Anesthesiology
66:524-530, 1987

Effects of Fentanyl on Peripheral and Cerebral Hemodynamics in Neonatal Lambs

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The effects of fentanyl on cardiovascular function, regional distribution of cardiac output, and the dose required for producing anesthesia were studied in ten previously catheterized, newborn lambs. In addition, the effects of fentanyl on cerebral blood flow and oxygen utilization were examined. Fentanyl in cumulative doses as high as 4.4 mg/kg (average plasma levels of 646 ± 95 ng/ml, maximum plasma level of 862 ng/ml) did not reliably produce anesthesia as assessed by tail and foot clamping, although it did cause profound respiratory depression. With normocapnia maintained by mechanical ventilation, fentanyl did not alter cerebral oxygen delivery or consumption, and the two remained coupled. Fentanyl did not affect cardiac output, heart rate, or mean arterial blood pressure at the highest dose level, nor did it reduce blood flow to specific organ beds, other than the kidney. Thus, the hemodynamic stability seen with fentanyl in the lamb does not occur at the expense of reduced blood flow to organs, such as the gastrointestinal tract or brain, that are particularly vulnerable in the neonate. (Key words: Anesthetics, intravenous; fentanyl. Anesthesia: pediatric. Brain: blood flow; carbon dioxide tension; metabolism. Heart: blood flow, myocardial.)

AT EQUIPOTENT DOSES (ED_{50}, MAC), most anesthetic agents cause a high incidence of unacceptable side effects in neonates.[1] Studies in adults of various species (dog,[2] rat,[3] human[4]) have demonstrated that high doses of fentanyl and related synthetic narcotics act as complete, single-agent, intravenous anesthetics (*i.e.*, they provide unconsciousness, analgesia, and amnesia), and do so with remarkable circulatory stability. Robinson and Gregory[5] used heart rate and blood pressure responses as an index of adequate anesthesia to demonstrate that human premature infants undergoing ductal ligation could be anesthetized with fentanyl (0.03–0.05 mg/kg) and with concomitant circulatory stability.

The purpose of this study was to investigate the physiologic consequences of a high dose of fentanyl in a newborn animal model in which the narcotic is the only anesthetic agent used. Specifically, we examined: 1) the dose requirements for producing anesthesia as determined by tail and foot clamping, 2) the regional distribution of cardiac output to assess whether the circulatory stability reported with fentanyl occurs at the expense of blood flow to major organs, 3) how fentanyl affects cerebral blood flow (CBF), cerebral oxygen uptake and the coupling of CBF to oxygen utilization when no other drugs are administered, and 4) whether the effects of fentanyl were reversed by naloxone.

Methods and Materials

SUBJECTS AND PREPARATION

All animals (n = 10) were healthy newborn lambs of mixed breed (2.9–6.0 kg) and less than 1 week old. Approval for this study was obtained by the Institution's Animal Care and Use Committee. Following inhalation induction of anesthesia using halothane (2–4%), nitrous oxide, and oxygen (30%) the lambs were orally intubated, and then ventilated with a Harvard small animal ventilator. Anesthesia was maintained with 2–3% halothane, 30% oxygen, and 67–68% nitrous oxide. All catheters were placed under sterile conditions.

A left ventricular catheter was placed *via* a femoral artery for microsphere injection. Placement of this catheter was determined by pressure monitoring. The opposite femoral artery was cannulated, and the catheter advanced 6–8 cm into the abdominal aorta. A catheter was placed in each subclavian artery *via* the brachial artery. These catheters were advanced into the left ventricle, and then withdrawn so that their tip was 4–5 cm above the aortic valve. One femoral vein was catheterized with a #5 French, triple lumen, thermodilution, balloon-tipped catheter which was advanced into the pulmonary artery while the pressure tracing was monitored to ensure proper placement. The other femoral vein was used to place a catheter in the right atrium. The catheters were filled with heparin, tunneled subcutaneously, and exteriorized in an external pouch. In addition, a burr hole was drilled in the skull, and the superior sagittal sinus was cannulated with the catheter tip placed approximately 1 cm anterior to the confluence of sinus, as described previously.[6] Following surgery and anesthesia, the lambs received intramuscular antibiotics (300,000 U of procaine Penicillin), recovered, and were returned to their ewes. All catheter placements were verified at autopsy.

