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Modification by Dipyrone (Noramidopyrine Methanesulphonate) of Stone-Induced Ureteric Hyperperistalsis in the Dog

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Summary. Implantation of a stone in the ureter of the dog by ureterotomy results in focal hyperperistalsis which is accentuated by administration of norepinephrine, and reduced by administration of phenoxybenzamine or isoproterenol. Administration of dipyrone reduces the hyperperistalsis, but this action does not appear to be that of either a β-agonist or an α-antagonist.

Key words: Ureteric colic, Dipyrone.

Although doubt has been expressed as to the existence or nature of the dynamic response of the ureter to the presence of a calculus (8, 13), clinical and experimental studies (6, 10, 11) have demonstrated spasm, hyperperistalsis, and ineffective transport of urine in association with ureteric calculi. The evidence may not be totally convincing, but many urologists appear to accept the notion of stone-induced hypermotility by inclusion of some sort of antispasmodic medication in the treatment of ureteric colic (1, 8, 10, 11, 15, 16).

In Europe, dipyrone is widely used as a spasmolytic agent in both human and veterinary medicine. However, the potent analgesic properties of dipyrone obscure the interpretation of presumed spasmolytic activity. Experimental studies are meagre (2-4, 12, 14), and with rare exception (9) are limited to effects on motility of the gastrointestinal tract. This paper reports a study of the action of dipyrone on the ureter *in vivo*.

The experiments were designed to:
1. Develop an experimental model demonstrating the dynamic characteristics of a calculus in the ureter.
2. Validate the response obtained, by modifying it with agents known to affect ureteric peristalsis.
3. Ascertain what effect, if any, is produced on the dynamic response by the administration of dipyrone.
4. Explore the mechanism by which dipyrone produces any effect noted.

METHODS

1. Development and Characterisation of Model

Mongrel dogs weighing 12-25 kg were denied food and fluid for 12 h, anaesthetised with halothane, maintained on mechanical ventilation via an endotracheal tube, and subjected to midline laparotomy. Both ureters were cannulated at about the midpoint of the ureter by transmural insertion of an 18 gauge catheter over a 21 gauge needle. Approximately 2 cm distal to the tip of the catheter the right ureter was opened by longitudinal ureterotomy with a No. 15 scalpel, a stone was inserted proximally, and the incision was closed with sutures of 6-0 silk. The stones were selected empirically from a handful of coarse Arizona riverbed sand. The left femoral artery was cannulated for blood pressure recording.

The catheters were connected to transducers and recordings of arterial and ureteric pressure waves were made on a Hewlett-Packard 7700 recorder (Fig. 1).[1]

Normal saline solution was administered by intravenous infusion throughout the experiments at a rate of 2.5 ml/min.

[1] The model is remarkably similar to that of Peters and Eckstein (11). At the time of presentation of the method and early results to the American Urological Association on 13 May 1975 we were unaware of their concurrent work

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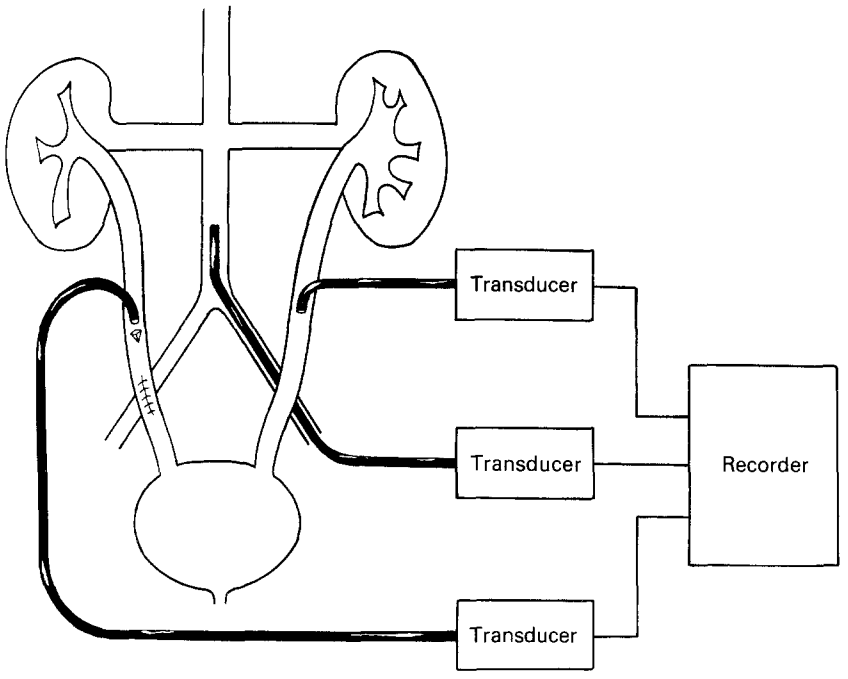

