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Effect of Oxybutynin on Reflex Micturition in the Decerebrate Dog as Determined by Urodynamic Evaluation

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The effect of oxybutynin on reflex micturition in the decerebrate dog was investigated by cystometric and striated urethral sphincter EMG studies. Reflex micturition consisting of bladder contraction and relaxation of the striated urethral sphincter occurred when a critical degree of filling was reached in the absence and presence of cumulative doses of 30, 100, and 300 μg/kg of oxybutynin. Oxybutynin at doses of 30, 100, and 300 μg/kg produced a significant increase in threshold volume during the collecting phase in a dose-dependent manner. In the urodynamic parameters of the emptying phase considered to be influenced greatly by cholinergic activity there was a small but significant decrease in the maximum bladder pressure only at a dose of 300 μg/kg. The present study supports urodynamically clinical usefulness of oxybutynin for the relief of symptoms associated with detrusor instability and hyperreflexia.

Key words: cystometry, sphincter EMG, detrusor instability and hyperreflexia

INTRODUCTION

Oxybutynin is a tertiary amine with a distinct peripheral anticholinergic activity, strong papaverinelike direct smooth muscle relaxant action, and local analgesic effect [Fredericks et al., 1975; Fredericks, 1978]. This drug has been clinically used for the relief of symptoms associated with detrusor instability and hyperreflexia [Diokno and Lapides, 1972; Moisey et al., 1980; Kawabe et al., 1986; Gajewski and Awad, 1986]. But, in previous studies, urodynamic evaluation of the effect of oxybutynin has not been thoroughly carried out. We attempted to investigate the effect of oxybutynin on the urodynamic parameters of both the collecting and emptying phase of the reflex micturition cycle in the decerebrate dog with cystometric and striated urethral sphincter EMG studies.

MATERIALS AND METHODS

Seven mongrel dogs were anesthetized with sodium thiamylal (15 mg/kg body weight, i.p.). The general experimental techniques were similar to those reported

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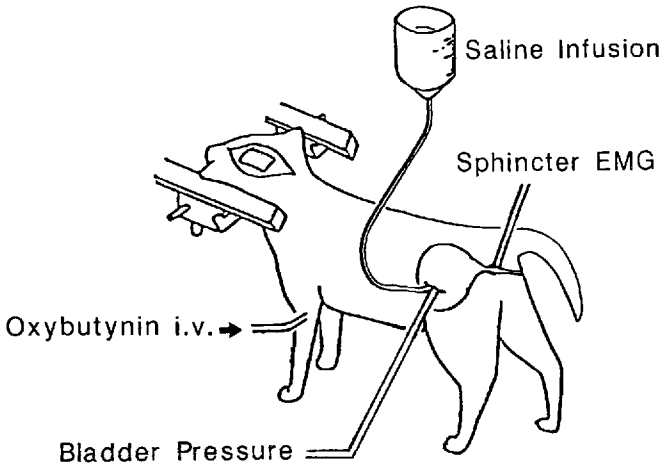

Fig. 1. Schematic diagram of experimental setup.

previously [Nishizawa et al., 1986, 1988]. A cannula through which oxybutynin could be intravenously administered was inserted into the cephalic vein. The trachea was intubated through a tracheostomy to assure an adequate airway and to allow enflurane anesthesia. The bilateral carotid arteries were ligated for future decerebration. The systemic blood pressure was monitored with a cannula in the carotid artery. Through a midline incision of the abdomen, the bladder, urethra, and ureters were exposed. Both ureters were divided and cannulated to drain urine. The bladder volume was maintained by only external infusion. A double lumen catheter was inserted through the dome into the bladder in order to empty the bladder freely from the urethra at the time of bladder contraction. One channel was connected to a Statham P50 transducer to measure bladder pressure, and the other was used to fill the bladder with warm saline at a rate of 1–6 ml/min by using an infusion pump (Nihon Kohden, TFV-1200A). Two hooked stainless-steel wire electrodes (diameter 0.1 mm) were inserted into the urethral wall to measure the striated urethral sphincter EMG. After closure of the incised abdomen, the animals were decerebrated at the precollicular-postmammillary level through a craniotomy in the prone position in order to create a reflex micturition in response to bladder filling. Next, after discontinuation of the enflurane anesthesia, the dog was placed in the standing position by fixing the vertebrae of the thoracic segments and pelvis in a stereotaxic instrument (Narishige, SN-2).

