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Effect of Prostaglandin on Urethral Resistance and Micturition

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Summary. The effect of four exogenous prostaglandins, PGA_1, PG802, PGE_2 and $PGF_{2\alpha}$, upon the lower urinary tract was investigated in female mongrel dogs without neurogenic lesions in vivo. The urethral resistance was studied by means of a urethral pressure profile, and the bladder function by evaluating whether or not the micturition was triggered. The reduction of urethral resistance in terms of the maximum urethral closure pressure was most significant with PGE_2 given intraarterially. Micturition was most frequently provoked by the intravenous administration of PG802, a derivative of PGE_1. PGE series seemed to be the most potent for the evacuation of urine in female dogs.

Key words. Prostaglandin, Urethral resistance, Micturition, Urodynamics, Dog experiment.

Introduction

Euler in 1936 demonstrated the biological properties of prostaglandin (PG) extracted from the mammalian prostate and seminal vesicle [7]. During the past 10 years the effect of this substance upon the urogenital tract has been the subject of clinical investigation. PGs have been found to play a role in maintaining the tonus of smooth muscle [8]. It has also been shown that the detrusor muscle contracts in response to PGE and F series [1, 4, 5] and that the tone of the urethral smooth muscle increases with the addition of $PGF_{2\alpha}$ and decreases with PGE_2 [1, 3, 9]. The clinical application of PGs to facilitate micturition has been attempted in the form of bladder instillation with PGE_2 [4] and $PGF_{2\alpha}$ [6] and in the form of intravenous administration with PG995, a derivative of $PGF_{2\alpha}$ [14]. While the former seemed to be of effect, the latter failed to provoke micturition in spite of the elevated bladder tonus in chronic neurogenic bladders. In an attempt to study further the effect of various PGs given intravenously and intraarterially upon the bladder and urethra, the following animal investigation in vivo was carried out.

Materials and Methods

Female mongrel dogs, weighing 7 to 25 kg, were anaesthetised with intravenous thiamylal sodium, 15 mg/kg, and connected to a mechanical respirator. Small additional doses were injected as required. An episiotomy was made to allow easy access to the urethral orifice. The hind limbs were loosely fixed in a supine position.

Urethral Resistance

The urethral resistance was evaluated by means of our urethral pressure profile technique [13]. A 10FG rubber catheter with two side holes was mechanically pulled out of the bladder at a speed of 50 mm/min with an infusion rate of 2.5 ml/min. The blood pressure was monitored via a small tube whose tip was advanced into the abdominal aorta through the femoral artery. The pressure recording was made on an electric manometer through strain gauge transducers. When the urethral pressure profile was traced twice, succinylcholine chloride in a dose of 1 mg/kg was given intravenously. Succinylcholine was found essential to obtain reliable experimental data which otherwise would have been influenced by the contraction of the striated muscle component of urethral sphincter and by hyperventialtion. The urethral pressure profile under the muscle relexant was taken as the control. The effect of four PGs, i.e. PGA_1, PG802 (a derivative of PGE_1), PGE_2 and $PGF_{2\alpha}$, were investigated in three different doses (o.1, 1.0 and 10.0 microgram/kg). Each PG, dissolved in 5 ml of distilled water, was given succesively in a few seconds through the blood pressure monitoring channel. Ten minutes elapsed between subsequent doses. One minute after each PG administration the urethral profile was recorded, where three parameters were chosen for comparison with the control; the maximum urethral closure pressure, functional profile length and mean blood pressure.

Micturition

Micturition in response to exogenous PGs was assessed in association with the continuous monitoring of bladder and blood pressure. Residual urine being removed, the distilled water stained blue with