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Received from the Department of Anesthesiology/Critical Care Medicine, The Johns Hopkins Medical Institutions, 600 N. Wolfe Street, Baltimore, Maryland 21205. Accepted for publication November 26, 1986. Supported in part by USPHS NIH Grant NS20020 and by an ASA Research Starter Grant entitled "Narcotic 'Anesthesia' in Newborn Lambs." The fentanyl for this project was supplied by Janssen Pharmaceuticals, as was the analysis of plasma levels.

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Experimental Protocol

Each animal was studied approximately 24 h after surgery. The lamb was removed from the ewe, weighed, and placed in an environmental chamber that minimized external stimulation and kept the lamb calm. The lamb was free to sit and stand, but not to turn about. The lamb was unsedated, unstimulated, and left quiet and resting for 30 min. After obtaining baseline measurements, the ten animals received at 20-min intervals 0.1, 0.3, 1.0, and 3.0 mg/kg fentanyl for a cumulative dose of 4.4 mg/kg. All drugs were administered through the femoral venous catheter. Approximately 3 min after each increment of fentanyl was administered, cardiac output determinations were made. Five minutes after each fentanyl increment was administered, blood samples for blood gases, *p*H, oxygen content, and hematocrit were obtained from the subclavian artery and sagittal sinus catheters. Eight minutes after each fentanyl increment was administered, radiolabelled microspheres were injected in seven animals. Blood losses due to sampling were replaced with stored autologous blood after collecting each microsphere reference sample. Ten minutes following each fentanyl increment, anesthesia was assessed by noting the animal's level of consciousness and response to foot and tail clamping with a hemostat. Consciousness was inferred if the lamb's eyes were open, if it vocalized ("baaed"), and if it alerted to sound (hand clap, shout). Responses to foot and tail clamping included withdrawal of the stimulated foot (or non-withdrawal); gross purposeful muscular movement, usually of the head (jerking or twisting); and increases (or no change) in systolic arterial blood pressure. Following the full fentanyl loading, 0.1 mg/kg naloxone was given. Blood samples for hematocrit, blood gas, and oxygen content were obtained from the subclavian artery and sagittal sinus catheters. Cardiac output was measured, and a final microsphere injection was made. Three lambs, who did not receive microsphere embolization, had arterial and venous blood samples for fentanyl levels drawn at 2 and 15 min following each fentanyl administration.

All animals breathed spontaneously. When respiratory depression occurred, that is, an increase in arterial CO_2 tension (Pa_{CO_2}) of 20% or greater above baseline, or a fall in arterial oxygen content of 20% or greater from baseline, the animals were orally intubated and ventilated with a Harvard small animal ventilator to return to baseline levels of Pa_{CO_2} and arterial O_2 content.

Measurements

Regional blood flow measurements were made with radiolabelled microspheres (15 ± 1.5 μm diameter) using the reference sample technique.[7] Approximately 1–1.5 × 10^6 of each microsphere isotope (^{153}Gd, ^{51}Cr, ^{113}Sn, ^{103}Ru, ^{95}Nb, and ^{46}Sc) was injected into the left ventricle over a 30-s period, followed by a 10 ml saline flush over 15 s. The reference withdrawal blood samples were collected simultaneously from the subclavian artery and abdominal aorta at 2.5 ml/min beginning 15 s before the injection and lasting for 3 min. This injection technique does not alter aortic blood pressure, cardiac output, blood gases, heart rate, or *p*H, and has been used previously in our laboratory.[6]

