Effects of High-Dose Fentanyl on Renal Haemodynamics in Conscious Dogs

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The renal haemodynamic effects of high doses of fentanyl were examined in 17 unanaesthetized, chronically implanted dogs, in order to avoid the confusing effects of superimposed anaesthesia and acute surgical procedures. Ten to fourteen days prior to the study, a Doppler flow probe was positioned around the left renal artery and a Tygon catheter was placed into the lower abdominal aorta through a lumbar arterial side branch. During the experiments, the trained animals were lying quietly on their right side. Following steady-state awake baseline measurements, an intravenous fentanyl infusion, $25 \mu\text{g}\cdot\text{kg}^{-1}$ (lower dose), or $50 \mu\text{g}\cdot\text{kg}^{-1}$ (higher dose) was administered over a ten-minute period. Arterial pressure, renal blood flow, calculated renal vascular resistance and arterial blood gases were measured for 20 minutes following the infusion. Observations were made during spontaneous and controlled ventilation, with $\text{FIO}_2 = 0.21$ or 1.0 . Fentanyl increased arterial pressure 10–40 per cent in all groups and did not, as a rule, significantly affect renal blood flow. Thus renal vascular resistance was increased. There were no significant differences between effects of the $25 \mu\text{g}\cdot\text{kg}^{-1}$ and the $50 \mu\text{g}\cdot\text{kg}^{-1}$ doses of fentanyl. It is concluded that these doses of fentanyl, given to the conscious, normovolaemic dog, result in renal vasoconstriction. Renal blood flow does not decrease, however, implying that autoregulation remains intact. These changes are a result of fentanyl, per se, rather than secondary to changes in oxygenation and carbon dioxide levels in the blood and do not appear to have a dose response relationship in the dosage range studied.

Key Words

ANAESTHETICS, INTRAVENOUS: Fentanyl; KIDNEY: Blood Flow.

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High-dose morphine has been advocated for use in patients with compromised cardiovascular status in order to achieve better haemodynamic stability.¹ Subsequent investigations have indicated that, although generalized haemodynamics may remain stable under such conditions, undesirable changes in regional haemodynamics can occur.² The cardiovascular system seems to be more hyperdynamic during anaesthesia with narcotic drugs than it does during traditional inhalation anaesthesia.³ Fentanyl has been recommended because it appears to offer even greater haemodynamic stability than morphine.^{4–7} This apparent stability might be related to less release of histamine with fentanyl than with morphine.⁸ However, one must still be concerned about the stability of regional haemodynamics when high doses of fentanyl are given. Recent data related to myocardial perfusion substantiates this concern.⁹ The renal vasculature has received little attention in this regard. One study in dogs anaesthetized with thiopentone, using a PAH clearance technique, has indicated that high doses of fentanyl do not decrease renal plasma flow. However, urine output and free water clearance were diminished along with an increase in urine osmolality indicating an ADH mechanism.¹⁰ More recently, in a study in man, it was reported that fentanyl did not change creatinine clearance, urine osmolality, or blood vasopressin concentrations.¹¹ The intent of the present study was to examine the effects of high-dose fentanyl on renal perfusion in a chronically implanted conscious animal model in which the pharmacological effects of fentanyl would not be influenced by the simultaneous presence of other anaesthetic agents, stress or the surgical procedure.

Methods

This study was done on 17 healthy, mongrel dogs of either sex weighing 20–30 kg. The animals had no

respiratory infections, had minimum haematocrits not lower than 40 volumes per cent and were double serum negative for dirofilaria of heart worms. Implantation of the animals was done under endotracheal halothane/nitrous oxide anaesthesia with spontaneous breathing. With the animals in the supine position, a midline laparotomy was done. A four- or six-millimeter Doppler ultrasonic flow probe (L&M Electronics, Daly City, CA) was positioned around the left main renal artery. A small Tygon catheter was introduced via a lumbar arterial side branch and positioned into the lower abdominal aorta with its tip facing proximally. The instrumentation wires and catheter were then run subcutaneously and exteriorized at an intrascapular site. The animals were then allowed to recover for 10–14 days. During that time, they were positioned on the experiment table three times a week. This enabled them to become accustomed to the experimental surroundings and conditions.

