Anesthesiology
63:166–171, 1985

Cardiovascular and Pharmacodynamic Effects of High-dose Fentanyl in Newborn Piglets

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To understand better the hemodynamic effects of fentanyl anesthesia on the developing newborn, the authors studied the changes in cardiac output and its four determinants (preload, afterload, heart rate, and contractility) and plasma fentanyl kinetics in newborn piglets following the administration of high-dose fentanyl with or without atropine premedication. Twenty-five healthy farm piglets were divided into four groups. Hemodynamic studies were conducted on five who received 50 μg/kg intravenous fentanyl, five controls who received only 0.01–0.03 mg/kg intravenous atropine, and nine who received both agents. Fentanyl pharmacokinetics were determined by radioimmunoassay in six additional piglets.

Mean plasma fentanyl concentrations were 25.4, 12.7, and 7.9 ng/ml at 5, 15, and 30 min postbolus, respectively, with an elimination phase half-life of 35.8 min. In piglets given fentanyl alone, the maximum significant ($P < 0.05$) hemodynamic changes from baseline occurred at 5 min: mean aortic pressure (MAP) +42%, cardiac output −42%, heart rate −36%, left ventricular end-diastolic pressure +81%, and total peripheral resistance index +93%. The latter four hemodynamic variables were highly correlated with the logarithm of the plasma fentanyl concentration ($R^2 > 0.96$, $P \leq 0.05$). In control animals given atropine alone, only MAP changed significantly (+12–14%) during the study. Contractile indices (echocardiographic shortening fraction and left ventricular peak dP/dT) did not change significantly in any group. Piglets given fentanyl–atropine had no significant hemodynamic change during the study other than a 7–15% increase in MAP. (Key words: Anesthesia: pediatric. Anesthetics, intravenous: fentanyl. Heart: myocardial function.)

HIGH-DOSE fentanyl anesthesia has become popular for adults undergoing coronary artery bypass surgery in order to avoid major adverse hemodynamic effects caused by potent volatile inhalation agents. Moderate-to-high dose fentanyl anesthesia (25–50 μg/kg) is commonly used for infants undergoing thoracotomy for ligation of patent ductus arteriosus or open-heart surgery.[1,2] When fentanyl is given with pancuronium, heart rate (HR) and blood pressure changes are usually minimal. For example, premature infants with congestive heart failure due to patent ductus arteriosus given fentanyl (30–50 μg/kg) and pancuronium had only a 5% decrease in systolic blood pressure and HR.[1] Using slightly higher doses of fentanyl (50–75 μg/kg) with pancuronium, Hickey and Hansen documented a 9% decrease in mean arterial pressure and HR in infants undergoing open-heart surgery.[2] However, such clinical studies provide little insight into the effect of fentanyl on cardiac output or its determinants. We were interested in extending these clinical findings by evaluating changes in cardiac output and its four determinants (preload, afterload, heart rate, and contractility) in healthy newborn piglets during the first elimination half-life following the administration of 50 μg/kg intravenous fentanyl with or without atropine premedication.

Methods

Animal Preparation

Twenty-five farm piglets, ages 2–15 days, weighing 1.1–3.3 kg, were divided into four groups. Hemodynamic studies were conducted on five who received 50 μg/kg intravenous fentanyl citrate, five control piglets who received 0.01–0.03 mg/kg intravenous atropine sulfate, and nine who received both agents. Fentanyl pharmacokinetics were determined in six other animals. This study was approved by our institutional review board for animal studies.

