Yara Marcondes Machado Castiglia,
José Reinaldo Cerqueira Braz, Pedro Thadeu Galvão Vianna,
Lino Lemonica, Luiz Antonio Vane

Effect of high-dose fentanyl on renal function in dogs

Departamento de Anestesiologia da Faculdade de Medicina de Botucatu - UNESP - São Paulo, Brazil

Our objective was to determine the effects of high-dose fentanyl on canine renal function (RF). We anesthetized with sodium pentobarbital (SP) 16 dogs, randomly divided into 2 groups: in G1, SP was given alone, and in G2, combined with 0.05 mg.kg^{-1} fentanyl. All animals were ventilated artificially and had catheterized left and right femoral veins and left femoral artery for fluid infusion, drug administration, blood collection, and hemodynamic measurement. Urine was collected throughout the experiment. Attributes of RF were studied. SP did not alter RF, which was significantly altered by fentanyl. In G2, slower heart rates, mean arterial pressure, creatinine clearance, urinary output, osmolar clearance and fractional excretion of sodium and potassium were observed. G1 had a behavior attributed to extracellular volume expansion and no RF alterations. In G2, we observed significant decreases in RF due to opioid-induced hemodynamic changes, not discarding the possible action of aldosterone.

UNITERMS: High-dose fentanyl. Renal function. Dog.

INTRODUCTION

High-dose fentanyl anesthesia is often used because this technique is usually associated with a stable cardiovascular hemodynamic course. However, there are few reports on the effects of high-dose fentanyl on renal function (RF) and authors have not obtained similar results, performing their studies on man as well as on dogs.[1-4] Fentanyl has also been used in combination with other drugs known to alter RF.

The primary aim of this study is to report the renal response of dogs to a high dose of fentanyl. These dogs were compared to a reference group receiving sodium pentobarbital (SP), a drug which does not alter RF.[5,6]

Anddress for correspondence:
Profa. Dra. Yara Marcondes Machado Castiglia
Deptº de Anestesiologia da FMB - UNESP
Distrito de Rubião Junior - Caixa Postal 530
Botucatu/SP - Brasil - CEP 18618-970

MATERIAL AND METHODS

Anesthesia was induced in 16 healthy male mongrel dogs (8 to 20 kg) with 30 mg.kg^{-1} of SP. In the first experimental phase, anesthesia was maintained with SP (5 mg.kg^{-1}). In the second phase, animals were randomly divided into 2 groups of 8 dogs and were differentiated as follows:

Group 1 (**G1**) - control group, maintenance with SP only, and;

Group 2 (**G2**) - maintenance with SP and 0.05 mg.kg^{-1} fentanyl.

A cuffed endotracheal tube was inserted, and the animals received pancuronium bromide (0.08 mg.kg^{-1} in the first dose and 0.03 mg.kg^{-1} for maintenance). Ventilation was controlled by a K. Takaoka model 660 apparatus with room air and adjusted to maintain normal blood-gas pressures. Left and right femoral veins were catheterized for fluid infusion, drugs administration, blood collection and measurement of inferior vena cava pressure (ICP). Channelization of the left femoral artery was carried out for measurements of mean arterial pressure (MAP) (Hg manometer). Urethral catheterization was performed.

CASTIGLIA, Y.M.M.; BRAZ, J.R.C.; VIANNA, P.T.G.; LEMONICA, L.; VANE, L.A. - Effect of high-dose fentanyl on renal function in dogs

São Paulo Medical Journal/RPM 115(3): 1433-1439, 1997

During the first phase, the animals received Ringer's solution (0.4 ml.kg^{-1}.min^{-1} - extracellular volume expansion) for 30 min, followed by a prime dose of 30 mg.kg^{-1} creatinine and 4 mg.kg^{-1} para-aminohipuric acid (PAH). Immediately afterwards, a solution of 0.15 percent creatinine and 0.06 percent PAH in Ringer (0.6 mg.kg^{-1}.min^{-1} creatinine and 0.24 mg.kg^{-1}.min^{-1} PAH) was administered by continuous drip infusion with a Gilson pump model Hp1, until the end of the experiment. There were 4 clearance periods, each lasting 15 min.

Forty-five min after prime, the first clearance period began with V measurement (always after emptying the bladder), venous blood collection and determinations of MAP, ICP, and heart rate (HR). After the first clearance period end, the second phase of the experiment started with the second clearance period immediately after fentanyl administration. The third clearance period began immediately after the end of the second, and the fourth started 30 min after the end of the third.