Aortic pressure was measured from the previously implanted Tygon catheter with a mercury-calibrated P23ID strain gauge manometer (Statham Instruments Inc., Oxnard, CA). Renal arterial blood flow was measured with a Doppler ultrasonic flow meter (L&M Electronics, Model 1012, Daly City, CA) using a hardwire connection to the implanted probes. This system has an accurate electronic zero. Prior to implantation, all probes were calibrated with a mechanical perfusion system. Specifically, a probe was placed around a section of dog iliac artery. Then flow through that artery was accomplished with a variable speed roller pump using heparinized dog blood. The flow was precisely quantitated with a graduated cylinder and stopwatch over a range of 50–350 ml/minute and a regression curve was established for each flow probe. Data were continuously recorded on a Gould-Brush direct writing oscillograph (Gould-Brush, Cleveland, OH). Renal vascular resistance was calculated by dividing the mean arterial pressure in millimeters of mercury by the mean renal blood flow in milliliters per minute. Samples for analysis of arterial partial pressure of oxygen (PaO_2) and carbon dioxide (PaCO_2) were withdrawn from the arterial catheter and analyzed on an Instrumentation Laboratory model 813, pH blood gas analyzer.

The animals were divided into three groups. Group I breathed room air spontaneously. Group II

breathed room air spontaneously for an initial set of controls and then breathed 100 per cent oxygen spontaneously through a canine anaesthesia mask connected to a semiclosed circle system. In this group a second set of controls was recorded while the animals were breathing oxygen, before the administration of fentanyl. Group III breathed room air for an initial set of controls, then breathed 100 per cent oxygen through the canine anaesthesia mask while a second set of controls was taken as did the animals in Group II. Then, one-quarter of the way through the administration of fentanyl, a point at which the animals showed signs of significant sedation, 0.1 mg/kg of dimethyltubocurarine was administered intravenously. This facilitated control of the animal's ventilation for the remainder of the experimental period. Dimethyltubocurarine was chosen because it does not produce significant haemodynamic changes.¹² Controlled manual ventilation (CMV) was accomplished with the canine anaesthesia mask connected to a semiclosed circle system. The lungs were ventilated manually with a bag; ventilation was aided by an in-line Wright respirometer on the expiratory limb to quantitate tidal volumes. At the end of the experiment dimethyltubocurarine was reversed with appropriate doses of neostigmine and atropine and manual ventilation continued until the animals breathed adequately on their own.

In all three groups, 25 $\mu\text{g}\cdot\text{kg}^{-1}$ or 50 $\mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl were administered over a ten-minute period. Data were collected for an additional 20 minutes after the end of the infusion for a total recording period of 30 minutes from the start of drug infusion. Changes were measured at 2½, 5, 10, 15, 20 and 30 minutes in all three groups and were compared statistically with the room air control value of each group by use of Student's paired t-test. Thus each animal served as its own control. The room-air breathing control was used because there were no significant changes in renal haemodynamics on transition from breathing room air to oxygen. Statistically significant changes were indicated by a p value of less than 0.05. Both dosages were administered to each animal in a random sequence on separate days. Intervals of 24 hours were allowed to elapse after an animal had received the lower dose of fentanyl, and 48 hours after receiving the higher dose of fentanyl, before the next experiments were done in that animal.

FIGURE 1 Renal Haemodynamic Effects of $25 \mu\text{g} \cdot \text{kg}^{-1}$ and $50 \mu\text{g} \cdot \text{kg}^{-1}$ of Fentanyl While Animals Breathed Room Air Spontaneously. Illustrated here are the mean per cent changes from control in aortic pressure, renal blood flow and renal vascular resistance for the Group I animals breathing air. The insets refer to the mean actual control values $\pm$ SEM for that variable. Time is plotted on the abscissa in minutes. The infusion took place during the first ten minutes and variables were measured for an additional 20 minutes. Open circles refer to the lower dose of fentanyl, closed circles refer to the higher dose of fentanyl. Asterisks indicate statistically significant changes ($p < 0.05$) within groups from that group's actual control value. Double crosses indicate statistically significant differences at any one time point between the low- and high-dose animals.

