

## *Effects of Fentanyl and Droperidol on Canine Left Ventricular Performance*

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The effects of fentanyl and droperidol on left ventricular performance were evaluated in the neurally intact dog right-heart-bypass preparation under conditions of constant cardiac output, arterial pressure, and heart rate. Fentanyl, .01 and .02 mg/kg body weight, and droperidol, 0.5 mg/kg, did not affect left ventricular performance. However, 1.0 mg/kg droperidol caused a significant ( $P < .05$ ) increase in left ventricular end-diastolic pressure and a small decrease in maximum left ventricular  $dP/dt$  ( $.05 < P < .10$ ). No significant change in myocardial oxygen consumption was observed. This study indicates that large doses of droperidol may depress left ventricular performance and may account for a portion of the hypotension observed after its administration in man. (Key words: Anesthetics, intravenous, fentanyl; Anesthetics; intravenous, droperidol; Heart, function, fentanyl; Heart, function, droperidol.)

THE COMBINATION of fentanyl, a potent short-acting narcotic analgesic, and droperidol, a butyrophenone, has achieved

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clinical acceptance for the production of a dissociative analgesic state, "neuroleptanalgesia." The basic pharmacology of fentanyl citrate was described by Cardoeki and Yelnosky,<sup>1</sup> and that of droperidol by Yelnosky, Katz and Dietrich.<sup>2</sup> While there have been numerous investigations of these drugs alone and in various combinations,<sup>3-9</sup> their individual effects on left ventricular performance in a reflexly intact preparation have not been described.

### Methods

Mongrel dogs, weighing 15 to 25 kg, were anesthetized with a warmed mixture of chloralose (60 mg/kg) and urethane (600 mg/kg), administered intravenously. The trachea was intubated with a cuffed endotracheal tube and respiration maintained with a volume-controlled Emerson ventilator using 100 per cent O<sub>2</sub>. The chest was opened through a median sternotomy, and right-heart bypass<sup>10</sup> was instituted as follows:

The systemic venous return from the cannulated superior and inferior venae cavae was directed to a reservoir from which the blood was warmed, oxygenated (Temptral Q-100, adult, or Q-110, pediatric, disposable blood oxygenator, Bentley Laboratories) and returned to the pulmonary artery via an occlusive calibrated roller pump. Cardiac output was determined by the rate at which blood was pumped back into the pulmonary artery. Aortic pressure was maintained constant (when desired) by a pressure-bottle apparatus in communication with the cannulated left subclavian artery. A snare ligature was placed around the descending thoracic aorta above the diaphragm to abolish blood flow to the abdominal viscera before right-heart bypass was established.

The prime was freshly drawn, heparinized, mongrel dog blood. If additions to the prime were necessary during the experiment, either fresh ACD mongrel dog blood or lactated

Ringer's solution was used. The hematocrit of the prime was maintained at 30 per cent or higher.

Reflexes originating in the aortic and carotid baroreceptors were tested by suddenly changing arterial blood pressure by varying the output of the pump and observing the change in heart rate on the electrocardiogram. Only animals demonstrating reflex activity by this maneuver were used in the subsequent experiments. After establishing the presence of reflex activity, heart rate was controlled by oversewing or crushing the sinoatrial node and using sequential electrical pacing (Medtronic R wave-coupled pulse generator, model 5837) of the right atrium and the right ventricle. Synchronization of the two pulses resulted in a constant A-V delay that was always shorter than the prevailing PR interval. Heart rate was calculated from the electrocardiogram.

The isolated right heart received only the coronary venous drainage, which was drained from the cannulated right ventricle via a Shipley-Wilson rotameter to the venous reservoir. The rotameter readings were calibrated against timed volumetric collections of coronary blood flow (CBF). Coronary arteriovenous O<sub>2</sub> difference (A-V<sub>O<sub>2</sub></sub>) was continuously monitored using a Guyton A-V<sub>O<sub>2</sub></sub> analyzer (Oxford Instrument Co., Jackson, Mississippi), which was calibrated by the method of Van Slyke and Neill. Care was taken to keep the animals' arterial P<sub>O<sub>2</sub></sub>'s below 200 torr, since above this value the analyzer readings become artifactual. A Radiometer digital acid-base analyzer (Type BMS 3 or PHM 72b, Radiometer, Copenhagen, Denmark) was used to monitor arterial pH, P<sub>O<sub>2</sub></sub> and P<sub>CO<sub>2</sub></sub> values of the experimental preparations. By appropriate infusion of NaHCO<sub>3</sub> and the use of a 97 per cent O<sub>2</sub>-3 per cent CO<sub>2</sub> gas mixture to oxygenate the blood, pH and P<sub>CO<sub>2</sub></sub> were maintained within physiologic ranges. Left ventricular end-diastolic pressure (LVEDP) was measured by a short Y-shaped metal cannula introduced into the left ventricle through the apex, and attached to a Statham P23 Db strain gauge. The rate of rise of left ventricular pressure (dp/dt) was recorded electronically and calibrated as previously described.<sup>10</sup> Systemic arterial pressure was measured in the aorta

via the left carotid artery with a Statham P23Db strain gauge. All data were recorded on an eight-channel Beckman type S-II direct-writing Dynograph.

