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Urological Research

Effects of prostaglandin synthetase inhibitors on the upper urinary tract

Experimental studies on isolated preparations and urodynamic measurements in men

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Summary. Prostaglandin inhibitors such as indomethacin have been used for the treatment of renal colic. While opioids have a central analgesic effect, the effects of indomethacin are mainly peripheral, acting directly on the kidney. Pharmacourodynamic investigations of the upper urinary tract in men have demonstrated that intravenous indomethacin reduces renal pelvic pressure. These effects are more intense with indomethacin than with metamizol and are not found with hyoscine butylbromide. We have determined that indomethacin reduces the smooth muscle activity of human renal pelvis preparations in a tissue bath. These findings may represent a further possible direct effect of indomethacin on the upper urinary tract during the treatment of renal colic.

Key words: Upper urinary tract – In vitro – Relaxation – Urodynamics – Indomethacin – Metamizol

Renal colic is caused by increasing intraluminal pressure and wall tension within the renal pelvis above an obstructing stone [11, 13]. This increased pressure in the upper urinary tract is dependent on the renal synthesis and secretion of prostaglandins, which increases renal blood flow and counteracts the effect of the antidiuretic hormone [8, 11]. Both of these prostaglandin effects increase diuresis and raise the intrapelvic pressure.

Prostaglandin synthetase inhibition by indomethacin or diclofenac may relieve pain in cases of renal colic, mainly due to a decrease in the renal pelvic pressure [11, 15]. Another contributing factor in pain relief might be a direct effect of prostaglandin synthetase inhibitors on the smooth muscle activity of the ureter and the renal pelvis [2, 4, 17, 21]. The present study was designed to evaluate influences of indomethacin and metamizol on human smooth muscle tension in the urinary tract.

Up to now, in vivo urodynamic effects of prostaglandin synthetase inhibitors on renal pelvic pressure of obstructed kidneys have only been evaluated in an animal model [1, 7]. Comparable investigations in humans have not yet been published and will be presented in this study.

Materials and methods

Experiments on isolated muscle strips of the human urinary tract

Isometric contractions of isolated strips of smooth muscle tissue from the human urinary tract were analyzed in a tissue bath (Rhema Labortechnik, Hofheim/Taunus, FRG) using oxygenated Krebs-Henseleit solution (113.8 mmol/l NaCl, 22 mmol/l $NaHCO_3$, 4.7 mmol/l KCl, 1.2 mmol/l KH_2PO_4, 1.1 mmol/l $MgSO_4$, 2.5 mmol/l $CaCl_2$ and 5.5 mmol/l glucose) at a constant temperature 37 °C.

One end of the muscle strip preparation was secured to a holding device, and the other end was attached to an isometric force transducer by a monofilament suture. The isometric tensions were continuously registered with a pen recorder (Hellige, Freiburg, FRG). After mounting, the isolated strips were allowed to equilibrate for at least 1 h until a stable tension level was reached. Then, prostaglandin PGF2α (MinprostinF2α, Upjohn, Heppenheim, FRG) was added with increasing concentrations and the isometric tensions were evaluated.

The prostaglandin solution was then washed out and the initial tension level was again reached. A second group of studies was performed with indomethacin or metamizol to varying levels of PGF2α concentration and isometric tension was again tested. Statistical analyses were performed using the Wilcoxon test.

Acquisition of tissue samples

The human strips of renal pelvis were obtained after radical nephrectomy for renal cell carcinoma in one pole of the kidney. In patients with ureteral reflux undergoing ureteroneocystostomy, small strips of the bladder dome were removed for analysis. The tissue pieces measured 1–3 to 5–10 mm.

Pharmacourodynamic experiments

In vivo experiments were performed in 26 adult patients who had radiographically documented complete ureteric obstruction due to a ureteral calculus and therefore underwent placement of a percutaneous nephrostomy tube (8.5 F, Angiomed, Karlsruhe, FRG). The patients (10 men, 16 women, ages 25 to 66 years) had their nephrostomy tubes placed 2–21 days before the study. The period of hydronephrosis before insertion of the nephrostomy tubes could not be exactly determined (1 day to several weeks).

