

# Urodynamic changes following intrathecal administration of morphine and fentanyl to dogs

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تغيرات الديناميات البولية بعد حقن المورفين والفنتانيل داخل القرباب (داخل الجافية) في أدمغة الكلاب

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خلاصة: تمت دراسة تأثير حقن المورفين والفنتانيل داخل القرباب (داخل الجافية) على المثانة، عن طريق تسجيل صورة المثانة بالطريق الراجع في 18 كلباً تحت التخدير. وقد أجريت الفحوص قبل حقن محلول ملحي في داخل القرباب (المجموعة الأولى) وكذلك بعد الحقن بستين دقيقة ثم بعد 120 دقيقة. وفي المجموعة الثانية حقن بدلاً من المحلول الملحي 0.03 ميليغرام/كيلوغرام من المورفين. وحقنت المسرعة الثالثة بمقدار 1.5 ميكروغرام/كيلوغرام من الفنتانيل. وقد لوحظت زيادة كبيرة في الحجم الأقصى للمثانة ودرجة مطاوعتها، وانخفاض في ضغط إفراغ البول، الأمر الذي يثبت حدوث ارتخاء في الطبقة العضلية المغلفة للمثانة بعد حقن المورفين أو الفنتانيل داخل القرباب. وقد أدى حقن المورفين إلى ارتخاء مثاني أكبر درجة وأطول أمداً عما حدث بعد حقن الفنتانيل. ونستنتج من ذلك أن حقن المورفين والفنتانيل داخل القرباب (داصل الجافية) يؤدي إلى درجات مختلفة من احتباس البول. ولما كان الفنتانيل قد أدى إلى ارتخاء مثاني أخف وأقصر مما حدث بعد حقن المورفين، فقد يكون استعماله أنفع في المصابين باضطرابات بولية.

**ABSTRACT** The effect of intrathecal (IT) injection of morphine and fentanyl on the urinary bladder was studied by ascending cystogram in 18 anaesthetized dogs. Examinations were performed before and 60 and 120 minutes after IT injection of saline (group I), 0.03 mg/kg morphine (group II) and 1.5 µg/kg fentanyl (group III). A significant increase in maximal volume and compliance and a decrease in voiding pressure were observed, indicating relaxation of the detrusor muscle after IT administration of morphine or fentanyl. IT morphine produced greater and more prolonged bladder relaxation than IT fentanyl. We conclude that IT morphine and fentanyl cause variable degrees of urinary retention. As fentanyl produced milder and shorter bladder relaxation than morphine, it may be useful in patients with urinary disturbances.

## Modifications urodynamiques suite à l'administration intrathécale de morphine et de fentanyl à des chiens

**RESUME** L'effet de l'injection intrathécale (IT) de morphine et de fentanyl sur la vessie a été étudié par cystogramme à doses croissantes sur 18 chiens anesthésiés. Des examens ont été réalisés avant et 60 et 120 minutes après l'injection intrathécale de solution salée (groupe I), de 0,03 mg/kg de morphine (groupe II) et de 1,5 µg/kg de fentanyl (groupe III). Une augmentation significative du volume maximal et de la compliance et une diminution de la pression permictionnelle ont été observées, ce qui indique une relaxation du muscle détenseur après l'administration IT de morphine et de fentanyl. La morphine IT a produit une relaxation plus importante et plus prolongée de la vessie urinaire que le fentanyl IT. Nous concluons que la morphine et le fentanyl IT provoquent des degrés variables de rétention urinaire. Le fentanyl ayant produit une relaxation plus douce et plus courte de la vessie que la morphine, il peut être utile chez les patients souffrant de troubles urinaires.

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## Introduction

The discovery of opioid receptors and the subsequent development of the technique of epidural and intrathecal (IT) opioid administration are undoubtedly two of the most significant advances in pain management in recent decades. The use of spinal opioids is widespread and increasing. The technique is used widely to treat intraoperative, postoperative, traumatic, obstetric, chronic and cancer pain [1]. It is also used in treatment of severe pain in chronic pancreatitis [2]. Reports of selective and long-lasting analgesia following spinal administration of opioids have nevertheless been tempered by documentation of a number of side-effects, such as pruritus, nausea and vomiting, urinary retention, hypoventilation, and both early and late respiratory depression [3,4].

