Urol Res (1986) 14:37–40

Urological Research

The Effect of Ritodrine and Glucagon on the Acutely Obstructed Canine Ureter

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Accepted: April 30, 1985

Summary. The effects of 22 μg/kg/h glucagon and 240 μg/kg/h ritodrine infusions on the electrical activity and the intraluminal pressure of an acutely obstructed canine ureter have been studied. Acute obstruction of the ureter increased the rate of peristalsis from 7.05 (±0.61) to 19.87 (±0.47) per minute and the intraluminal pressure rose to a maximum of 124 cm water. Glucagon and ritodrine infusions reduced the rate of peristalsis to 6.32 (±0.73) and 5.83 (±0.84) respectively, whilst the intraluminal pressure was reduced by 43% during the glucagon infusion and 51% during the ritodrine infusion. The effect of ritodrine was more prolonged than that of glucagon.

Key words: Ureter, Glucagon, Propanolamines.

Introduction

Glucagon has been shown to inhibit the peristaltic activity of the canine ureter [1, 13], and two clinical reports have suggested that it may be beneficial in the treatment of ureteric colic [5, 8]. Mayo and Halbert [6] reported that glucagon was less effective than diazoxide in reducing the raised intraluminal pressure induced by acute obstruction in the canine ureter.

The effect of ritodrine on ureteric activity has not been previously studied, although this drug is widely used to inhibit premature labour. Ritodrine is a beta agonist, as is terbutaline which has been demonstrated to inhibit canine ureteric activity [10].

We previously described a method of recording canine ureteric action potentials extraluminally [13] and found it to be reliable and accurate in both acute and chronic studies. Using this method the effect of glucagon and ritodrine on ureteric function in the acutely obstructed canine ureter was studied.

* M. J. Stower was in receipt of a grant from Novo Industries

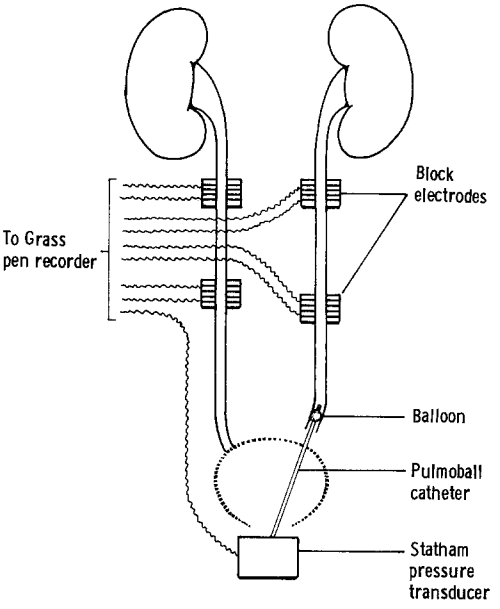

Fig. 1. The experimental model. Both ureters have been placed into two bipolar electrodes and the left ureter cannulated with the balloon catheter which can be inflated to produce obstruction

Material and Methods

In eight female greyhound dogs, weighing between 25–32 kg, anaesthesia was induced with 20 mg/kg thiopentone. The dogs were intubated and anaesthesia maintained with nitrous oxide/oxygen 2:1 and 0.5% or 1% halothane. The dogs were placed on a heated operating table to minimise heat loss and an intravenous infusion of 5 ml/kg/h 0.9% sodium chloride was given throughout the study.

The block electrodes were constructed from 5 mm thick perspex measuring 10 mm x 10 mm into which a channel 3–4 mm deep and 7 mm wide was made. Four silver wires were inlaid transversely so that they were flush with the surface of the channel (Fig. 2). The silver wires were soldered to Teflon insulated lead wires and this area was covered with Epoxy adhesive. The silver wires were chlorided by electrolysis, thus creating two bipolar electrodes in very close proximity.