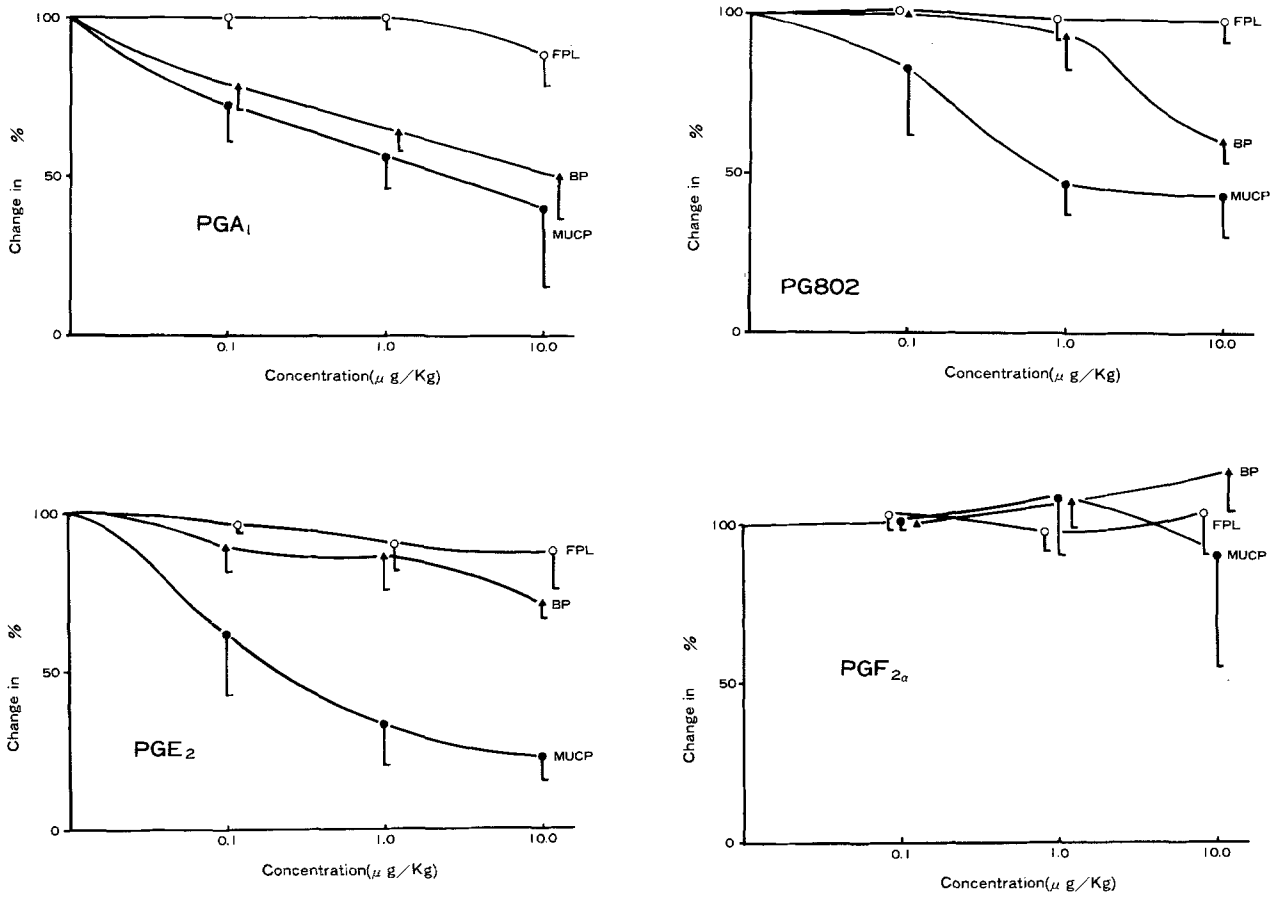

Fig. 1. Response of urethral pressure profile and blood pressure to four prostaglandins (PGs). MUCP stands for the maximum urethral closure pressure, FPL functional profile length, and BP blood pressure. Vertical bars represent the standard deviation

