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The Effect of Various Drugs on Canine Ureteric Peristalsis

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Summary. Using an intact concious animal model the effect of various drugs on the rate of canine ureteric peristalsis was studied. The drugs found to reduce consistently the rate of ureteric peristalsis were diazoxide, terbutaline, and ritodrine. Ritodrine was the most consistent, having a prolonged effect and reducing the rate of ureteric peristalsis to 50% of the rates observed in control experiments.

Key words: Ureter, Propanolamines.

Introduction

Ureteric colic is a common and painful condition which is usually treated with powerful analgesics, which do not modify the underlying problems of hyperperistalsis and distension of the upper urinary tract. Anticholinergics have been used for their presumed inhibitory effect on the ureter, but many workers have shown them to have little or no effect [1, 4, 14, 16]. This study uses an established method previously described by us [16] to record the effect of drugs which have an action on ureteric smooth muscle.

Methods

Three extraluminal bipolar silver/silver chloride electrodes were sutured longitudially to the serosal surface of both ureters, and a single strain gauge was sutured to the right ureter in 5 female greyhound dogs weighing between 27–32 kg (Fig. 1). The teflon coated leadwires were exteriorised by means of a stainless steel cannula sutured to each flank. The animals were allowed to recover for 8–10 days before any studies were performed.

Ureteric electrical and mechanical activity were monitored using a multichannel pen recorder (Grass Instruments, Quincy, Mass., USA). The dogs were trained to empty their bladders before the study commenced and stood quietly in a specially constructed cage for the duration of the recording. After a control period of 20 min the test drug was given intravenously via a suitable peripheral vein either as a bolus injection or in the case of ritodrine as an infusion for 45 min. After the bolus injection recordings were continued for a further 45 min and in the case of the ritodrine infusion for 30 min after the infusion had been stopped. Only one drug was given to each dog on any one day to minimise the possibility of interaction.

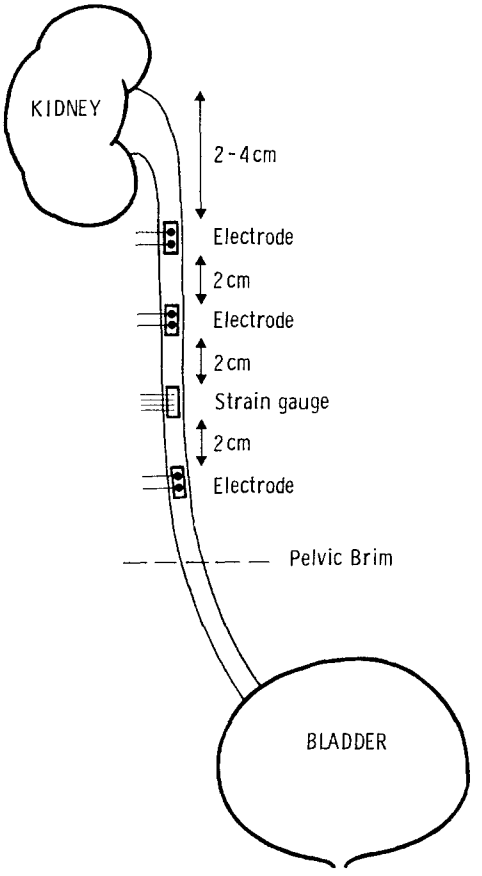

Fig. 1. The position of the electrodes and strain gauges on the ureter

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Table 1. Drugs studied for their effect on canine ureteric peristalsis

Drug	Dose
Aminophylline	7.0 mg/kg
Chlorpheniramine	0.2 mg/kg
Diazoxide	3.0 mg/kg
Metoclopramide	0.14 mg/kg
Ouabain	0.02 mg/kg
Propanolol	0.08 mg/kg
Phentolamine	0.30 mg/kg
Ritodrine	0.1 mg/min (infusion)
Salbutamol	0.04 mg/kg
Terbutaline	0.1 mg/kg
Verapamil	0.2 mg/kg
Placebo	5 ml 0.9% Saline