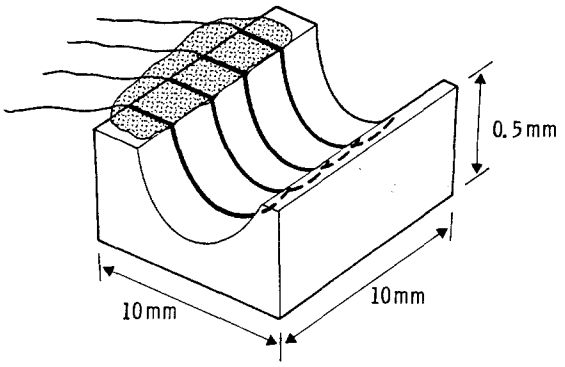

Fig. 2. Two pairs of electrodes inlaid in a perspex block (see text for detailed description)

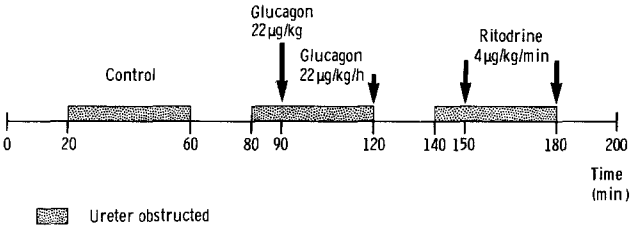

Fig. 3. The experimental protocol to study the effect of glucagon and ritodrine on the acutely internally obstructed ureter

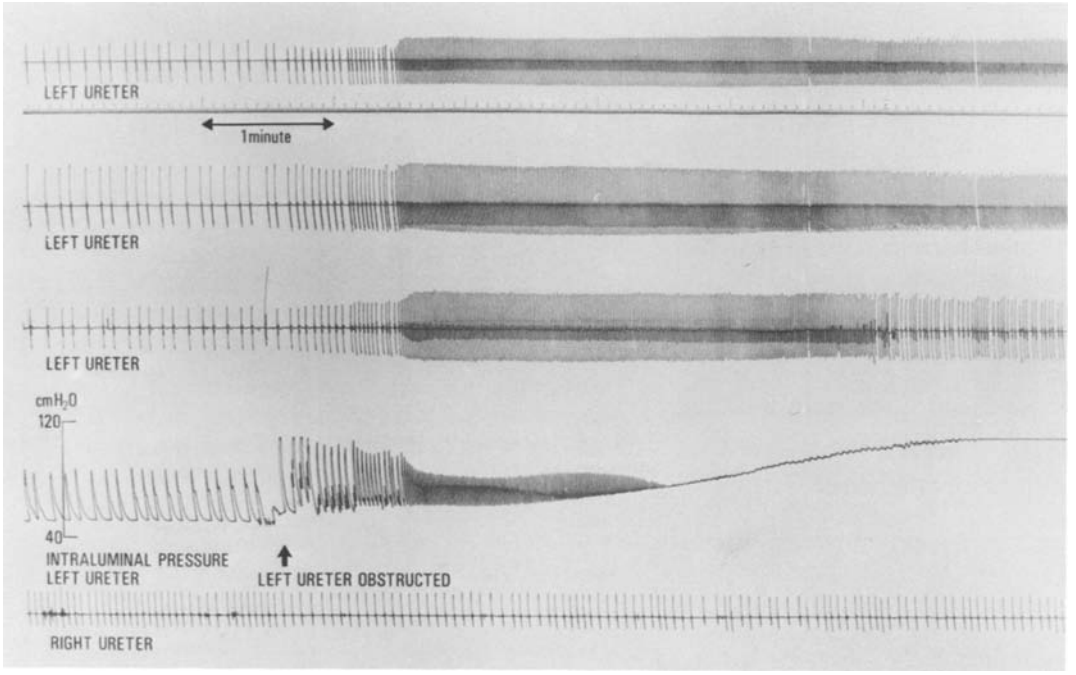

Fig. 4. The effect of acute internal obstruction on the canine ureter. For clarity only three electrodes from the left (obstructed side) and one electrode from the right (unobstructed side) are shown (subject 2). Note that the peristaltic rate in this example is faster than the mean of 19 per minute from all studies

Both ureters were identified via a midline incision and two block electrodes were positioned under each ureter. The most distal portion of the left ureter was dissected free from the wall of the bladder and then cut across, allowing a Vygon Pulmoball pulmonary arterial catheter size French 5 (Vygon U.K. Ltd., Bridge Road, Cirencester, Gloucester.) to be advanced 4 cm into the ureter. This catheter consists of an open central channel through which intraluminal ureteric pressure could be measured using a Gould Statham transducer (Gould Medical U.K., Lutterworth, Leicester.) and a ballon sited at the tip of the catheter which could be distended with 0.5–0.7 ml of air to totally obstruct the ureter, whilst still measuring the intraluminal pressure (Fig. 1).

All the signals from the electrodes and the transducer were amplified and displayed using a Grass 8 channel recorder (Grass Instruments Inc., Quincy, Mass.).

The experiment was divided into three phases, control, glucagon (Novo) and ritodrine (Duphar), allowing time for basal conditions to be achieved before starting each phase (Fig. 3).

