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Comparison of the mode of action of prostaglandin E_2 (PGE_2) and sulprostone, a PGE_2-derivative, on the lower urinary tract in healthy women*

A urodynamic study

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Summary. The influence of intravesical administration of PGE_2 (1,500 µg) and sulprostone, a PGE_2 derivative (1,000 µg) on urodynamic parameters of the lower urinary tract was tested on six healthy female patients. PGE_2 and sulprostone significantly decreased the urethral closure pressure at rest. PGE_2 increased the detrusor opening pressure as well as the detrusor pressure during maximum flow. Sulprostone, in contrast, slightly decreased these parameters. Both substances caused a strong urgency sensation resulting in an equally reduced bladder capacity and leading to a measurable bladder instability in both cases. This gives rise to the assumption that frequency, urgency and bladder instability may be the result of intravesical relaxation. By 24 h after administration all urodynamic parameters had returned to pretreatment values, thus indicating that long-term changes in urodynamic parameters are not found after either prostaglandin.

Key words: Sulprostone – Prostaglandin E_2 – Influence on urodynamic parameter – Lower urinary tract – Healthy females – Detrusor instability

Bultitude et al., in 1976, were the first to report on single intravesical and intraurethral administration of natural prostglandins (PGs). Since then various publications have demonstrated their clinical and urodynamic effect in the treatment of urinary retention of various etiologies in female patients [1, 7, 9, 11]. Some studies, however, did not prove a clinical benefit of intravesical administration of these natural prostaglandins [8, 17, 20]. The major reason may be found in the short duration of action of these substances. Therefore, the use of long-acting prostaglandins may offer a solution. The long-acting PG derivative 15-methyl-PGF_2-alpha proved to be clinically effective in the treatment of patients with reflex bladder [19].

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The PG_2 derivative sulprostone has gained world-wide acceptance for the induction of abortion at all gestational ages [12, 13]. Its tissue selectivity to the uterine muscle [10] causes a major reduction of systemic side effects [14]. Intravenous doses of 200 µg/h and 500 µg/h resulted in a significant reduction of bladder capacity [15]. Intravesical application of increasing doses showed the same results. A maximum effect was achieved with a dose of 700 µg [15].

It was the purpose of this study to evaluate the influence of sulprostone on urodynamic parameters of the bladder and urethra in healthy females subjects compared with that of PGE_2. Special interest concerns the separation of short- and long term effects of both substances on the lower urinary tract in order to avoid further controversial results.

Materials and methods

The study group consisted of six healthy female volunteers with an average age of 28 years (min. 23 years, max. 45 years). All the women had had their last menstrual period 6–10 days before, and pregnancy had been ruled out by a negative serum β-HCG level. No symptoms affecting the lower urinary tract were present. A single dose of PGE_2 (1,500 µg) or sulprostone (1,000 µg) in a solution of 50 ml 0.9% NaCl at body temperature was given intravesically by way of a transurethral catheter.

Urodynamic measurements were performed according to ICS standards [2–4]. Urethrometry was achieved by a perfusion technique devised by Brown and Wickham [6]. The filling speed of the bladder was 55 ml per min. The following parameters were recorded:

Intravesical pressure (p_v)
Rectal pressure (p_{abd})
Detrusor pressure (p_v-p_{abd})
Urinary flow
Voided volume
Urethral pressure at rest
Functional urethral length

Micturition studies were performed in the sitting position and urethrometry in the supine position.

An intravesical instillation of 50 ml plain 0.5% NaCl solution was initially given as a placebo and 30 min later filling of the bladder

Table 1. Influence of intravesical administration of prostaglandin E_2 (PGE_2) (1500 µg) and sulprostone (1000 µg) on urodynamic parameters in the urethra

	PGE_2			Sulprostone		
	Before	After		Before	After	
Urethral closure pressure at rest (cmH_2O)	96.6 ± 13.2	85.8 ± 10.9	*	95.4 ± 12.9	83.3 ± 12.4	*
Functional urethral length (mm)	35.5 ± 3.0	34.9 ± 3.4	n.s.	34.2 ± 3.4	32.7 ± 2.5	n.s.