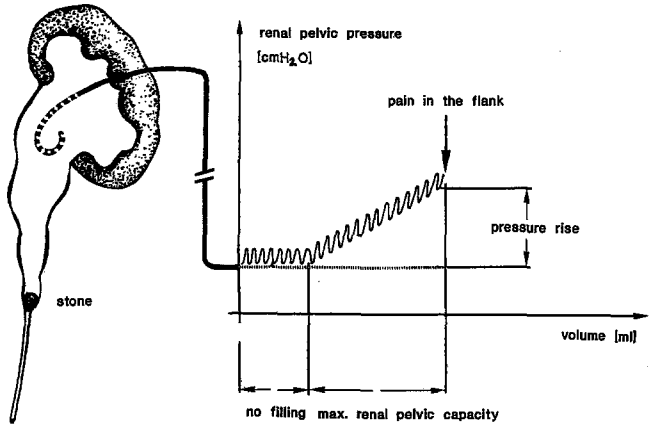

Fig. 1. Parameters relating to upper urinary tract urodynamics

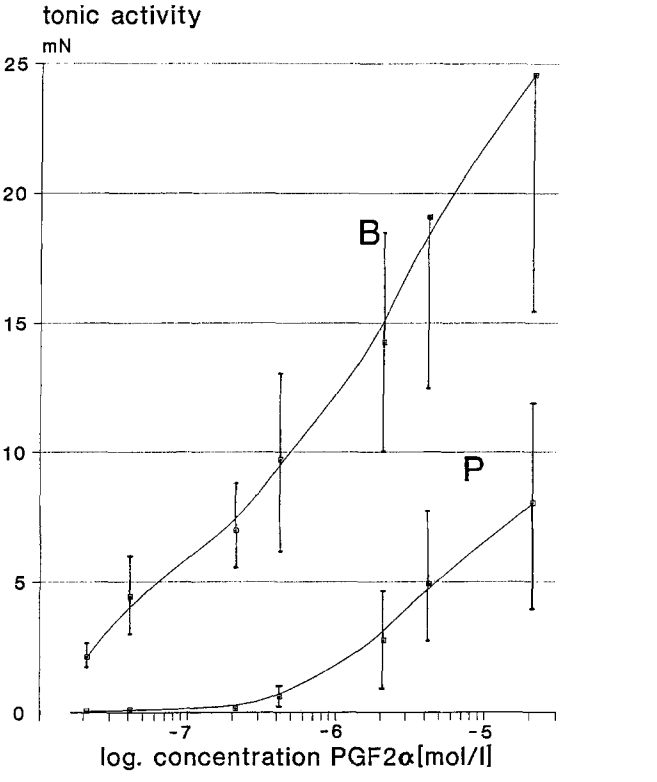

Fig. 2. Dose-response curves for prostaglandin F2α on isolated human renal pelvic (*P*, $n=28$) and human urinary bladder (*B*, $n=10$) strips. *Vertical bars* represent standard error of mean (SEM)

During the study, the nephrostomy tubes were connected to a system for filling the renal pelvis and to a Statham transducer. As the ureteral obstruction still persisted, an acute obstruction of the kidney was recreated by filling the upper urinary tract with sterile normal saline (0.9%) using a constant infusion rate of 5 ml/min. The infusion was stopped when the patient complained of flank pain. These experiments determined the maximal rise in renal pelvic pressure and the maximal renal pelvic capacity (Fig. 1). During all procedures, a Foley catheter was kept in the urinary bladder. Blood pressure was measured continuously during drug application.

Determinations of renal pelvic pressure and renal pelvic capacity were determined before and 5 minutes after intravenous application of 2.5 g metamizol (Novalgin, Höchst, FRG) 50 mg indomethacin

