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Interaction of Fentanyl and Pentobarbital on Peripheral and Cerebral Hemodynamics in Newborn Lambs

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The effects of 3.0 mg·kg^{-1} fentanyl on cerebral and peripheral hemodynamics, alone and when combined with subanesthetic doses of pentobarbital (4.0 mg·kg^{-1}), were studied in 11 unanesthetized, newborn lambs, in whom catheters had been previously inserted. After a control period, drugs were administered at 20-min intervals by intravenous bolus injection. Group 1 animals (n = 5) received fentanyl, pentobarbital, and naloxone (0.01 mg·kg^{-1}), whereas Group 2 animals (n = 6) had the order of fentanyl and pentobarbital reversed. All animals responded to pain (withdrawal to tail clamping) and appeared conscious (eyes open, alert to sound) when either fentanyl or barbiturate was given alone. The combination of drugs, however, produced complete unresponsiveness. All of these effects were reversed by naloxone. Cardiac output did not change after either fentanyl or pentobarbital was administered individually but decreased significantly (29% in Group 1, 21% in Group 2) after administration of the combination of both. Mean arterial pressure and heart rate were unchanged. Cerebral blood flow, oxygen (O_2) transport, and O_2 consumption did not change after either administration of fentanyl or pentobarbital alone but decreased significantly after both (22%, 30%, 19%, respectively, in Group 1 and 35%, 40%, 38%, respectively, in Group 2). The decrease in cerebral O_2 transport nearly paralleled the decrease in cerebral O_2 consumption such that the ratio, the fractional O_2 extraction, increased slightly. Fentanyl decreased kidney blood flow alone (24%) and in combination with pentobarbital (25%), although pentobarbital did so only when combined with fentanyl. Neither drug affected blood flow to the stomach or to the small or large intestines when given alone but did decrease flow significantly when combined (27%, 27%, 34%, respectively, in Group 1; and 36%, 32%, 21%, respectively, in Group 2). Thus, blood flow to major organs may not be sustained at normal levels when fentanyl is combined with subanesthetic doses of pentobarbital. (Key words: Anesthesia: pediatric. Anesthetics, intravenous: fentanyl; pentobarbital. Brain: blood flow; carbon dioxide tension; metabolism. Heart: blood flow, myocardial.)

STUDIES IN ADULTS of various species (dog,[1–3] rat,[4] human[5,6]) have shown that fentanyl and related synthetic opiates may act as complete, single-agent, intravenous anesthetics (*i.e.*, they provide unconsciousness and analgesia) and preserve circulatory stability. We recently reported our inability to produce anesthesia (movement to noxious stimulation) in chronically catheterized, newborn lambs when fentanyl was given alone in cumulative doses as high as 4.4 mg·kg^{-1}.[7] Our inability to produce anesthesia and reliable analgesia in newborn lambs appears to contradict the findings of other investigations.[1–5] However, some of these investigations used acute surgical preparations in which the animal is prepared for experimentation with barbiturate or inhalational anesthesia.[1–3] Residual brain tissue levels of these other anesthetics, although not sufficient to produce anesthesia by themselves, may significantly potentiate the effect of subsequently administered fentanyl on consciousness and withdrawal to painful stimuli. Alternatively, the barbiturates may antagonize the antinociceptive effects of the opiates and thereby increase opiate requirements.[8,9]

In addition to the experimental controversies cited above, the question of how fentanyl interacts with other anesthetics, such as pentobarbital, is important in clinical anesthesia. Fentanyl is increasingly being used as the sole or major component of newborn anesthesia[10] and is often combined with a barbiturate. Thus, it is imperative to ascertain if the peripheral and cerebral hemodynamic stability reported with fentanyl is preserved when it is administered in combination with a barbiturate.

The purpose of this study was to determine the physiologic consequences of combining pentobarbital with fentanyl in newborn animals. Specifically, we examined whether fentanyl alone or in combination with a subanesthetic dose of pentobarbital could do the following: 1) produce anesthesia, as determined by movement in response to tail clamping and/or response to sound; 2) affect circulatory stability and the regional distribution of cardiac output; and 3) affect cerebral blood flow, cerebral oxygen consumption (CMR_{O_2}) and the coupling of cerebral blood flow to CMR_{O_2}.

Methods and Materials

SUBJECTS AND PREPARATION

Eleven healthy lambs, 2–4 days old, weighing 4.8 kg (range, 2.8–6.6 kg), were chronically catheterized for blood flow determinations by the radiolabeled microsphere technique during halothane–nitrous oxide anesthesia as described previously.[7] Axillary arteries, femoral arteries, and femoral veins were cannulated. A catheter was also inserted into the sagittal sinus. In six of the an-

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imals, a thermistor catheter was inserted into the pulmonary artery *via* a femoral vein for thermodilution determinations of cardiac output. The catheters were filled with heparin, tunneled subcutaneously, and exteriorized in an external pouch. After surgery and anesthesia the lambs received intramuscular antibiotics (300,000 U of procaine penicillin), recovered, and were returned to their ewes. All catheter positions were verified at autopsy.