It was possible to keep the conditions of the left ventricular myocardium in a steady state since: 1) cardiac output was equal to pump effluent; 2) arterial blood pressure was kept constant by the pressure-bottle apparatus; 3) atrioventricular pacing maintained a steady heart rate. Left ventricular function was evaluated by measuring left ventricular maximum dp/dt and LVEDP at constant cardiac output, aortic pressure, and heart rate. Myocardial oxygen consumption (MV<sub>O<sub>2</sub></sub>) was expressed as the produce of coronary blood flow and coronary A-V<sub>O<sub>2</sub></sub> difference in ml/100 g left ventricle/min. Left ventricular weight was obtained directly following completion of the study and sacrifice of the animal.

### Protocol

The drugs investigated were fentanyl, 0.01 and 0.02 mg/kg, and droperidol, 0.5 and 1.0 mg/kg. All dogs in the fentanyl study received the low dose first, then, after a recovery period, the high dose. No dog received fentanyl after droperidol. Three dogs in the low-dose droperidol group and two in the high-dose droperidol group had previously received infusions of fentanyl. There was no observed difference between responses to droperidol of dogs that had received fentanyl and those that had not. Only one dose of droperidol was administered to any individual animal. After control measurements were recorded, the drug to be evaluated was injected over a period of 1 minute into the cannula perfusing the pulmonary artery to avoid administering a bolus of the drug. Hemodynamic measurements were made 1, 3 and 5 minutes from the end of injection. Control and experimental values were evaluated for statistical significance using a t test for paired data.

### Results (Table 1)

There was no significant change in ventricular performance or myocardial oxygen consumption after fentanyl (0.01 mg/kg and 0.02 mg/kg) and droperidol (0.5 mg/kg).

TABLE I. Effects of Fentanyl and Droperidol on Left Ventricular Function (Means  $\pm$  SD)\*

	Control	Post-injection		
		1 Minute	3 Minutes	5 Minutes
Left ventricular end-diastolic pressure (cm H <sub>2</sub> O)				
Fentanyl, 0.01 mg/kg (5)†	6.26 $\pm$ 2.04	5.70 $\pm$ 1.55	6.66 $\pm$ 1.70	6.32 $\pm$ 1.97
Fentanyl, 0.02 mg/kg (5)	6.72 $\pm$ 2.81	6.26 $\pm$ 2.64	6.26 $\pm$ 2.49	6.16 $\pm$ 2.55
Droperidol, 0.5 mg/kg (12)	6.49 $\pm$ 3.80	6.53 $\pm$ 3.68	6.28 $\pm$ 3.43	6.45 $\pm$ 3.63
Droperidol, 1.0 mg/kg (10)	6.98 $\pm$ 2.97	8.19 $\pm$ 4.02‡	8.11 $\pm$ 3.10‡	8.02 $\pm$ 2.88‡
LV dP/dt (torr/sec)				
Fentanyl, 0.01 mg/kg (5)	3,306 $\pm$ 994	3,492 $\pm$ 742	3,301 $\pm$ 746	3,264 $\pm$ 637
Fentanyl, 0.02 mg/kg (5)	2,535 $\pm$ 614	2,618 $\pm$ 599	2,564 $\pm$ 671	2,618 $\pm$ 599
Droperidol, 0.5 mg/kg (12)	3,330 $\pm$ 732	3,302 $\pm$ 858	3,353 $\pm$ 817	3,334 $\pm$ 739
Droperidol, 1.0 mg/kg (10)	2,666 $\pm$ 931	2,566 $\pm$ 911	2,573 $\pm$ 800	2,610 $\pm$ 778
MV <sub>O</sub> (ml O <sub>2</sub> /100 g left ventricle/min)				
Fentanyl, 0.01 mg/kg (4)	13.42 $\pm$ 1.16	13.24 $\pm$ 1.40	13.21 $\pm$ 1.62	12.78 $\pm$ 1.42
Fentanyl, 0.02 mg/kg (4)	10.51 $\pm$ 3.09	10.55 $\pm$ 3.15	10.49 $\pm$ 3.17	10.40 $\pm$ 3.08
Droperidol, 0.5 mg/kg (10)	8.29 $\pm$ 2.99	8.73 $\pm$ 3.48	8.60 $\pm$ 3.20	8.42 $\pm$ 3.24
Droperidol, 1.0 mg/kg (7)	13.42 $\pm$ 13.0	12.51 $\pm$ 11.25	12.52 $\pm$ 11.85	12.48 $\pm$ 11.64

\* Reflexly intact canine right-heart bypass preparation: cardiac output, arterial blood pressure and heart rate constant.