Fig. 1. Diagrammatic representation of experimental model

Table 1. Agents and doses

		N[a]
Epinephrine	0.1 to 7.5 μg/kg	22
Norepinephrine	0.1 to 7.5 μg/kg	9
Isoproterenol	5.0 to 15 μg/kg	11
Propranolol	50 to 400 μg/kg	11
Phenoxybenzamine	1 mg/kg	2

[a] N = number of experiments with each agent

2. Validation of Dynamic Response

With the exception of phenoxybenzamine, which was administered by continuous infusion at a rate of 20 μgm/kg/min, the adrenergic agents and doses indicated in Table 1 were given by intravenous bolus through an injection port in the infusion set, and flushed by resumption of the saline flow.

3. Effect of Dipyrone

Dipyrone was administered by intravenous bolus in dosages of 100 and 200 mg/kg.

4. Exploration of Mechanism of Effect of Dipyrone

Agents and doses indicated in Table 1 were administered before and after dipyrone to mongrel dogs prepared as described above. In addition, female greyhounds weighing 20-25 kg were prepared for adrenergic agent bolus series determination of sensitivity to minimal ventricular arrhythmia after the method of Koehntop et al. (7). Minimal arrhythmic dosage determinations were made before and after administration of dipyrone and phenoxybenzamine: 30 min and 60 min after dipyrone, and immediately after completion of the infusion of phenoxybenzamine. Starting bolus levels were: epinephrine 62.5 ng/kg/bolus; norepinephrine 62.5 ng/kg/bolus; phenylephrine 6.25 μgm/kg/bolus.

RESULTS

Development of the preparation required the expenditure of 12 dogs in trial-and-error determination of proper stone size and shape. Stones too small or too smooth passed without inducing significant changes in ureteric peristalsis. Larger stones blocked the ureter and peristalsis ceased. Like Peters and Eckstein (11) we ultimately selected a number of suitable stones: roughly tetrahedral in shape, averaging 3.5 x 3.0 x 2.0 mm in size (Fig. 2).

Implantation in the ureter of a stone of the proper size and shape induced peristaltic contraction waves of markedly higher pressure than waves recorded in the control ureter (Fig. 3). With removal of the stone the hyperperistalsis ceased (Fig. 4). After the initial development we succeeded in inducing unilateral ureteric hyperperistalsis in 46 of 48 experiments.

The response of the induced hyperistaltic contractions to adrenergic agonists and antagonists

Fig. 2. A typical stone

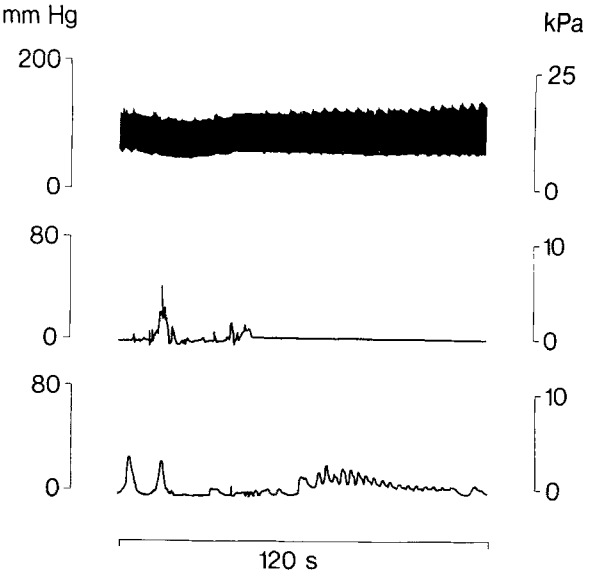

Fig. 4. Cessation of hyperperistalsis after removal of stone from ureter. Artifacts in control ureter tracing from operative procedure (as Fig. 3)