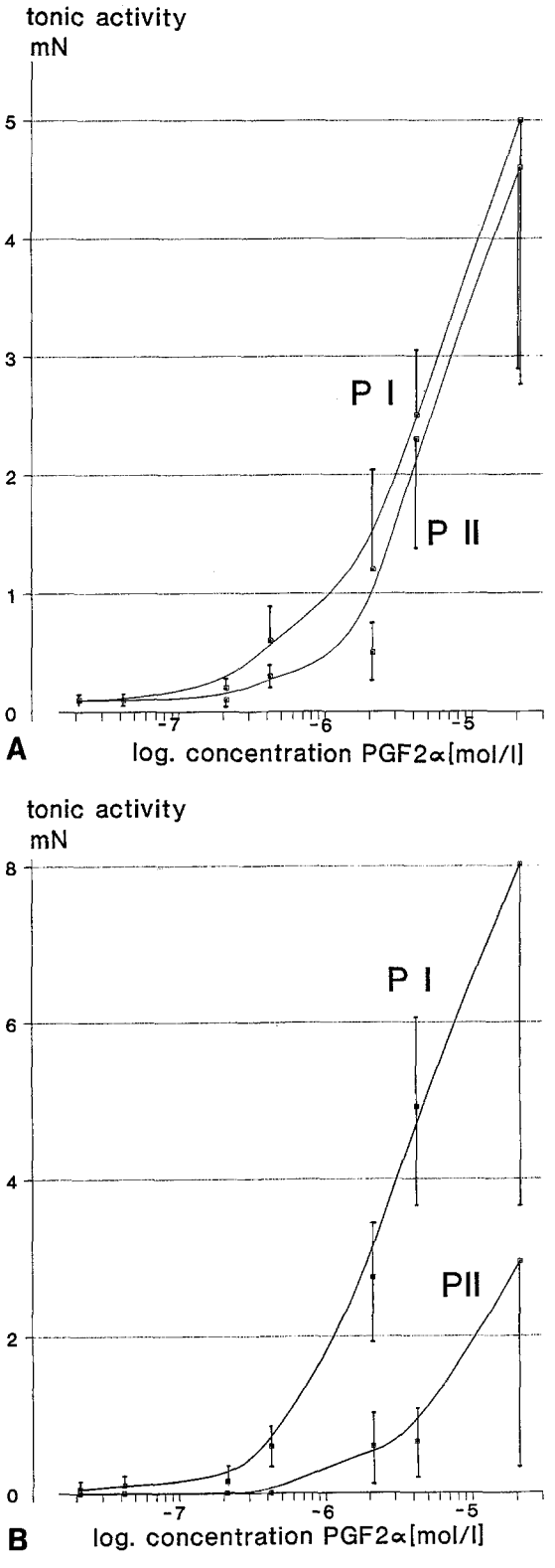

Fig. 3. **A** Dose-response curves of prostaglandin F2α on isolated human renal pelvic strips before (*PI*) and after (*PII*) incubation with metamizol (3×10^{-4} mol/l). $P<0.05$ for PI vs PII. (*Vertical bars* represent SEM, $n=8$). **B** Dose-response curves of prostaglandin F2α on isolated human renal pelvic strips before (*PI*) and after (*PII*) incubation with indomethacin (3×10^{-4} mol/l). $P<0.01$ for PI vs PII (*vertical bars* represent SEM, $n=8$)

Table 1. Pharmaco-urodynamic results recorded in the upper urinary tract after (1) hyoscine butylbromide (9 patients), (2) metamizol (9 patients) and (3) indomethacin (8 patients)

Drug administration	$\bar{X} \pm$ SEM before			$\bar{X} \pm$ SEM after		
	1	2	3	1	2	3
Rise in renal pelvic pressure (cm H_2O)	16.3 ± 3.2	21.1 ± 4.9	14.6 ± 0.7	15.0 ± 3.7	16.6* ± 5.1	9.1** ± 2.3
Renal pelvic capacity (ml)	57.0 ± 9.5	63.4 ± 12.3	65.0 ± 10.5	53.4 ± 8.6	72.8 ± 13.8	81.0 ± 16.3

* $P < 0.05$ (difference from before to after metamizol administration)
** $P < 0.01$ (difference from before to after indomethacin administration)