Urodynamic studies [5,6] have demonstrated that epidural and IT morphine relaxes the smooth muscle of the bladder with little or no effect on the internal and external urethral sphincter. However, not all opioids behave in a similar manner in terms of their action on the detrusor or urethral musculature [7]. The present study was undertaken to investigate the effect of IT morphine and fentanyl on urinary bladder function in dogs.

## Methods

The study was carried out on 18 male dogs weighing 14–20 kg. Urodynamic parameters were recorded before and after IT injection of saline, morphine and fentanyl. These experiments did not consider the analgesic effect of IT opiates.

The dogs were classified into 3 groups each containing 6 dogs:

- Group I (control): dogs received IT saline (0.9% sodium chloride)
- Group II (morphine): dogs received IT morphine (0.03 mg/kg) [5]
- Group III (fentanyl): dogs received IT fentanyl 1.5 µg/kg [8]

Anaesthesia was induced by intravenous thiopentone (15–20 mg/kg) followed by tracheal intubation and was maintained by mechanical ventilation using nitrous oxide and oxygen. Pancuronium bromide (0.1 mg/kg) was used to produce complete muscle paralysis to exclude the effect of changes in intra-abdominal pressure on the urinary bladder. Supplementary doses of pancuronium were given as required.

Saline, morphine and fentanyl were administered IT through a fine spinal needle to dogs. The lumbar cistern of the spinal subarachnoid cavity envelops the spinal nerves of the cauda equina. The cistern is narrow at the level of the lumbosacral foramen, gradually tapers to a point, and ends at the level of the first sacral vertebra [9]. Fankhauser states that one can obtain a few drops of cerebrospinal fluid (CSF) by lumbar puncture in dogs [10]. Correct placement of the needle was confirmed by the appearance of CSF. The injected volume of saline was 1 mL, while the injected dose of morphine or fentanyl was diluted in saline to a volume of 1 mL.

The urodynamic parameters were recorded before, and 60 and 120 minutes after IT injection of saline (group I), morphine (group II) and fentanyl (group III).

An ascending cystogram was formed as follows. After insertion of an 8F urinary catheter through the urethra, the bladder was evacuated. The catheter was then connected by a three-way connection to a pressure transducer, then to the oscil-

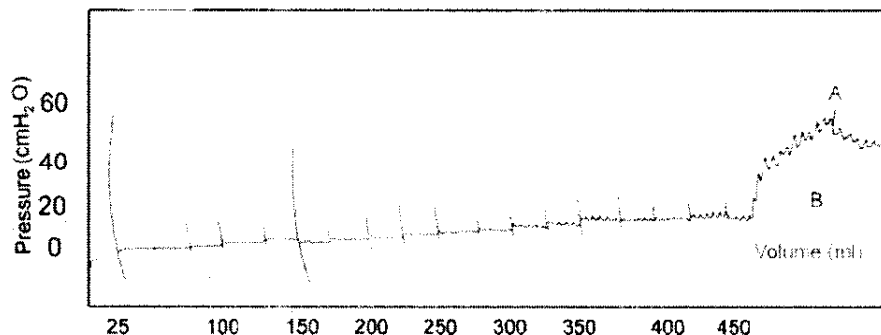


Figure 1 Representative cystogram in a dog showing the maximal volume (B), the volume at which a sharp incline in the curve occurs, and the maximal pressure (A), the highest pressure at which voiding occurs.

lograph and to an infusion set. Saline was infused at a rate of 9 mL/minute. The cystogram was performed by continuously filling the bladder with saline and simultaneously measuring the intravesical pressure. During filling the pressure in the bladder increased gradually until a sharp incline in the plotted curve, indicating that overfilling was imminent. At this point the infusion was halved before voiding occurred and before the stretched fibres of the detrusor muscle could be damaged [6].

