achieve a relatively higher success rate for TWOC. Moreover, the addition of distigmine bromide to acotiamide did not appear distinctive to the adverse events (AEs) of diarrhea and diaphoresis using distigmine bromide during the short medication period. This study alludes to the safety and tolerability of this treatment combination particularly given the advanced age of our patient cohort, where the mean age was 78.2 years. However, we must be careful because we do not know fully the risks of developing AE after long-term administration of this treatment combination.

Finally, we did not perform pressure flow studies in this report; therefore, we cannot conclude the extent of effects

of acotiamide on detrusor function at this time. However, urodynamic studies will be an integral part of our future studies for female AUR patients treated with acotiamide. A prospective randomized study is also necessary to determine whether this combination therapy is superior to that of urapidil/distigmine bromide.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Klarskov P, Andersen JT, Asmussen CF, et al. Acute urinary retention in women: a prospective study of 18 consecutive cases. *Scand J Urol Nephrol.* 1987;21(1):29–31.
2. Edwards JR, Peterson KD, Andrus ML, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007. *Am J Infect Control.* 2007;35(5):290–301.
3. Manikandan R, Srirangam SJ, O’Reilly PH, Collins GN. Management of acute urinary retention secondary to benign prostatic hyperplasia in the UK: a national survey. *BJU Int.* 2004;93(1):84–88.
4. Kumar S, Tiwari DP, Ganesamori R, Singh SK. Prospective randomized placebo-controlled study to assess the safety and efficacy of silodosin in the management of acute urinary retention. *Urology.* 2013;82(1):171–175.
5. Maldonado-Avila M, Manzanilla-Garcia HA, Sierra-Ramirez JA, et al. A comparative study on the use of tamsulosin versus alfuzosin in spontaneous micturition recovery after transurethral catheter removal in patients with benign prostatic growth. *Int Urol Nephrol.* 2014;46(4):687–690.
6. Turner-Warwick R. Impaired voiding efficacy and retention. *Clin Obstet Gynaecol.* 1978;5(1):193–207.
7. Yamanishi T, Yasuda K, Kamai T, et al. Combination of a cholinergic drug and an alpha-blocker is more effective than monotherapy for the treatment of voiding difficulty in patients with underactive detrusor. *Int J Urol.* 2004;11(2):88–96.
8. Yoshii K, Hirayama M, Nakamura T, et al. Mechanism for distribution of acotiamide, a novel gastroprokinetic agent for the treatment of functional dyspepsia, in rat stomach. *J Pharm Sci.* 2011;100(11):4965–4973.
9. Doi Y, Murasaki O, Kaibara M, et al. Characterization on functional effects of Z-338, a novel gastrokinetic agent, on the muscarinic M1, M2, and M3 receptors expressed in *Xenopus* oocytes. *Eur J Pharmacol.* 2004;505(1–3):31–35.
10. Sugimoto K, Akiyama T, Shimizu N, et al. A pilot study of acotiamide hydrochloride hydrate in patients with detrusor underactivity. *Res Rep Urol.* 2015;7:81–83.

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