Results

Group One [Air with Spontaneous Ventilation, $n = 12$, (Figure 1)]

With the animal breathing room air spontaneously, both doses of fentanyl caused significant elevation of arterial pressure during the first 5 to 15 minutes of the observation period. During the latter portion of the observation period, arterial pressure returned to values not significantly different from controls. With the exception of the change at ten

minutes, there were no significant differences between the low and high doses for arterial pressure in this group. Renal blood flow did not change significantly from the control value during the entire observation period with either dose of fentanyl, although it increased slightly during the last fifteen minutes. Renal vascular resistance was significantly elevated at five and ten minutes with both dosages of fentanyl, but only at the five minute point was the difference between the two dosages significant.

Group Two [Oxygen with Spontaneous Ventilation, $n = 5$, (Figure 2)]

There were no significant changes in arterial pressure, renal blood flow or renal vascular resistance in the transition from breathing room air to breathing 100 per cent oxygen during the control periods. Both dosages of fentanyl slightly decreased arterial pressure at $2\frac{1}{2}$ minutes. Thereafter, arterial pressure increased significantly for most of the remainder of the observation period. There were no significant differences between the two dosages for this variable. Renal blood flow showed no statistically significant changes from the control levels with the exception of the five-minute value in the high dose group, when it was significantly decreased by 16 per cent. As in the room-air-breathing animals, renal blood flow increased late in the observation period, but not to a significant degree. There were also no statistically significant differences between the two dosages for this variable. Renal vascular resistance was significantly elevated from 5 to 15 minutes. During the latter part of the observation period it returned to levels not significantly different from control values. There were no differences between dosages for this variable as well.

Group Three [Oxygen with Controlled Manual Ventilation, $n = 5$, (Figure 3)]

Again there were no significant differences in blood pressure, renal blood flow or renal vascular resistance in the transition from breathing room air to breathing oxygen during the control period. During the oxygen breathing portion the tidal volume and respiratory rate were measured with the in-line Wright respirometer. Early in this study, at the time of starting controlled manual ventilation, we attempted to reproduce that amount of ventila-

tion that had been observed during spontaneous breathing with oxygen before drug administration. Despite this, we found that the PaCO_2 increased after fentanyl had been given. To maintain normocarbida during fentanyl, it was necessary to ventilate the animals 30–40 per cent more than they had breathed during spontaneous ventilation. At 2½ minutes, arterial pressure was significantly decreased in the low-dose group. Thereafter, arterial pressure increased significantly in this group at 10 and 15 minutes. In the high-dose group arterial pressure was significantly elevated for most of the observation period. These elevations were significantly greater than those in the low-dose group at 10, 15 and 20 minutes. Renal blood flow was not significantly changed from its control value in the low-dose group, but in the high-dose group renal blood flow was significantly increased from control at 15, 20 and 30 minutes. However, these changes were not statistically different between the two dosage groups. Renal vascular resistance was significantly decreased with both dosages at 2½ minutes. Thereafter it increased significantly at five and ten minutes in the high-dose group and at ten minutes in the low-dose group. Later, renal vascular resistance returned to values not significantly different from the baseline. There were no significant differences between dosages for renal vascular resistance.

The data related to blood gases are contained in Table 1. In Group I breathing room air, the PaCO_2 was significantly increased with both dosages of fentanyl. There was a significantly greater degree of elevation of PaCO_2 in the high-dose group at 5, 10, and 15 minutes. The PaO_2 decreased significantly with both dosages while breathing RA and to a significantly greater degree in the high-dose group at 10 and 15 minutes. In Group II breathing oxygen, PaCO_2 increased significantly in both dosage groups and there was a statistically greater difference between dosages at ten minutes. With both changes however, the PaCO_2 elevation was significantly greater than the comparable dose in the room air group. As anticipated, PaO_2 increased while breathing oxygen and remained elevated during fentanyl administration. In Group III, which breathed oxygen and had a normal PaCO_2 maintained by controlled manual ventilation, PaCO_2 did not change in the transition from breathing RA to breathing oxygen during the control period.