Approval for this study was obtained by the Institution's Animal Care and Use Committee.

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. Thirty milliliters of blood was collected from the femoral venous catheter for future transfusion and replaced with 100 ml of Ringer's lactated solution. The lamb was unsedated, unstimulated, and left quiet and resting for 20 min. After baseline measurements were obtained (time 0), five animals (Group 1) received 3 $mg \cdot kg^{-1}$ fentanyl (time, 20 min), 4 $mg \cdot kg^{-1}$ pentobarbital (time, 40 min), and 0.1 $mg \cdot kg^{-1}$ naloxone (time, 60 min). Six animals (Group 2) received 4 $mg \cdot kg^{-1}$ pentobarbital (time, 20 min), 3 $mg \cdot kg^{-1}$ fentanyl (time, 40 min), and 0.1 $mg \cdot kg^{-1}$ naloxone (time, 60 min). All drugs were administered through a femoral venous catheter. Approximately 3 min after each drug administration, cardiac output was measured. Five minutes after each drug administration, blood samples for blood gas, *p*H, oxygen (O_2) content, and hematocrit were obtained from the subclavian artery and sagittal sinus catheters. Seven minutes after each drug administration, radiolabeled microspheres were injected into the left ventricular catheter. Blood losses resulting from sampling were replaced with stored blood after each microsphere reference sample was collected. Ten minutes after each drug, anesthesia was assessed by noting the animal's level of consciousness in response to foot and/or tail clamping with a 10-inch hemostat clamped to the first ratchet for 30 seconds. Consciousness was inferred if the lamb's eyes were open, if the lamb vocalized ("baaed"), and if it was alert to sound (hand clap, shout). Responses to foot and tail clamping included purposeful withdrawal of the stimulated foot (or nonwithdrawal); gross purposeful muscular movement, usually of the head (jerking or twisting); and increased (or no change) systolic arterial blood pressure. All animals breathed spontaneously. When apnea or respiratory depression occurred, that is, an increase in arterial CO_2 tension (Pa_{CO_2}) of 20% or greater above baseline or a decrease in arterial O_2 content of 20% or greater from baseline, the animal's trachea was orally intubated and the lungs 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 radiolabeled microspheres (16 ± 0.5 μm diameter) (DuPont, New England Nuclear Products) with the use of the reference sample technique.[10] Approximately 1–1.5 × 10^6 microspheres of each isotope was injected into the left ventricle over a 30-s period, followed by a 10-ml saline flush over 15 s. Four of the following six isotopes were injected per animal: ^{153}Gd, ^{51}Cr, ^{113}Sn, ^{103}Ru, ^{95}Nb, and ^{46}Sc. 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.[7]

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 heart, kidney, stomach, small intestine, and large intestine were obtained to average spatial inhomogeneities and to ensure that calculations were based on the presence of at least 1,000 microspheres for each organ. 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 with the use of differential spectroscopy by the simultaneous equation method.[11] Tissue blood flow ($\dot{Q}_t$) was calculated as the product of this corrected tissue count (C_t) and the arterial reference withdrawal rate (Q_r) divided by the counts in the reference sample (C_r) and by the weight of the tissue (W); that is, $\dot{Q}_t = (C_t \cdot Q_r)/(C_r \cdot W)$. Blood flow to cephalic tissues was calculated using the subclavian arterial reference sample. Blood flow to the abdominal and lower body tissues were calculated using the abdominal aortic reference sample.

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 with the use of 3 ml of iced saline injected into the central venous pressure port of a 5-Fr thermodilution catheter (Edwards Laboratories). This procedure did not change body temperature or hemodynamics. The thermodilution technique for cardiac output measurement compares favorably with other

TABLE 1. Blood Gas, *p*H, Hematocrit, and Arterial and Cerebral Venous O_2 Content Values Following Fentanyl (3.0 mg/kg), Pentobarbital (4.0 mg/kg), and Naloxone (0.1 mg/kg) Administration

	Control	Fentanyl	Fentanyl and Pentobarbital	Naloxone
Group 1 (n = 5)				
Time (min)	0	20	40	60
Pa_{CO_2} (mmHg)	33 ± 1	31 ± 2	34 ± 3	34 ± 1
Pa_{O_2} (mmHg)	73 ± 5	73 ± 7	75 ± 5	72 ± 6
*p*H	7.37 ± 0.03	7.33 ± 0.02	7.33 ± 0.02	7.35 ± 0.05
Hematocrit (%)	29 ± 3	28 ± 3	26 ± 2*	25 ± 2*
Ca_{O_2} (ml · 100 ml^{-1})	12.6 ± 2.0	12.0 ± 1.7	11.2 ± 1.5*	10.6 ± 2.0*
$C\bar{v}_{O_2}$ (ml · 100 ml^{-1})	7.2 ± 1.7	7.3 ± 1.6	5.5 ± 1.2*	6.3 ± 1.7*
Group 2 (n = 6)				
Time (min)	0	20	40	60
Pa_{CO_2} (mmHg)	34 ± 1	37 ± 5	33 ± 2	38 ± 5
Pa_{O_2} (mmHg)	79 ± 5	75 ± 6	70 ± 7	70 ± 4
*p*H	7.37 ± 0.01	7.35 ± 0.01	7.31 ± 0.02	7.28 ± 0.03*
Hematocrit (%)	27 ± 1	27 ± 1	26 ± 1	25 ± 1*
Ca_{O_2} (ml · 100 ml^{-1})	12.5 ± 0.5	11.8 ± 0.4	10.3 ± 0.4*	10.4 ± 0.4*
$C\bar{v}_{O_2}$ (ml · 100 ml^{-1})	6.3 ± 0.5	5.6 ± 0.4	4.4 ± 0.2*	5.1 ± 0.7*