After the anesthetic effect wore off in the decerebrate state, a series of experiments were performed. By using cumulative dosing, the effects of oxybutynin on the reflex micturition induced by bladder filling were studied. As a control study, the cystometry and striated urethral sphincter EMG were performed during the reflex micturition in response to bladder filling in the absence of oxybutynin. After cumulative doses of oxybutynin (30, 100, 300 μg/kg) cystometric and striated urethral sphincter EMG studies were repeated during reflex micturitions induced by bladder filling (Fig. 1). The measurements were started 1 min after the administration of the drug. The bladder filling was stopped when the flow from the external meatus was observed.

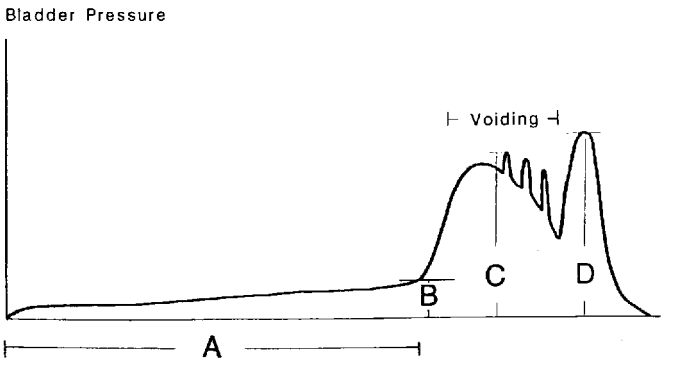

Fig. 2. Schematic diagram of urodynamic parameters. A: Threshold volume. B: Threshold pressure. C: Maximum bladder pressure. D: After-voiding bladder contraction pressure.

The following urodynamic parameters were evaluated: threshold volume, threshold pressure, voided volume, residual volume, maximum bladder pressure, voiding time, and after-voiding bladder contraction pressure. Figure 2 shows a schematic diagram of threshold volume, threshold pressure, maximum bladder pressure, and after-voiding bladder contraction pressure. The voiding time was measured by stopwatch with observation of the flow from the external meatus. The paired t-test was used to compare the urodynamic parameters obtained in control condition and after cumulative doses of oxybutynin, and $P < .05$ expressed significant statistical difference.

RESULTS

Figure 3 shows a representative recording of cystometric and striated urethral sphincter EMG studies performed in the control condition and after cumulative doses of oxybutynin (30, 100, 300 μg/kg). In the control condition and after cumulative doses of oxybutynin, reflex micturition with bladder contraction and relaxation of the striated urethral sphincter occurred when a critical degree of filling was reached. The prominent finding was an increase in the threshold volume and a decrease in the after-voiding bladder contraction pressure. The threshold volume was increased from 48 ml in the control condition to 52, 57, and 61 ml and after-voiding bladder contraction pressure was changed from 36 cmH_2O in the control condition to 40, 24, and 20 cmH_2O at cumulative doses of 30, 100, and 300 μg/kg of oxybutynin, respectively. There is no evident change in blood pressure, respiration, or heart rate.