FIGURE 2 Renal Haemodynamic Effects of $25 \mu\text{g}\cdot\text{kg}^{-1}$ and $50 \mu\text{g}\cdot\text{kg}^{-1}$ of Fentanyl While Animals Breathed Oxygen Spontaneously. Illustrated here are the mean per cent changes from control in aortic pressure, renal blood flow and renal vascular resistance for the Group II animals breathing oxygen. Two sets of controls were taken before fentanyl – one while breathing room air and one while breathing oxygen. The insets refer to the mean actual control values $\pm$ SEM for that variable while breathing room air. Time is plotted on the abscissa in minutes. The infusion took place during the first ten minutes and variables were measured for an additional 20 minutes. Open circles refer to the lower dose of fentanyl, closed circles refer to the higher dose of fentanyl. Asterisks indicate statistically significant changes ($p < 0.05$) within groups from that group's actual room air control values.

The PaCO_2 , with the exception of the 2½-minute value in the high-dose group, did not change significantly during fentanyl. The PaCO_2 was significantly less than it was in the animals spontaneously breathing room air or oxygen. The PaO_2 in this group was not significantly different from the PaO_2 in group II breathing oxygen spontaneously.

Discussion

The results of this study demonstrated that when $25 \mu\text{g}\cdot\text{kg}^{-1}$ to $50 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl were admin-

FIGURE 3 Renal Haemodynamic Effects of $25 \mu\text{g}\cdot\text{kg}^{-1}$ and $50 \mu\text{g}\cdot\text{kg}^{-1}$ of Fentanyl During Controlled Manual Ventilation (CMV) with Oxygen. Illustrated here are the mean per cent changes from control in aortic pressure, renal blood flow and renal vascular resistance for the Group III animals whose ventilation was controlled. Two sets of controls were taken before fentanyl and CMV — one while the animal was breathing room air spontaneously and one while breathing oxygen spontaneously. The insets refer to the mean actual control values $\pm$ SEM for that variable while breathing room air. Time is plotted on the abscissa in minutes. The infusion took place during the first ten minutes and variables were measured for an additional 20 minutes. Open circles refer to the lower dose of fentanyl, closed circles refer to the higher dose of fentanyl. Asterisks indicate statistically significant changes ($p < 0.05$) within groups from that group's actual room air control values. Double crosses indicate statistically significant differences at any one time point between the low- and high-dose animals.

istered to conscious, normovolaemic dogs, renal blood flow was preserved. This occurred in spite of changes in arterial pressure. If autoregulation is defined as a stable flow over a range of perfusion pressures then autoregulatory ability remained

intact in the renal vascular bed with these doses of fentanyl.

The mechanism of these changes was not examined in this study. It would appear there is a biphasic renal vascular response to fentanyl. In an isolated perfused dog hind limb preparation, it has been shown that, initially, intra-arterial doses of fentanyl produced a vascular smooth muscle relaxation followed by a constrictor-type effect.¹³ In the present study, initially arterial pressure and renal vascular resistance decreased slightly, to be followed by an elevation of both. These early dilation effects were probably related to a direct relaxant action of fentanyl on renal resistance vessels. This was followed by constriction not only in the renal bed itself, but also systemically. This latter effect was most likely due to a centrally mediated catecholamine release. Several human studies have examined catecholamine levels after fentanyl. The results are conflicting and range from no change,¹⁴ to a decrease,^{11,15} to a large increase¹⁶ in catecholamines. The reason for these discrepancies is not clear. There are technical difficulties related to the measurement of catecholamines. Differences in technique may be the explanation. These were all human data and there are no comparable studies in dogs related to catecholamine levels and fentanyl. Likewise, there is a scarcity of data describing the generalized cardiovascular effects of fentanyl in conscious animals. Studies in dogs previously anesthetized with thiopentone or pentobarbitone showed that high-dose fentanyl depressed cardiac output. This should have resulted in reflex increases in peripheral resistance to maintain blood pressure. In actuality, peripheral resistance remained unchanged and blood pressure decreased.^{4,10,17} Such a response was not seen in our conscious animals as blood pressure always increased after fentanyl. This was probably due to an increase in total peripheral resistance which is not seen in the animal whose brain stem has been depressed by preceding administration of barbiturates. Morphine, like fentanyl, is a central nervous system sedative, yet it has been shown to release catecholamines from both the adrenal medulla,¹⁸ as well as from peripheral nerves.¹⁹ Our hypothesis is that fentanyl has a similar action that becomes masked when other anesthetic drugs are present. In fact under such conditions, it may even appear to be sympatho-inhibitory.^{20,21} In conscious animals, the adrener-

