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# ORIGINALS

## Possible Pharmacological Means of Treating Renal Colic

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Summary. The effects of various drugs on the partially obstructed ureter were investigated in a new model experiment which permitted the calculation of peripheral resistance. After the administration of noradrenaline, the local spasm of the ureter in the region of the obstruction was increased and the urinary flow fell. After administration of the α-blocker phentolamine and of the β-receptor stimulant orciprenaline there was a reduction of the peripheral resistance and an increase in urinary flow due to spasmolysis. Because of its lower side-effect rate, phentolamine is worth investigating in further clinical studies.

Key words: Ureteral colic, spasmolytic agents, ureteral resistance.

According to the currently held opinion on the control of ureteral dynamics, the impulse formation in the renal pelvis and the impulse transmission are predominantly of myogenic origin (6, 10, 14, 17). The peristalsis is, however, subject to modifying neurogenic impulses via the autonomic nervous system (4). Starting from a hypothetical pace-maker centre in the renal pelvis, the peristalsis develops as a segmentally progressing wave of contractions down the ureteral muscle. The impulse transmission takes place on the one hand as the result of the mechanical stimulus of a sudden rise in pressure in the distal segment and on the other hand as the result of the stimulus, i.e. membrane depolarisation. This causes excitation of the neighbouring cell in the region of the "nexus" (14). Neurogenic effects can have a considerable influence on the formation and transmission of the impulses. The influence of the sympathetic system has been demonstrated by numerous morphological and pharmacological investigations, whilst the importance of the parasympathetic nervous system is still disputed (4, 10). According to Ahlquist's classification (1), there are activating α- and inhibitory β-2-receptors in the ureter (3, 10).

The aim of the present investigation was therefore to see if it was possible to obtain a pharmacological effect on the ureter with α-receptor-blocking agents.

### Methods

A major difficulty in investigations on ureteral peristalsis is the interpretation of the measurements, as there are numerous intra- and extraureteral factors that can affect the results. An attempt was therefore made to keep constant as many parameters as possible using a new experimental procedure.

The experiments were carried out on 36 mongrel dogs under anaesthesia. After intravenous induction with 25 mg/kg body weight pentobarbitone, the anaesthesia was maintained with a nitrous oxide-oxygen mixture in the ratio 2.8 : 1. After opening the abdomen, the renal calices were opened up in situ without further preparation via a 1 cm nephrotomy. During this procedure, the renal artery and vein were temporarily compressed manually. Concretions with a diameter of 2.6 to 3.3 mm were introduced into the upper end of the ureter via the nephrotomy by means of fine forceps. They were then pushed further into the middle region of the ureter with a probe. The concretions were 3 different sizes of jagged grains of sand. Which

of the 3 concretions was used was decided according to the anatomical conditions. Subsequently, a perfusion catheter (2 mm diameter) was sewn into the renal pelvis using a purse-string suture so that the perfusion fluid could only flow into the ureter.

The urine produced by the kidney, which was initially strongly contaminated with blood, was drained via a second nephrotomy catheter placed in the lower calices. The nephrotomy was closed without much loss of blood with 3 stitches in the parenchyma (see Fig. 1). This procedure protected the nerves in the region of the hilum. Prior investigations had shown that the peristalsis is less impaired by this procedure than by an incision in the renal pelvis or by cutting through the ureter.

Ringer solution was used for the perfusion. The perfusion pressure was kept constant by maintaining the height in an interposed T-unit at a given level. Only the quantity of the perfusate, which was supplied from a reservoir according to the level of fluid in the T-unit, was varied and was recorded in ml/30 sec. The usual pressure parameters (basal pressure, amplitude, frequency, form and duration of the contraction) were measured below the concretion by means of an endoluminal probe (internal diameter 0.5 mm, external diameter 1 mm) to which a Statham element was attached and which was passed into the distal segment of the ureter after opening the urinary bladder. The probe used had not caused any stasis in the ureter in preliminary investigations. Recording was carried out with a UV recorder. All the results were analysed for statistical significance by means of the t-test.