A pressure/volume curve was generated in increments of 25 mL until the maximum capacity was reached. The maximal volume (the volume at which a sharp incline in the curve was observed) and the maximal pressure (the highest pressure at which voiding occurred) were recorded. The bladder compliance was calculated from maximal volume/maximal pressure.

Data were expressed as mean  $\pm$  standard deviation. Analysis of variance (ANOVA) was performed, followed by a Scheffe test to analyse and compare the data.  $P < 0.05$  was considered statistically significant.

## Results

Figure 1 shows a representative cystogram in a dog, indicating the maximal volume and maximal voiding pressure. As shown in Table 1, the change in all variables studied in the group at 60 minutes and 120 minutes post-injection of saline compared to the pre-injection values was not statistically significant ( $P > 0.05$ ). However, IT injection of morphine significantly increased the maximal volume at 60 and 120 minutes compared to the pre-injection (baseline) value. The increase in maximal volume at 120 minutes was also significantly higher than at 60 minutes ( $P < 0.05$ ).

In terms of the effect of IT morphine on voiding pressure, there was no significant difference between 60 and 120 minutes, but the value at both time points was significantly less than the baseline value ( $P < 0.05$ ). The effect of morphine on bladder compliance was similar to the effect on maximal volume.

IT injection of fentanyl caused an elevation in the maximal volume of the bladder significantly higher than the pre-injection

**Table 1 Maximum volume, voiding pressure and bladder compliance before and after intrathecal (IT) injection of saline (0.9% sodium chloride), morphine (0.03 mg/kg) and fentanyl (1.5 µg/kg)**

Variable	Before IT injection (baseline)		After IT injection (60 minutes)		After IT injection (120 minutes)		F-value	P-value	Scheffe test
	Mean	s	Mean	s	Mean	s			
<i>Maximum volume (mL)</i>									
Saline (control)	249.00	41.42	246.83	42.45	247.67	41.65	0.23	> 0.05	
Morphine	243.00	38.71	396.83	36.56	461.50	38.12	87.60	< 0.05*	S <sup>a</sup>
Fentanyl	246.83	37.31	345.67	32.98	304.17	43.52	12.17	< 0.05*	(II=III) > I
<i>Voiding pressure (cmH<sub>2</sub>O)</i>									
Saline (control)	50.50	6.09	45.00	8.10	43.50	8.14	1.44	> 0.05	
Morphine	56.17	8.89	33.67	11.27	22.33	8.45	28.70	< 0.05*	(II=III) < I
Fentanyl	51.17	8.89	24.33	11.18	36.83	6.94	16.80	< 0.05*	S <sup>a</sup>
<i>Bladder compliance (mL/cm H<sub>2</sub>O)</i>									
Saline (control)	4.72	0.91	4.87	0.21	4.90	1.03	0.16	> 0.05	
Morphine	4.33	1.03	9.33	1.03	16.83	3.71	64.19	< 0.05*	S <sup>a</sup>
Fentanyl	5.50	1.23	12.00	2.61	8.00	3.03	39.49	< 0.05*	S <sup>a</sup>

<sup>a</sup>S = all significant.

\*Significant at P < 0.05.

s = standard deviation.

**Table 2 Comparison of the changes in the bladder functions after intrathecal (IT) injection of saline (0.9% sodium chloride), morphine (0.03 mg/kg) or fentanyl (1.5 µg/kg)**

Variable	Saline (control)		Morphine		Fentanyl		F-value	P-value	Scheffe test
	Mean	s	Mean	s	Mean	s			
<i>Maximum volume (mL)</i>									
60 minutes after IT injection	-0.86	3.56	66.41	28.87	42.42	23.51	14.96	< 0.05*	(II=III) > I
120 minutes after IT injection	-0.43	3.53	93.44	31.98	25.28	22.45	27.52	< 0.05*	(I=III) < II
<i>Voiding pressure (cmH<sub>2</sub>O)</i>									
60 minutes after IT injection	-11.38	6.21	-39.30	20.41	-51.81	21.93	8.24	< 0.05*	(II=III) > I
120 minutes after IT injection	-14.39	6.52	-60.88	12.27	-27.73	9.58	36.19	< 0.05*	(I=III) < II
<i>Bladder compliance (mL/cmH<sub>2</sub>O)</i>									
60 minutes after IT injection	6.02	18.41	120.83	28.26	121.55	41.62	27.74	< 0.05*	(II=III) > I
120 minutes after IT injection	5.03	21.19	295.56	87.09	44.88	43.08	45.15	< 0.05*	(I=III) < II

\*Significant at P < 0.05.

s = standard deviation.

