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The effect of indomethacin and metamizole on ureteral motility and urine flow in sheep

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Summary. The objective of this study was to evaluate the effect of two non-steroid anti-inflammatory drugs, indomethacin and metamizole, on ureteral peristalsis during acute occlusion similar to the situation in renal colic. In 12 pentobarbital anesthetized sheep, both ureters were cannulated and the frequency of ureteral contractions, urine flow, mean ureteral pressure and blood pressure were recorded during 10-min control and i.v. drug administration periods. Both indomethacin (1–2 mg/kg) and metamizole (60–120 mg/kg) showed a dose dependent reduction in peristaltic frequency without reduction of the mean pressure. In addition, the pressure amplitude of the peristaltic waves was also lowered, particularly with indomethacin. Only indomethacin reduced the urine flow. Arterial blood pressure was elevated by both drugs, particularly after the first dose of indomethacin. It can be concluded that indomethacin and metamizole reduce ureteral peristaltic frequency, probably blocking the impulse transmission at the ureteropelvic junction.

Key words: Indomethacin – Dipyrone – Prostaglandins – Anti-inflammatory agents – Ureteral obstruction – Ureter

The clinical observation of the therapeutic usefulness of non-steroidal anti-inflammatory drugs (NSAID) in the treatment of renal colic [5, 10] prompted this study. The possible mechanism of action may involve the well-known analgesic actions of NSAID associated with prostaglandin synthesis inhibition [4] or reduction in ureteral motility and an antidiuretic effect on the kidney, as has been demonstrated in pigs with acute experimental obstruction [11].

By in vitro experiments on isolated human ureters obtained from nephrectomies and sheep ureters we showed a dose-dependent inhibition of ureteral motility with different NSAIDs [2, 3, 14], which was related to prostaglandin-synthesis inhibition [16]. It is important, however, to carry out in vivo experiments that allow both ureteral peristalsis and urine production to be monitored since both of these parameters are interrelated in pain-producing distension of the renal pelvis. The present experiments were designed to assess these parameters simultaneously in the obstructed and non-obstructed ureters of anaesthetized sheep. As NSAIDs, indomethacin and metamizole, two drugs that have been used clinically in the treatment of renal colic, were chosen [5, 6]. Metamizole, a dipyrone (Na phenyl-dimethyl-pyrazolone-methylamino-methane-sulphonate) is an effective analgesic, antipyretic and anti-inflammatory drug.

Materials and methods

Twelve Australian merino sheep (11 castrated males and one female) were used that weighed 29–36 kg. General anesthesia was given with pentobarbital sodium i.v. (30 mg/kg) and maintained with additional doses as required. The trachea was intubated via a tracheotomy to ensure a free airway and the animal respired spontaneously. A midline laparotomy was performed, and the ureters were ligated 5 cm above the bladder and cannulated with 26 cm polyethylene catheters of 1.5 mm OD. Twenty minutes prior to cannulation, 10 ml/kg saline was administered i.v. through a catheter in the jugular vein. One ureteric catheter was connected to a Statham pressure transducer to enable measurement of occluded ureteral pressure, while the contralateral side was drained via a 23 gauge needle. Urine flow and blood pressure were continuously recorded on a Gilson 5/6 chart recorder. Ureter pressure was intermittently recorded every 10 min, followed by release of obstruction and drainage for 5 min. Two 10 min control periods were recorded prior to drug administration.

Indomethacin and metamizole were administered by i.v. bolus injection in separate experiments at doses of 1 and 2 mg/kg and 60 and 120 mg/kg. respectively.

Calculations

Six experiments were carried out for each drug. In these, the frequency of ureteral phasic contractions, the mean ureter pressure and the pressure amplitude were determined from one ureter during

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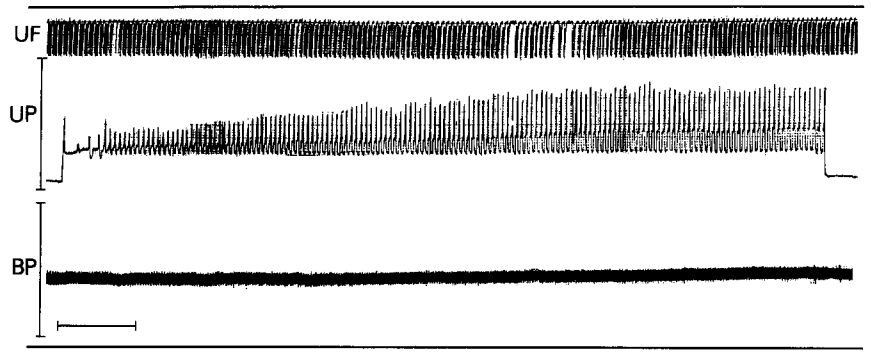

Fig. 1. Control experiment: urodynamic parameters and arterial blood pressure during urether occlusion. Note immediate rise of ureter pressure after occlusion. UF, Urinary flow (each deflection corresponds to one drop); UP, ureteral pressure (calibration: 50 mmHg; BP, arterial blood pressure calibration: 200 nmHg, time of interval: 1 min)