Table 2. The effect of drugs on canine ureteric peristalsis in 5 dogs

Drug	Effect of drug		
	Decrease	Increase	No effect
Placebo	0	0	5
Aminophylline	0	0	5
Chlorpheniramine	1	0	4
Diazoxide	2	0	3
Metoclopramide	0	0	5
Ouabain	0	1	4
Phentolamine	1	1	3
Propanolol	0	1	4
Ritodrine	4	0	1
Salbutamol	3	0	2
Terbutaline	3	0	2
Verapamil	1	0	4

(Only changes of more than 33% are considered)

The drugs and doses whose effect on ureteric peristalsis were tested are shown in Table 1. All the drugs were given in a 5 ml aliquot of 0.9% sodium chloride.

The records were counted manually expressing ureteric peristalsis as a rate per minute (± S.E.M.).

Results

The mean rate of ureteric peristalsis for all the dogs during the initial control period was 8.69 (± 0.46) per minute.

Placebo. The placebo, 5 ml 0.9% sodium chloride, altered the rate of ureteric peristalsis by nearly 30% in 2 of the 5 dogs, but there was no effect in the group overall (Table 2).

As these results have shown that the rate of peristalsis is variable and can be altered considerably by giving a placebo drug, only a change of greater than 33% induced by a test drug has been taken as relevant.

Aminophylline. Aminophylline (7.0 mg/kg) caused no significant change in the rate of peristalsis in any of the dogs.

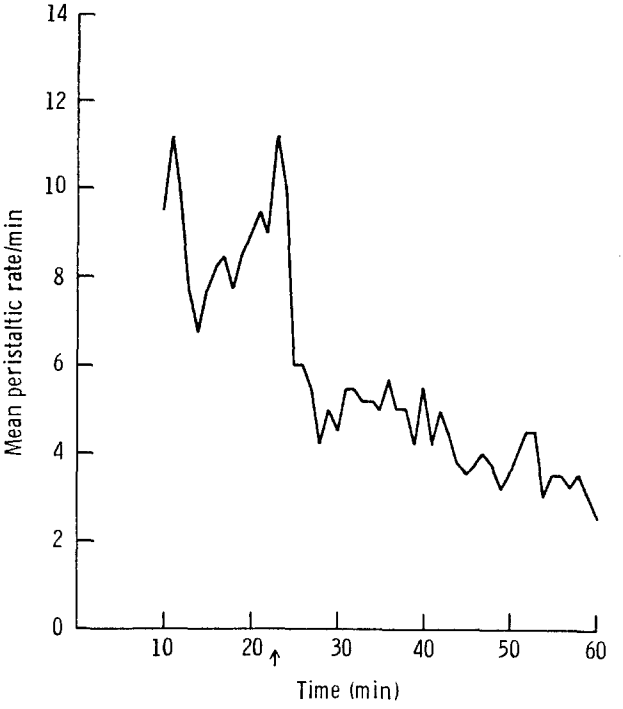

Fig. 2. The effect of Ritodrine infusion (0.1 mg/min) on the rate of ureteric peristalsis. (↑ = start of infusion)

Chlorpheniramine. Chlorpheniramine (0.2 mg/kg) decreased the rate of peristalsis in 1 dog by 41%, but there was no effect in any of the other dogs.

Diazoxide. Diazoxide (3 mg/kg) slowed the rate of peristalsis overall in all 5 dogs by 34%. It also had a long duration of action and it more than halved the initial rate in 2 dogs (54 and 64%).

Metoclopramide. Metoclopramide (0.14 mg/kg) caused no significant changes in the rate of peristalsis in any of the dogs.

Ouabain. Ouabain (0.02 mg/kg) increased the rate of peristalsis in 1 of the 5 dogs studied by 60%, but no effect was seen in the others.

Phentolamine. Phentolamine (0.3 mg/kg) had a variable effect on the ureter. In one dog there was a significant decrease in the rate of 43%, whilst in another dog there was a significant increase in the rate of 41%. No significant effects were seen in the other three dogs.