Pa_{CO_2} = arterial CO_2 tension; Pa_{O_2} = arterial O_2 tension; Ca_{O_2} = arterial O_2 content; $C\bar{v}_{O_2}$ = sagittal sinus O_2 content. In all animals the tracheas were intubated and the lungs were mechanically ventilated after fentanyl administration. Each value represents the mean ± SE.
* $P < 0.05$ from control.

techniques in newborn lambs.[12] 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 arterial–sagittal sinus oxygen content difference. Cerebral fractional oxygen extraction was calculated as the arteriovenous oxygen content difference divided by arterial oxygen content. Cerebral oxygen transport was calculated as the product of arterial oxygen content and cerebral blood flow.

STATISTICAL ANALYSIS

The effect of fentanyl and pentobarbital administration, alone and in combination, as well as 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 plus or minus standard error.

Results

BEHAVIORAL EFFECTS

In the baseline condition, the lambs stood or laid down, rolled their heads, spontaneously vocalized, were alert to sound, spontaneously closed and opened their eyes, and moved when lightly touched. Additionally, they responded to painful stimuli (tail clamping) by brisk, purposeful withdrawal and with increased blood pressure. When pentobarbital (4.0 mg · kg^{-1}) was administered alone (Group 2), behavioral responses were unchanged from baseline conditions in all six animals. On the other hand, when 3.0 mg · kg^{-1} fentanyl was given alone (Group 1), all five lambs appeared "catatonic," that is, their eyes were open, they lay on their sides with extension of their limbs, and they no longer vocalized spontaneously. Nevertheless, these lambs with fentanyl alone still were alert to sound and purposefully responded to painful stimuli. The combination of fentanyl and barbiturate produced complete unresponsiveness to both painful stimuli and sound in all 11 lambs. These effects were completely reversed by naloxone. After naloxone administration, all lambs immediately stood up, vocalized, and became fully responsive to tail clamping.

RESPIRATORY EFFECTS

Table 1 shows arterial blood gases, *p*H, hematocrit, and arterial and cerebral venous oxygen content data from both groups. There was no significant effect on respiration when pentobarbital was given alone. The effects produced by fentanyl on respiration, on the other hand, were pronounced, whether it was given alone or after pentobarbital administration. Indeed, all animals became apneic and required immediate tracheal intubation and ventilation after fentanyl administration. Thus, the blood gases obtained after fentanyl administration (table 1) represent the effects of mechanical ventilation.