The bladder was emptied and urine always collected at the end of each period. Blood samples were collected in the middle of each period. The mean values of the readings were calculated from those obtained at the beginning and end of each clearance period. The following attributes were recorded:

- Hemodynamics - HR, MAP, ICP, PAH clearance (C_{PAH}), renal blood flow (RBF) and renal vascular resistance (RVR);
- Blood - hematocrit (Ht)and plasma osmolarity (P_{osm};
- Renal function - creatinine clearance (C_{cr}), filtration fraction (FF), urinary output (V),urinary osmolarity (U_{osm}), osmolar clearance (C_{osm}), free water clearance (C_{H2O}), and fractional excretion of sodium (Na) and potassium (K)(FE_{Na} and FE_K).

The attributes were studied at the following times:

- 1st phase: M1, control time for each animal obtained 45 min after prime of creatinine and PAH;
- 2nd phase: M2, immediately after the end of M1; M3, immediately after M2; M4, 30 min after the end of M3.

In G2, M2, M3 and M4 were obtained immediately, 15 and 60 min after fentanyl administration.

PS and pancuronium maintenance dose was carried out 30 min before M1 and M4.

All serum and urine samples were later assayed for creatinine and PAH concentrations using colorimetric techniques.[7,8] Osmolarity was obtained through cryoscopic lowering. Na and K levels were determined using a flame photometer with oxyacetylene.

From this information, the following were derived: clearance (C) = U.V/P where U and P are the urine and plasma substance concentration (mg.ml^{-1}); FF = C_{cr} / C_{PAH}; C_{osm} = U_{osm} V/P_{osm}; C_{H2O} = V - C_{osm}; FE = C / C_{cr} x 100; RBF = C_{PAH} / (1-Ht); and RVR = MAP / RBF.

Statistical analysis was carried out using the profile analysis.[9,10] For attributes presenting a high coefficient of variation (greater than 40 percent), the transformations were studied according Kempthorne.[11] A value of p < 0.05 was considered statistically significant. The α prefixed was 0.05.

RESULTS

Among the hemodynamics attributes of G1, MAP (Fig. 2) was higher at M4 and C_{PAH} was lower at M4. With respect to RF, V (Fig. 4) increased from M2 to M3 and M4. U_{osm} (Fig. 5) decreased from M1 on, C_{H2O} (Fig. 7) increased from M1 on, and FE_{Na} and FE_K (Figs. 8, 9) increased from M2 to M4 (Table 1).

In comparison with the baseline values, HR (Fig. 1) and MAP (Fig. 2) decreased immediately after 0.05 mg.kg^{-1} of fentanyl (G2). All values of C_{cr}, V, C_{osm}, FE_{Na} and FE_K (Figs. 3, 4, 6, 8, 9) decreased after fentanyl. On the other hand, all values of C_{H2O} increased from M2 onwards (Table 1). There were no consistent changes in any of the remaining attributes over the experimental period.

DISCUSSION

SP is a useful agent to induce and maintain anesthesia for experimental research and does not produce significant RF changes.[5,6] In small- to medium-sized dogs, such as the ones we used, HR is between 60-120 beats per minute.[12] In our study, the early observed increase in HR was attributed to a sympathetic[13] or vagolytic[14] origin or reflex through the arterial baroreceptor.[15]

The increase in MAP only at M4 was probably due to a superficial anesthesia level. Greater sympathetic activity as well as an increase in RVR (not significant) and a decrease in C_{PAH} (is actually indexed to renal plasma flow) may have occurred from M3 to M4. The large extracellular volume expansion performed in order to obtain high urinary output and more reliable results of C_{PAH} and C_{cr} actually resulted in high V. Examination of the literature shows that the observed hemodynamic changes

are similar to those reported in dogs by other investigators. They observed decreases in V only 15 min after the injection of SP into dogs.[6,16] Lower U_{osm} was attributed to increasing values of V, which is not evidence of water diuresis, since C_{H2O} increased, yet continued negative, and there was a progressive increase in C_{osm}, FE_{Na} and FE_K.

Greater venous return and preload due to extracellular volume expansion cause aterial distention with liberation of arterial natriuretic peptide, which has natriuretic and diuretic actions. There is inhibition of vasopressin release by arterial distention and also of renin release by extracellular volume expansion. Thus, with the increase in extracellular volume, as expected there was greater elimination of water, and also of solutes.