Results are expressed as a mean ± S.E.M. and the Mann Whitney U test has been used to test for statistical significance.

Results

The mean rate of ureteric peristalsis during the first control period was 7.05 (±0.61) per minute and this increased to 19.87 (±0.47) per minute after balloon obstruction of the ureter.

Fig. 4 shows the effect of an acute internal obstruction on ureteric function; the rate of ureteric peristalsis increased very rapidly once the ureter was obstructed. Pressure steadily rose to reach a plateau at 3–6 min. The peaks of pressure normally associated with each peristaltic wave disappeared

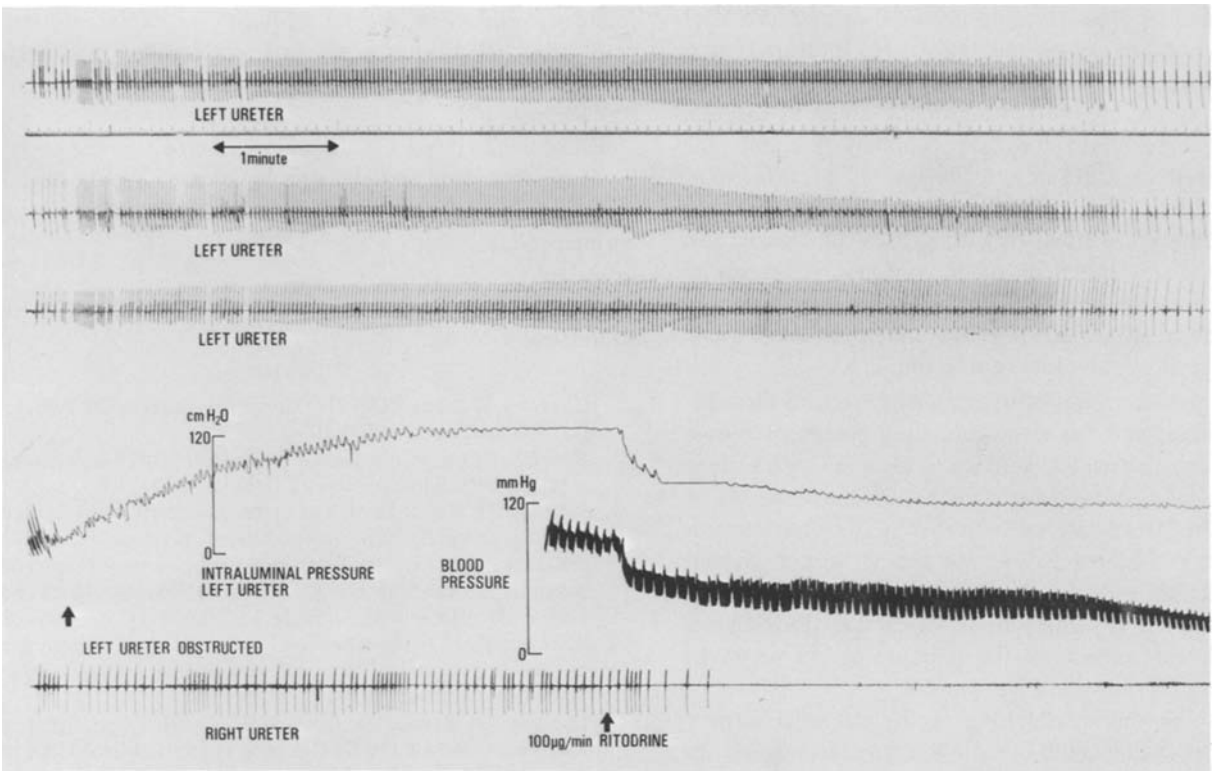

Fig. 5. The effect of a ritodrine infusion on the acutely obstructed ureter. For clarity only three electrodes from the left and one electrode from the right are shown. Also the period of obstruction has been shortened so that the continuous sequence of events can be seen (Subject 4)

Table 1. Effect of glucagon and ritodrine on the intraluminal pressure of the acutely obstructed canine ureter

	Median intraluminal pressure cm water
Max pressure during control obstruction	84.5 (60–124)
Max pressure before glucagon	56.5 (31–123)
Max pressure during glucagon infusion	28.0 (10–87)
Max pressure before ritodrine	76.5 (32–95)
Max pressure during ritodrine infusion	31.0 (16–50)

when the plateau was reached. There was no compensatory rise in the rate of peristalsis of the unobstructed ureter during this period.