At the conclusion of the experiment, the animal was killed by an overdose of sodium pentobarbital followed by KCl, and the brain and internal organs were removed. The brain was dissected into the following regions: medulla, pons, midbrain, diencephalon, caudate nucleus, white matter, and cerebral hemispheres. Multiple samples of skin, muscle, heart, kidney, stomach, and small and large intestine were obtained to average spatial inhomogeneities and to insure that calculations were based on the presence of at least 1000 microspheres in each tissue sample. Samples were counted in a Packard Multichannel Autogamma Scintillation Spectrometer (Model 9042), and backscatter from higher energy isotopes into windows of lower energy emission was subtracted for a corrected count value using differential spectroscopy by the simultaneous equation method.[8] Blood flow was calculated as the product of this corrected tissue count and the arterial reference withdrawal rate divided by the counts in the reference sample and by the weight of the tissue. Blood flow to cephalic tissues utilized the subclavian arterial reference sample, whereas the abdominal aortic reference sample was used for calculating blood flow to lower body tissues.

Aortic blood pressure was continuously monitored with a Statham pressure transducer referenced to the level of the right atrium. Cardiac output was determined in triplicate by thermodilution using 3 ml of iced saline injected into the central venous pressure port of a 5 French thermodilution catheter (Edwards Laboratories). This procedure did not change body temperature or hemodynamics. The thermodilution technique for cardiac output measurement compares favorably with other techniques in newborn lambs.[9] Arterial and sagittal sinus P_{O_2}, P_{CO_2}, and *p*H were measured with Radiometer BMS3 electrodes and analyzer, and O_2 content was measured with a Lex-O_2-Con (Lexington Instruments). Cerebral oxygen consumption (CMR_{O_2}) was calculated as the product of hemispheric blood flow and the arteriovenous oxygen content difference. Cerebral fractional oxygen extraction was calculated as the arteriovenous oxygen content difference divided by arterial oxygen content.

Fentanyl levels were determined on plasma separated from whole blood by centrifugation and frozen at −20° C until analyzed for fentanyl concentrations. Plasma levels of fentanyl were measured by gas chromatography using a Hewlett-Packard 5710A gas chromatograph equipped

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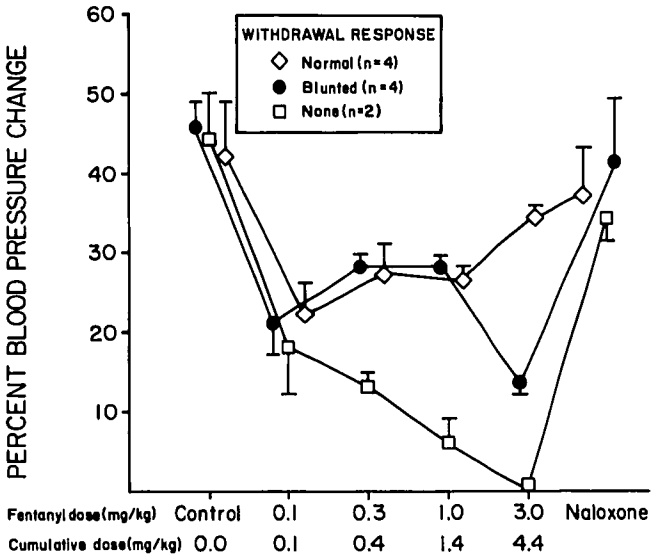

FIG. 1. Response to foot and tail clamping at each fentanyl increment as well as following naloxone administration is depicted as the percent change in systolic blood pressure. These changes in blood pressure corresponded to the behavioral responses seen (normal, weak, and no limb withdrawal). Each line represents the average blood pressure response of the non-responders (n = 2), the blunted responders (n = 4), and the full responders (n = 4). Bars represent the standard error.

with a nitrogen/phosphorus detector, and was performed by Janssen Laboratories according to the method of Woestenborghs *et al.*[10] The precision of this technique, expressed as coefficient of variation, is between 4 and 10% in the concentration of interest. The sensitivity of this technique is 0.1 ng/ml.

Statistical Analysis

The effect of incremental doses of fentanyl and of naloxone administration on each measured variable was examined by one-way analysis of variance with repeated measurements. Multiple comparisons of mean values were made by the Duncan Multiple Range Test. Probability values of less than 0.05 were considered significant. All results are presented as the mean ± standard error.