The administration of fentanyl to the well-anesthetized dogs of G2 resulted in rapid decreases in HR and MAP. Because fentanyl has no significant direct peripheral cardiovascular effects, the HR decrease must have been due to a central effect - a reduction of efferent neurogenic and humoral sympathetic tone. It follows that the higher the preexisting sympathetic activity, the greater the possibility for cardiovascular depression from fentanyl.[17] However, the mechanism involved may be bradycardia caused by fentanyl mediated by vago.[18-20]

Hypertension seems to be dependent on action on sympathetic nerv terminals,[21] or fentanyl may even lower the plasma levels of techolamines[17,22]

Table 1
Hemodynamic and renal function attributes [mean (SD)] in G1 (control) and G2 (fentanyl).

	M1	M2	M3	M4
HR (beats.min^{-1})				
Group 1	144 (18)	145 (19)	150 (18)	146 (23)
Group 2	138 (35)	106 (24)*	107 (25)*	104 (31)*
MAP (mmHg)				
G1	114 (2)	113 (2)	112 (2)	121 (2)*
G2	115 (3)	82 (2)*	76 (2)*	82 (2)*
ICP (cmH$_2$O)				
G1	5.4 (2.2)	5.5 (2.3)	5.4 (2.3)	5.5 (2.2)
G2	5.4 (2.3)	5.5 (1.9)	5.7 (2.4)	5.8 (2.0)
C_{PAH} (ml.min^{-1}.kg^{-1})				
G1	14 (7)	14 (6)	16 (5)	11 (6)*
G2	14 (8)	13 (6)	13 (7)	11 (4)
RBF (ml.min^{-1}.kg^{-1})				
G1	17 (11)	19 (10)	20 (9)	14 (8)
G2	20 (12)	19 (10)	19 (11)	15 (7)
RVR (mmHg.ml^{-1}.min^{-1})				
G1	0.41 (0.17)	0.39 (0.16)	0.35 (0.12)	0.51 (0.18)
G2	0.44 (0.22)	0.35 (0.20)	0.36 (0.23)	0.38 (0.16)
Ccr (ml.min^{-1}.kg^{-1})				
G1	3.7 (1.1)	4.0 (1.3)	3.8 (1.3)	3.4 (1.7)
G2	3.6 (1.5)	2.8 (1.0)*	3.2 (1.5)*	2.9 (1.4)*
V (ml.min^{-1}.kg^{-1})				
G1	0.09 (0.06)	0.10 (0.06)	0.14 (0.08)*	0.15 (0.09)*
G2	0.13 (0.09)	0.11 (0.09)*	0.09 (0.08)*	0.08 (0.08)*
Uosm (mOsm.kgH$_2$O^{-1})				
G1	711 (283)	550 (201)*	506 (196)*	466 (225)*
G2	578 (162)	556 (101)	560 (125)	526 (111)
Cosm (ml.min^{-1})				
G1	2.8 (1.1)	2.6 (1.5)	3.2 (1.8)*	3.2 (2.0)*
G2	2.5 (1.8)	1.5 (1.1)*	1.3 (1.1)*	1.3 (0.9)*
C_{H2O} (ml.min^{-1})				
G1	- 1.5 (1.4)	- 1.0 (0.7)*	- 1.1 (0.7)*	- 0.9 (0.7)*
G2	- 1.1 (0.7)	- 0.6 (0.5)*	- 0.6 (0.5)*	- 0.5 (0.4)*
FE_{Na} (%)				
G1	1.8 (1.1)	2.2 (1.3)	3.2 (1.8)*	3.7 (2.4)*
G2	3.3 (4.4)	1.9 (2.5)*	1.4 (1.8)*	1.8 (2.5)*
FE_K (%)				
G1	22.5 (16.4)	23.6 (13.1)	32.2 (17.3)*	42.7 (29.6)*
G2	25.4 (12.6)	17.6 (9.3)*	15.2 (7.8)*	27.6 (17.3)

*$p < 0.05$

HR = heart rate; MAP = mean arterial pressure; ICP = inferior vena cava pressure; C_{PAH} = PAH clearance; RBF = renal blood flow; RVR = renal vascular resistance; C_{cr} = creatinine clearance; V = urine output; U_{osm} = urinary osmolarity; C_{osm} = osmolar clearance; C_{H2O} = free water clearance; FE = fractional excretion. M1 = control moment (G1 and G2); M2 = immediately after fentanyl (G2); M3 = 15 min after fentanyl (G2); M4 = 60 min after fentanyl (G2).