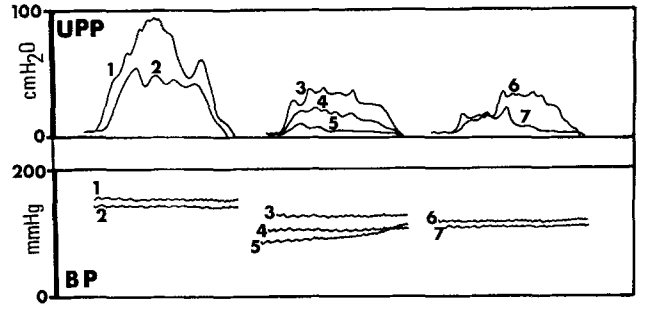

Fig. 2. Consecutive recordings of urethral pressure profile (UPP) and mean blood pressure (BP) in response to intravenous thiamylal sodium, intravenous succinylcholine and intrarterial PGE_2. Curve 1 demonstrates the effect of thiamylal sodium, 2 succinylcholine 1 mg/kg, 3 PGE_2 0.1 μg/kg, 4 PGE_2 1.0 μg/kg, 5 PGE_2 10.0 μg/kg, 6 change in urethral profile 20 min after the curve 5, and 7 another succinylcholine 1.0 mg/kg

indigocarmine solution for easy identification, was infused slowly into the bladder cavity via a small tube placed in the urethra up to the amount of 50 to 100 ml, depending upon the size of dog. When the bladder pressure was equilibrated, PG was intravenously injected into the forearm in 2 to 3 min. The same four PGs were tested in various doses, 10 to 60 microgram/kg, diluted in 10 ml of distilled water. The bladder response to a given PG was evaluated up to 30 min or until micturition occurred.

Results

Urethral Resistance

This was investigated in five dogs for each PG (Fig. 1 and 2). Dose-dependent reduction in the maximum urethral closure pressure and mean blood pressure was observed in all PGs except $PGF_{2\alpha}$, which, on the contrary, showed a slight vasocontracting effect. The effect of $PGF_{2\alpha}$ on the maximum urethral closure pressure was not consistent – a pressure rise in four out of five dogs with a dose of 1.0 microgram/kg, and a pressure fall in four out of five with a dose of 10.0 microgram/kg. The change in functional profile length with PG administration was negligible in all instances. The reduction of urethral resistance in terms of the maximum urethral closure pressure was most significant with PGE_2 followed by PG802.

Micturition

For each PG eight to 10 dogs were used and the mean dose was 36 to 46 microgram/kg (Table 1 and Fig. 3). Micturition was most frequently encountered with PG802, in eight out of 10 dogs. The highest volume voided as a percentage of

Table 1. Bladder response to 4 PGs given intraveously. Micturition was most frequently provoked with PG802, and the largest volume voided was encountered with PGE_2

PGs	Mean dose in μg/kg (range)	No. of dog voided (%)	Volume voided[a] (range)	Time voided[b] (range)
A_1 (n = 8)	46 (33–55)	0%	–	–
PG802 (n = 10)	40 (10–50)	80%	45% (20%–70%)	14 min (4–30 min)
PGE_2 (n = 10	43 (30–50)	30%	83% (50%–100%)	16 min (3–28 min)
$PGF_{2\alpha}$ (n = 10)	36 (10–55)	20%	74% (48%–100%	25 min (21–30 min)