Results

Behavioral Effects

Eight of the ten lambs appeared conscious throughout the study, in that their eyes were open, they would alert to sound, and they would move when lightly touched. Nevertheless, all of the lambs were visibly different following the 3.0 mg/kg dose of fentanyl in that they appeared "catatonic." In the baseline condition, the lambs stood or laid down, rolled their heads, and "baaed." Following the full fentanyl loading dose of 3.0 mg/kg (4.4 mg/kg cumulative dose), the animals all lay on their side with extension of their limbs and stopped "baaing." At 0.1, 0.3, and 1.0 mg/kg of fentanyl, all animals continued to withdraw normally to painful stimuli, and showed increases in blood pressure (fig. 1). At 3.0 mg/kg of fentanyl, however, animals were found to fall into three groups of normal, weak, and no-limb-withdrawal response. The strength of the withdrawal reflex and the rise in arterial pressure were related in these three groups (fig. 1). At the highest fentanyl dose, two animals became completely unresponsive to pain; that is, they neither withdrew their limbs nor increased their systolic aortic blood pressure; four animals had blunted responses to pain, that is, they weakly withdrew their limbs, but did not move their heads or jerk away, and increased their systolic aortic blood pressure by less than 15%; and four animals remained normally responsive to foot clamping in that they had gross purposeful withdrawal movements and increased their systolic aortic blood pressure by 20% or more. The effects of fentanyl on consciousness and response to pain were completely reversed by naloxone. All lambs immediately stood up, "baaed," and became fully responsive to foot clamping.

Respiratory Effects

Table 1 shows the blood gas, *p*H, and arterial and cerebral venous oxygen content data with fentanyl administration for all animals studied. The respiratory effects of fentanyl were pronounced. Although there was no CO_2 retention in the 0.1 mg/kg dose range, there were significant increases in Pa_{CO_2} and decreases in Pa_{O_2} following the 0.3 mg/kg and 1.0 mg/kg doses. All ten animals required oral intubation and mechanical ventilation for apnea or Pa_{CO_2} increases of greater than 20%. One animal was orally intubated at 0.3 mg/kg, four at 1.0 mg/kg, and the remaining five at 3.0 mg/kg. Thus, the improvement in blood gases seen (table 1) following 3.0 mg/kg fentanyl represents the effects of mechanical ventilation. Truncal rigidity was never seen, although extension of the limbs was evident. The lambs did not resist or struggle during intubation or during ventilation. Naloxone completely reversed the respiratory depression produced by fentanyl. Following naloxone administration, all lambs were extubated and breathed spontaneously.

Cardiovascular Effects

The cardiovascular effects measured 3 min after each incremental dose of fentanyl are shown in table 1. Cardiac output and heart rate were unchanged from control at any dose level of fentanyl. Mean aortic pressure increased at the intermediate fentanyl doses when hypoxia, hypercarbia, and/or light anesthesia were present. However, aortic pressure was not altered from control at 3.0 mg/

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TABLE 1. Blood Gas, *p*H, Hematocrit, and Arterial and Cerebral Venous O_2 Content Values and Hemodynamics with Fentanyl and Naloxone Administration

	Control	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	Naloxone
Pa_{CO_2} (torr)	34 ± 1	37 ± 1	40 ± 1*	38 ± 2*	38 ± 2	34 ± 1
Pa_{O_2} (torr)	76 ± 5	67 ± 3	57 ± 4*	65 ± 4*	69 ± 4	72 ± 5
*p*H	7.38 ± .01	7.35 ± .01	7.29 ± .02*	7.34 ± .03	7.36 ± 0.02	7.32 ± 0.02*
Hematocrit (%)	30 ± 3	30 ± 2	29 ± 2*	29 ± 2*	28 ± 3*	27 ± 2*
Ca_{O_2} (ml/dl)	13.5 ± 1.0	13.1 ± 1.0	11.2 ± 0.9*	11.7 ± 1.4*	12.3 ± 1.2	11.5 ± 1.1*
Cv_{O_2} (ml/dl)	8.0 ± 0.9	8.0 ± 0.9	8.0 ± 1.0	7.5 ± 1.0	6.5 ± 0.8*	6.8 ± 0.9
Cardiac Output (ml/kg/min)	294 ± 13	349 ± 31	377 ± 31	383 ± 31	359 ± 29	351 ± 31
Mean aortic pressure (mmHg)	70 ± 2	88 ± 6*	93 ± 4*	90 ± 5*	79 ± 5	80 ± 5
Heart rate (beats/min)	200 ± 13	192 ± 17	226 ± 23	235 ± 22	242 ± 17	236 ± 17