(baseline) value ( $P < 0.05$ ). However, there was no significant difference between the values at 60 and 120 minutes post-injection. In the group administered fentanyl, the voiding pressure at 120 minutes was significantly higher than at 60 minutes, but both were significantly lower than the pre-injection (baseline) value ( $P < 0.05$ ). Furthermore, IT fentanyl significantly increased bladder compliance at 60 and 120 minutes post-injection compared to pre-injection (baseline) values ( $P < 0.05$ ), but decreased compliance at 120 minutes compared to 60 minutes.

Table 2 shows the comparison between the effect of saline, morphine and fentanyl on the cystogram (mean percentage change at 60 and 120 minutes from pre-injection value). At 60 minutes there was no significant difference between morphine and fentanyl in their effects on maximal

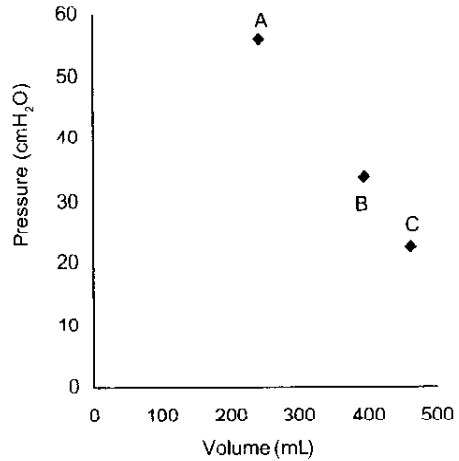


Figure 3 Representative cystogram for intrathecal morphine: (A) before administration (baseline); (B) 60 minutes after administration; (C) 120 minutes after administration.

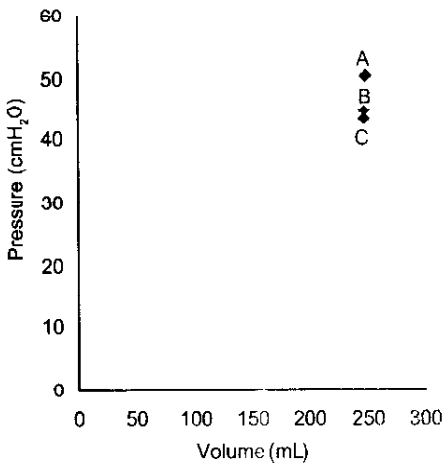


Figure 2 Representative cystogram for saline (control): (A) before administration (baseline); (B) 60 minutes after administration; (C) 120 minutes after administration.

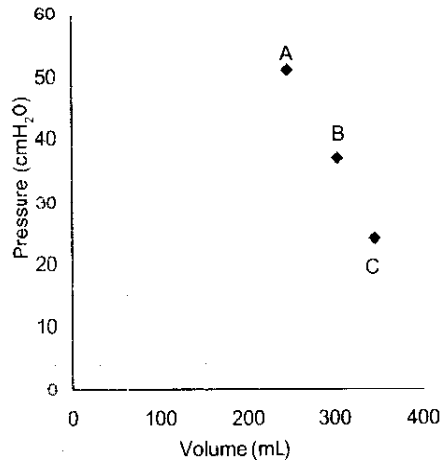


Figure 4 Representative cystogram for intrathecal fentanyl: (A) before administration (baseline); (B) 60 minutes after administration; (C) 120 minutes after administration.

volume, while both provoked significantly higher values than the control ( $P < 0.05$ ).

Similar results were obtained for the effect of both drugs on voiding pressure and bladder compliance. At 120 minutes, there was no significant difference between saline and fentanyl on maximal volume, voiding pressure or bladder compliance, and both injections had significantly less effect than morphine at 120 minutes post-injection ( $P < 0.05$ ).