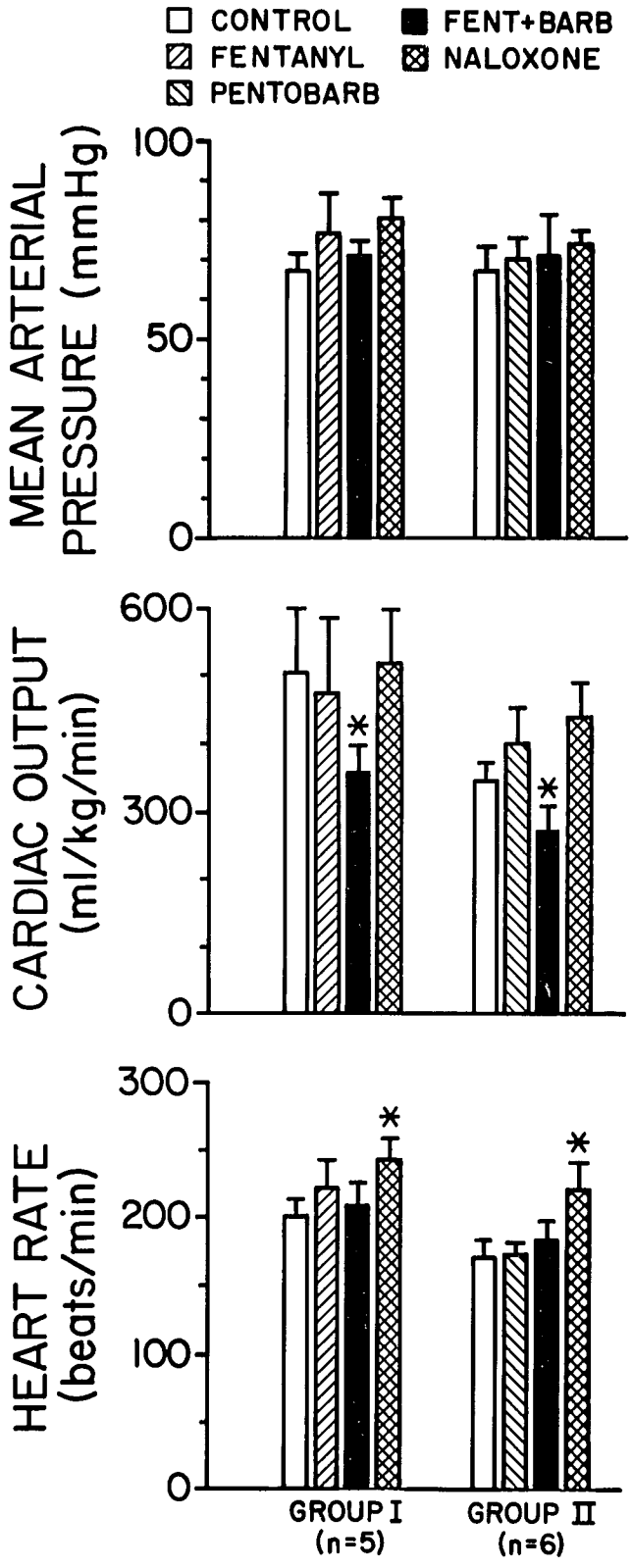

FIG. 1. Mean arterial pressure, cardiac output, and heart rate responses at control (open bar) and 3 min after administration of 3.0 mg·kg^{-1} fentanyl (left diagonal bar), 4.0 mg·kg^{-1} pentobarbital (right diagonal bar), the combination of 3.0 mg·kg^{-1} fentanyl and 4.0 mg·kg^{-1} pentobarbital (solid bar), and 0.1 mg·kg^{-1} naloxone (cross-hatched bar) are depicted. Group 1 (n = 5) received fentanyl first. Group 2 (n = 6) received pentobarbital first. Bars represent the standard error. An asterisk represents $P < 0.05$ from control.

The lambs did not resist or struggle during tracheal intubation or ventilation after administration of the combination of both drugs (Group 2). However, after the administration of fentanyl alone (Group 1), the lambs responded to tracheal intubation with head withdrawal and, because laryngeal function remained intact, with glottic closure and coughing. After intubation, the animals were calm, although they chewed on their endotracheal tubes during mechanical ventilation.

Naloxone completely reversed the respiratory depression produced by fentanyl. After naloxone administration, all lambs had their tracheas extubated and they breathed spontaneously.

Cardiovascular Effects

The cardiovascular effects measured 3 min after each drug dose are shown in figure 1. Cardiac output did not change after administration of either fentanyl or barbiturate individually but decreased (29% in Group 1 and 21% in Group 2) after administration of the combination of both agents. Mean arterial pressure and heart rate did not change after administration of either drug, alone or in combination. Naloxone administration restored cardiac output and produced a modest tachycardia.

The effects of 4.0 mg·kg^{-1} pentobarbital and 3.0 mg·kg^{-1} fentanyl, alone and when combined, on regional blood flow are shown in figure 2. Neither drug affected blood flow to the stomach, small intestine, or large intestine when given alone but decreased flow when combined (27%, 27%, 34%, respectively, in Group 1; and 36%, 32%, 21%, respectively, in Group 2) (fig. 1). On the other hand, renal blood flow decreased when fentanyl was given alone (24%) and when combined with barbiturate (25%). Pentobarbital reduced kidney blood flow only when combined with fentanyl. Right and left ventricular blood flow increased (103% and 116%, respectively) when fentanyl was given alone but then returned to near baseline levels when fentanyl was combined with pentobarbital (fig. 2). After naloxone administration, right and left ventricular blood flow was increased above baseline (123% and 110%, respectively, in Group 1; and 89% and 54%, respectively, in Group 2).

Cerebral Effects

Cerebral blood flow, cerebral O_2 transport, and CMR_{O_2} did not change after either fentanyl or barbiturate