All animals were restrained and given metocurine (0.3 mg/kg) by ear vein injection before intubation. Controlled ventilation was accomplished with the use of a proximal inspiratory pressure of about 20 cmH_2O, end-expiratory pressure 2 cmH_2O, a respiratory rate appropriate to maintain normocapnea,[3] and oxygen as the carrier gas. Core temperature, hematocrit, and blood glucose concentrations were maintained within the normal limits for species and age that we previously established (unpublished observations). All animals received maintenance fluids at 4 $ml \cdot kg^{-1} \cdot h^{-1}$ (including bolus thermodilution injections) during the study. Vascular catheters were inserted into the central circulation through the left internal carotid artery, left external jugular vein, and femoral artery with the use of 0.5% lidocaine (total dose <4 mg/kg).[4] The position of the

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Received from the Departments of Anesthesiology and Pediatrics, Children's Hospital of Pittsburgh and Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Accepted for publication March 19, 1985. Supported by BRS Grant S07 RR05507-20, awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health; American Heart Association (Lancaster, Pennsylvania, Chapter); and MH30915.

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catheters in the central circulation was established by waveform analysis and verified by postmortem examination.

Hemodynamic Measurements

Thermodilution cardiac output was measured in duplicate with the use of 1.5-ml aliquots of 0° C solution injected into the superior vena cava and sensed by a thermistor placed in the descending aorta (Model 9520E Cardiac Output Computer®, Edwards Laboratories, Inc., Santa Ana, California). Mean reproducibility between paired cardiac output measurements in newborn piglets previously studied in this laboratory was 4.1%. Cardiac output (CO) was reported as measured cardiac output divided by body weight. No intracardiac shunts were detected by analysis of the thermodilution curves. Phasic and electronically integrated mean aortic pressures (MAP) were measured continuously with the use of a fluid-filled system zeroed to midchest level (Model 1290A Quartz Physiologic Pressure Transducer®, Hewlett-Packard Co., Waltham, Massachusetts).

Left ventricular (LV) contractility was estimated by two methods. LV peak dP/dT, the maximum instantaneous rate of pressure rise during isovolumic contraction, was electronically derived from the LV pressure signal obtained with the use of micromanometer-tipped catheter (PC-450 Catheter®, Millar Instruments, Inc., Houston, Texas). M-mode echocardiography was used to assess LV shortening fraction (SF), the difference between the LV internal minor axis diameters at end-diastole ($LVID_d$) and end-systole ($LVID_s$), indexed to the end-diastolic dimension, to describe the fractional reduction of LV cavity size during systole: $(LVID_d - LVID_s)/LVID_d$. Echocardiographic studies were performed with the use of a 5.0-mHz, 6-cm nonfocused transducer and recorded at 75 mm/s from the left or right parasternal position (ContinuTrace and System II, Irex, Inc., Ramsey, New Jersey). A "T-scan" was performed to locate the true minor axis.[5] Measurements were made according to established standards, and the mean value of at least three cardiac cycles during expiration was recorded.[6]

Preload was estimated by measuring $LVID_d$ and LV end-diastolic pressure (LVEDP) at end-expiration with the use of the high-fidelity catheter while recording at high gain. The electronic zero baseline was calibrated to equal atmospheric pressure initially and reestablished before each reading. Our measurement of baseline pressure drift was less than 0.2 mmHg/h. Afterload was estimated from the total peripheral resistance index (TPRI), the quotient of MAP and CO. HR was counted from the continuous electrocardiogram. Stroke volume index (SVI) was CO/HR. Pressures were recorded simultaneously on a multichannel strip chart recorder at 25 or 50 mm/s (Model 7754A Medical Recorder®, Hewlett-Packard Co.).

Since fentanyl invariably caused bradycardia when given alone, we attempted to isolate the chronotropic from the inotropic and other influences on cardiac output. In pilot studies, atrial pacing did not reestablish the baseline heart rate because of the occasional occurrence of Type I (Wenckebach) second-degree AV block. We considered ventricular pacing unsatisfactory due to the potential reduction of cardiac output associated with the loss of atrial systole. We therefore chose to use atropine.