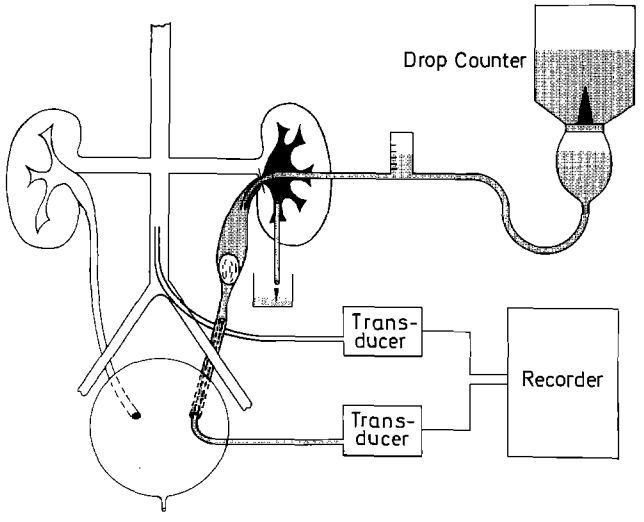


Fig. 1. Diagramatic representation of the experimental conditions. Perfusion of the ureter at constant pressure. The urine produced by the kidney itself is led off via another catheter

## Results

The intravenous administration of 20-40 ug/kg body weight noradrenaline produced the well-known and reproduceable positive inotropic and chronotropic actions on the ureteral musculature (2, 9, 10). However, because of the constriction of the lumen and lack of co-ordination in the contractions, the "urinary flow" is reduced (see Fig. 2). This reduction in the flow occurs both in the non-obstructed (n = 39) as well as in the partially obstructed ureters (see Fig. 3). These changes are significant ($p < 0.01$).

These results raise the question whether α-receptor blockers or β-stimulants would have the theoretically expected opposite effect. At a dose of 0.4 mg/kg i.v. body weight, phentolamine led to a highly significant increase in the flow of urine in the partially obstructed ureter (n = 15, $p < 0.001$, see Fig. 4).

The effect started after 30-60 sec and lasted for about 20-25 min and was accompanied by a transient fall in blood pressure. The frequency of the ureteral contractions fell, whilst the basal pressure and contraction amplitude did not exhibit any uniform behaviour. In some of

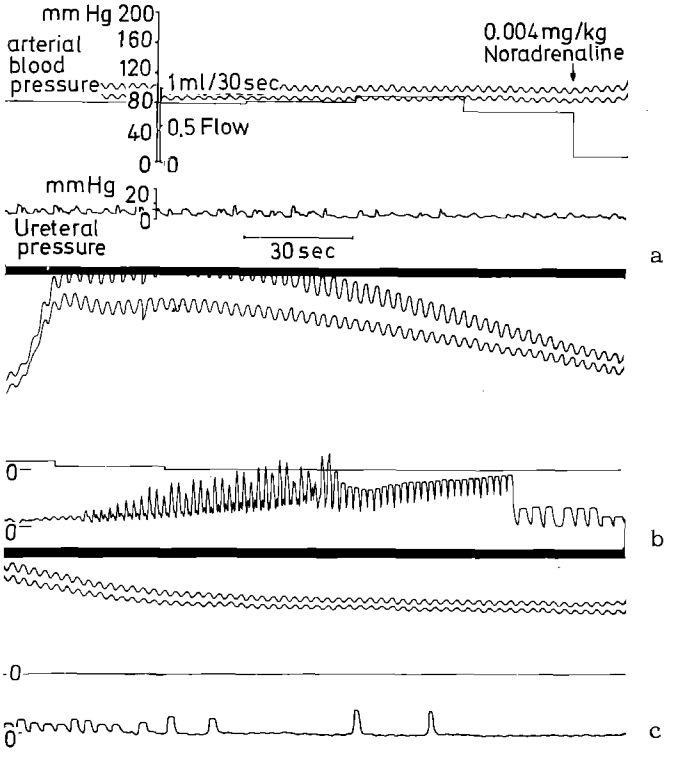


Fig. 2. After administration of noradrenaline there is a positive chronotropic and inotropic action on the ureter (lower curve). Simultaneous recording of the arterial blood pressure (upper curve) and of the perfusion volume, which falls to zero (middle curve) (a, b and c from a continuous trace)