The collected data of the urodynamic parameters in control conditions and after cumulative doses of oxybutynin are shown in Table I. Figures 4 and 5 show the effect of cumulative doses of oxybutynin on the urodynamic parameters during collecting and emptying phases for each individual dog. There was a significant increase in threshold volume during the collecting phase at doses of 30, 100, and 300 μg/kg of oxybutynin in a dose-dependent manner ($P < .05$). There was a small but significant decrease in maximum bladder pressure during the emptying phase at dose of 300 μg/kg of oxybutynin ($P < .05$). In five out of seven dogs, after-voiding bladder contraction with pressures of 47.2 ± 18.8 cmH_2O (means±S.D.) occurred in the

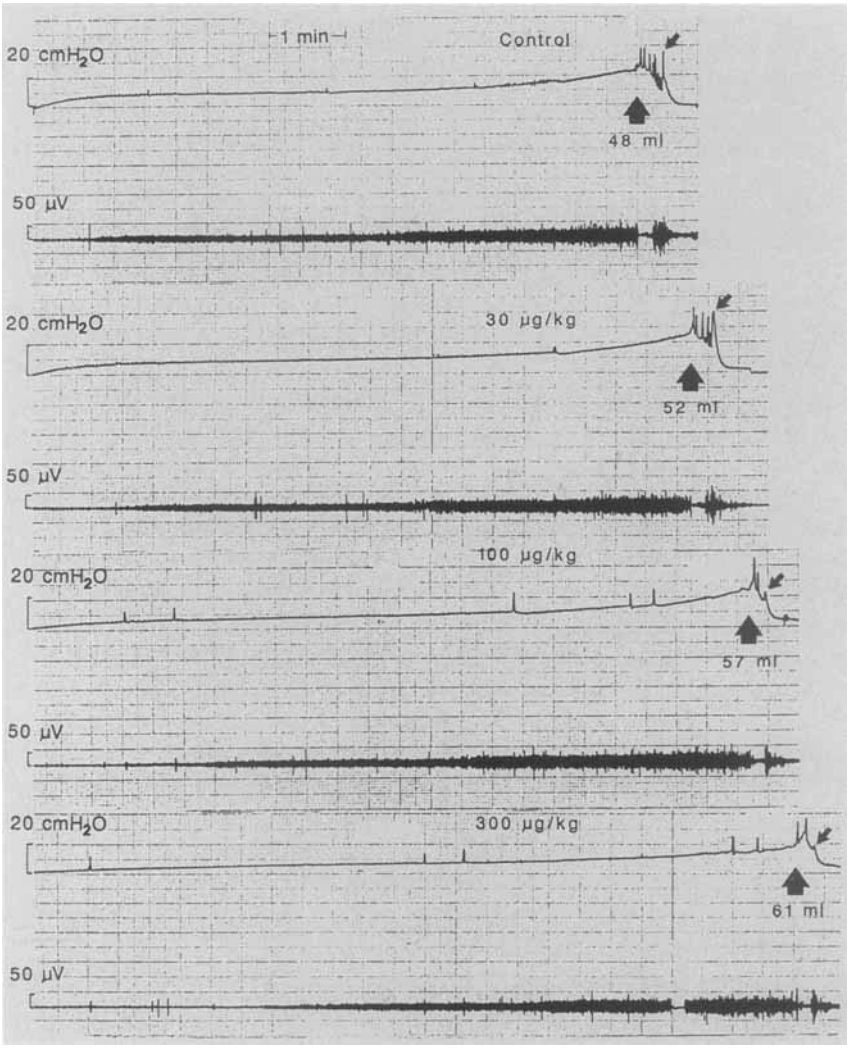

Fig. 3. Representative recording of cystometry and urethral sphincter EMG in control and after oxybutynin. Large arrows indicate start of reflex micturition, and small arrows indicate after-voiding bladder contraction. Threshold volume was 48, 52, 57, and 61 ml in control condition and at cumulative doses of 30, 100, 300 μg/kg of oxybutynin, respectively.

control condition and was decreased to pressures of 20.8±29.7, 10.4±14.3, and 4.0±8.9 cmH_2O at cumulative doses of 30, 100, and 300 μg/kg of oxybutynin, respectively. Significant decrease was founded at doses of 100 and 300 μg/kg ($P < .05$).