Hemodynamic Study Protocol and Data Analysis

After obtaining a resting hemodynamic profile (T_0), we intravenously administered either of the following: 1) 50 μg/kg fentanyl over 5 min; 2) 0.02 mg/kg atropine by bolus; or 3) 0.01 mg/kg atropine bolus followed by 50 μg/kg fentanyl over 5 min. In the last group, any animal whose heart rate decreased more than 10% below control value during the administration of fentanyl received an additional 0.01 mg/kg atropine bolus immediately; one piglet required two additional doses (0.03 mg/kg total dose). Fentanyl was delivered over 5 min, without a subsequent continuous infusion, in order to reproduce an administration technique commonly used by pediatric anesthesiologists. We recorded the hemodynamic profile of each animal 5, 15, and 30 min following the end of all drug administrations (T_5, T_{15}, and T_{30}, respectively).

Statistical analysis was performed by using repeated measures analysis of variance followed by Student-Newman-Keuls multiple range test ($\alpha = 0.05$) to determine the significance of any hemodynamic changes noted between any two time periods.[7]

Pharmacokinetic Study Protocol and Data Analysis

To estimate the pharmacokinetics of fentanyl, arterial plasma fentanyl concentrations were determined in quadruplicate in six piglets 1, 3, 5, 7.5, 10, 15, 30, 45, and 60 min after the administration of a rapid intravenous bolus of 50 μg/kg fentanyl alone. Hemodynamic and pharmacokinetic studies were not performed on the same animals because a reproducible, accurate radioimmunoassay was not available to us at the time the cardiovascular studies were done. We used a refined radioimmunoassay, which we and others developed.[8,9] This assay accurately detects 0.1 ng/ml fentanyl with an interassay coefficient of variation less than 6% for all concentrations measured. Fentanyl pharmacokinetic data

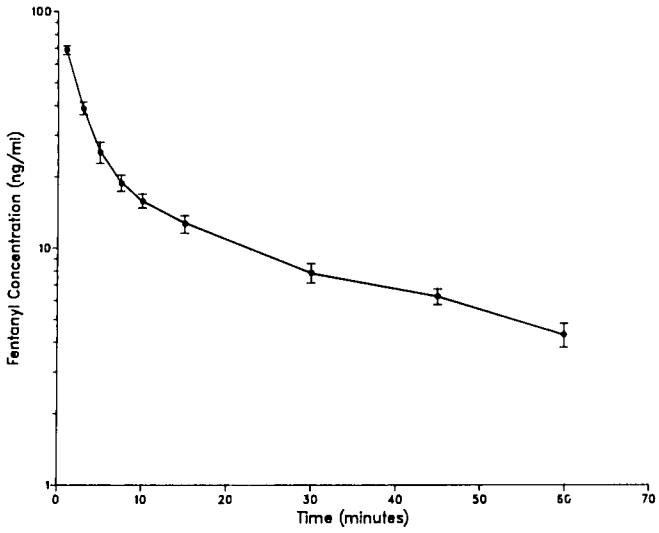

FIG. 1. Plasma fentanyl concentration decay curve. The data fit a biexponential, two-compartment model. N = 6; dose = 50 μg/kg; A = 84.1 ng/ml; B = 18.1 ng/ml; α = 0.49; β = 0.018; area under curve = 11.51 $mg \cdot ml^{-1} \cdot min^{-1}$, $T_{1/2}\alpha = 2.1 \pm 0.7$ (SEM) min; $T_{1/2}\beta = 35.8 \pm 8.2$ min, volume of distribution (steady-state) = 2,414 ml. Abbreviations explained in text.

were analyzed by the ESTRIP computer program to determine an initial estimate of the number of exponents the polyexponential equation required to describe the data best and to determine the goodness of fit.[10,11] These initial parameters were used to generate a new data set; both sets were then used to define the final exponential equation with the use of a nonlinear regression program.[12] The latter program also calculated α and β, the slopes of the distribution and elimination curves, respectively, and A and B, the maximum conceivable concentrations (at T_0) for the distribution and elimination phases, respectively. $T_{1/2}\alpha$ and $T_{1/2}\beta$, the half-lives of the distribution and elimination phases, respectively, the volume of distribution between compartments at the steady state (V_d), the area under the curve (AUC) representing the total amount of drug present, and the total body clearance rate (total dose/AUC) were calculated as described by Niazi.[13] Simple linear regression analysis was used to calculate the correlation coefficient (r) of the logarithm of plasma fentanyl concentration and the hemodynamic variables.