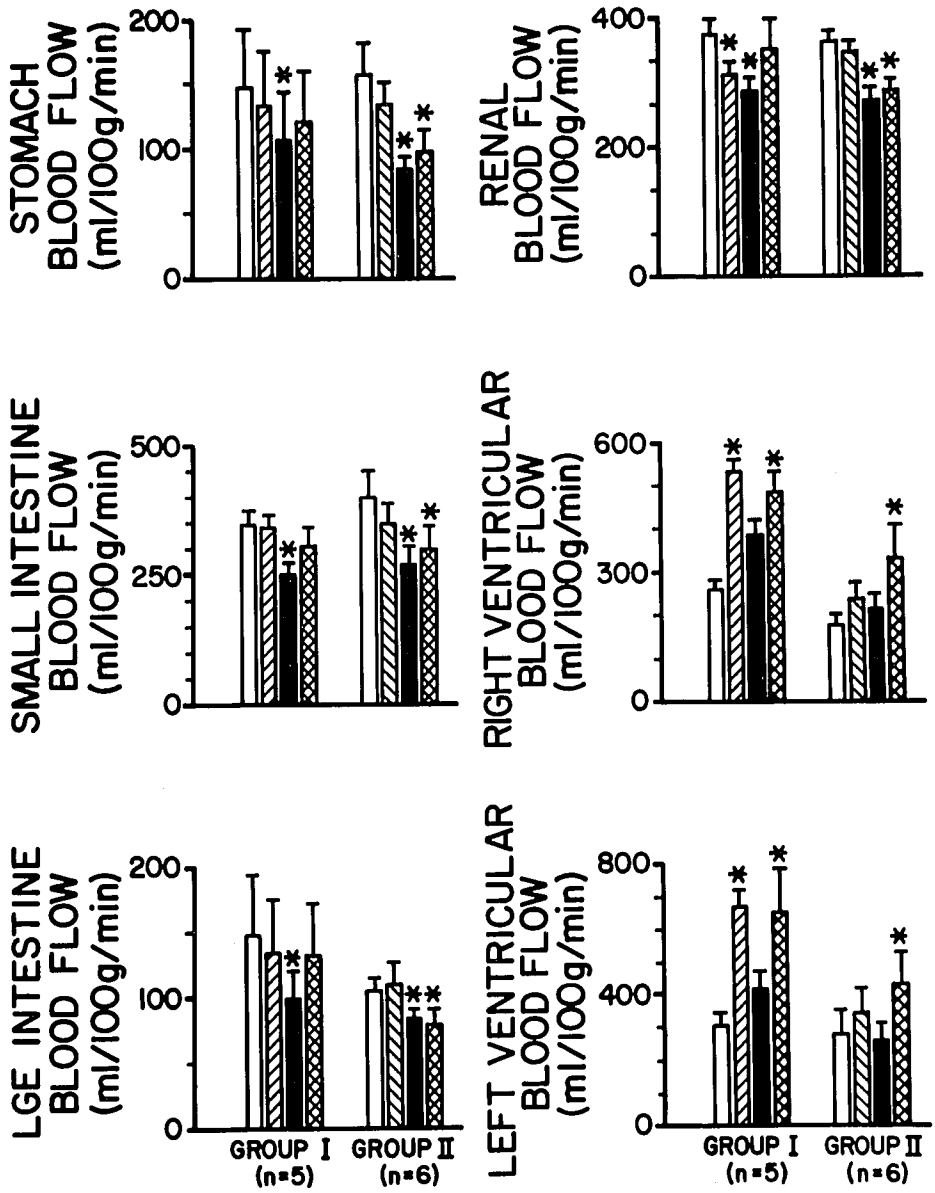

FIG. 2. Organ blood flow ($ml \cdot 100\ g^{-1} \cdot min^{-1}$) at control (open bar) and 7 min after administration of 3.0 $mg \cdot kg^{-1}$ fentanyl (left diagonal bar), 4.0 $mg \cdot kg^{-1}$ pentobarbital (right diagonal bar), the combination of 3.0 $mg \cdot kg^{-1}$ fentanyl and 4.0 $mg \cdot kg^{-1}$ pentobarbital (solid bar), and 0.1 $mg \cdot kg^{-1}$ naloxone (cross-hatched bar) are depicted. Group 1 (n = 5) received fentanyl first. Group 2 (n = 6) received pentobarbital first. Bars represent the standard error. An asterisk represents $P < 0.05$ from control.

administration when either drug was given alone. However, the combination of drugs decreased cerebral blood flow, cerebral O_2 transport, and CMR_{O_2} (22%, 30%, 19%, respectively, in Group 1; and 35%, 40%, 38%, respectively, in Group 2) (fig. 3). The decrease in cerebral O_2 transport nearly paralleled the decrease in CMR_{O_2} such that the ratio, the fractional O_2 extraction, increased slightly. After naloxone administration, cerebral blood flow and cerebral O_2 transport increased when compared with the combination of fentanyl and pentobarbital (fig. 3).

Analysis of blood flow to specific brain regions, expressed as percent change from control, is shown in figure 4. Blood flow to specific brain regions was not different from control after either fentanyl or pentobarbital administration alone. Regional brain blood flow decreased after the combination of the two drugs. After naloxone administration, all brain regions had higher blood flows compared with the flows after the combination of fentanyl and barbiturate as well as with those of control. The increased cerebral blood flow above baseline values may have resulted, in part, from the decrease in arterial hematocrit and oxygen content that occurred at the end of the experiment (table 1).