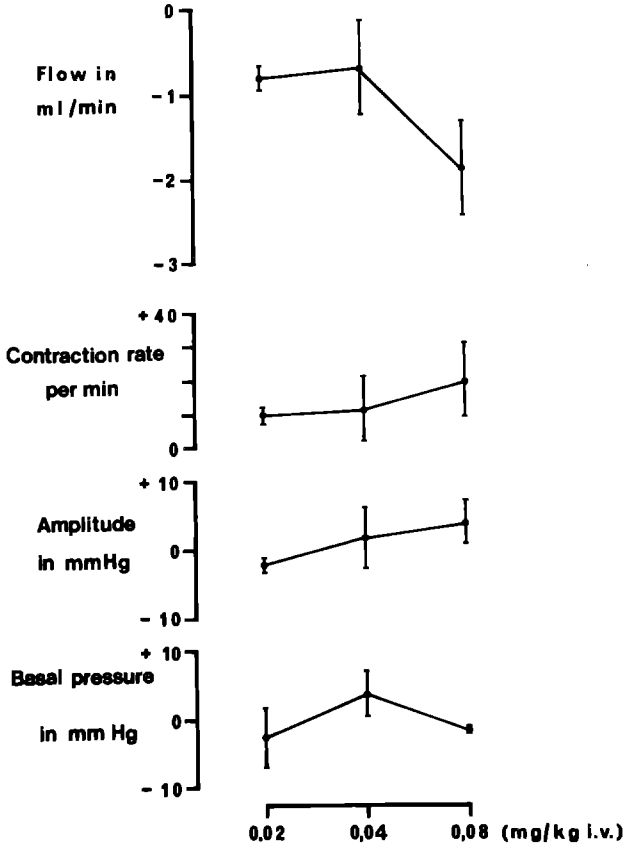


Fig. 3 Urodynamic parameters after administration of noradrenaline. The dose-dependent changes are plotted with standard deviations ($s_x$)

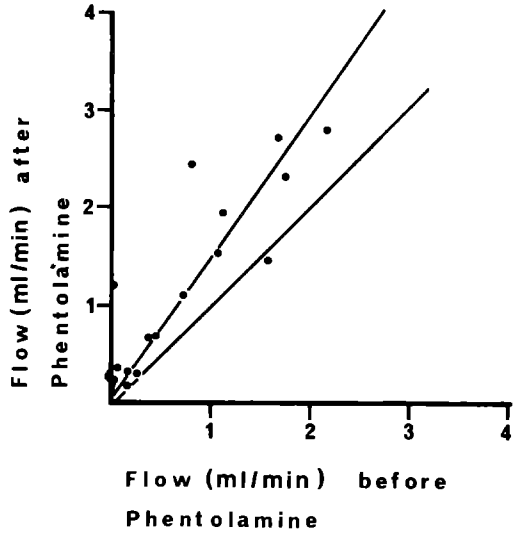


Fig. 4. Changes in the urine flow after phentolamine administration. The lower straight line has a slope of 1. All values above this line show an increase in the perfusion rate

the experiments the amplitude was reduced, but generally the basal pressure and the contraction amplitude increased as a result of the increased urinary flow. The myogenic factors were in these cases superimposed on the neurogenic effect.

Orciprenaline, a β-receptor stimulator (0.02-0.04 mg/kg i.v. body weight), produced an increase in urinary flow in ureters perfused at constant pressure (n = 14). Whilst the increase with 0.02 mg/kg was highly significant ($p < 0.001$), the increase at higher dosages was no longer significant. Possibly, the negative inotropic and chronotropic effects exerted a greater influence at this level (see Fig. 5).

If one regards the ureter as a suction pump (17) then its performance (L) can be calculated from the formula:

$$\Delta L = \Delta p \times \frac{\Delta V}{\Delta t}$$

For the 60-sec observation period conversion to integral calculation is required, i.e.