Results

Mean plasma fentanyl concentration decreased in a biexponential manner over time (fig. 1). The mean plasma fentanyl concentration was 25.4 ± 2.6 (SEM) ng/ml at 5 min, 12.7 ± 1.1 ng/ml at 15 min, and 7.9 ± 0.8 ng/ml at 30 min. $T_{1/2}\alpha$ = 2.1 ± 0.7 min and estimated $T_{1/2}\beta$ = 35.8 ± 8.2 min.

Five minutes following the administration of fentanyl alone, HR and CO decreased and MAP, LVEDP, and TPRI increased significantly (table 1 and fig. 2). MAP and TPRI remained significantly above and HR significantly below their baseline values at each time period. At 30 min, CO and LVEDP were not significantly different from their baseline readings. SF, dP/dT, SVI, and $LVID_d$ did not change significantly.

Atropine alone produced no significant change other than a 12–14% increase in MAP. Fentanyl alone caused significant changes in CO, HR, LVEDP, and TPRI not seen in the control animals given only atropine. In animals given fentanyl alone, HR, CO, LVEDP, and TPRI (but not MAP) were highly correlated ($R^2 > 0.96$, $P \leq 0.05$) with the logarithm of the fentanyl concentration (table 2).

Fentanyl with atropine (fig. 3) produced no significant change in any variable, other than a small increase in MAP (maximum +15% at 15 min). As seen in table 1, values of the fentanyl–atropine group variables were not statistically different from those of the atropine group alone, with one exception: atropine decreased TPRI while fentanyl–atropine increased it at 5 min. Comparing the fentanyl–atropine group with the fentanyl group, HR, CO, LVEDP, dP/dT, and TPRI differed significantly at 5 min and occasionally later, although MAP, SVI, SF, and $LVID_d$ did not differ.

Discussion

The newborn piglet is a representative model of newborn human cardiovascular physiologic development. Many aspects of its cardiovascular system are similar to those of humans, including the coronary circulation,[14] the delayed maturation of neurogenic cardiovascular reflexes,[15] and intracardiac anatomy.

The dose of fentanyl used in these animals is simlar to that used as the sole or principal anesthetic/analgesic in infants undergoing cardiac surgery. Peak plasma concentrations in piglets are similar to those we measured in infants given 50 μg/kg fentanyl prior to cardiopulmonary bypass (unpublished data). To enable our hemodynamic results in piglets to be compared with those of other studies at corresponding times, we obtained all cardiovascular measurements within the first elimination half-life.

Plasma fentanyl concentrations correlate well with the degree of analgesia[16,17] and respiratory depression.[17,18] Our study demonstrated that fentanyl concentration correlated well with changes in CO, HR, LVEDP, and TPRI. Contractility (SF and LV dP/dT) remained essentially unaffected.

We postulate that fentanyl induced peripheral vasoconstriction, causing TPRI and MAP to increase. Hypertension increased baroreceptor activity, causing reflex bradycardia unless blocked by atropine. A sudden in-

TABLE 1. Fentanyl Hemodynamic Data. Mean ± SD and Significance within and between Piglet Groups (Repeated Measures Analysis)