* Significant difference

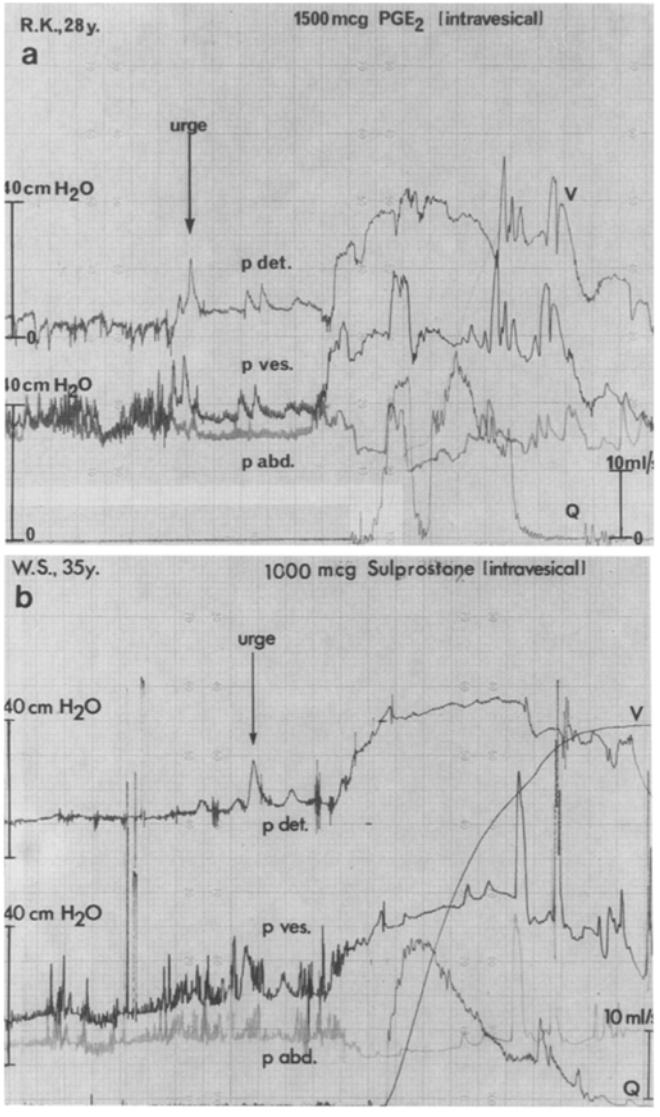

Fig. 1 a, b. Uninhibited detrusor contractions during bladder filling after application of **a** PGE_2 (1,500 µg), **b** sulprostone (1,000 µg). p_v = Intravesical pressure; p_{abd} = intraabdominal pressure; p_{det} = detrusor pressure; V = voided volume; Q = urinary flow

and micturition were performed twice. More than 10% variation between the two runs in maximum bladder capacity, first desire to void, peak flow rate or flow time was not permitted. A change in the type of micturition was also defined as an exclusion criterion. However, none of the women had to be excluded.

In a second trial, following the placebo treatment mentioned above, either sulprostone or PGE_2 dissolved in 50 ml 0.9% NaCl was instilled into the bladder, and 30 min later filling of the bladder and micturition were again performed twice. Three women were randomly assigned to treatment with PGE_2 and the others with sulprostone. Every patient received both treatments at least 14 days apart. The women taking part had no knowledge of the type of treatment. They also had no information about possible drug-related symptoms on the lower urinary tract.

Urethrometry was performed before and after the placebo trial as well as after the drug trial. The average of the two measurements of every urodynamic parameter was used in the analysis.

Statistical analyses were performed with the Wilcoxon matched pairs signed ranks test. The level of significance was 0.05.

Results

The urethral closure pressure obtained after treatment had decreased significantly, from 96.6 cm H_2O to 85.8 cm H_2O (means), after PGE_2 and from 95.4 to 83.3 cm H_2O after sulprostone treatment. The functional urethral length remained unchanged (Table 1). The decrease in closure pressure was not confined to any particular part of the urethra, but occurred over the whole profile. The outcome was identical in both groups. Although there was no significant change in bladder compliance during the filling phase, both drugs induced a significant reduction in bladder capacity, because the desire to void was felt earlier. All women described much stronger sensation felt earlier than normally. The increased desire to void disappeared immediately after the trial in three cases. The remaining three women had continuing symptoms for 3–12 h regardless of the substance given. Uninhibited detrusor contractions between 14 and 22 cm H_2O occurred either after PGE_2 or sulprostone in four of the six women. In three women detrusor contractions were induced by both drugs (Fig. 1 A, B). In no case were detrusor contractions accompanied by leakage of urine.