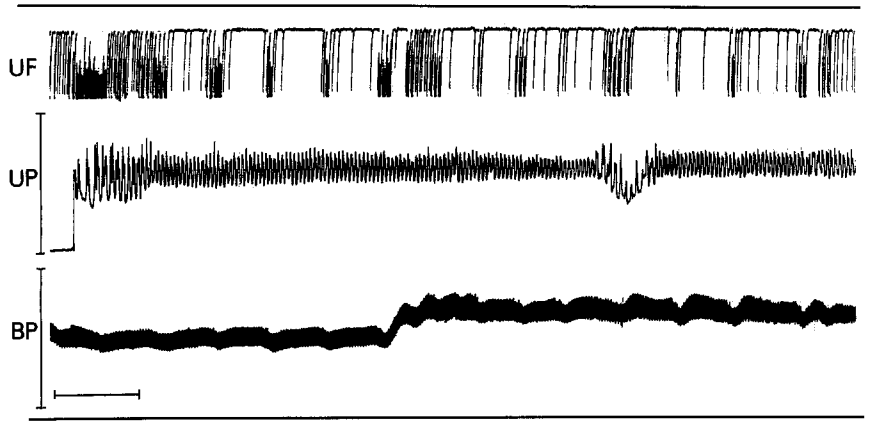

Fig. 2. The effect of indomethacin (0.8 mg/kg i.v.) on ureteral pressure. Indomethacin administered at 4 min (left side of panel). (Same calibration as in Fig. 1)

a 10-min period of obstruction. Urine flow was determined on the contralateral side by counting the drops from the analogue output of the chart record, multiplied by the volume of one drop. The mean ureter pressure was calculated as the trough level plus 50% of the pressure amplitude. The mean blood pressure was calculated as the diastolic pressure plus one-third of the blood pressure amplitude. The frequency of ureter contractions was counted as the number of primary (large) deflections per minute.

The uro- and hemodynamic parameters were assessed for each consecutive minute and the mean value and standard errors for the whole period of obstruction calculated. Statistical comparison was made for the control period preceding the drug administration period. Standard statistical methods were used and level of significance indicated as follows: <0.05*, <0.01**, and <0.001***.

Drugs

Indomethacin was supplied as sterile powder in Confortid vials (Dumex, Denmark) containing indomethacin sodium (50 mg) and monosodium phosphate (27.1 mg). Indomethacin solution was obtained by reconstitution of the vial with 10 ml sterile, distilled water; the solution had a pH of 7.7 Metamizole (Hoechst, FRG) was obtained as a powder and dissolved in distilled water.

Results

During the 10-min control period prior to drug administration, occlusion of the urine flow after attachment of the ureteral catheter to the pressure transducer resulted in an increase in pressure and clearly visible contractile peristaltic waves (Fig. 1).

Figure 2 and Table 1 show the effect of indomethacin on the parameters measured. The most noticeable effect was that of increased arterial blood pressure, particularly after the first dose. Urine flow successively declined and there was also a reduction in the frequency and amplitude of peristaltic contractions. The ureteral mean pressure, however, did not decline.

The changes observed after administration of metamizole were similar and are shown in Fig. 3 and Table 2. Metamizole had less effect on arterial blood pressure, but it induced a dose-dependent reduction in the frequency of ureteral contractions. There was a transient slight increase of ureter pressure amplitude after the first dose and no change after the second dose. Ureteral mean pressure was slightly elevated. Matamizole did not affect diuresis.

In a separate experiment, the pressure in the partially occluded catheter used for urine flow determination was measured and found to be $32.7 \pm 3.0\%$ of that of the totally occluded ureter.

Discussion

The present study showed that intravenous administration of both indomethacin and metamizole reduces the frequency of ureter contractions on a dose-dependent basic. Only indomethacin, however, significantly lowered diuresis and the amplitude of ureteral pressure.

In an earlier study on sheep, but without prior infusion of saline, we noted similar changes with indomethacin. In these experiments urine flow was not recorded simul-

Table 1. Effect of two doses of indomethacin on blood pressure and ureter dynamics in sheep experiments ($n = 6$). Data represent arithmetic means (±) standard errors of the mean. p values express degree of statistical significance in relation to control

Parameters	Control	0.8 mg/kg	p	2.4 mg/kg	p
Mean blood pressure (mmHg)	99.7 ± 0.3	123.5 ± 2.4	**	119.2 ± 0.5	**
Urine flow (ml/min)	0.33 ± 0.01	0.27 ± 0.02	*	0.23 ± 0.03	*
Ureter frequency (c/min)	16.5 ± 0.08	16.3 ± 0.14	NS	13.4 ± 0.06	**
Ureter amplitude (mmHg)	21.0 ± 0.5	16.4 ± 0.5	**	17.6 ± 0.4	**
Ureter mean pressure (mmHg)	32.6 ± 0.2	32.9 ± 0.1	NS	32.4 ± 0.1	NS