CASTIGLIA, Y.M.M.; BRAZ, J.R.C.; VIANNA, P.T.G.; LEMONICA, L.; VANE, L.A. - Effect of high-dose fentanyl on renal function in dogs

São Paulo Medical Journal/RPM 115(3): 1433-1439, 1997

through a central effect - a reduction in efferent neurogenic tone and humoral sympathetic tone. However, Priano[4] believes fentanyl liberates catecholamines from the adrenal medulla and peripheral nerves by central mediation, which may explain the increase he observed in the RVR of dogs to which only fentanyl (25 and 50 $\mu g.kg^{-1}$) had been administered. Results differing from these may be due to the previous administration of other drugs such as barbiturates, which cause central depression and sympathetic inhibition.

Taneyama et al.,[23] in a denervation study performed in dogs, reported that the reduction of MAP produced by fentanyl may be mainly due to the reduction of sympathetic outflow. Flacke et al.[17] demonstrated that fentanyl alone decreased plasma catecholamine levels, which might indicate lower sympathetic nerve activity. The decreased MAP in G2 may have caused lower glomerular capillary hydrostatic pressure and thus reducing C_{cr}, which is an estimation of glomerular filtration rate (GFR). GFR influences urine output more than any other one factor.
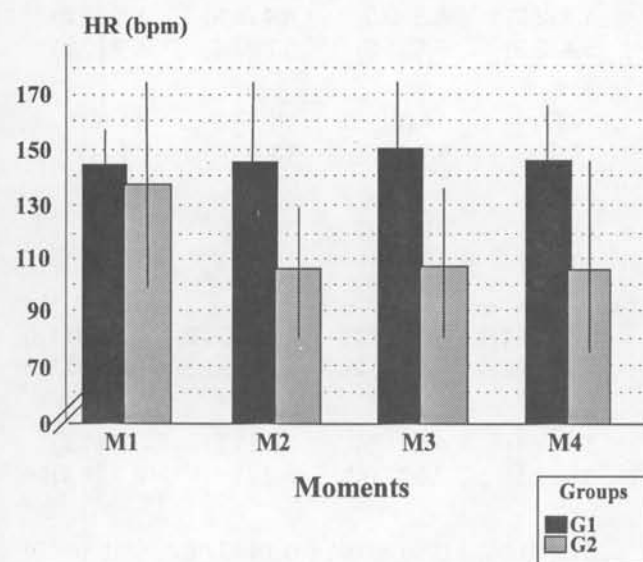
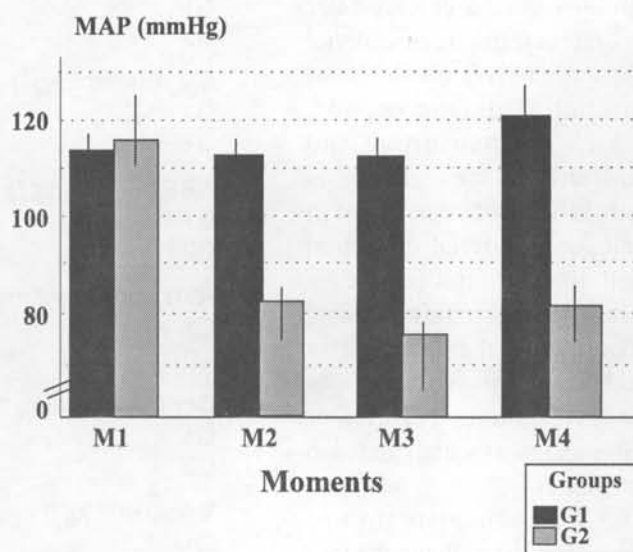Figure 1 - Heart rate in G1 (SP) and G2 (fentanyl)