Discussion

The major finding of this study is that subanesthetic doses of pentobarbital and fentanyl, when administered

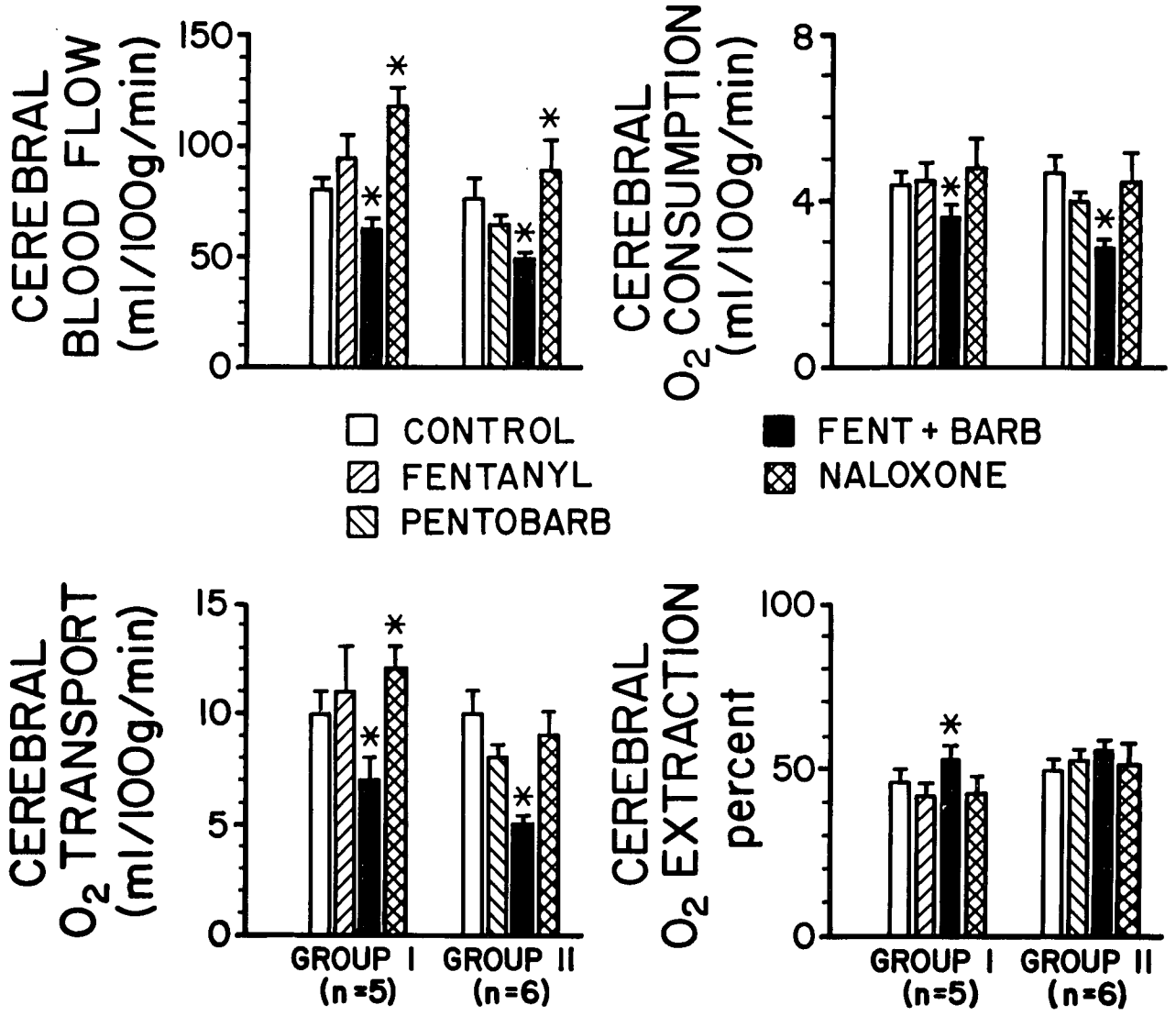

FIG. 3. Hemispheric cerebral blood flow, cerebral oxygen consumption, cerebral oxygen transport, and cerebral oxygen extraction at control (open bar) and after administration of 3.0 mg · kg^{-1} fentanyl (left diagonal bar), 4.0 mg · kg^{-1} pentobarbital (right diagonal bar), the combination of 3.0 mg · kg^{-1} fentanyl and 4.0 mg · kg^{-1} pentobarbital (solid bar), and 0.1 mg · kg^{-1} naloxone (cross-hatched bar) are depicted. Group 1 (n = 5) received fentanyl first. Group 2 (n = 6) received pentobarbital first. Bars represent the standard error. An asterisk represents $P < 0.05$ from control.

in combination, produce unconsciousness and analgesia in newborn lambs. The resulting anesthesia is associated with concomitant reductions of CMR_{O_2}, cerebral blood flow, cardiac output, and splanchnic and renal blood flows.

Our observation that a high dose of fentanyl (3.0 mg · kg^{-1}), when given alone, does not consistently produce unconsciousness, analgesia, or decreased CMR_{O_2}, despite producing profound effects on the control of ventilation, confirms our previous findings in newborn lambs.[7] The inability of fentanyl, when administered alone, to produce anesthesia in lambs may be related to species or to the age and maturational level of the animal. However, other reports have not shown consistent findings, even within the same species. For example, Arndt and colleagues,[13] found that fentanyl administration (0.167 mg · kg^{-1}) in trained dogs reliably blocked all somatic and cardiovascular responses to tail clamping, whereas Bailey *et al.*,[14] using untrained dogs, could neither duplicate the results of Arndt *et al.*[13] nor reliably produce anesthesia with fentanyl until doses as high as 3.0 mg · kg^{-1} were used. Shingu *et al.*[4] achieved anesthesia with lower doses of fentanyl (0.05 mg · kg^{-1}) in nonpretreated rats.