* $p < 0.05$
** $p < 0.01$

Table 2. Effect of two doses of metamizole on blood pressure and ureter dynamics in sheep experiments ($n = 6$). Data represent arithmetic means (±) standard errors of the mean. p values express degree of statistical significance in relation to control

Parameters	Control	60 mg/kg	p	120 mg/kg	p
Mean blood pressure (mmHg)	93.9 ± 0.3	98.3 ± 0.1	**	104.1 ± 0.1	**
Urine flow (ml/min)	0.54 ± 0.01	0.59 ± 0.01	NS	0.53 ± 0.03	NS
Ureter frequency (c/min)	17.3 ± 0.1	15.8 ± 0.2	**	14.7 ± 0.17	**
Ureter amplitude (mmHg)	15.5 ± 0.3	16.8 ± 0.6	*	15.4 ± 0.7	NS
Ureter mean pressure (mmHg)	27.9 ± 0.3	29.4 ± 0.1	**	29.7 ± 0.1	**

* $p < 0.05$
** $p < 0.01$

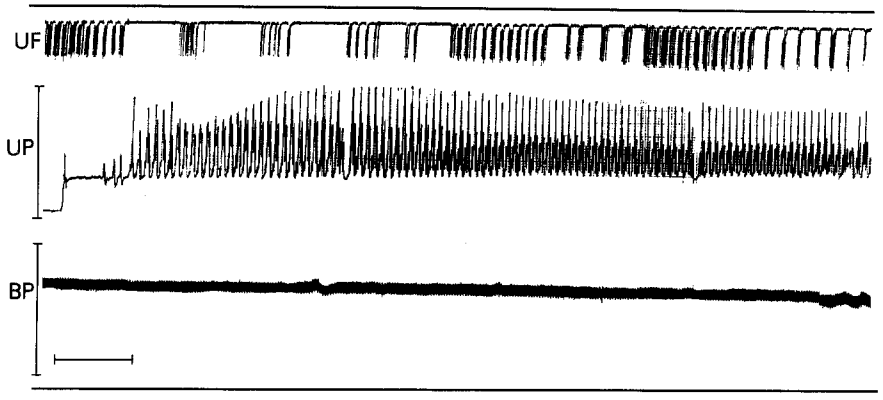

Fig. 3. The effect of metamizole (120 mg/kg i.v.) on ureter pressure, urine flow and arterial blood pressure. Metamizole administered at 4 min. (Same calibration as in Fig. 1)

taneously, and it was therefore difficult to come to any conclusions about the mechanism of action [1]. In the present study urine flow ureter dropped by 30% after the second dose of indomethacin, but there was no change after metamizole.

The reduction in diuresis after administration of a non-steroid anti-inflammatory agent can be explained by inhibition of prostaglandin synthesis in the obstructed kidney [3]. The moderate reduction observed in the present study might be related to the fact that the ureter from which the flow was recorded was only partially blocked due to the impediment of outflow passing through a 23 gauge needle. The reduction on the totally obstructed side from which the pressure was recorded could not be assessed for obvious reasons.

Due to preoperative hydration of the animals, the inhibition of vasodilator prostaglandins may have been blunted [12]. One would expect that the significant reduction in urine flow observed in the present series of experiments would be associated with simultaneous lowering of the mean ureter pressure and amplitude. This was not observed in our study and there was only a moderate reduction in the amplitude of peristaltic pressure waves. This seems to indicate that the NSAID used in this study did not significantly affect the smooth muscle tension of the ureter.

The reduction in ureter peristaltic frequency is an interesting observation and can be explained by two alternative mechanisms: (1) that the drugs primarily reduce the pacemaker frequency in the renal pelvis or (2) that the NSAID blocks impulse transmission in the ureter. The pacemaker is known to be located in the pelvis [17] and an inhibition of impulse transmission normally occurs at the ureteropelvic junction [8]. An increased

transmission block seems to be the most likely explanation since we have recently shown that propagation of contractile impulses in the ureter is under the control of prostaglandins [15].

When comparing the effect of indomethacin with metamizole, it is apparent that indomethacin-reduced diuresis was only recorded in the partially obstructed ureter from which the urine flow was actually recorded. This effect must be related to an intrarenal mechanism. It is known that acute obstruction of the ureter is associated with increased renal blood flow and diuresis, which is mediated by increased intrarenal prostaglandin production [13]. This response obviously can be blocked with cyclooxygenase inhibitors like indomethacin [12]. Therefore, it can be concluded that indomethacin has a dual renal and ureteral effect, whereas metamizole only seems to influence the frequency control of the ureter.

The consistent finding of elevated arterial blood pressure, particularly after administration of indomethacin, can be explained on the basis of a block in the release of vasodilator prostaglandins, notably prostacyclin, which is normally continously released from the pulmonary vasculature [7]. Although the resting levels are not sufficient to play an important role in blood pressure homeostasis, increased autonomic tone, such as in the present experimental situation, may elicit conditions with a higher output of prostaglandins [9].

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