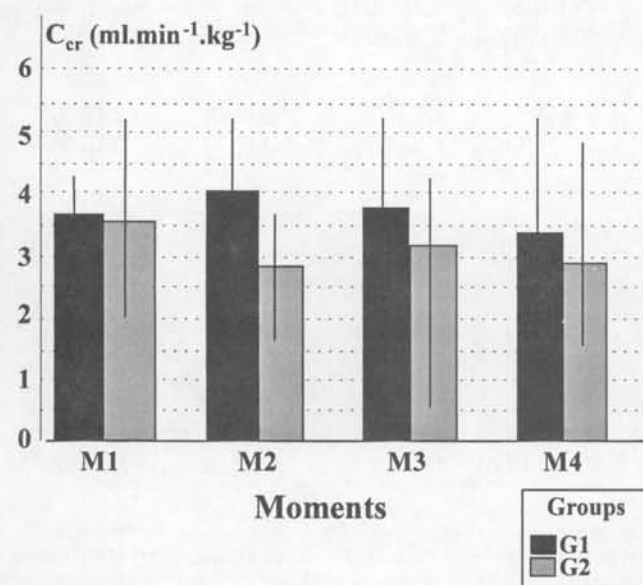Figure 2 - Medium arterial pressure in G1 (SP) and G2 (fentanyl)

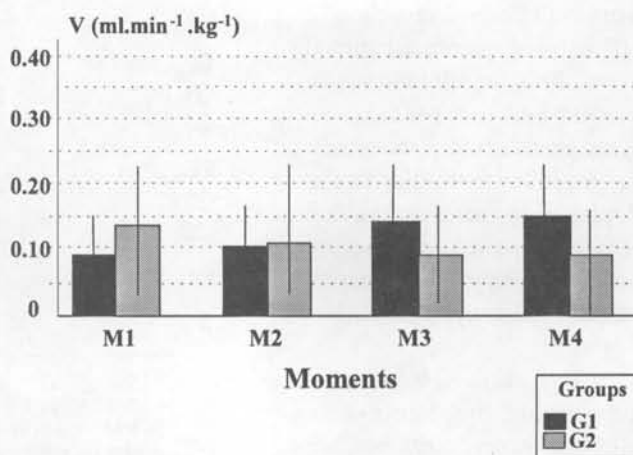Figure 3 - Creatinine clearance in G1 (SP) and G2 (fentanyl)

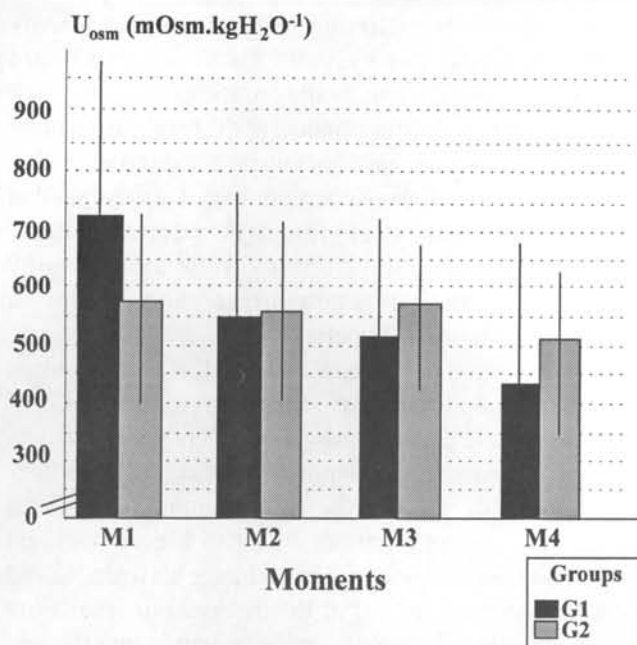Figure 4 - Urinary output in G1 (SP) and G2 (fentanyl)

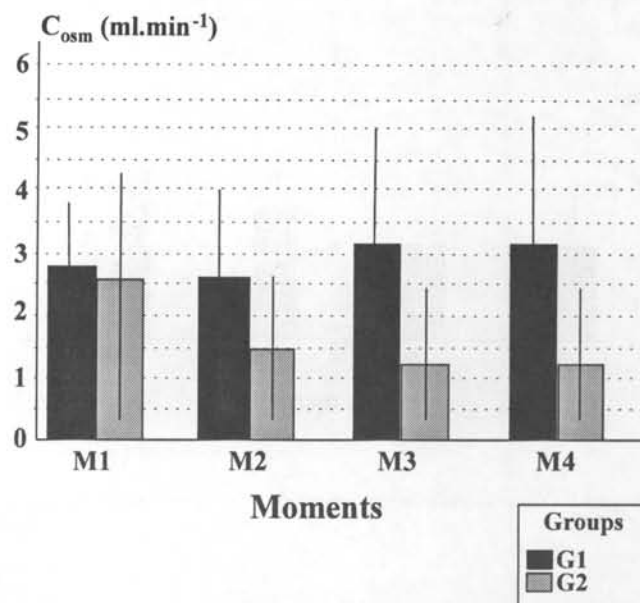**Figure 5 -** Urinary osmolarity in G1 (SP) and G2 (fentanyl)