Pa_{CO_2} = arterial CO_2 tension; Pa_{O_2} = arterial O_2 tension; Ca_{O_2} = arterial O_2 content; Cv_{O_2} = sagittal sinus O_2 content.
All animals were intubated & mechanically ventilated at the 3.0 mg/kg dose.
* $P < 0.05$ from control.
Each value represents the mean ± SE of 10 animals.

kg fentanyl when the maximum effects of fentanyl on spontaneous respiration, pain withdrawal, and consciousness were seen, and when ventilation was controlled in all animals.

The effects of 3.0 mg/kg fentanyl and naloxone on regional blood flow are shown in figure 2. There was no change in blood flow to the stomach, small intestine, large intestine, muscle, or skin. On the other hand, flow to the right and left ventricles increased, while renal blood flow decreased when compared to control. Following naloxone administration, renal blood flow increased compared to the 3.0 mg/kg fentanyl dose.

CEREBRAL EFFECTS

CBF, CMR_{O_2}, and cerebral O_2 delivery did not change from control following the highest fentanyl dose (fig. 3). In the subpopulation of lambs (n = 2) who became unresponsive to painful stimuli, there was a 38 ± 1% decrease in CBF, a 36 ± 1% reduction in CMR_{O_2}, and a 40 ± 1% decrease in oxygen delivery. In all lambs, the cerebral fractional extraction of oxygen was unchanged following fentanyl. Following naloxone administration, CBF increased significantly when compared to 3.0 mg/kg fentanyl, although not when compared to control (fig. 3). Arterial O_2 content and hematocrit were reduced about 10–15% by this point in the experiment, and part of the rise in CBF may be secondary to this relative anemia. Cerebral O_2 delivery was not elevated following naloxone relative to either control or fentanyl.

Analysis of blood flow to specific brain regions, expressed as percent change from control for all seven lambs, is shown in figure 4. Although blood flow to the cerebrum was unchanged at the 3.0 mg/kg dose of fentanyl, there were significant decreases in blood flow and O_2 delivery to spinal cord, cerebellum, medulla, diencephalon, and