	T_0		T_5			T_{15}			T_{30}		
	Mean	SD	Mean	SD	Per Cent Change	Mean	SD	Per Cent Change	Mean	SD	Per Cent Change
HR (beats/min)											
F	192*	17	123†	62	−36%	139†‡	40	−27%	155‡	28	−19%
A	209*§	21	230*§	29	+10%	231*§	17	+11%	238§	20	+14%
F-A	226*§	55	221*§	53	−2%	221*§	51	−2%	222*§	51	−2%
MAP (mmHg)											
F	75*	43	107†¶	23	+42%	107‡¶	10	+42%	103§¶	9	+37%
A	85*	5	96†¶	13	+13%	96‡¶	6	+12%	97§¶	9	+14%
F-A	86*	12	98†¶	13	+14%	99‡¶	19	+15%	92§¶	20	+7%
CO ($l \cdot min^{-1} \cdot kg^{-1}$)											
F	0.322†	0.087	0.188‡	0.049	−42%	0.250*	0.081	−22%	0.272*†	0.086	−16%
A	0.262*	0.066	0.298*†	0.067	+14%	0.298*†	0.068	+14%	0.288*†	0.072	+10%
F-A	0.268*	0.092	0.257*	0.087	−4%	0.266*	0.093	−1%	0.252*	0.089	−6%
LVEDP (mmHg)											
F	5.4*†	1.8	9.8‡	3.3	+81%	8.2‡§	4.3	+52%	6.8†§	3.8	+26%
A	3.2*¶	1.6	3.4*¶	1.5	+6%	3.6*¶	1.9	+13%	3.2*¶	1.3	0%
F-A	2.7*¶	1.8	4.1*¶	2.9	+52%	2.3¶	1.6	−15%	1.9¶	1.8	−30%
dP/dT (mmHg/s)											
F	3,960*†	440	3,280*	600	−17%	3,960*†	640	0%	4,120*†	440	+4%
A	3,360*†	640	4,040*†	740	+20%	3,920*†	520	+17%	4,000*†	920	+19%
F-A	3,660*†	1,060	4,360†	360	+19%	4,320†	720	+18%	4,100*†	1,080	+12%
SF (%)											
F	29.9	13.1	28.8	2.9	−4%	36.7	10.0	+23%	40.7	6.7	+36%
A	45.7	10.2	45.8	10.5	0%	42.3	9.4	−7%	42.8	10.0	−6%
F-A	34.4	7.7	33.0	6.6	−4%	40.0	10.3	+16%	35.1	10.8	+2%
TPRI ($mmHg \cdot l^{-1} \cdot min \cdot kg$)											
F	302.4*	117.0	583.4¶	113.6	+93%	471.4§	178.0	+56%	419.2†‡§	161.8	+39%
A	340.4*†‡	78.6	321.6*†	97.6	−6%	342.2*†‡	87.6	+1%	346.0*†‡	61.0	+2%
F-A	370.2*†‡	184.4	427.8‡§	168.5	+16%	410.4†‡§	163.6	+10%	413.1†‡§	187.4	+12%
SVI ($ml \cdot kg^{-1} \cdot beat^{-1}$)											
F	1.68	0.50	1.64	0.39	−2%	1.88	0.60	+12%	1.74	0.44	+4%
A	1.32	0.29	1.36	0.30	+3%	1.34	0.25	+2%	1.28	0.31	−3%
F-A	1.37	0.70	1.43	0.70	+4%	1.37	0.67	0%	1.30	0.73	−5%
$LVID_d$ (cm)											
F	1.73	0.39	1.93	0.32	+12%	1.73	0.48	0%	1.71	0.34	−1%
A	1.37	0.19	2.30	1.88	+68%	2.23	1.82	+63%	1.32	0.17	−4%
F-A	1.41	0.19	1.42	0.11	+1%	1.30	0.16	−8%	1.38	0.18	−2%

For each variable, mean values with shared symbols were not significantly different ($P > 0.05$). SF, SVI, and $LVID_d$ did not change significantly. Per cent change describes deviation from T_0. F = fentanyl; A = atropine; F-A = fentanyl with atropine; CO = cardiac output; MAP = mean aortic pressure; dP/dT = maximum rate of isovolumic left ventricular pressure rise; TPRI = total peripheral resistance index; LVEDP = left ventricular end-diastolic pressure; HR = heart rate; SF = shortening fraction; SVI = stroke volume index; $LVID_d$ = LV internal diastolic diameter.