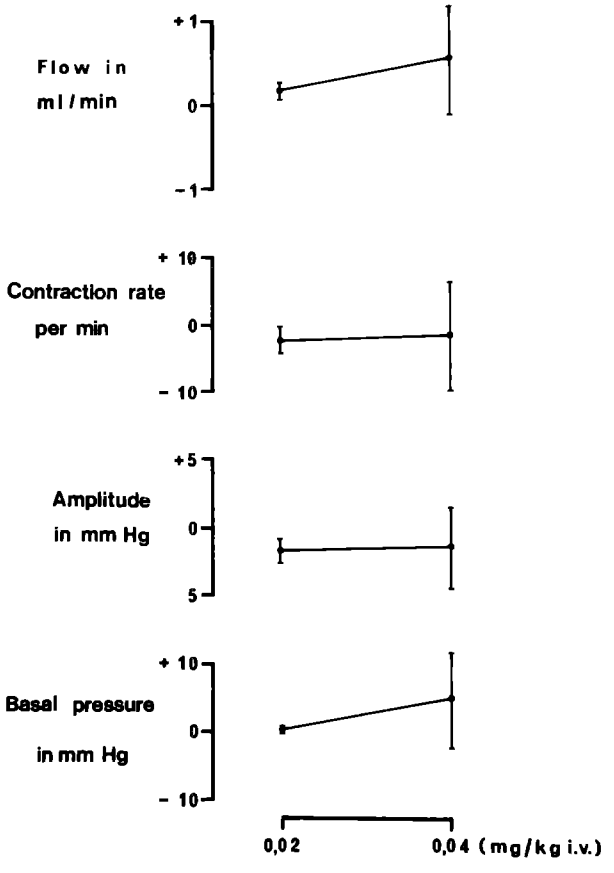


Fig. 5. Urodynamic parameters after intravenous injection of orciprenaline. Graphical presentation of the increase in urine flow, frequency, amplitude and basal pressure with standard deviations ($s_x$)

$$\bar{L} = \dot{V} \times \frac{1}{T}\int_{o}^{60\ sec} p\ (t)\ dt \qquad \text{where} \qquad \dot{V} = \frac{dV}{dt}$$

The volume per unit time could be determined in ml/min because of the special experimental conditions. The pressure below the concretion was measured with a probe and the pressure curve was determined planimetrically. It was thus possible to determine the performance of the ureter mathematically.

The driving force of a fluid in a tube is the pressure applied (p) and the resistance (W) which counteracts it. This model can be applied approximately to the congested ureter above the concretion. The flow intensity (I) of a fluid with friction is

$$I = \frac{p_2 - p_1}{W}$$

$P_2$ was kept constant by means of the experimental conditions. The pressure $p_1$ in the urinary bladder was equal to that of atmospheric pressure.

$$W = \frac{p_2 - p_1}{I}$$

As $I = \dot{V}$ by definition, it follows that

$$W = \frac{p_2 - p_1}{\dot{V}} = \frac{(p_2 - p_1)\ \frac{1}{T}}{\bar{L}} \int_{o}^{T} p\ (t)\ dt$$

The resistance is inversely proportional to the performance. As the resistance of a partially obstructed ureter is predominantly caused by the concretion and the local spasm of the ureter, the effect of spasmolytic drugs can readily be assessed by calculating the reduction in resistance. Fig. 6 and Table 1 show the effects of noradrenaline, phentolamine and orciprenaline on the partially obstructed ureter. Phentolamine and orciprenaline lead to a dilatation of the lumen of the ureter at the level of the concretion and thus to a reduction in the resistance and to an increased urine flow. This spasmolysis relieves the pressure on the kidney and improves the possibility of passage of the concretion.