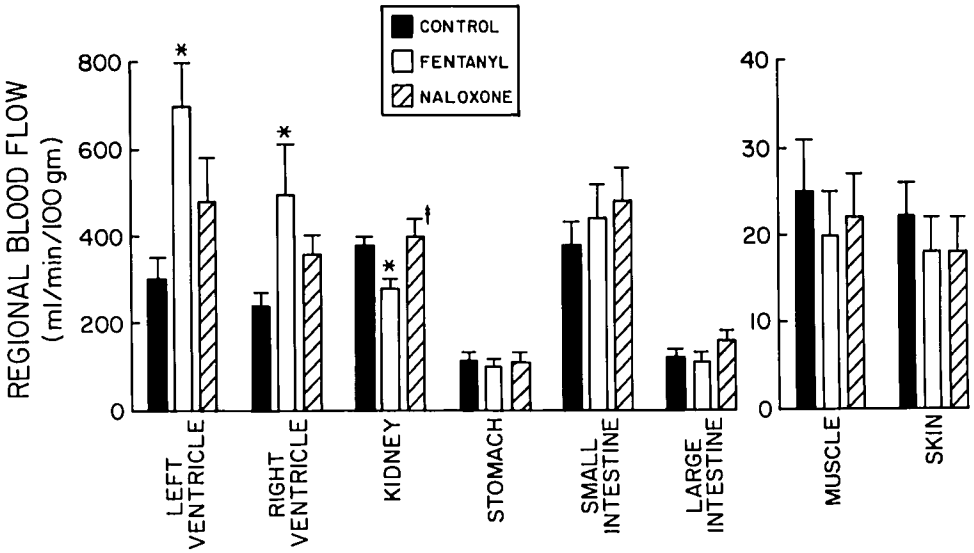

FIG. 2. Regional blood flow (ml/min/100gm) at control (closed bars), at 3.0 mg/kg fentanyl (cumulative dose 4.4 mg/kg) (clear bars), and following naloxone (striped bars) administration are shown. The mean for all animals (n = 7) is depicted. Bars represent the standard error. Statistical significance, $P < 0.05$, compared to control is represented by an asterisk (*), whereas comparison of naloxone effect to maximum fentanyl effect is represented by a cross (‡).

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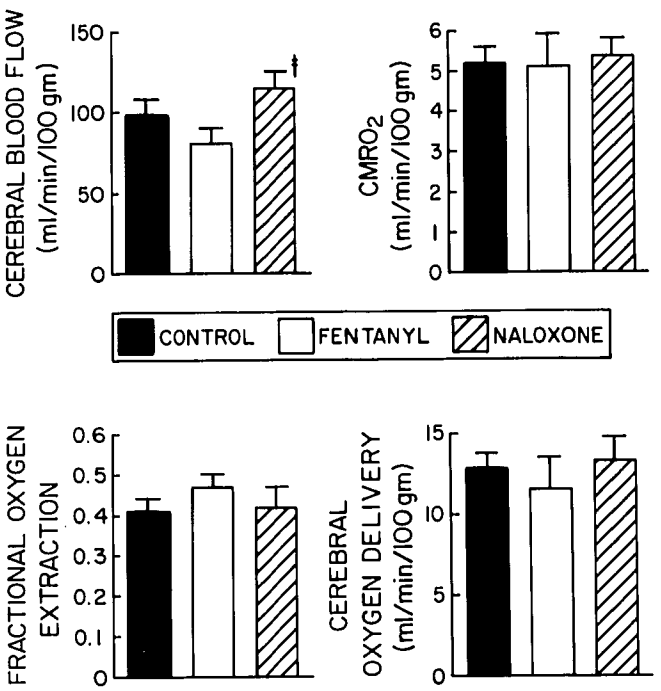

FIG. 3. Cerebral blood flow, CMR_{O_2}, oxygen delivery, and cerebral fractional O_2 extraction at control (closed bars), at maximum fentanyl (cumulative dose 4.4 mg/kg) (clear bars), and following naloxone (striped bars) administration are shown. The mean for all animals (n = 7) is depicted. Bars represent the standard error. Statistical significance, $P < 0.05$, compared to control is represented by an asterisk (*), whereas comparison of naloxone effect to maximum fentanyl is represented by a cross (‡).

subcortical white matter. Following naloxone administration, all brain regions had significantly higher blood flows compared to the highest fentanyl dose. These blood flows, however, were not different from control. The response to naloxone was not equivalent in all regions. The caudate nucleus had significantly higher blood flow (as a percent of control) compared to cerebrum and white matter.

Arterial blood levels of fentanyl obtained from three animals were high. The levels obtained averaged 37 ± 15, 99 ± 41, 321 ± 95, and 646 ± 95 ng/ml at 2 min after the administration of 0.1, 0.3, 1.0, and 3.0 mg/kg fentanyl, respectively.

Discussion

Fentanyl, acting as a single intravenous anesthetic agent in the newborn lamb, did not reliably produce unconsciousness, prevent limb withdrawal, or block hemodynamic responses to painful stimuli following incremental doses of fentanyl as high as 3.0 mg/kg. Indeed, this lack of anesthesia occurred despite a cumulative fentanyl dose of 4.4 mg/kg and an average arterial plasma level of 646 ± 95 ng/ml (maximum plasma level of 862 ng/ml). Other investigators have produced anesthesia with fentanyl in other animal models at much lower fentanyl doses.[2,3] Our inability to produce anesthesia and reliable analgesia in newborn lambs appears to contradict the findings of other investigations. There are several possible reasons for this: 1) differences in species; 2) different preparations; 3) concomitant use of other anesthetic agents; and 4) age.