In contrast to the identical effect of the two drugs during the filling phase, their effects on micturition were different. After the administration of PGE_2, detrusor pressure at maximum flow and the opening pressure

Table 2. Influence of intravesical administration of PGE_2 (1500 µg) and sulprostone (100 µg) on urodynamic parameters during filling phase and micturation

	PGE_2			Sulprostone			Difference between post treatment values
	Before	After		Before	After		
Bladder capacity (ml)	725.0 ± 113.1	554.7 ± 163.2	*	734.7 ± 113.4	557.8 ± 107.9	*	n.s.
Compliance (ml/cmH_2O)	91.5 ± 18.8	87.2 ± 21.3	n.s.	84.8 ± 17.4	70.7 ± 33.0	n.s.	n.s
Opening time (s)	5.9 ± 1.5	5.6 ± 1.8	n.s.	5.2 ± 0.9	4.8 ± 2.5	n.s.	n.s.
Detrusor opening pressure (cmH_2O)	29.2 ± 6.0	34.3 ± 7.5	n.s.	27.8 ± 4.4	25.7 ± 7.7	n.s.	*
Detrusor pressure at maximum flow (cmH_2O)	37.5 ± 13.6	41.5 ± 11.3	n.s.	33.8 ± 14.6	27.0 ± 9.7	*	*
Maximum flow rate (ml/s)	24.1 ± 6.9	24.3 ± 14.6	n.s.	26.4 ± 5.7	23.2 ± 5.4	*	n.s.
Average flow rate (ml/s)	11.3 ± 4.4	13.9 ± 8.7	n.s.	13.8 ± 3.5	11.1 ± 4.0	n.s.	*

increased, whereas sulprostone treatment brought about a decrease in both parameters (Table 2). As a result all flow parameters decreased after sulprostone and the average flow rate increased after PGE_2. A comparison of the post-treatment values with both drugs showed statistical significance for the differences in detrusor opening pressure, pressure at maximum flow, and average flow rate.

Urodynamic control examinations after 24 h showed no residual drug effects.

Discussion

This study demonstrates for the first time the influence of PGE_2 and that of the PGE_2 derivative sulprostone on urodynamic parameters in healthy women. In contrast to the findings of Delaere et al. who did not find a change in bladder capacity, maximum flow rate and maximum flow pressure for PGE_2 [8], our data show a significant decrease in urethral closure as well as an increase in detrusor pressure. This confirms in vivo studies with PGE_2 treatment of patients suffering from urinary retention. When the women in our study group were examined 24 h after administration of the test substances, the urodynamic parameters had returned to pretreatment values. The patients' strong desire to void, which in all cases was related to the PGE_2, administration, returned to normal within 3–12 h. Therefore, a long-term effect of PGE_2 on the lower urinary tract which has been described by others [7, 9] cannot to be explained by our urodynamic results.

Although sulprostone is a PGE_2 derivative, its mode of action on the female lower urinary tract is different from that of PGE_2. While the decrease in urethral closure pressure is quantitatively equal to that with PGE_2, detrusor pressure at maximal flow is reduced. In vitro studies suggest that this finding is not due to a detrusor-relaxant effect of sulprostone [16], but has to be interpreted as the result of infravesical relaxation. Both prostaglandins induce a significant reduction in bladder capacity, which is due to an earlier urgency to void. Furthermore, three of the six women developed uninhibited detrusor contractions not only after PGE_2 but also after sulprostone application. The fact that the detrusor pressure after sulprostone is even reduced contributes to the assumption that frequency, urgency and even bladder instability may also be due to infravesical relaxation [5, 18].

Although sulprostone applied locally to the uterine muscle has an action that is of long duration, this is not so when it is applied to the urethra. The systemic i.v. dose needed to achieve an effect on the lower urinary tract is in excess of 200 µg/h and is therefore accompanied by severe side effects, especially in the gastrointestinal tract [12]. Therefore, the PGE_2 derivative offers no advantage over natural PGE_2.

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