DISCUSSION

Our experimental model is suitable for urodynamic evaluation on the effect of oxybutynin for several reasons. 1) The reflex micturition induced by bladder filling in the decerebrate dog exhibits highly reproducible urodynamic parameters during

TABLE I. Effect of Oxybutynin on the Urodynamic Parameters (Mean ± S.D.)

	Threshold		Maximum bladder	Voided	Voiding	Residual
	Volume (ml)	Pressure (cmH_2O)	pressure (cmH_2O)	volume (ml)	time (sec)	volume (ml)
Control (n=7)	15.3 ± 15.5	20.3 ± 6.5	37.7 ± 7.3	13.8 ± 6.4	10.3 ± 3.6	1.4 ± 2.8
30 μg/kg	18.0 ± 15.7*	21.4 ± 5.9	37.7 ± 8.8	14.4 ± 15.2	10.3 ± 1.8	3.6 ± 3.4
100 μg/kg	19.3 ± 17.3*	21.7 ± 7.6	35.4 ± 8.0	11.4 ± 9.8	10.7 ± 3.1	8.1 ± 10.4
300 μg/kg	20.6 ± 18.3*	21.7 ± 7.2	34.0 ± 7.1*	10.4 ± 8.4	11.7 ± 5.7	8.1 ± 10.4

*$P < .05$.

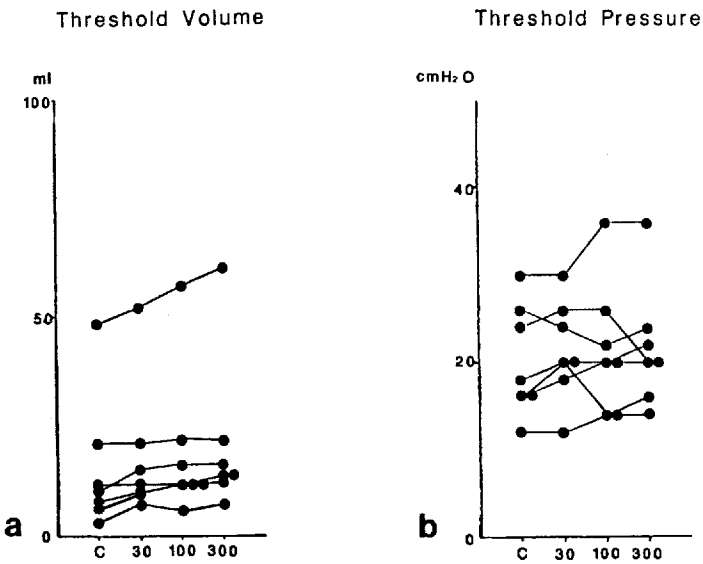

Fig. 4. Urodynamic parameters of collecting phase (a) before and (b) after oxybutynin. C, control.

both the collecting and emptying phases [Nishizawa et al., 1986]. 2) The reflex micturition developed by the function of pontine micturition center [Nishizawa et al., 1988] without cerebral control resembles the detrusor instability and hyperreflexia in the clinical case. 3) The dog is fixed in the standing position, which is more physiologically demanding than the conventional prone position.

Our results show that reflex micturition with bladder contraction and relaxation of striated urethral sphincter occurred in the control condition and after cumulative doses of 30, 100, and 300 μg/kg of oxybutynin in all seven decerebrate dogs. Oxybutynin at cumulative doses of 30, 100, and 300 μg/kg which are likely to be almost equal to the doses of 3–15 mg/day in the clinical application [Diokno and Lapides, 1972; Moisey et al., 1980; Kawabe et al., 1986; Gajewski and Awad, 1986] has no undesirable adverse effect for a clinical use to depress totally detrusor contractility, resulting in an impairment of bladder-emptying function.