During the ten minutes of ureteric obstruction before glucagon was given the mean peristaltic rate for all the subjects was 19.02 (±0.52) per minute, this fell to a mean of 6.32 (±0.72) during the glucagon infusion. This decrease in the rate of peristalsis was always seen within 50 s of the start of the infusion. Complete inhibition of ureteric activity was seen in five dogs for 3.0 (±0.63) minutes after the start of the glucagon infusion, but the rate of peristalsis tended to increase towards the end of the infusion.

Before the ritodrine infusion was given the mean rate of peristalsis for all the subjects in the obstructed ureter was 19.12 (±0.63) per minute which fell to 5.83 (±0.84) per minute during the infusion. This effect usually took 3–5 min to become apparent as is seen in Fig. 5. Ritodrine had a much longer duration of action, and inhibition of ureteric activity occured for at least 30 min after the infusion was stopped. There was no statistical difference between glucagon and ritodrine in their inhibition of electrical activity.

The median maximum intraluminal pressures measured during the study are shown in Table 1. Glucagon induced a fall of 43.1% ($p = 0.047$), compared to a fall of 51.2% ($p = 0.008$) during the ritodrine infusion. This difference between glucagon and ritodrine was not significant.

Discussion

Different techniques have been used to study the effect of acute obstruction on ureteric function. Calculi have been inserted via a nephrostomy tube into the upper ureter [12, 3], but this can lead to damage of a major blood vessel with a subsequent alteration of renal haemodynamics. Lindsey et al. [4] described a method whereby the ureter was opened longitudinally and a calculus inserted into the ureter which was then closed, but using this method it is difficult to obtain a watertight seal and it has been shown to alter the rate of peristalsis [9]. Stainless steel spheres have been pushed up the ureter [2], but could damage the ureteric mucosa

and intraluminal pressure could not be measured proximal to the obstruction. Mayo and Halbert [6] measured intraluminal pressure via a tube inserted at the upper end of the ureter, whilst causing obstruction of the ureter by external clamping. This method does not accurately reproduce the situation seen in acute obstruction caused by a calculus. Therefore the use of the pulmonary arterial catheter reflects more accurately the effect of a ureteric calculus whilst also allowing the measurement of the intraluminal pressure proximal to the obstruction. The balloon was distended in the lower third of the ureter as this is the position in which the majority of calculi cause obstruction.

The bipolar electrodes gave high quality records throughout the studies and the electrical action potentials always preceeded any mechanical activity as recorded by a change in intraluminal pressure. Due to the known short half-life of glucagon, the 30 min interval between the two drug infusion periods was considered to be long enough to prevent any drug interaction, and in view of the long half-life of ritodrine glucagon was always given first. There was variation between different subjects in the response of the ureter to obstruction as is shown in Figs. 4 and 5.

Glucagon produced inhibition of the electrical activity of the ureter during acute obstruction, an effect which has already been shown in the unobstructed ureter [13]. Glucagon reduced intraluminal ureteric pressure by 43% but this effect was not so pronounced towards the end of the infusion. Mayo and Halbert [6] reported that a bolus injection of 12.5 μg/kg glucagon, a smaller dose than was used in this study, caused a fall of 24% in the intraluminal pressure in an obstructed ureter.

Ritodrine also induced inhibition of the electrical activity of the ureter, while at the same time it induced a fall of 51% in the intraluminal pressure. This effect was seen throughout the infusion and for at least 30 min after the infusion was stopped.

Ritodrine also produced a fall of intra-arterial pressure which would alter renal pressures and hence the transmitted pressure to the ureter. The fall of intraluminal ureteric pressure induced by ritodrine may be mediated both by a direct action on the ureteric smooth muscle and a fall of blood pressure. Diazoxide which lowers intraluminal ureteric pressure also lowers blood pressure [6].

There are no previous studies on the effect of ritodrine on the ureter, but isoproterenol [1, 10, 11] and orciprenaline [9] which are also beta-adrenergic agonists decrease the amplitude and or the frequency of canine ureteric peristalsis. Terbutaline, a selective beta 2 agonist, has been studied and found to produce prolonged inhibition of canine ureteric peristalsis [10]. Isoproterenol and orciprenaline have been shown to reduce the rate and magnitude of ureteric peristalsis in man [7].

Ritodrine, as it has a more prolonged effect on the acutely obstructed canine ureter than glucagon, should be investigated further for its efficacy in the management of ureteric colic.

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