TABLE I Arterial Blood Gases

Variable	Group	Actual Control Value		Time After Start Infusion: Data Expressed in Actual Values						
		RA	O ₂	24 min	5 min	10 min	15 min	20 min	30 min	
PaCO ₂ ± SEM (torr)	RA	L-32 ± 1		34 ± 1a	37 ± 1a	39 ± 2a	40 ± 1a	40 ± 1a	40 ± 1a	
		H-32 ± 1		36 ± 1a	40 ± 1a,b	44 ± 1a,b	44 ± 2a,b	43 ± 2a	42 ± 2a	
	O ₂	L-32 ± 2	35 ± 1	37 ± 3	44 ± 3a,c	47 ± 3a,c	45 ± 4a	46 ± 2a,c	43 ± 2a	
		H-33 ± 1	35 ± 2	41 ± 2a,c	47 ± 5a	60 ± 4a,b,c	57 ± 4a,c	50 ± 3a	47 ± 3a	
	O ₂ + CMV	L-34 ± 2	34 ± 2	33 ± 2	33 ± 3e	33 ± 4e	31 ± 6d,e	31 ± 6d,e	34 ± 5	
		H-30 ± 2	32 ± 1	35 ± 1a	32 ± 4d	32 ± 5d	28 ± 4d	31 ± 5d	31 ± 5d	
PaO ₂ ± SEM (torr)	RA	L-94 ± 1		81 ± 3a	72 ± 5a	70 ± 3a	79 ± 3a	82 ± 2a	87 ± 2a	
		H-94 ± 1		76 ± 3a	64 ± 3a	59 ± 4a,b,c	67 ± 4a,b	76 ± 3a	81 ± 3a	
	O ₂	L-99 ± 3	317 ± 35a	341 ± 48a,c	346 ± 46a,c	370 ± 26a,c	359 ± 24a,c	348 ± 15a,c	344 ± 29a,c	
		H-98 ± 3	334 ± 36a	372 ± 31a,c	343 ± 51a,c	349 ± 23a,c	368 ± 32a,c	322 ± 35a,c	334 ± 37a,c	
	O ₂ + CMV	L-96 ± 3	283 ± 42a	305 ± 41a,d	322 ± 47a,d	346 ± 50a,d	328 ± 50a,d	336 ± 50a,d	351 ± 52a,d	
		H-92 ± 3	294 ± 41a	306 ± 44a,d	327 ± 48a,d	344 ± 52a,d	333 ± 50a,d	350 ± 52a,d	354 ± 74a,d	
Fentanyl Infusion										

Fentanyl Infusion

PaCO₂ = mean arterial partial pressure CO₂, PaO₂ = mean arterial partial pressure O₂, RA = spontaneous ventilation with room air, O₂ = spontaneous ventilation with oxygen, CMV = controlled manual ventilation with oxygen. L = low-dose (25 µg·kg⁻¹), H = High-dose (50 µg·kg⁻¹).