Propanolol. Propanolol (0.08 mg/kg) only caused a significant change in 1 dog, increasing the rate by 38.5%, whilst no significant effects were seen in the other dogs.

Ritodrine. Ritodrine was given as a continuous infusion in accordance with the manufacturers instructions at a rate of 0.1 mg/min which is equivalent to 0.3 mg/min in man and is the maximum recommended dose. Figure 2 shows that

the effect of ritodrine is not evident for 3–5 min, but once an effect had occurred it consistently slowed the rate of peristalsis an effect which was significant in 4 of the subjects. Ritodrine caused an overall reduction in the rate of ureteric peristalsis of 57.5% and also had a prolonged and consistent effect.

Salbutamol. Salbutamol (0.04 mg/kg) induced a significant reduction in 3 of the dogs (33, 39 and 40%), but had little effect on the others.

Terbutaline. Terbutaline sulphate (0.1 mg/kg) caused an overall decrease of the rate by 38% and proved to be one of the most exciting drugs, causing a reduction in all the dogs and this reached significance in 3 (33, 41 and 54%).

Verapamil. Verapamil (0.2 mg/kg) decreased the rate of peristalsis in 4 dogs, but inexplicably it increased the rate in one dog. Overall this drug caused a decrease in peristalsis by 22%.

Table 2 summarises the results for all the drugs given.

Discussion

This method gives reliable and easily reproducable recordings from the conscious and unrestrained animal [16]. The method also overcomes the problems of intraluminal catheters which have been shown to alter ureteric peristalsis [5], while it also allows repeated recordings to be taken from each subject without explanting the bladder which is required for repeated recordings using intraluminal catheters [2, 14]. The presence of extraluminal electrodes and force strain guages did not appear to alter ureteric function as the recordings obtained six weeks after implantation were the same as those obtained initially. We have also previously reported that intravenous urograms performed after long term implantation showed no signs of ureteric dilatation or obstruction [16].

All the results and conclusions presented here and in other papers on the pharmacology of the ureter should be interpreted carefully as in this study it was found that a placebo of 5 ml 0.9% saline produced some marked changes in the peristaltic rate and it appears to be the only study to have used a placebo drug. This effect may be due to two factors. Firstly it has been shown that nor-adrenaline and adrenaline have an excitory effect on the ureter and these hormones are released under stress. It was noticeable that the rate of peristalsis increased on some occasions whilst the intravenous injection was being administered. Therefore this effect may modify the initial action of some of the less powerful drugs, but it must be remembered that a patient with ureteric colic is under severe stress so that a drug which consistently overcomes this possible effect of stress may have a therapeutic role. Secondly it was noticed that the mean peristaltic rate during the control period varied from day to day in the same individual subject, suggesting that there are naturally occuring changes in the rate of peristalsis which may give statistically spurious results.

With aminophylline, a xanthine bronchodilator, Boyarsky and Labay [2] concluded that in dogs there was no clear cut response with doses ranging from 1 mg/kg upwards, which is the same as was seen in this study using 7 mg/kg. The effect on the rabbit ureter would appear to be more pronounced, causing inhibition [9, 20].

Histamine has been shown consistently to increase the frequency and/or amplitude of the dog and pig ureteric peristalsis in vivo and in vitro [3, 4, 17], but the antihistamine decreased the rate in only one dog in this study. Another antihistamine, diphenhydramine, has been shown to inhibit competitively the effects of histamine [4]. Chlorpheniramine had little effect in this study as no histamine was given before it and as the ureter was under normal conditions histamine should not have been produced locally.

Diazoxide reduced the rate of peristalsis in 2 of the dogs in which it was tested, and overall it produced a slowing of 34%. Boyarsky and Labay [2] reported a similar result on the canine ureter, observing that diazoxide consistently slowed ureteric peristalsis and lowered the force of peristaltic contraction. Slowing or cessation of peristalsis could be elicited by doses of between 1 mg/kg and 4 mg/kg I.V. though the observed periods of aperistalsis were only 2–8 min. Diazoxide 3 mg/kg did not induce any periods of complete inhibition in this study which may be due to the fact that all of Boyarsky and Labay's dogs were anaesthetised. Mayo and Halbert [11] found that 3 mg/kg diazoxide produced complete inhibition of ureteric activity for 16.44 min, but once again this was in the anaesthetised dog.