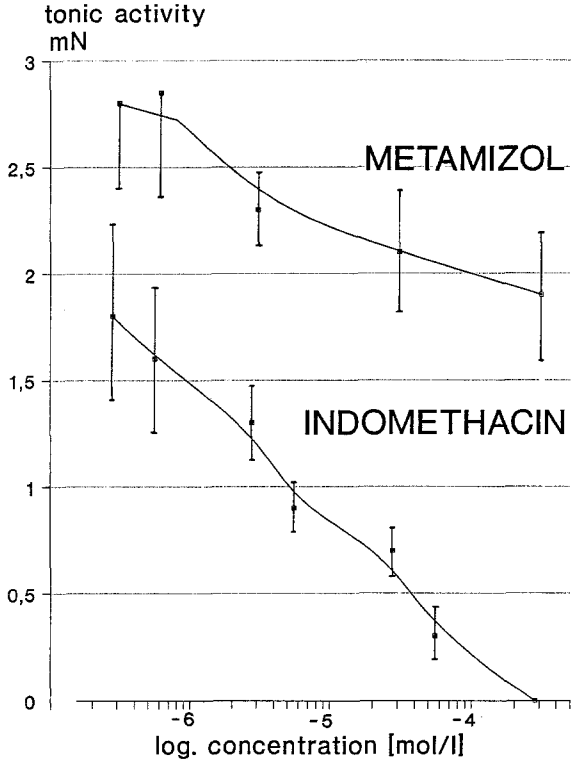

Fig. 4. Effects of indomethacin and metamizol on response of isolated human renal pelvic strips to prostaglandin F2α (3×10^{-6} mol/l). *Vertical bars*, SEM, $n = 8$. $P < 0.001$ without indomethacin vs with 3×10^{-4} mol/l indomethacin

(Confortid, Dumex, Denmark) and 20 mg hyoscinbutylbromide (Buscopan, Boehringer, FRG). Each patient received only one drug during one experiment, so that interactions between the medications were avoided. The drug dosage used in these studies corresponds to the usual amount given for the treatment of renal colic. Statistical analysis of the results before and after drug administration was performed with the Wilcoxon test.

Results

Experiments on isolated strips of the urinary tract

Prostaglandin F2α was found to cause a dose-related contraction on tissue strips from the human renal pelvis. Even stronger contractions were noted with the human urinary bladder strips (Fig. 2).

Metamizol did not significantly change the contractile tonic response produced by PGF2α in renal pelvis strips (Fig. 3A). Yet, after adding indomethacin the dose-related contractions of the pelvis strips with PGF2α changed significantly ($P < 0.01$) (Fig. 3B). With increasing concentrations of indomethacin, the contractions of the renal pelvis preparations produced by PGF2α (3×10^{-4} mol/l) were significantly reduced, and indomethacin at a concentration of 3×10^{-4} mol/l was shown to completely abolish the contractile response to PGF2α (Fig. 4). Metamizol had no effect on the contractile response.

Pharmacourodynamic experiments

Results of the pelvic pressure and volume measurements are shown in Table 1. There was no difference in the rise in pelvic pressure before and after application of hyoscine butylbromide, whereas the renal pelvic pressure significantly decreased after administration of metamizol ($P < 0.05$) and indomethacin ($P < 0.01$). The capacity of the renal pelvis did not change significantly with the administration of metamizol, indomethacin or hyoscine butylbromide. No major changes in blood pressure were noted in any patients.

Discussion

Treatment of renal colic should eliminate pain and possibly produce smooth muscle relaxation of the upper urinary tract [9, 14]. Whereas opioids have a central analgesic action, the effects of prostaglandin synthetase inhibitors are mainly peripheral, acting directly on the kidney [14].

It is known that an increase in renal pelvic pressure due to an acutely obstructed kidney stimulates the synthesis of prostaglandins, especially PGE_2 in the kidney, which in turn cause a temporary increase in renal blood flow and diuresis, producing a further rise in renal pelvic pressure [8, 11]. In experimentally obstructed ureters [1, 7, 11] prostaglandin synthetase inhibitors have been shown to reduce renal pelvic pressure. In six mongrel dogs with complete ureteral obstruction caused by a Fogarty bal-

loon catheter passed retrograde into the distal ureter, Gasparich produced a significant decrease in renal pelvic pressure using several prostaglandin synthetase inhibitors [7].

In our pharmacourodynamic experiments on conscious subjects with complete ureteral obstruction due to stones, the renal pelvis was drained by a percutaneous nephrostomy tube. During the studies the renal pelvis was filled with a sterile saline infusion until pain was registered. Thus, an acute obstruction of the upper urinary tract was produced, causing a rise in renal pelvic pressure. The maximal rise in renal pelvic pressure was determined before and after drug application. The increase in renal pelvic pressure was diminished after metamizol and more so after indomethacin administration. There was no change in renal pelvic pressure after application of hyoscine butylbromide. This may be explained by the fact that acetylcholine antagonists have only minimal effect on the renal pelvis and ureter [4, 10]. It has also been shown that anticholinergic treatment alone is not an effective therapy for renal colic [9, 17].

