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ORIGINAL ARTICLE

Human urine with solifenacin intake but not tolterodine or darifenacin intake blocks detrusor overactivity

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Abstract The objective of the study was to evaluate the local effects of three antimuscarinics excreted into human urine after oral ingestion. Two normal adult collected their voided urine after taking oral doses of tolterodine, darifenacin, and solifenacin for 7 days with a 14-day washout period. The urodynamic effect of intravesically administered human urine on carbachol-induced bladder overactivity was studied in female rats. Cystometric parameters were measured during continuous infusion of saline and human urine and then a mixture of carbachol (30 μM) and human urine. Carbachol significantly reduced the intercontraction interval and bladder capacity in the control (urine taken in the absence of oral antimuscarinics) and tolterodine- or darifenacin-administered groups. However, human urine obtained after taking solifenacin prevented the carbachol-induced detrusor overactivity. Urine excreted after oral ingestion of solifenacin provides a localized pharmacological advantage for the treatment of the overactive bladder syndrome.

Keywords Detrusor overactivity · Antimuscarinics · Solifenacin · Darifenacin · Tolterodine

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Introduction

The overactive bladder (OAB) syndrome is a common and challenging global medical problem [1, 2]. Pharmacological treatment with muscarinic receptor antagonists has been the main stay of therapy for patients suffering from this syndrome [3, 4]. It is widely known that the efficacy of these drugs is mediated through the blockade of the muscarinic receptor in the detrusor muscle and the urothelium [3, 4]. Historically, the pharmacological site of action for these drugs has ignored the impact of the localized effects in the bladder urothelium. Evidence shows that muscarinic mechanisms are also involved in the bladder sensory function, which supports the idea of a localized pharmacological action on the bladder urothelium [5–7].

Following oral administration, currently available antimuscarinic agents are excreted into the urine following metabolism to varying degrees of inactive and active metabolites [8]. Trospium has 60% of an active metabolite excreted into the urine, which has shown a significant inhibitory effect over tolterodine LA and oxybutynin in a rat model of detrusor overactivity [9]. Solifenacin succinate has approximately 15% active compound excreted into the urine as compared to 3% and less than 1% with darifenacin and tolterodine LA, respectively [10]. We hypothesized that antimuscarinic agents excreted into the urine might have different degrees of local inhibitory effects on muscarinic

receptors in the urothelium and suburothelial sensory fibers and suppress bladder overactivity.

Materials and methods

Drugs and evaluation

Drugs used in this study were clinically approved solifenacin, tolterodine, darifenacin, and carbachol. Oral tablets of darifenacin 7.5 mg, tolterodine LA 4 mg, and solifenacin succinate 5 mg were taken once daily for 7 days by two healthy adult volunteers. The volunteers were maintained on usual fluid and dietary intake with no other concurrent medications. Urine was collected on the seventh day for darifenacin, tolterodine LA, and solifenacin. The drugs were taken in random order with a 14-day washout period between drugs. The collected urine from the two volunteers was then mixed together and subsequently tested intravesically on the rats (N=6, for each group) in a blinded fashion. Human urine taken in the absence of antimuscarinics (and other drugs) served as the control. Carbachol was used to stimulate detrusor overactivity and confirmed the effects of cystometric parameters following the instillation of the urine containing the various agents [9].

Animal model

For this study, female Sprague–Dawley rats weighing 200–250 g were anesthetized with a subcutaneous injection of urethane (1.1 g/kg). An abdominal midline incision was performed, and the ureters were ligated followed by placement of a tranvesical catheter with a fire-flare tip (PE-50).

Cystometography

The transvesical catheter was inserted into the dome of the bladder for bladder filling and pressure recording after abdominal closure. A three-way stopcock was connected to the transvesical catheter to monitor bladder pressure. Cystometry was performed with physiological saline at room temperature at an infusion pump rate of 0.04 mL/min (Harvard Apparatus, Holliston, MA, USA). Four parameters were measured: (1) intercontraction interval (ICI; time between two voiding cycles), (2) pressure threshold (bladder pressure immediately before micturition), (3) maximum voiding pressure (the maximum bladder pressure during micturition), and (4) bladder capacity. After baseline cystometry with saline infusion was performed, human urine was infused into the bladder to examine the effects of antimuscarinics excreted in the urine on normal bladder activity. Following this, human urine mixed with 30 μM carbachol chloride (Sigma Chemical, St. Louis, MO, USA) was infused into the bladder at the same rate. The cystometric parameters were evaluated and compared during continuous infusion of saline and urine with and without carbachol for 1 h.