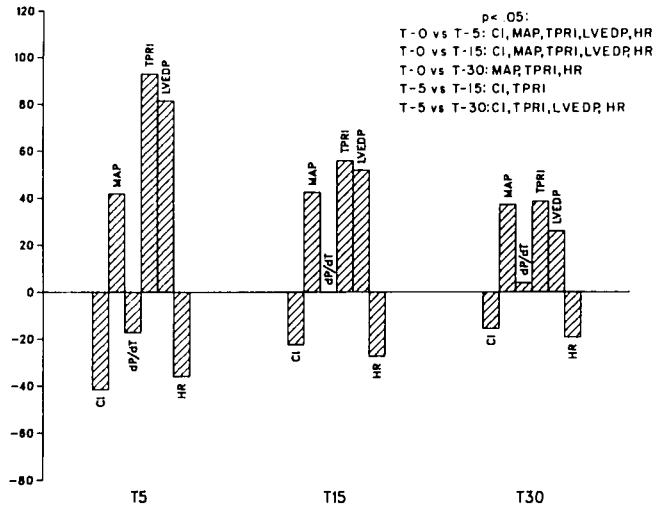

FIG. 2. Hemodynamics of fentanyl alone. Histogram shows per cent changes from control values at 5, 15, and 30 min following administration of 50 μg/kg fentanyl. Statistical analysis within piglet group noted here; see table 1 for analysis between piglet groups. CO = cardiac output; MAP = mean aortic pressure; dP/dT = maximum rate of isovolumic left ventricular pressure rise; TPRI = total peripheral resistance index; LVEDP = left ventricular end-diastolic pressure; HR = heart rate. No statistically significant change in shortening fraction (SF); stroke volume index (SVI); or LV internal diastolic diameter ($LVID_d$) occurred.

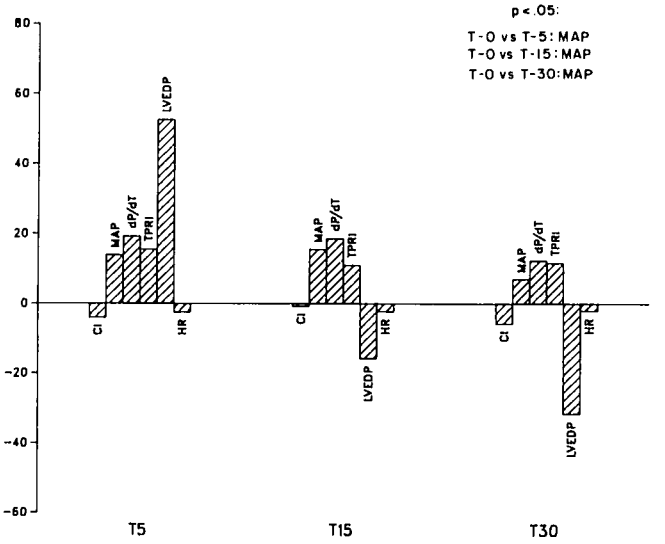

FIG. 3. Hemodynamics of fentanyl and atropine, expressed as per cent change from control values. Only MAP had statistically significant differences ($P < 0.05$): T_0 *versus* T_5, T_0 *versus* T_{15}, and T_0 *versus* T_{30}. See table 1 for statistical analysis between piglet groups. CO = cardiac output; MAP = mean aortic pressure; dP/dT = maximum rate of isovolumic left ventricular pressure rise; TPRI = total peripheral resistance index; LVEDP = left ventricular end-diastolic pressure; HR = heart rate.

crease in LV afterload increased LVEDP. CO decreased because no positive inotropic response or increase in SVI occurred to offset the reduction in HR. This chain of events depends on a functional baroreceptor reflex, which responds to hypertension by increasing its afferent output to the vagus nerve to slow the heart. Buckley *et al.*[19] demonstrated that piglets less than 1 week old lack baroreceptor function during halothane anesthesia, although 2-week-old piglets may have normal baroreceptor function. However, halothane may have reduced the baroreceptor responsiveness of these animals, just as it does in newborn rabbits.[20]

