Title: INTERACTION OF FENTANYL AND PENTOBARBITAL ON CEREBRAL AND PERIPHERAL HEMODYNAMICS IN NEWBORN LAMBS

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Introduction: The newborn who requires surgery poses special anesthetic challenges. Most inhalational anesthetics cause unacceptable side effects in human neonates. Fentanyl anesthesia on the other hand, is safe and effective as determined by heart rate and blood pressure.[1] The safety of fentanyl may be adversely affected when it is used with other anesthetic drugs such as the barbiturates. The purpose of this study was to investigate the effects of fentanyl alone and when combined with small doses of pentobarbital on cerebral and peripheral hemodynamics in a newborn animal model.

Methods: Eleven healthy, newborn lambs 2-4 days old, averaging 4.8 kg (range 2.8-6.6 kg) were chronically catheterized (under halothane-N_2O anesthesia) for: 1) blood flow determination (radiolabelled microsphere technique), 2) cerebral venous sampling (sagittal sinus), and 3) thermodilution determination of cardiac output (CO) (pulmonary artery) (N=7). 24 hours later, the lambs were placed in an environmental chamber that minimized external stimuli (control) (time 0). Group I (n=5) received 3.0 mg/kg fentanyl (time 20 min), 4.0 mg/kg pentobarbital (time 40 min), and 0.1 mg/kg naloxone (time 60 min). Group II (n=6) received 4.0 mg/kg pentobarbital (time 20 min), 3.0 mg/kg fentanyl (time 40 min) and 0.1 mg/kg naloxone (time 60 min). Apnea or increases in $PaCO_2$ of 20% above baseline values were treated with intubation and mechanical ventilation to restore $PaCO_2$ to control levels. Cerebral oxygen extraction was calculated as the difference between arterial oxygen content (CaO_2) and sagittal sinus oxygen content (CvO_2) divided by CaO_2. Cerebral oxygen consumption ($CMRO_2$) was calculated as the product of cerebral blood flow (CBF) and the difference between CaO_2 and CvO_2. Cerebral oxygen delivery was calculated as the product of CaO_2 and CBF. Data were analyzed using one-way analysis of variance with repeated measures. Multiple comparisons were made by the Duncan Multiple Range Test. $P < 0.05$ was considered significant (*). All data are represented as mean ± SE. Organ blood flow and cerebral O_2 delivery and consumption are represented in ml/100g/min and CO as ml/kg/min.

Results: All animals responded to pain (withdrawal to tail clamping) and appeared conscious (eyes open, alert to sound) when either fentanyl or barbiturate were given alone. The combination of drugs, however, produced complete unresponsiveness. The respiratory effects of fentanyl were pronounced; all animals required immediate intubation and ventilation. All of these effects were reversed by naloxone. CO did not change following either fentanyl or barbiturate individually but fell significantly (29% in Group I 21% Group II) following the combination of both (table). Mean arterial pressure and heart rate did not change following either drug, alone or in combination. CBF, cerebral O_2 delivery and $CMRO_2$ did not change following either fentanyl or barbiturate alone but decreased significantly following both (22%, 30%, 19% respectively in Group I and 35%, 40%, 38% respectively in Group II) (table). The difference in cerebral O_2 delivery nearly paralleled the decrease in $CMRO_2$ such that the ratio, the fractional O_2 extraction, increased slightly. Fentanyl decreased kidney blood flow alone (24%) and in combination with barbiturate (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 I and 36%, 32%, 21% respectively Group II) (table).

Discussion: We conclude that fentanyl when used as a single agent in newborn lambs in doses as high as 3.0 mg/kg does not produce anesthesia despite its profound respiratory depression. However, when combined with very small doses of barbiturate it produces anesthesia and significant reductions in CO, CBF, cerebral O_2 delivery, $CMRO_2$ and splanchnic 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 even small doses of other anesthetic drugs.

Ref: 1. Yaster M. Anesthesiology 66:433-35, 1987

	GROUP I			
	CONTROL	FENTANYL	PENTOBARB	NALOXONE
TIME	0	20	40	60
CO	504±92	475±109	359±49*	519±78
CBF	81±5	95±11	63±5	119±8*
$CMRO_2$	4.43±0.3	4.5±0.4	3.6±0.3*	4.8±0.7
Cer O_2 DEL	10±1	11±2	7±1*	12±1*
EXT	46±4	42±4	53±4*	43±5
KIDNEY	371±22	320±17	283±21*	348±47
STOMACH	148±45	134±42	108±36*	121±40
SM INTEST	345±28	342±22	252±22*	305±37
LG INTEST	147±46	133±41	97±22*	131±40

	GROUP II			
	CONTROL	FENTANYL	PENTOBARB	NALOXONE
TIME	0	20	40	60
CO	349±26	404±52	275±49*	445±47
CBF	77±9	65±4	50±2*	89±14*
$CMRO_2$	4.7±0.4	4.0±0.2	2.9±0.2*	4.5±0.7
CerO_2 DEL	10±1	8±4	5±3*	9±1*
EXT	50±3	53±3	56±3	52±6
KIDNEY	361±15	344±15	269±19*	284±17*
STOMACH	158±24	125±15	85±9*	93±17*
SM INTEST	400±51	349±38	271±34*	300±45*
LG INTEST	103±11	108±17	81±8*	78±11