Statistical analysis

The results are presented as mean±standard error (SE). A p value less than 0.05 was considered statistically significant. Statistical comparisons were conducted using Prism statistical software (GraphPad Software, San Diego, CA, USA). An analysis of variance was used to compare the cystometric parameters among the groups.

Results

Normal human urine (control) had no significant effects on cystometric parameters when instilled into the normal rat bladder. Human urine collected after oral intake of darifenacin, solifenacin, and tolterodine LA also had no significant effect on cystometric variables as shown in Fig. 1 and Table 1.

When bladders were infused with human urine containing carbachol to induce detrusor overactivity, the ICI was significantly reduced when urine excreted with darifenacin (1,042 vs 768 s, p=0.0009) or tolterodine LA (1,071 vs 706 s, p=0.02). In contrast, human urine containing carbachol increased the ICI when urine excreted with solifenacin (656 vs 728 s, p=0.607; Fig. 2).

The maximum voiding pressure and the pressure threshold were not statistically changed by intravesical infusion of human urines with or without carbachol in the solifenacin and tolterodine LA groups (Table 1). However, the maximum voiding pressure increased with all three agents but significantly increased when carbachol was added to urine with darifenacin (53 vs 62 cmH_2O, p= 0.0004). The clinical significance of this is unclear.

Statistical decreases in bladder capacity were noted with the control, tolterodine, and darifenacin groups (percentage decreases in bladder capacity 47%, 28%, and 26%, respectively). In contrast, the solifenacin group showed an increase in bladder capacity by 27% suggesting that solifenacin has unique localized bladder effects that can overcome and inhibit the effects of carbachol.

Discussion

The present study evaluated the effect of three antimuscarinic agents, tolterodine, darifenacin, and solifenacin, excreted into human urine to evaluate if parent drug and/