Control values are indicated in the left side of the table. For the animals breathing oxygen (Groups II, III) there are two sets of control data before fentanyl administration; one while breathing room air (RA) and one while breathing oxygen (O₂). All control values are expressed as the mean actual values ± SEM. Arterial PCO₂ and PO₂ after fentanyl, are also indicated as the mean actual values ± SEM. For all statistical comparisons, significant differences were considered to be $p < 0.05$. The subscripts indicate:

a = $p < 0.05$ from that group's RA control value.

b = $p < 0.05$ L vs H doses within groups, i.e. RA, O₂, O₂ + CMV.

c = $p < 0.05$ for L vs L or H vs H RA vs O₂.

d = $p < 0.05$ for L vs L or H vs H RA vs O₂ CMV.

n's: RA = 12, O₂ = 5, O₂ + CMV = 5.

There were no significant differences for low versus high or high versus high doses between Group II and Group III.

gic stimulation from fentanyl is allowed to become manifest and vascular resistance increases as noted here specifically in the kidney, as we did not measure cardiac output. In addition to direct vasoconstrictor effects of catecholamines, it is possible that they are also acting indirectly by releasing renin, with a subsequent elevation of angiotensin-II. This too could contribute to the changes in renal vascular resistance noted here. Patients who received $100 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl did not show a statistically significant change in their renin levels; however, the mean values presented did increase 35 per cent.¹¹

No attempt was made here to assess renal function as this requires placement of a bladder catheter for urine samples. This was considered undesirable in our conscious unrestrained animal model. One other study has examined renal function in dogs anaesthetized with thiopentone, then given $100\text{--}1000 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl. Decreases in urine volume and free-water clearance and increases in urine osmolality were noted leading to postulation of an ADH mechanism.¹⁰ A more recent study was not able to demonstrate increases in ADH in humans given $100 \mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl.¹¹ The results of the earlier study may have been influenced by the presence of barbiturates which can cause ADH release.²² These reports again illustrate the difference in pharmacologic results between anaesthetized and conscious subjects.

In those cases in which fentanyl is usually employed, there is often concern for the maintenance of renal perfusion yet few investigations have been done along these lines in animals or in humans. One other study of renal blood flow with fentanyl has been done in dogs, but the animals had received thiopentone. A PAH clearance-renal plasma-flow technique was used to index renal blood flow. These authors did not see a statistically significant change in RPF after fentanyl.¹⁰ However, a closer look at their data reveals that blood pressure decreased, RPF increased 11-25 per cent and calculated renal vascular resistance decreased 20-33 per cent. These changes are opposite to those seen here. Thiopentone could certainly account for the differences as it decreases renal vascular resistance.²³ Another possibility could be a drug interaction phenomenon.

In the present study, the results observed are most likely due to fentanyl itself, rather than to secondary

changes in the ventilation or oxygenation. When the decreases in PaO_2 were prevented by administration of oxygen (Group II), the renal haemodynamic events in response to fentanyl were the same as those seen in animals breathing room air (Group I). Hypoxaemia, then, was not the cause of the results. When oxygenation was maintained and increases in PaCO_2 prevented with controlled manual ventilation (Group III), the results were the same except for some small quantitative differences. The fact that arterial pressure was greater in Group III might be related to the fact that more fentanyl gets into the brain with normocarbica than when with hypercarbia.²⁴ This lack of effect of arterial blood gas changes on renal haemodynamics has been observed in previous studies.²⁵ In contrast to the brain and heart, the kidney is not an organ whose blood flow is regulated by metabolic mechanisms. In actual fact, it has luxury perfusion with the usual arterial-venous oxygen difference being two to three volumes per cent.

The arterial blood gas data obtained are interesting and perhaps warrant separate investigation. During the first ten minutes, the per cent decrease in PaO_2 exceeded the per cent increase in PaCO_2 , thus the hypoxaemia was not totally due to hypoventilation. Other explanations for this hypoxaemia include shunt and V/Q mismatch phenomena in the lung as well as cardiac output depression.²⁶ Additionally, in order to maintain normocarbica, it was necessary to ventilate the animals on controlled manual ventilation at minute volume 30-40 per cent greater than when the animals breathed by themselves. This might have been due to a bronchodilatory action of fentanyl itself or the released catecholamines both of which would increase physiologic deadspace. Another possibility could be increased CO_2 production associated with increased tissue metabolism due to catecholamine release.