In the urodynamic parameters of the collecting phase, there was a significant increase in threshold volume after oxybutynin. The increase in threshold volume after

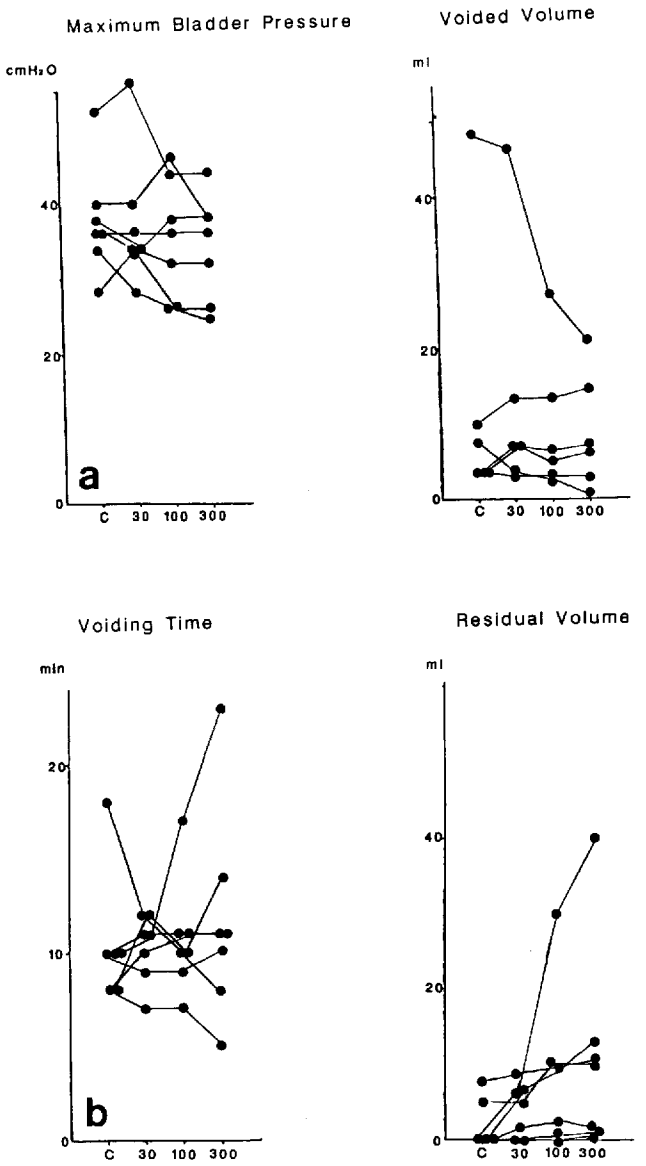

Fig. 5. Urodynamic parameters of emptying phase **(a)** before and **(b)** after oxybutynin.

oxybutynin seems to be consistent with the clinical results reported by Moisey et al. [1980], Kawabe et al. [1986], and Gajewski and Awad [1986]. Moisey et al. [1980] reported that the main urodynamic changes after oxybutynin 15 mg/day were increased in bladder volumes at first detrusor contraction and in total bladder capacity. Kawabe et al. [1986] reported that the prominent urodynamic improvements after 6 mg/day were increased in bladder volume at first desire to void and at the maximum desire to void. Gajewski and Awad [1986] reported that oxybutynin 15 mg/day produced an increase in maximum cystometric capacity. In the urodynamic parameters of the emptying phase considered to be influenced greatly by cholinergic

activity [Applebaum, 1980], there was a small but significant decrease in the maximum bladder pressure only at 300 μg/kg dose. Other parameters of the emptying phase did not show any significant change. The slight effectiveness of oxybutynin during emptying phase suggests that anticholinergic activity of oxybutynin is weak in this study. The anticholinergic activity of oxybutynin was reported to be about 1/7–1/10 of atropine in the muscle strip study [Aida et al., 1986].

No evident changes observed in blood pressure, respiration, or heart rate suggests safety for this drug for the cardiovascular system. Present study supports urodynamically clinical usefulness of oxybutynin for the relief of symptoms associated with detrusor instability and hyperreflexia.

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