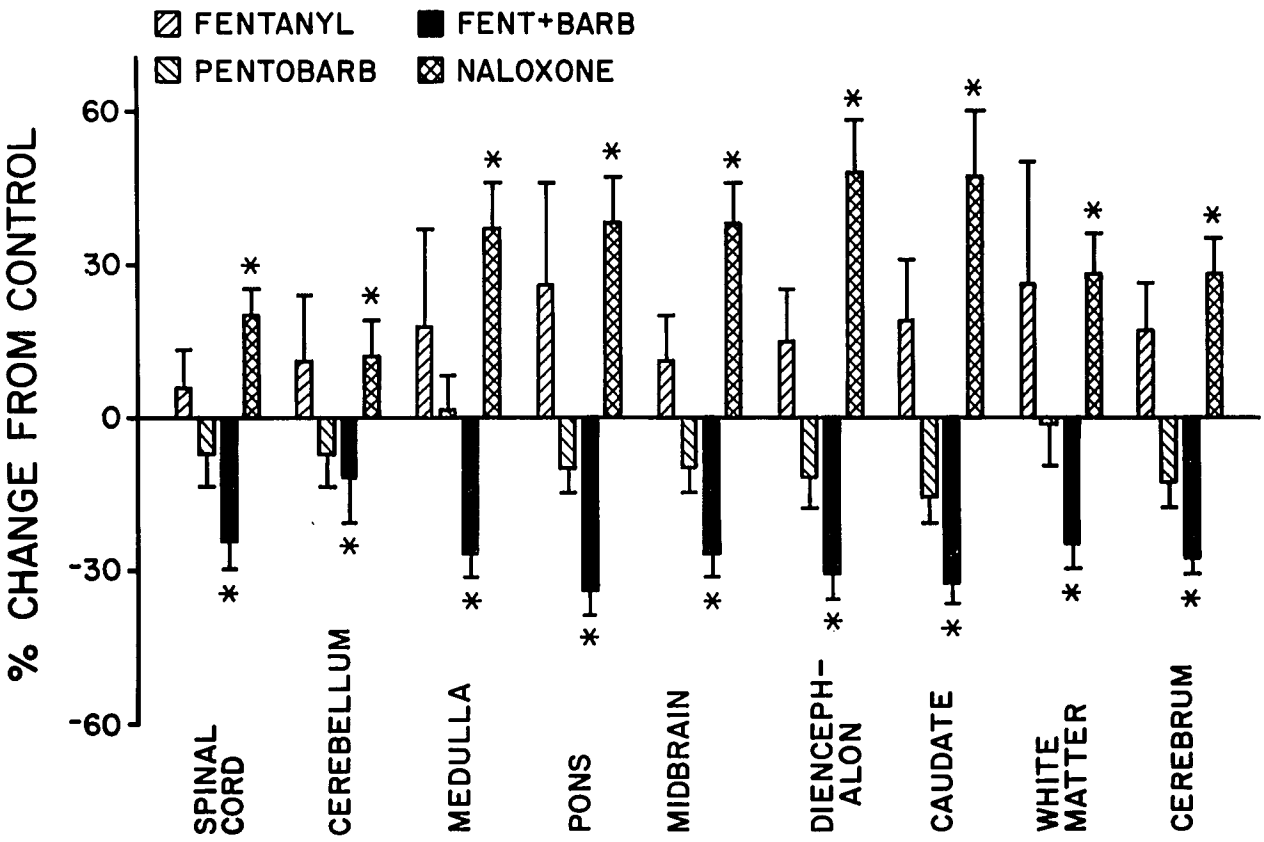

FIG. 4. Regional cerebral blood flow 7 min after administration of 3.0 mg·kg^{-1} fentanyl (left diagonal bar), 4.0 mg·kg^{-1} pentobarbital (right diagonal bar), the combination of 3.0 mg·kg^{-1} fentanyl and 4.0 mg·kg^{-1} pentobarbital (solid bar), and 0.1 mg·kg^{-1} naloxone (cross-hatched bar) are shown. Values are percent change (mean ± SE) from the control values. An asterisk represents $P < 0.05$ from 0%. After administration of the combination of fentanyl and pentobarbital, all brain regions had lower flows when compared with control.

These rats did not respond to tail clamping but appeared conscious. The ability of opiates to reliably produce sleep and amnesia when used alone in adult humans has been questioned as well.[15] Therefore, our inability to produce anesthesia with 3.0 mg·kg^{-1} fentanyl in the newborn lamb may not necessarily be unique to this species or age group.