## Discussion

Urodynamic investigations of the upper urinary tract always suffer from the variability of numerous intra- and extraureteral factors which can affect the results. With the procedure described it was possible to exclude variations in the secretion pressure of the kidney and at the same time to measure the artificial diuresis. This made a better assessment of the urody-

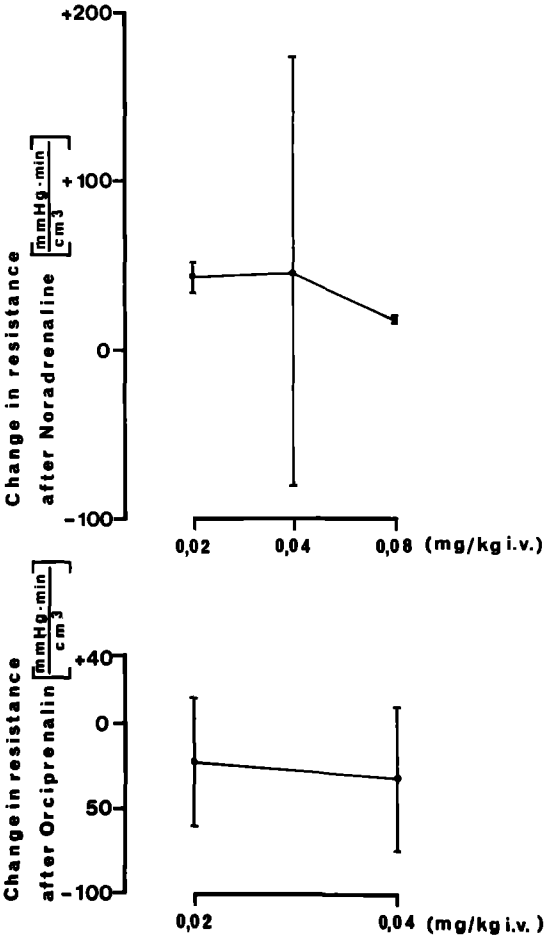


Fig. 6. Changes in the peripheral resistance in the ureter before and after administration of noradrenaline and orciprenaline with standard deviations ($s_x$)

Table 1. Changes in the resistance in the ureter before and after intravenous injection of phentolamine (0.4 mg/kg). Depending on the initial situation, 4 groups were formed. The higher the initial resistance, the greater the spasmolytic effect.

| Initial resistance in: mm Hg x sec / cm³ | | | Changes in resistance in: mm Hg x sec / cm³ | | |
|---|---|---|---|---|---|
| $\bar{x}$ | $s_{\bar{x}}$ | $s_x$ | $\bar{x}$ | $s_{\bar{x}}$ | $s_x$ |
| 19,27 | ±1,29 | ±2,58 | -3,39 | ±2,02 | ±4,04 |
| 38,36 | ±4,12 | ±8,24 | -17,04 | ±3,97 | ±7,94 |
| 132,04 | ±33,10 | ±66,20 | -23,98 | ±6,79 | ±13,58 |
| 1803,98 | ±924,53 | ±1849,06 | -1710,89 | ±940,03 | ±1880,06 |

$s_{\bar{x}}$ = standard deviation of the mean

$s_x$ = standard deviation

namic parameters possible. In order to be able to make statements about ureteral dynamics during acute renal obstruction with a concretion, a stone was introduced into the ureter without touching the nervous connections of the ureter and without breaking its continuity. External compression of the ureter or obstruction with a thick ureteral catheter is not suitable for simulating an obstruction of the ureter (7).

The flow in the ureter is normally laminar. If there are corpuscular objects in the urine bolus, they do not have any effect on the ureter peristalsis if they move freely in the centre of the stream. However, if there is mechanical alteration of the mucosa due to larger concretions, then the ureter may react with a local spasm which leads to total obstruction (12, 16). Inflammatory edema and microhaemorrhages in the mucous membrane are the result. Because of the continuing urine production the basal pressure in the ureter proximal to the obstruction rises. The ureter reacts to this rise in pressure with a high frequency fibrillatory peristalsis (6, 15). The rise in pressure leads to an increase in the friction which counteracts the passage of the concretion (5).

It is possible to use pharmacological agents in this situation in various ways. In addition to non-specific spasmolytics, such as papaverine, the peripheral resistance can be lowered with α-blocking agents or β-stimulating drugs as shown in the present study. Their action is explained by the dilatation of the ureter in the region of the obstruction or by abolition of the local spasm caused by mechanical changes. This had already been demonstrated for β-stimulants (11, 12). Clinical use, however, had failed because of side-effects. Initial clinical experiments with phentolamine appear to be promising (8).

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