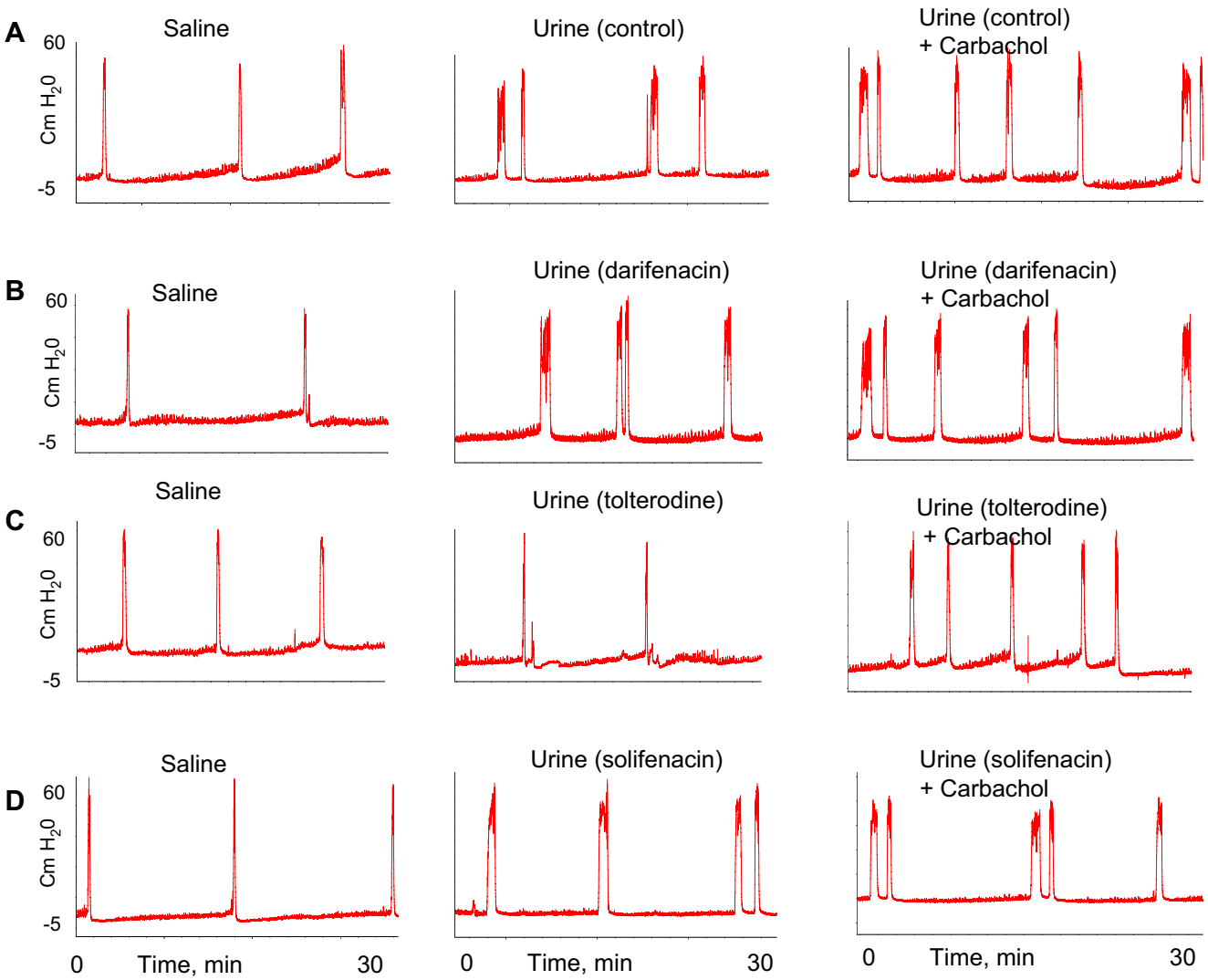

Fig. 1 Representative cystometrograms during intravesical instillations of urine from humans taking antimuscarinics. The intercontraction interval was decreased with intravescial instillation of the control human urine with carbachol chloride (30 μM) compared to prior infusion of human urine without carbachol (**a**). Urine from humans taking solifenacin succinate (**d**) showed no decrease in intercontraction intervals on carbachol instillation. In contrast, darifenacin (**b**) and tolterodine (**c**) demonstrated actions similar to those with the control urine

or drug metabolites produced a local inhibitory effect in the rat model of detrusor overactivity. In our current study, we demonstrated that urine collected from the humans who had taken solifenacin suppressed carbachol-induced bladder overactivity, including an increase in the ICI and bladder capacity. However, urine collected after intake of tolterodine LA or darifenacin did not suppress carbachol-induced bladder overactivity. We suggest that the oral administration of solifenacin may have a local bladder effect during the storage phase.

Muscarinic receptors have been found on bladder urothelium cells and the suburothelium structure in addition to the detrusor muscle [11]. Yoshida et al. demonstrated that a basal release of acetylcholine from human bladder tissue is partly from the urothelium but not from a neural origin. Acetylcholine in association with other neurotransmitters from the urothelium, such as adenosine triphosphate and nitric oxide, has been demonstrated to have effects on afferent nerve endings [5, 7, 12]. Kim et al. demonstrated that intravesical antimuscarinic agents suppressed carbachol-induced ICI reduction but had no effect on normal bladder storage and contractile function [13], thus separating the local inhibitory effects of antimuscarinic agents during the storage phase from a reduction in voiding pressure. Furthermore, a recent study revealed that intravenous administration of darifenacin, an M3-selective muscarinic antagonist, reduced bladder afferent activity [14]. Thus, it appears that the beneficial therapeutic effects of antimuscarinic drugs may be partially mediated by their actions on sensory nerves [15].

Table 1 Cystometric variables of intravesical instillation of saline and human urine without and with carbachol; data are the mean±SE for six rats in each group

Variable and drugs taken	Intravesical instillation		
	Saline	Urine	Urine with carbachol
Intercontraction interval (s)			
Control	760±100	752±115	425±90*
Solifenacin	687±72	656±97	728±119
Tolterodine	1090±133	1071±140	706±93*
Darifenacin	1090±93	1042±82	768±70*
Bladder capacity (mL)			
Control	0.49±0.05	0.47±0.05	0.25±0.06*
Solifenacin	0.45±0.06	0.45±0.05	0.57±0.05
Tolterodine	0.66±0.09	0.64±0.08	0.46±0.04*
Darifenacin	0.72±0.07	0.69±0.10	0.51±0.10*
Maximum voiding pressure, cmH_2O			
Control	40.2±1.5	39.7±1.9	41.9±1.7
Solifenacin	49.4±3.8	51.0±3.9	55.9±1.5
Tolterodine	46.6±2.4	46.8±2.6	50.5±3.3
Darifenacin	52.8±1.9	54.3±1.6	62.4±2.5*
Pressure threshold (cmH_2O)			
Control	9.4±1.1	10.1±0.8	11.3±0.9
Solifenacin	10.8±1.0	11.7±1.1	11.5±1.3
Tolterodine	10.2±1.1	10.54±1.2	10.3±1.2
Darifenacin	13.5±1.6	12.9±1.2	13.4±1.6