† Number of studies.

‡  $P < 0.05$ .

However, after 1.0 mg/kg of droperidol, there was a significant ( $P < .05$ ) increase in LVEDP of approximately 1 cm H<sub>2</sub>O and a small decrease ( $.05 < P < .10$ ) in left ventricular maximum dP/dt of approximately 100 torr/sec (3 per cent change). Although the decrease of dP/dt was small, it was larger than any other change of this variable observed throughout the study.

### Discussion

These studies were undertaken to evaluate the separate effects of fentanyl and droperidol on left ventricular performance. Dixon and associates<sup>3</sup> reported that Innovar (fentanyl, 0.01 mg/kg, and droperidol, 0.5 mg/kg) has no direct effect on left ventricular function. The present data indicate that fentanyl in doses of 0.01 and 0.02 mg/kg does not affect left ventricular performance in reflexly intact animals. This finding is in contrast to the findings of Goldberg and Padgett,<sup>11</sup> who demonstrated decreases of contractility of the isolated saline-perfused rat trabeculae carnae muscle by both fentanyl and morphine. The same dichotomy, *i.e.*,

depression of contractility of saline-perfused cardiac muscle strips<sup>11</sup> and lack of depression of a blood-perfused heart (heart-lung preparation),<sup>12</sup> has been described with morphine, the prototypical opiate. The reasons for these disparate observations concerning both drugs are not apparent.

Droperidol, in doses of 0.5 and 1.0 mg/kg, is reputed not to affect ventricular contractility. However, the present study suggests that droperidol in a dose of 1.0 mg/kg minimally, but reproducibly, diminishes left ventricular performance. Although the dose that caused depression of ventricular contractility is large when extrapolated to man, it is within the range used clinically, especially when we consider that it was diluted by the pump-priming volume, which expanded circulating blood volume two- to threefold. Yelnosky, Katz and Dietrich<sup>2</sup> observed depression of contractile force with 2 and 4 mg/kg of droperidol in the intact dog anesthetized with sodium pentobarbital (30 mg/kg, iv). The data thus suggest that myocardial depression may be a factor in the hypotension seen in patients when droperidol is administered, although this occurrence has previously been

ascribed solely to the effect on the peripheral vasculature mediated by blockade of alpha-adrenergic receptors.

Recent work suggests that droperidol may be an alpha-adrenergic blocker in man,<sup>13</sup> as originally postulated by Yelnosky, Katz and Dietrich for droperidol in dogs. Dixon and associates have shown that Innovar (fentanyl, 0.01 mg/kg, and droperidol, 0.5 mg/kg) produces an immediate moderately severe decrease in peripheral arterial resistance, and a moderate increase in capacitance of the peripheral vascular bed, but these investigators did not study each drug separately. In the present experiments no systematic attempt was made to quantify the effects of fentanyl and droperidol on the systemic vasculature. Nevertheless, in every instance following injection of fentanyl or droperidol during right-heart bypass, the constant-pressure apparatus had to be activated and blood added to the system to expand intravascular volume in order to maintain a stable mean arterial blood pressure. Several initial experiments with droperidol were terminated by the resultant massive vasodilation of the peripheral vasculature. This experimental difficulty was overcome by ligation of the thoracic aorta above to the diaphragm.

The preparation of a right-heart bypass obviously requires anesthesia. The present experiments were performed on animals basally anesthetized with chloralose and urethane, an anesthetic regimen that produced minimal circulatory depression and preserves reflex activity.<sup>14</sup> However, we cannot entirely rule out a contribution of the chloralose-urethane to the reported observations.

In summary, results of this study indicate that fentanyl, 0.01 and 0.02 mg/kg, and droperidol, 0.5 mg/kg, have no effect on left ventricular performance in the chloralose-urethane-anesthetized canine right-heart-bypass preparation. Droperidol in a dose of 1.0 mg/kg causes a suggestion of myocardial depression. The data emphasize the impor-

ance of considering the interaction of drugs on the entire cardiovascular system when evaluating their effects.

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