The effects of anesthetics may be species specific. Shingu *et al.*,[3] using unpretreated rats, achieved anesthesia with fentanyl. These rats did not respond to tail clamping, but appeared, by the authors' own description, "conscious" throughout the experimental procedure. McPherson and Traystman[11] could not reliably produce unconsciousness in dogs with fentanyl, although analgesia was present. Sebel *et al.*[12] showed that the EEG response of lorazepam premedicated, paralyzed human patients to 0.05–0.07 mg/kg fentanyl administration produced predictable EEG changes, which were associated with unconsciousness and a lack of response to surgical stimulation. The ability of single-agent narcotics, such as fentanyl, to reliably produce sleep and amnesia in adult humans has been questioned by others.[13]

Many investigations of fentanyl use acute animal preparations in which the animal is prepared for experimen-

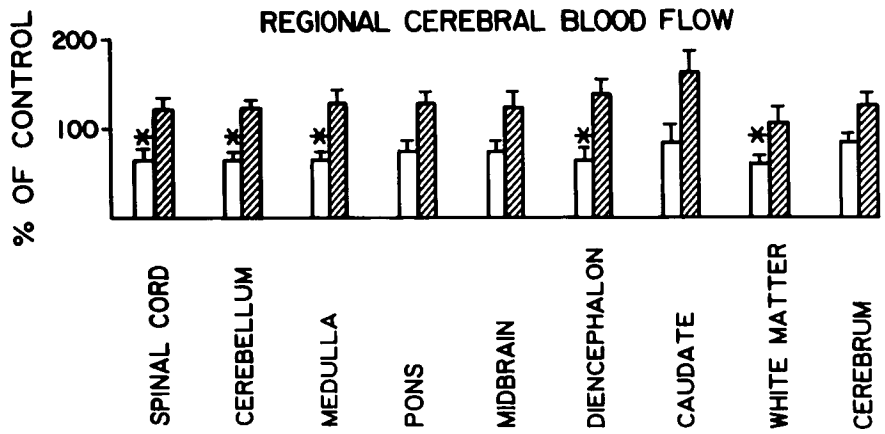

FIG. 4. Regional cerebral blood flow (ml/min/100 gm) following 3.0 mg/kg of fentanyl (cumulative dose 4.4 mg/kg) (clear bars) and naloxone (striped bars) administration are shown. Values are percent change (mean ± SE) from the control values. Asterisks (*) depict significant difference ($P < 0.05$) from control. Following naloxone administration, all brain regions had higher blood flows when compared to fentanyl. These blood flows were not different than control.

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tation under barbiturate or inhalational anesthesia.[14] The concomitant use of other anesthetic agents such as barbiturates, halothane, or nitrous oxide in animal preparations may significantly potentiate the effect of fentanyl on unconsciousness and non-withdrawal to painful stimuli.

Finally, there is the issue of age. Standards and results of adult model drug research may not apply to newborn and young animals, because the young have developmentally different metabolism, volumes of distribution, excretion, and central nervous system maturity.[15] Most studies of the anesthetic effect of fentanyl have utilized adult animals.

Although fentanyl did not reliably produce anesthesia, it did cause profound respiratory depression, and it did so without any evidence of chest wall rigidity. This respiratory depression was completely reversible by naloxone. A number of studies[16,17] suggest that the respiratory depression and analgesia produced by opiates involve different receptor subtypes, and these receptors change in number in an age-related fashion and can be blocked by naloxone. Pasternak *et al.*,[16,17] working with newborn rats, showed that 14-day-old rats are 40 times more sensitive to morphine analgesia than 2-day-old rats. Nevertheless, morphine depresses the respiratory rate in 2-day-old rats more effectively than in 14-day-old rats. Thus, the dichotomy between analgesia and respiratory depression may be an age-related receptor phenomenon. On the other hand, profound analgesia and apnea can easily be achieved without producing anesthesia in adult humans as well. Stanley *et al.*[18,19] showed that anesthetic doses of pure agonist narcotics completely terminate involuntary breathing. These patients, however, were responsive to verbal command, and were able to initiate normal tidal volumes when requested to do so. Thus, the profound respiratory depression seen without concomitant loss of consciousness in the newborn lamb and its reversibility with naloxone is consistent with previous studies in adult humans.