From the results presented here, it would seem unlikely that metoclopramide should ease the pain of ureteric colic, as has been recently claimed in a small study [7]. In the dog, metoclopramide had very little effect on peristalsis, whilst in man it has been claimed that metoclopramide actually stimulates ureteric peristalsis [15] Ouabain, a short acting cardiac glycoside, has been shown to increase the activity of the isolated cat ureter [19], whereas in the guinea pig it has been shown to produce inhibition of ureteric activity [18]. In vitro ouabain has been shown to increase the rate of contraction of the dog ureter [2], and in this study ouabain increased the rate of peristalsis in only 1 out of 4 dogs, suggesting that the action of ouabain is different in vivo.

The alpha blocker, phentolamine, produced very variable results in this study, decreasing the rate in one dog and increasing it in another, but Peters and Eckstein [13] found in the acutely obstructed canine ureter that phentolamine 0.4 mg/kg decreased the rate of ureteric peristalsis and also allowed more urine to pass the obstruction. These differences may be explained by the different experimental methods and doses used. Boyarsky and Labay [2] found that the longer acting alpha blocker phenoxybenzamine caused a slight transient acceleration of ureteric peristaltic frequency but Malin et al. [10] and Reid et al. [14] found no effect caused by this drug. It might also explain why

the results obtained in a clinical trial of phentolamine by Kubacz and Catchpole [8] are no better than those obtained with pethidine alone.

Propanolol increased the rate of peristalsis in one dog, which is contrary to other studies [2, 14] in which higher doses of propanolol were used. In this study the increase seen was small, and it must therefore be concluded that propanolol has little effect on the canine ureter.

The selective beta 2-adrenoceptor stimulants, salbutamol, terbutaline and ritodrine, probably have the most therapeutic potential, especially the latter two which consistently reduced the rate of peristalsis. Another beta-adrenoceptor stimulant, isoproterenol, has been consistently shown to decrease the rate of canine ureteric peristalsis and more importantly an inhibitory effect has been observed in isolated segments of the human ureter [10]. Orciprenaline, a partially selective adrenoceptor stimulant, has also been shown to decrease ureteric activity [13].

Melchior et al. [12] have shown in 7 patients that isoproterenol and orciprenaline can reduce the rate and magnitude of ureteric persitalsis, but both caused a considerable rise in blood pressure and pulse. There are no previous studies of the action of salbutamol on the ureter, but Reid et al. [14] administered terbutaline 0.01 mg/kg to their experimental dogs and found that it abolished ureteric peristalsis for 2 to 15 min. Terbutaline 0.1 mg/kg was given in this study and did not have such a profound effect, but this may be due to the different methodology, Reid et al. used intraluminal catheters inserted via an explanted bladder.

Salbutamol and terbutaline have less effect on the cardiovascular system than isoproterenol and ocriprenaline as they are selective $beta_2$ adrenoceptor stimulants and terbutaline certainly deserves further study in man, as it may have a role to play in the management of ureteric colic.

Ritodrine is used extensively to inhibit premature labour, but has not been studied in other situations. This study has shown that it has a dramatic and consistent effect on ureteric peristalsis, inducing a considerable slowing of the rate and should be investigated further for its efficacy in the management of ureteric colic.

Verapamil has been shown to inhibit isolated guinea pig ureteric activity [6] an effect which perhaps could be predicted as this drug is a calcium channel blocker. Verapamil has not previously been studied in the intact animal, and it reduced the rate in only 1 out of 5 dogs.

Ritodrine, terbutaline, diazoxide, and veramapil would appear to warrant further clinical studies and from the results presented here ritodrine would seem to be the most promising.

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