Volume[a] and time[b] observed in the responding dogs

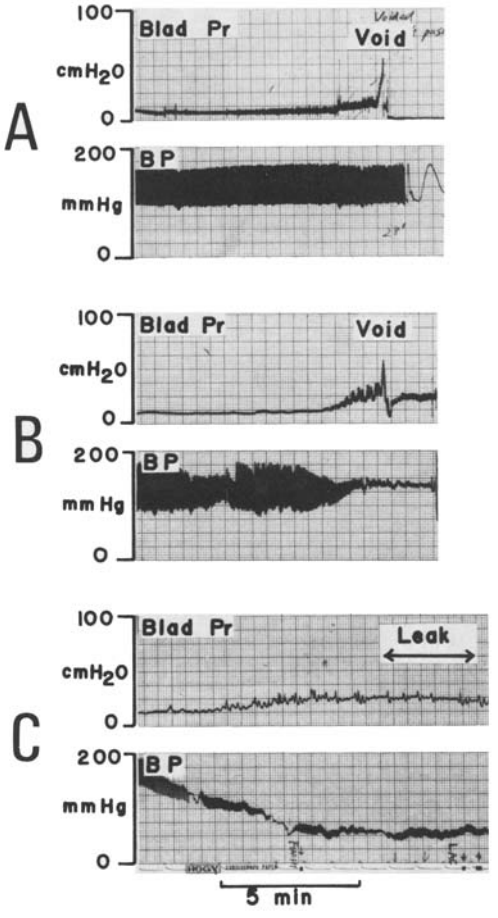

Fig. 3. Response of bladder in association with blood pressure to three prostaglandins. (*A*) PGE_2 50 μg/kg i.v., 100% of bladder volume voided 28 min later. (*B*) $PGF_{2\alpha}$ 50 μg/kg i.v., 100% of bladder volume voided 20 min later. (*C*) PG802 50 μg/kg i.v., 50% of bladder volume leaked around catheter 10 min later

bladder content was observed with PGE_2 (83%) followed by $PGF_{2\alpha}$ (74%). The average interval between the start of injection and micturition was 14 to 25 min. PGA_1 had no effect on micturition.

Discussion

The involvement of PGs in bladder physiology has been demonstrated in many ways. The exogenous PGE and F series have a contractile effect on detrusor strips [1, 3, 4]. The production and release of PGE and $F_{2\alpha}$ have been reported during bladder distension and after micturition in vivo [9, 11] and during spontaneous contraction in vitro [2]. The denervation supersensitivity of detrusor muscle in response to bethanechol [15] can be reproduced by the addition of PG995, a derivative of $PGF_{2\alpha}$, in chronic neurogenic bladder patients [14], which supports a close link between cholinergic receptors and PG action [10]. These results imply an important role played by PGE and F series upon the mechanism of bladder contraction and the maintenance of bladder tonus. However, it has not been determined whether they function through direct effect on the musculature [16], through specific receptors in detrusor muscle [12], or through a modulating effect on autonomic transmission to increase the release of the transmitter which is not yet identified [5].

There were two factors which had a significant influence upon the results of the present study. Firstly, shallow anaesthesia was mandatory to evaluate the bladder response to the exogenous PGs. Deep anaesthesia weakened or inhibited the reflex micturition and/or prolonged the interval between PG injection and micturition. Secondly, succinylcholine was necessary to prevent hyperventilation and voluntary contraction of striated muscle at the pelvic floor which often deformed the urethral pressure profile. By using this agent the maximum urethral closure pressure and functional profile length were reduced to an average of 65% and 83%, respectively, compared to those without muscle relaxant, confirming previous observations [18].

The fall of the maximum urethral closure pressure, i.e. the flattening of the profile, was quite obvious with PGA_1, PG802 and PGE_2, and was in accord with the result of Ghoneim et al. [9]. But this change was also accompanied by a fall of blood pressure which they did not mention. When the urethral profile was subsequently recorded for up to 20 min, blood pressure and the maximum urethral closure pressure showed a tendency to return to the original value but remained always lower than this value. These are schematically illustrated in Fig. 2. In view of the involvement of blood pressure on the tone of urethra, hypothesized by Tanagho and Meyers [17], it might be assumed that the vasodilating mechanism in these PGs was partly responsible for lowering the urethral resistance. $PGF_{2\alpha}$ seemed to have

a biphasic effect upon the maximum urethral closure pressure – an elevation up to a dose of 1.0 microgram/kg [9], and a fall with a higher dose.

Though the present study has been done on female dogs without any neurogenic lesions, the results obtained seem to suggest that PGE series are superior to other PGs in respect of lowering the urethral resistance (Fig. 1) and triggering micturition (Table 1). Micturition, if provoked, was preceded by gradual rise in bladder pressure of 10 to 15 cm of water in the majority of cases (Fig. 3A and B). When the detrusor contraction was weak, however, intermittent water leakage was observed in spite of the elevated bladder tonus (Fig. 3C). The bladder instillation therapy with PGE_2 reported by Bultitude et al. [4], who utilised a different route of administration from ours, was substantiated by our data. Since the abortifacient and vasodilating effects are inherent in PGE series, intravenous injection is not practical or safe. When another analogue of PGE series, absorbable from gastrointestinal tract, is developed, it might be of value in facilitating micturition in patients with bladder problems.

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