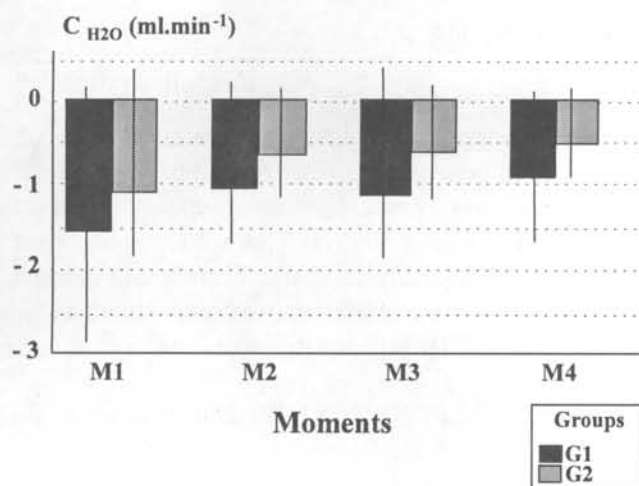**Figure 6 -** Osmolar clearance in G1 (SP) and G2 (fentanyl)

Figure 7 - Free water clearance in G1 (SP) and G2 (fentanyl)
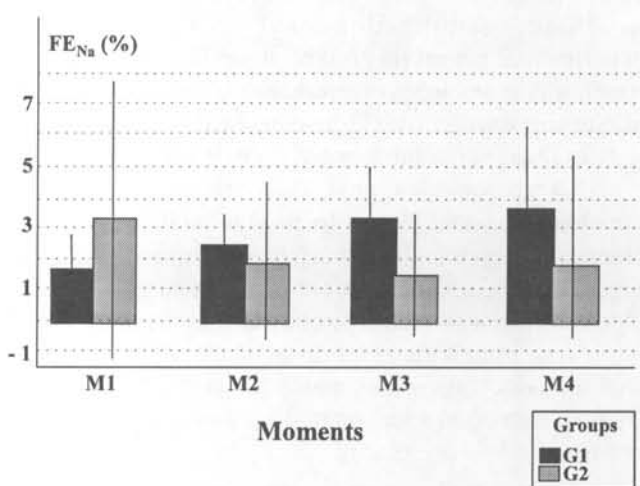

Figure 8 - Sodium fractional excretion in G1 (SP) and G2 (fentanyl)

There are two main mechanisms responsible for the preservation of renal perfusion in the presence of a decreased blood pressure. First, the normal kidney autoregulates its blood flow, keeping an almost constant RBF within a MAP range of 80 - 180 mmHg. The second possible mechanism is the intrarenal secretion of prostaglandins PGE_2 and PGI_2. Both are potent vasodilators.[24]

Our data suggest that these two responses may be preserved during high-dose fentanyl-induced hypotension. C_{PAH} and RBF did not change and RVR was only slightly (and not significantly) reduced, despite a marked decrease

in perfusion pressure. Thus, the significant decrease of GFR (C_{cr}) possibly was minimized.

Fentanyl, a μ opiate receptor agonist, diminishes V in the dog.[1,2] This effect, common to most opiates, has been attributed to the stimulation of vasopressin (an antidiuretic hormone) release.[25] More recent evidence suggests that this is not the decisive factor, although in this study mediated, may be a reduction in GFR.[26,27]