One disadvantage of a direct-measuring flow technique, such as the one used here, is that it does not give information about changes in intra-organ blood flow distribution as can be seen for instance with radioactive microspheres. The main goal of this study was to investigate the effects of fentanyl in a completely normal animal whose homeostasis had not been violated by other superimposed anaesthetics or surgical procedures. The flow-probe technique is the most practical and physiologic for use in chronic animals. Pentobarbital results in

deterioration of cardiac output and elevation of peripheral resistance with both spontaneous²⁷ and controlled²⁸ ventilation. Heart rate is grossly abnormal due to both a vagolytic and baroreceptor mechanism.²⁸ In addition, pentobarbital and other anaesthetics, commonly used in animal studies, markedly depress peripheral chemoreceptor reflexes.²⁹ All of those can have a significant impact on peripheral perfusion and thus influence pharmacologic studies of this nature.

In summary, this study has shown that high doses of fentanyl produce renal vasoconstriction. Renal blood flow is maintained probably through an autoregulatory mechanism. These changes do not appear to be dose-related and are independent of changes in ventilation and oxygenation. They can be contrasted with morphine and meperidine, both of which dilate the renal bed under similar experimental conditions and seem to do so in a dose-related manner.^{25,30} It is hypothesized that these changes are due to a centrally or a peripherally mediated increase in adrenergic activity. The precise mechanisms remain to be elucidated by future investigations.

Acknowledgements

The clerical expertise and patience of Sandra Doucette, who prepared the table and text, are greatly appreciated, as are the skills of Sandra Baxter and Byron Cline of the Medical Illustration and Photography division, Shriners Burns Institute, for their work on the figures. Special recognition is due Bettina Marrone for her invaluable technical support. Her care and attention to chronically instrumented animals as well as her skills related to their preparation for an actual performance of the experiments has been invaluable. Without such efforts, this study could not have been accomplished.

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Résumé

On a exploré les effets causés par de fortes doses de fentanyl chez 17 chiens non-anesthésiés, chroniquement préparés, afin d'éviter les effets incertains de l'anesthésie surajoutée et des opérations aiguës. De dix à quatorze jours avant notre expérience, une sonde Doppler a été placée autour de l'artère gauche et un cathéter Tygon a été inséré dans l'aorte du bas ventre à travers la branche lombaire artérielle du côté. Durant le cours de notre expérience, les animaux d'essais étaient couchés sans bouger sur le côté droit. Après avoir contrôlé les mesures de base des chiens éveillés, une infusion intraveineuse de fentanyl, $25 \mu\text{g}\cdot\text{kg}^{-1}$ (basse dose) et $50 \mu\text{g}\cdot\text{kg}^{-1}$ (dose plus forte) fut administrée pendant une période de dix minutes. La tension artérielle, le débit sanguin rénal, la résistance vasculaire rénale calculée et l'analyse artérielle des gaz du sang ont été mesurés pendant les vingt minutes suivant l'infusion. On a fait des observations pendant la ventilation spontanée et contrôlée avec le $\text{FIO}_2 = 0.21$ ou 1.0 . Le fentanyl augmenta la pression artérielle de 10 à 40 pour cent chez tous les groupes, mais n'influença pas de manière significative, comme d'usage, le débit sanguin rénal. Donc, la résistance vasculaire rénale augmenta. Il n'y a donc pas de différences significatives entre la dose de $25 \mu\text{g}\cdot\text{kg}^{-1}$ et celle de $50 \mu\text{g}\cdot\text{kg}^{-1}$ de fentanyl. Nous concluons donc que ces doses de fentanyl administrées aux chiens éveillés et normovolémiques influencent la vasoconstriction rénale. Le débit sanguin rénal ne baissa pas mais laisse cependant sous-entendre que l'autorégulation de la circulation rénale reste intacte. Ces changements sont donc produits par le fentanyl même, plutôt que les changements secondaires d'oxygénation et de gaz carbonique sanguins et n'apparaissent pas avoir de rapport avec la dose réponse des doses étudiées.