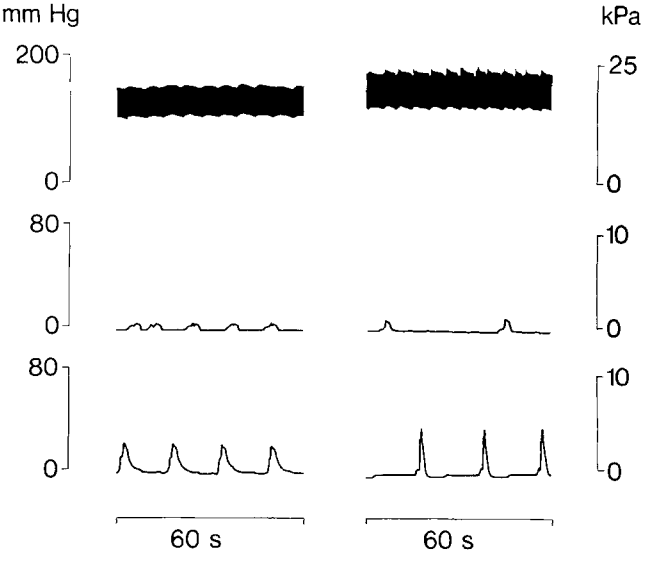

Fig. 3. Typical tracings from two different animals. Upper recording: blood pressure. Middle recording: control ureter. Lower recording: ureter with implanted stone.

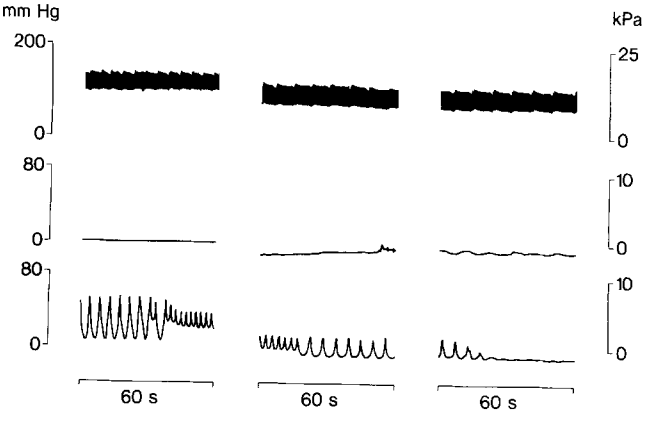

Fig. 5. Response to phenoxybenzamine, 1 mg/kg, infused at rate of 20 µgm/kg/min. Left: at start of infusion. Middle: after 45 min. Right: at 50 min (as Fig. 3)

was entirely consistent with the schema of the response summarised by Hannapel and Golenhofen (5) from data on normal ureteric peristalsis in unanaesthetised animals.

Phenoxybenzamine lysed the ureteric hyperperistalsis, at a cost of considerable reduction in blood pressure (Fig. 5). Isoproterenol lysed the hyperperistalsis, again with profound cardiovascular effects (Fig. 6). In doses higher than 2.5 µgm/kg epinephrine and norepinephrine consistently induced hyperperistaltic contractions in the stone-containing ureter (Fig. 7) during periods of sporadic quiescence, or when it had been rendered quiescent by isoproterenol or phenoxybenzamine. Propranolol alone had no observable effect, and appeared to be only transiently effective in blocking the effect of isoproterenol (Fig. 8).

In 22 of 32 experiments dipyrone fully lysed or

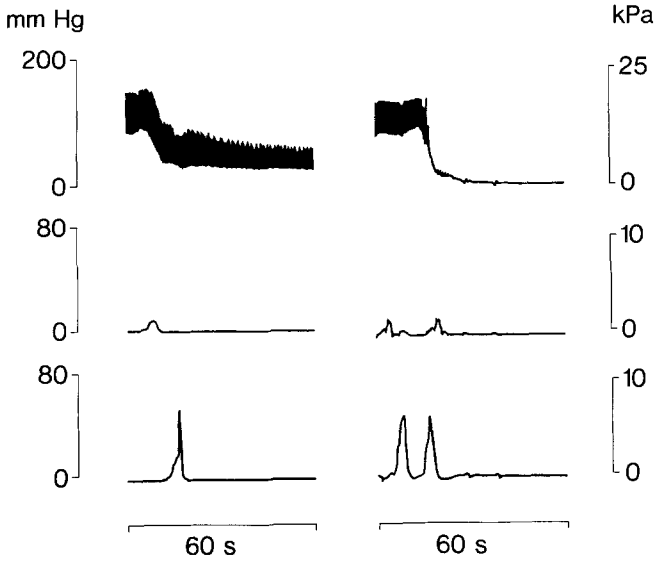

Fig. 6. Blood pressure and ureteric response to isoproterenol. Typical tracings from two different animals (as Fig. 3)