In our study, MAP and C_{cr} decreased in G2, while C_{PAH} and RBF did not. However, GRF begins to decrease at higher renal perfusion pressure than RBF. As diuresis is governed mainly by two physiological mechanisms - by
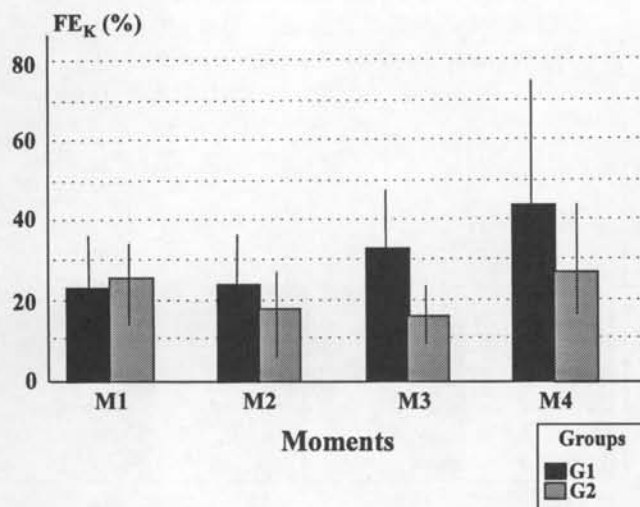
Figure 9 - Potassium fractional excreption in G1 (SP) and G2 (fentanyl)

regulation of the RBF and GFR (C_{cr}), and by variation of tubular reabsorption - these alterations would already be contributing to reducing V (as observed in G2).

Since stabilization of U_{osm} followed each experimental period (in control group U_{osm} decreased all time), it is possible that there was retention or water and also of solutes, because C_{osm} decreased after fentanyl. C_{H2O} did not change after the fentanyl dose (in G1, it increased).

These facts suggest aldosterone action. The hypotension would have activated the renin-angiotensin-aldosterone system; the end product of renin release is the production of angiotensin II, which in turn stimulates aldosterone release. Aldosterone impacts on renal salt and water retention; it increases distal tubular reabsorption of sodium, which decreases water excretion. Thus, in our study, V decreased after fentanyl administration, and urine presented stable osmolarity.

Another factor affecting renin-angiotensin activity is the prostaglandin system. These materials are synthesized from fatty acids and are secreted by the renal medulla. Apart from being dilators of the renal vasculature, they produce renin release but enhance sodium excretion by the tubules. On the contrary, our data demonstrate that FE_{Na} diminished after fentanyl administration. Prostaglandins can also be released from the kidney by angiotensin and norepinephrine and under a vasoconstrictive state (hypotensive).[24]

In contrast to what happened in G1, Na and K output decreased. Aldosterone normally enhances Na reabsorption and K secretion by the distal tubule. However, there is no mandatory coupling between these cellular mechanisms. In other words, the Na amount in the distal lumen tubule is not a limiting factor to K secretion, and there is no observed one-to-one exchange between Na and K at this nephron level. For this reason, our results are consistent with aldosterone having an important effect on Group 2.

CONCLUSIONS

In the population of dogs which received only SP, the observed behavior can be attributed to extracellular volume expansion. These animals were compared to others received high-dose fentanyl. There were significant decreases in RF, probably due to significant opioid-induced hemodynamic changes. However, we cannot eliminate the possibility of main action due to aldosterone.

RESUMO

Objetivos: Estudamos os efeitos de alta dose de fentanil (F) em atributos de função renal (FR) do cão. **Desenho:** Anestesiamos com pentobarbital sódico (PS) 16 cães divididos aleatoriamente em 2 grupos: manutenção com PS (G1) e PS com F (0,05 mg.kg^{-1}) (G2). **Intervenção:** os cães foram ventilados artificialmente e tiveram cateterizadas as veias femorais esquerda e direita e a artéria femoral esquerda para infusão de drogas e coleta de dados hemodinâmicos e de sangue para dosagens laboratoriais. Coletou-se urina durante todo experimento. **Mensuração:** Determinaram-se os valores de atributos de FR.. **Resultados:** PS não mudou a FR e o comportamento de G1 deveu-se à expansão do volume extracelular. O F diminuíu significativamente freqüência cardíaca, pressão arterial média, "clearance" de creatinina, volume urinário, "clearance" osmolar e excreção fracionária de sódio e potássio. **Conclusões:** A diminuição da FR foi provavelmente devida às alterações hemodinâmicas induzidas pelo F, não se descartando possível ação da aldosterona.

CASTIGLIA, Y.M.M.; BRAZ, J.R.C.; VIANNA, P.T.G.; LEMONICA, L.; VANE, L.A. - Effect of high-dose fentanyl on renal function in dogs

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CASTIGLIA, Y.M.M.; BRAZ, J.R.C.; VIANNA, P.T.G.; LEMONICA, L.; VANE, L.A. - Effect of high-dose fentanyl on renal function in dogs

São Paulo Medical Journal/RPM 115(3): 1433-1439, 1997