*$P<0.05$ vs saline and urine alone

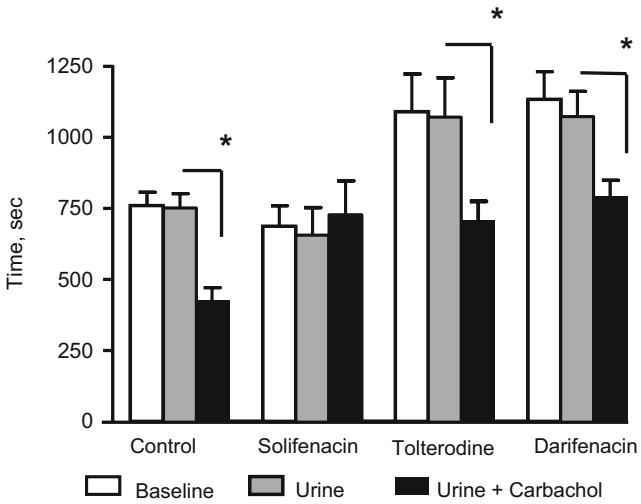

Fig. 2 Changes in the intercontraction interval with intravesical instillation of urine collected from humans who had taken antimuscarinics. Human urine with or without intake of antimuscarinic agents had no effect on intercontraction intervals when instilled into normal rat bladder. Intercontraction intervals were significantly decreased after the addition of carbachol to urine from humans who had taken tolterodine, darifenacin, or normal control urine ($P<0.005$). However, urine from humans who took solifenacin had prevented the effects of carbachol on intercontraction intervals

A previous study showed differences in the structure of the three antimuscarinics that result in different percentages of an intact compound excreted in the urine [10, 16]. Among them, solifenacin has the highest percentage of the intact compound excreted in the urine. Therefore, the current results showed that urine collected after taking solifenacin suppressed carbachol-induced detrusor overactivity, but the effect was not seen in the darifenacin and tolterodine group. Chapple et al. compared the therapeutic efficacy of solifenacin and tolterodine in treating OAB syndrome and found that flexible dosing with solifenacin is more effective in reducing OAB symptoms compared with the highest available dose of toleterodine [17]. In conjunction with the current study, we suggest that the clinical therapeutic advantage of solifenacin may partly relate to the local effect of solifenacin in the excreted urine.

One potential weakness of this study was the between-group differences in baseline ICI and bladder capacity. The causes that make the between-group differences are not clear. It could be due to various effects of anesthetics or transvesical catheter on micturition in the individual animal. However, the percentage of bladder capacity was decreased after adding carbachol into the control, tolterodine, and darifenacin groups (47%, 28%, and 26% decrease, respectively). In contrast, the solifenacin group showed an increase of 27%, which results might be beyond the impact of between-group differences in the baseline and suggest that solifenacin has a unique localized bladder effect that can overcome the effects of carbachol on reducing the ICI and bladder capacity.

Solifenacin when taken orally is up to 15% metabolically active when excreted in the urine [10]. However, since we only instilled the excreted urine for a short time, therefore, we suggest that the direct local action of the antimuscarinic drugs affect the muscarinic receptors in the urothelial or suburothelial tissues, rather than the detrusor smooth muscle. However, we cannot disregard that some fraction of the instilled antimuscarinic might affect muscarinic receptors in the detrusor smooth muscle. The present study seems to support that solifenacin, like trospium, may have a direct local action on muscarinic receptors in the urothelium, suburothelium, or sensory nerve.

Active urine metabolites or the parent compound of antimuscarinc agents and their local inhibitory effects on detrusor overactivity is an exciting research topic in neurourology. Antimuscarinic drugs such as solifenacin that are excreted into urine with active metabolites may produce a local topical effect in the bladder during the storage phase in addition to systemic effects on muscarinic receptors in the bladder wall. We postulate that excreted solifenacin in the urine might influence the bladder afferent activity and facilitate the relief of overactive syndrome. However, further experiments with intravesical instillation of solifenacin on bladder afferent activity are needed to be able to prove this hypothesis.

Conclusion

Following oral administration, each antimuscarinic agent exerts a range of effects on the bladder urothelium due to a variety of pharmacological activity from the parent compound, inactive or active metabolites following excretion into the bladder as studied in a rat detrusor overactivity model. Differences in localized bladder effects do exist among the antimuscarinic agents and may explain that those agents excreted into the urine with substantial activity might be more effective for treating bladder overactivity because of this local effect, in addition to the systemic effect effects on muscarinic receptors in the bladder wall.

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