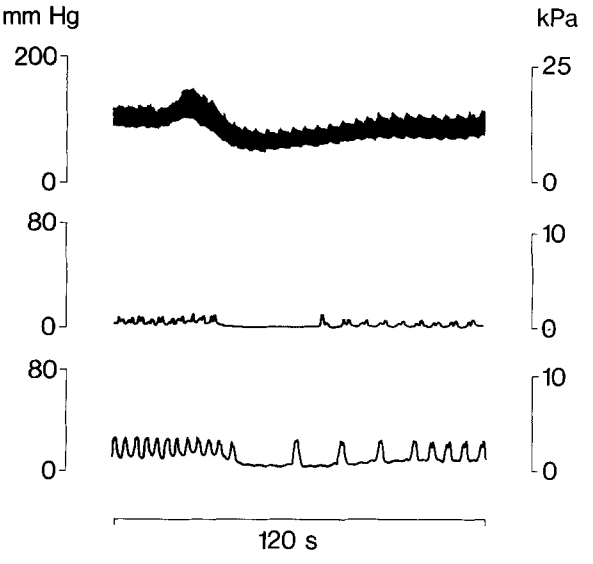

Fig. 8. Transient response of ureters to isoproterenol after propranolol (as Fig. 3)

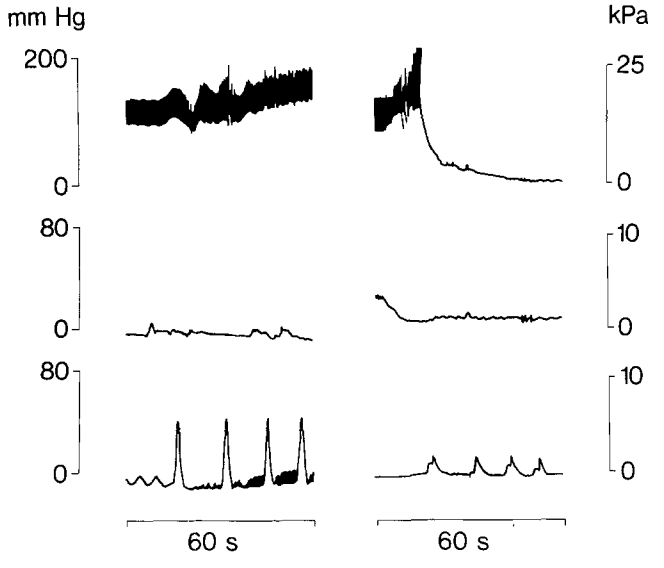

Fig. 7. Left hand tracings: blood pressure and ureteric response of quiescent ureter to epinephrine. Right hand tracings: postmortem induction of hyperperistalsis after lethal dose of epinephrine. Tracings from two different animals (as Fig. 3)

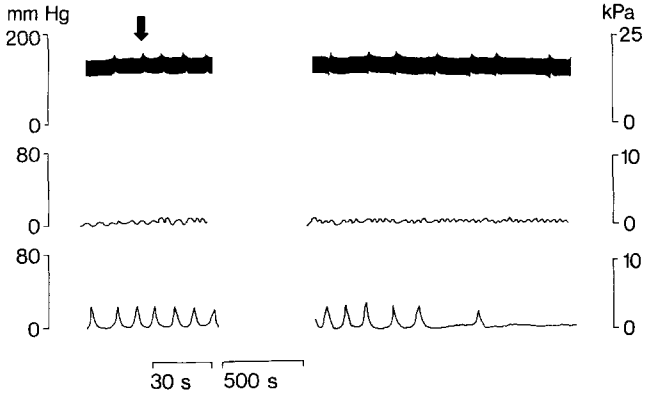

Fig. 9. Lysis of hyperperistalsis by dipyrone. Agent administered at time indicated by arrow (as Fig. 3)

markedly diminished the amplitude or the ureteric hyperperistaltic contractions. This effect was not impaired by propranolol. The lysed hyperperistalsis could be restored by administration of epinephrine or norepinephrine. In contrast to the immediate response of the hyperperistalsis to β-adrenergic agents, the effect of dipyrone was observed only after a delay of 2 to 10 minutes (Fig. 9).

Dipyrone produced no change in minimal arrhythmic dosage, and no change in the response of the blood pressure to the adrenergic agents administered (3 experiments). On the other hand, phenoxybenzamine administration resulted in a marked increase in the minimal adrenergic arrhythmic dosage (1 experiment).

DISCUSSION

Dipyrone administered by intravenous injection can reduce the dynamic response of the ureter to an implanted calculus. We are unable to explain why dipyrone was not effective in all experiments.

The mechanism of action of dipyrone is not clear. It does not act as a β-adrenergic agonist, nor does it act as an α-adrenergic antagonist. The experiments of Ruhnau (12) suggest a central mechanism, and the delay in effect raises the question of an indirect mechanism, or the possibility that a metabolite of dipyrone is the active.agent.

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