Figure 2 shows a nonsignificant correlation between maximal volume and voiding pressure in the control group, while Figures 3 and 4 both show a significant negative correlation between maximal volume and voiding pressure.

## Discussion

Urinary retention is considered to be the most troublesome of the nonrespiratory side-effects of IT morphine [11]. The reported incidence of urinary retention after epidural administration of morphine varies from 15% to 90% and is considered to be dose-related [12,13]. In itself, urinary retention is not usually a serious complication but untoward consequences might be expected if vesical catheterization led to urinary infection following surgical intervention [11].

In the present study, we observed that IT morphine (0.03 mg/kg) or fentanyl (1.5 µg/kg) in dogs caused bladder smooth muscle relaxation, indicated by a significant increase in maximal volume and compliance of the bladder, and a significant decrease in voiding pressure. On the other hand, IT injection of saline as a placebo showed insignificant changes in these cystogram parameters.

The effect of IT morphine and fentanyl on the canine urinary bladder in our work is similar to the changes in the vesical muscu-

lature reported after IT or epidural administration of morphine to humans [4,5] and dogs [6,14] and after IT administration of fentanyl to dogs [8].

Various modes and sites of action have been proposed to account for the effect of intrathecal opioids on the lower urinary tract function. One possible explanation may be the direct effect of IT morphine or fentanyl on opiate receptors possibly present in the urinary bladder [15], and on the cord modulating the sacral parasympathetic outflow to the urinary bladder [6]. IT opioids caused a depression of preganglionic neurons in the sacral parasympathetic nucleus, which resulted in reduced activity in the pelvic nerve and insufficient cholinergic activation of bladder smooth muscle. Transmission of afferent activity from the bladder is also believed to be impaired, because of activation of opioid receptors on primary afferent nerve terminals with the consequent inhibition of transmitter release in the spinal cord [16,17]. Spinal opioids may also act directly on the urinary tract through the sacral nociceptive neurons, which impair transmission in the sensory primary afferent component of this region, and may also have an effect on supraspinal centres [18].

A supraspinal inhibitory effect of IT opioids at the level of the pons where the primary micturition centre is located, and where opiate receptors are known to exist, may play a role in urinary retention [5,15]. But the rapid onset of detrusor relaxation favours a spinal site of action [5].

In our study, 120 minutes after IT morphine injection, bladder relaxation was more evident than after 60 minutes. However, bladder relaxation began to wear off 120 minutes after IT injection of fentanyl.

These results are in accordance with previous reports [6,8] that epidural morphine relaxes the detrusor within a short

time of injection leading to increased bladder capacity and urinary retention. Spontaneous recovery of bladder function occurs after about 14–16 hours on average [5]. After IT fentanyl, detrusor muscle relaxation also occurred and continued for at least 2 hours [8].

Payne et al. stated that IT administration of lipophilic opioids produces different CSF distributions than hydrophilic opioids [19]. Morphine has a low coefficient of lipid solubility and so large amounts of it remain in the CSF free to circulate towards the head [6]. However, fentanyl has a shorter duration of action and is more highly lipid-soluble than morphine. This accounts for its more rapid clearance and for the lower concentration of free drug concentration in the CSF [3], resulting in reduced migration to the supraspinal centres in the brain that mediate urinary tract control [8]. We observed that after 120 minutes, IT morphine produced more significant increases in maximal volume and bladder compliance and decrease in

voiding pressure than IT fentanyl. This may be explained if IT morphine causes an increase in tone of the external urethral sphincter, possibly by disinhibition of the somatic input to the sphincter [20]. IT fentanyl causes pronounced relaxation of the bladder neck musculature [15]. It is possible that the decrease in urethral resistance may partially counteract the effect of IT fentanyl on micturition. This effect might explain the observation that the incidence of urinary retention in human subjects is lower after spinal analgesia with fentanyl than it is with other opioids [21].

## Conclusion

IT administration of morphine and fentanyl produces variable degrees of urinary retention. As IT fentanyl causes a smaller degree of urinary retention lasting for a shorter period than IT morphine, it may be particularly useful for patients with disturbed urinary function.

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