Another factor that might explain some of the differences reported in the literature on the efficacy of fentanyl is the technique for assessing analgesia and anesthesia. Many investigators use response to tail clamping,[4,9,13,14,16,17] but differences in applying and interpreting tail clamp stimulation can influence results.[14] We used a 10-inch hemostat clamped to the first ratchet for 30 s at the base of the tail (to ensure the crushing of bone) and moved it and the tail continuously. Other studies used "sponge sticks,"[17] different durations of "clamp" time (10 s *vs.* 30 s),[13] and clamp ratchet position (full ratchet or partial ratchet closure),[14] all of which may affect the quality of the supramaximal stimulation. A submaximal stimulus may produce misleading results and conclusions about the ability of fentanyl to produce anesthesia. In addition, we used behavioral observations, such as response to loud noise and eye position, to assess the animal's level of consciousness. Indeed, Kissin and Brown used both the righting reflex as well as the purposeful movement response to tail clamp to demonstrate that the analgesic properties of opiates may not adequately reflect their anesthetic potencies.[18]

We found no changes in global or regional brain blood flow, CMR_{O_2}, cerebral O_2 transport, and cerebral O_2 extraction when subanesthetic doses of either fentanyl or pentobarbital were given alone. However, the combination of drugs produced a loss of consciousness and significant decreases in blood flow to the spinal cord, cerebellum, midbrain, diencephalon, white matter, and cerebrum. Cerebral blood flow, CMR_{O_2}, and cerebral O_2 transport decreased proportionately, such that O_2 transport and consumption of the brain remained coupled. Similarly, pentobarbital will produce a coupled reduction

in cerebral blood flow and O_2 consumption when it is administered alone in doses that produce a loss of consciousness.[19] When anesthetic doses of pentobarbital are given to dogs (30 $mg \cdot kg^{-1}$), further administration of fentanyl produces no deepening of the anesthetic state and no further reductions in cerebral blood flow and O_2 consumption.[20-22] Thus, the cerebral hemodynamic effects of both drugs are determined by their effects on consciousness. This is further supported by the fact that, in this study, after naloxone administration, all lambs regained consciousness and cerebral blood flow and O_2 consumption increased to preanesthesia levels.

The lambs receiving pentobarbital first (Group 2) had a greater reduction in cerebral blood flow and O_2 consumption than the lambs who received fentanyl first (Group 1). We may have missed the peak central nervous system effects of pentobarbital in the lambs who received fentanyl first (Group 1) because all of our measurements were obtained within 10 min of drug administration. Thus, the peak effects of pentobarbital may not have occurred in these lambs because of its slow anesthetic onset time. Furthermore, the maximum effects of fentanyl also may have dissipated in these Group 1 lambs at the time of measurement because of decreasing blood and tissue levels of fentanyl after bolus injection.

Heart rate, blood pressure, and cardiac output did not change after either fentanyl or pentobarbital administration when either drug was given alone. This hemodynamic stability is similar to the effects of fentanyl in humans (adults and newborn) and other animals.[2-7,10] Interestingly, the combination of drugs produced significant depression in cardiac output and is similar to the decrease seen when fentanyl is combined with nitrous oxide or diazepam in adult humans.[3,5]

Fentanyl had no significant effect on blood flow to the stomach, small intestine, and large intestine when given alone. These results are similar to our previous results[7] but differ from those of Twerskoy *et al.*,[23] who, with the use of isolated, perfused dog intestine, found that splanchnic blood flow increased after fentanyl administration. Alternatively, it is possible that the stress of intubation or positive pressure ventilation could have influenced cardiac output and its distribution. Although we cannot discount this possibility, we found in our previous study that doses of fentanyl that did not result in intubation and mechanical ventilation (0.1 $mg \cdot kg^{-1}$) did not alter cardiac output and gastrointestinal blood flow.[7]

The combination of fentanyl and pentobarbital, on the other hand, significantly decreased blood flow to the stomach and the intestines. Thus, blood flow to major abdominal organs may not be sustained at normal levels despite unchanged heart rate and arterial blood pressure when fentanyl is combined with even subanesthetic doses of pentobarbital. This is of special importance in newborns, because the newborn is particularly vulnerable to decreased blood flow to the gastrointestinal tract.[24] Fentanyl decreased kidney blood flow when given alone and in combination with pentobarbital and is consistent with the work of others using various anesthetic techniques.[7,25] The decrease in renal blood flow occurred despite the maintenance of normal mean aortic pressure and cardiac output.

In summary, we conclude that fentanyl, when used as a single agent in newborn lambs in doses as high as 3.0 $mg \cdot kg^{-1}$, does not produce anesthesia despite its profound effects on the control of ventilation. However, when combined with subanesthetic doses of pentobarbital, it produces loss of consciousness and responsiveness to painful stimuli and significant reductions in cerebral blood flow and O_2 consumption, cardiac output, and splanchnic and renal blood flow. Thus, blood flow to major organs may not be sustained at normal levels despite unchanged heart rate and blood pressure when fentanyl is combined with subanesthetic doses of pentobarbital.

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