There were some procedural differences between our studies and those of Gasparich and Mayo [7]. Gasparich and Mayo injected pharmacologic agents after the obstruction had been established, whereas in our studies, drugs were given before the obstruction was created. Our methodology was similar to that of Allen et al. [1], who gave dogs indomethacin by injection before establishing ureteral occlusion. He found that after indomethacin injection and ureteral occlusion the characteristic ipsilateral renal vasodilation did not occur and that the ureteral pressure remained significantly lower than corresponding pressures in control animals. We surmise that pathways for renal prostaglandin synthesis must be intact for renal vasodilation to occur in response to ureteral obstruction.

Furthermore, it would be interesting to analyze the changes in prostaglandin synthesis or diuresis during the experiments before and after application of the inhibitors. As the ureters were occluded in all patients, the effect of the drugs on urinary prostaglandin excretion or on urinary flow could not be studied.

The renal pelvic pressures attained in this study (with a maximum of 21 cmH_2O) are relatively modest and, according to Whitaker, are estimated to be borderline for obstruction [20]. But it is not correct to suggest that when the renal pelvic pressure does not increase noticeably during infusion there is no obstruction. In a completely closed collection system the pressure may increase sharply during filling of the upper urinary tract or it may remain low, since the pelvis and ureter have variable capacities depending on prior dilation and its duration. This influence of geometry has already been clearly illustrated by Coolsaet, who also demonstrated the influence of bladder volumes on ureteral pressure and flow [5]. Therefore, in our study, the bladders were kept empty with indwelling catheters. However, our results seem to indicate that the absolute renal pelvic pressure is not as important as the increase in renal pelvic pressures before and after drug administration.

The reduced rise in renal pelvic pressure combined with increased maximal pelvic capacity appeared to be the main reason for the analgesic effect of prostaglandin synthetase inhibitors and may explain the success of using these drugs in the treatment of renal colic [11, 16].

It is not clear whether there are further mechanisms that reduce pain and how the use of different medications may affect stone progression through the urinary tract [7]. In addition to local anti-inflammatory effects on the renal pelvis and ureter around the stone [9, 10], prostaglandin synthetase inhibitors also seem to have a further direct effect on the upper urinary tract by reducing the smooth muscle activity [4, 15, 17]. In our experiments on isolated preparations of the urinary tract, human strips of the renal pelvis and the bladder, both reacted with dose-related tonic contractions after addition of prostaglandin F2α.

Metamizol did not significantly alter the response of isolated renal pelvic strips when contractions were produced by prostaglandin F2α. These findings confirm the results of Hertle, who found that on isolated preparations of the upper urinary tract metamizol in concentrations up to 10^{-3} mol/l did not have influence on the contractile activity produced by high concentrations of potassium or norepinephrine [9]. In the case of human bladder strips, muscle relaxation was found with high concentrations of metamizol ($10^{-3} - 10^{-2}$ g/mol) [3]. These high concentrations might make this response of dubious physiological significance. A further explanation as to why metamizol does not work in muscle strip experiments might be its immediate change into metabolites with variable inhibitory activities [19].

On the other hand, we found that indomethacin was able to abolish isometric tonic contractions produced by PGF2α. It is not clear how this relaxation can be explained. Experiments in isolated sheep and human ureters have shown that spontaneous contractions or contractile response to electrical field stimulation can be inhibited by indomethacin. It was suggested that these contractions might be due to a continuous release of local prostaglandins and the contractions could be inhibited by prostaglandin synthesis inhibitors [4, 17. 18]. Exogenous prostaglandins have been used in our experiments in the tissue bath and have already been shown to restore contractile responsiveness after suppression with indomethacin [15, 17] or may increase phasic and tonic components of the electrically stimulated contractions [4]. Therefore, our findings with PGF2α causing contractions of human renal pelvic preparations confirm the aforementioned in vitro results. But, with the results it cannot be concluded that exogenous prostaglandins are directly antagonized by indomethacin although endogenous prostaglandin synthesis may be inhibited by indomethacin.

Although the results of isolated preparation experiments cannot be directly correlated to the in vivo response, our results with the direct effects of indomethacin on smooth muscle activity of the upper urinary tract and the results of the pharmacourodynamic investigations confirm clinical experience and clinical reports indicating that indomethacin is useful and effective in the treatment of renal colic [6, 11, 16].

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