Cardiac output did not change, despite very high plasma levels of fentanyl. This hemodynamic stability is similar to the effects of fentanyl in humans (adults and newborn) and other animal models.[2-5] Fentanyl had no significant effect on blood flow to the stomach, small intestine, and large intestine, despite high doses and blood levels. This is of particular importance in newborns, since the newborn is particularly vulnerable to decreased blood flow to the gastrointestinal tract.[20] The decrease in blood flow to the kidney is consistent with the work of others using various anesthetic techniques.[21] The decrease in kidney blood flow was reversed with naloxone. The decrease in renal blood flow occurred despite the maintenance of normal mean aortic pressure and cardiac output.

At the 3 mg/kg dose of fentanyl, there were significant decreases in blood flow in the spinal cord, cerebellum, medulla, diencephalon, and white matter. However, blood flow to the cerebrum, CMR_{O_2}, cerebral oxygen delivery, and cerebral fractional oxygen extraction did not change from control in those lambs who remained conscious and responsive to painful stimuli and in whom ventilation was controlled. But, in the two lambs who became unresponsive to painful stimuli, CBF, CMR_{O_2}, and cerebral oxygen delivery decreased 38 ± 1%, 36 ± 1%, and 40 ± 1%, respectively. In both subgroups of lambs, cerebral fractional extraction of oxygen was unchanged. The effects of fentanyl on brain blood flow and oxygen utilization may thereby be related to the effects of the drug on consciousness and response to tail and foot clamping. In this way, it may act like other anesthetic agents, such as the barbiturates, which decrease both CBF and CMR_{O_2} only when consciousness is lost.[22,23] This is further supported by the fact that, following naloxone administration, all lambs became fully responsive, and blood flow and O_2 delivery were restored to control in brain regions where it had been reduced.

Other investigators[14] have found decreased CBF and CMR_{O_2} following fentanyl administration in the presence of other anesthetics. However, it is this additive effect of different agents that may have decreased CMR_{O_2} and CBF. This view is supported by the work of McPherson and Traystman,[11] who used an acute dog model, but one that utilized pentobarbital either alone (30 mg/kg) or combined with fentanyl (fentanyl 0.1 mg/kg and pentobarbital 3–5 mg/kg). Following fentanyl administration (0.025 mg/kg), there was no change in CBF, because there was no further deepening of the anesthetic state. On the other hand, our results are different from those of Carlsson *et al.*,[24] who, using a rat model, found that CBF and CMR_{O_2} decreased by 50 and 35%, respectively, following fentanyl administration when compared to nitrous oxide-oxygen ventilated controls. The use of nitrous oxide-oxygen ventilated rats as controls resulted in control CBF of 180 ml/min/100 gm, which is considerably higher than the CBF reported for this animal by others (110–120 ml/min/100 gm).[25,26] This level of blood flow (180 ml/min/100 gm) in the nitrous oxide-oxygen ventilated controls is the blood flow seen in unanesthetized rats subjected to immobilization stress.[27] Indeed, the reduced flow reported by Carlsson *et al.*[24] for fentanyl is the accepted control CBF in their previous investigations. Thus, fentanyl may have had no effect, or it may have caused a reduction in flow by preventing immobilization stress in the rat.

In summary, we conclude that fentanyl, when used as a single anesthetic agent in newborn lambs in cumulative doses as high as 4.4 mg/kg, does not reliably produce anesthesia despite its profound respiratory depression. At the highest dose utilized, it does not change CBF, cerebral O_2 delivery, or consumption unless responsiveness is lost.

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Nevertheless, oxygen delivery and consumption of the brain remain essentially coupled. Finally, the hemodynamic stability seen with fentanyl does not occur at the expense of reduced blood flow to the gastrointestinal tract or brain, organs that are particularly vulnerable in the neonate.

The authors would like to thank Sue Eller for her excellent technical assistance. The authors are grateful to Nancy Martin for her exceptional patience in preparing this document.

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