Preload was estimated in this study by $LVID_d$ and LVEDP, which were affected differently by fentanyl. Preload may only be estimated in the intact heart, since direct measurements can be performed only on isolated cardiac muscle strips. In the intact heart, measurements of LV end-diastolic volume give the best estimate of preload. $LVID_d$ predicts LV volume if the LV cavity is assumed to be spheric. However, we observed the piglet LV cavity to be long and narrow during two-dimensional echocardiographic studies. Therefore, $LVID_d$ may be a poor predictor of LV volume here and an even worse predictor of preload. If LVEDP is used to estimate LV volume, the LV pressure/volume ratio must be constant. In this study, fentanyl increased LVEDP while $LVID_d$ did not change, suggesting an increase in this ratio due to a sudden increase in afterload. However, another study, using more precise and accurate techniques to measure instantaneous LV pressure and volume changes, is needed to prove this hypothesis.

TABLE 2. Comparison of Mean Log Fentanyl Concentration with Mean Hemodynamic Variable

	Log Fentanyl Concentration *versus*:			
	HR	CO	LVEDP	TPRI
r	−0.995	−0.987	0.998	0.995
P	0.03	0.05	0.02	0.03

Conflicting hemodynamic effects of fentanyl have been reported in studies of muscle strips, animals, and adult humans. A negative inotropic response was observed in muscle strips exposed to a fentanyl concentration several orders of magnitude greater than the usual.[21,22] In concentrations similar to those present in patients, contractile indices were unchanged.[23] Most studies of intact adult dogs are biased by the use of basal anesthesia. Most hemodynamic studies in adult humans are flawed by the use of atropine premedication, pancuronium, or propranolol. Also, their cardiovascular responses to stress may have been altered by coronary artery disease.

Several other studies are in concert with our results. The direction and magnitude of HR and MAP change in animals given atropine alone was confirmed in other newborn piglets after bilateral cervical vagotomy.[24] Awake, adult dogs given fentanyl had hypertension, bradycardia, and reduced cardiac output when incre-

mental drug doses resulted in a plasma fentanyl concentration of 31 ng/ml.[17] Merin *et al.*[25,26] showed that mature pigs given fentanyl had systemic hypertension develop. Fentanyl impairs storage of norepinephrine in intraneuronal storage vesicles and blocks neuronal uptake of norepinephrine.[27] The additional norepinephrine present might cause peripheral vasoconstriction and systemic hypertension if it were not quickly metabolized within the neuron. Although systemic hypertension has been reported occasionally in adults, it is not clear whether this is due to fentanyl or to pain from inadequate anesthesia and analgesia.[28]

Newborn piglets given fentanyl and atropine had remarkable hemodynamic stability. In contrast, newborn piglets given halothane anesthesia had a major reduction in CO, MAP, and LV contractile indices.[4] Although critically ill newborn infants may respond to anesthetics in a different manner or degree than healthy newborn piglets, high-dose fentanyl with atropine seems appropriate for newborns in whom preservation of cardiac output, myocardial contractility, preload, afterload, and heart rate is essential and where postoperative mechanical ventilation is anticipated.

The authors appreciate the technical assistance of Patricia Boyle, Denise McNeil, David Nace, Anne Namnoum, and Anne Sugden. Irex and Edwards Laboratories, Incs., generously loaned them equipment vital to this project. The authors especially thank Richard Michaels, M.D., for loaning them laboratory space. Sephali Chakravort, Ph.D., measured plasma fentanyl concentrations with the use of material provided by Janssen Pharmaceutica, Inc. Robert P. Hirsch, Ph.D., provided biostatistical advice, and Frank Briesz performed the computer analyses.

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