

**A1097**

**TITLE:** RESPIRATORY SENSITIVITY TO HYPOXIA AND HYPERCAPNIA AFTER BRIFENTANYL.  
**AUTHORS:** M. Cigada, M.D., M.S. Afifi, M.D., P.S.A. Glass, M.D., B. Esposito, R.N., E.M. Camporesi, M.D.  
**AFFILIATION:** Department of Anesthesiology, SUNY Health Science Center, Syracuse NY.

Respiratory depression limits the use of narcotics for pain control whenever ventilation is not assisted. The need for improving the "analgesia/respiratory depression" ratio leads to the search for new synthetic narcotics. In this randomized double blind study, the respiratory effects of Brifentanyl, a new short acting piperidine derivative, were compared to Alfentanil and normal saline.

After IRB approval, 12 healthy volunteers gave informed consent. On four different days separated by at least a week, they received Brifentanyl 10 mcg/kg (Brif10), Brifentanyl 30 mcg/kg (Brif30), Alfentanil 30 mcg/kg (Alf30) or normal saline (placebo) i.v.. Normocapnic hypoxia and normoxic hypercapnia were induced modifying the composition of the gases the subjects were breathing in a closed bag-in-box circuit. Tidal volume (Vt), respiratory rate (RR), pulse oximetry (SatO2), end tidal CO2 (PetCO2), heart rate (HR), EKG, FiO2, and airway pressure were continuously monitored. SatO2 was brought to a lowest level of 70% to test for hypoxic response and PetCO2 to a peak value of 60 mmHg to test for hypercapnic response. Data were corrected to BTPS and minute ventilation (Ve) was calculated on a breath-to-breath basis. Ventilatory challenges were performed at 0, 15, 60, 90, and 180 min after injection for hypoxia and at 0, 30, 75, 105, and 195 min for hypercapnia. Respiratory sensitivity was evaluated as the slope of the regression line (O2 Slope) between Ve and (100-SatO2) and (CO2 Slope) between Ve and PetCO2, as well as the value of Ve at SatO2=80% (V80) and at PetCO2=55 mmHg (V55).

Drug injections and respiratory tests were well tolerated by all subjects. Ventilatory responses after Brif10 were always comparable to placebo. At equianalgesic doses, both Alf30 and Brif30 significantly reduced hypoxic and hypercapnic responses at 15-30 min, with the exception of O2 slope for Brif30. Alf30 displayed a prolonged respiratory effect with significant reduction of V80 and V55 up to 90-105 min. Brif30, on the contrary, did not produce significant depression after the first 15-30 min. Absolute values are reported in the following table as Mean±1sem.

Time	O2 Slope (l/min/% SatO2)		V80 (l/min)	
	Alf30	Brif30	Alf30	Brif30
Control	2.1±1.4	2.2±0.5	66.9±11.8	74.1±14.5
15 min	0.8±0.2*	1.4±0.5	28.2± 3.6*	39.8± 8.6*
60 min	1.4±0.3	1.6±0.5	40.9± 6.0*	67.2±14.0
90 min	1.5±0.3	2.3±0.6	51.1± 9.0*	82.5±17.3
180 min	2.0±0.4	2.4±0.5	63.9±11.1	82.8±16.2

Time	CO2 Slope (l/min/mmHg PetCO2)		V55 (l/min)	
	Alf30	PetCO2	Alf30	Brif30
Control	3.8±0.5	3.8±0.6	60.6± 7.3	58.4± 7.1
30 min	2.7±0.5*	2.5±0.3*	31.3± 4.5*	40.3± 4.7*
75 min	3.0±0.4	3.8±0.7	40.1± 4.6*	52.6± 5.4
105 min	3.4±0.4	3.7±0.6	49.9± 6.4*	57.1± 5.8
195 min	4.2±0.7	4.1±0.5	58.4± 7.6	62.4± 7.1

\*: p<0.05 when compared to Control.

Side effects were similar after Alf30 and Brif30, but longer lasting after Alf30. We conclude that Brifentanyl is a potent narcotic with short respiratory depressant effect. It may thus represent a valuable product in the appropriate clinical settings. Supported in part by a Grant from Anaquest Inc.

**A1098**

**TITLE:** VENTILATORY RESPONSE AT FOUR LEVELS OF SUSTAINED HYPOXIA  
**AUTHORS:** J.A. Temp\*, M.D., B. Bigoni, D.S. Ward, M.D., Ph.D.  
**AFFILIATION:** Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778

The ventilatory response to sustained hypoxia in humans is biphasic, consisting of an initial brisk increase followed by a gradual decline reaching a steady state over twenty to thirty minutes.<sup>1</sup> Prior studies of hypoxic ventilatory decline (HVD) in humans have examined only one level of hypoxia, generally 80% saturation, although milder degrees of desaturation are also common in the recovery period.

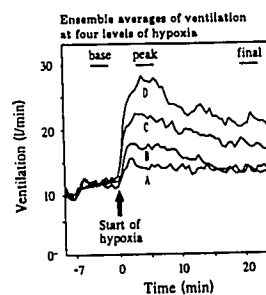
The ventilatory response to isocapnic hypoxia was measured at four levels of hypoxia in seven healthy males aged 18 to 32 years on two separate days. P<sub>ET</sub>CO<sub>2</sub> was held 1-2 mmHg above the control value for a seven minute baseline period. Thereafter, P<sub>ET</sub>O<sub>2</sub> was abruptly lowered to one of the four hypoxic levels for twenty-five minutes. At the end of each run, subjects breathed 100% O<sub>2</sub> for seven minutes to prevent accumulation of hypoxic depression.<sup>2</sup> The four levels were induced in either ascending or descending order during the first day and in the opposite order during the second day. Data for minute ventilation, tidal volume and frequency were analyzed by repeated measures ANOVA at the baseline, peak, and final time periods.

The average P<sub>ET</sub>CO<sub>2</sub> was 43.0 ± 1.7 mmHg and did not differ significantly across time periods or hypoxic levels. The arterial saturations were calculated on a breath-to-breath basis from the Severinghaus equation which matches arterial blood gas samples in healthy volunteers more accurately than does pulse oximetry.<sup>3</sup> The acute increases in ventilation (Table & Graph) resulted from increases in both tidal volume and respiratory rate, and were approximately linear with respect to the drop in saturation. HVD occurred through changes in tidal volume alone. HVD did not occur at the highest level of saturation.

Even though HVD occurred at moderate levels of hypoxia, it did not occur at the mildest level, a level which consistently did produce hypoxic stimulation. Although the initial increase was proportional to the level of desaturation, HVD was more variable. The findings are consistent with a threshold effect for HVD and/or a multiplicative model of the interaction between hypoxic stimulation and hypoxic depression.

Level	% Sat (s.d.)	Ventilation (L/min ± s.d.)		
		Baseline	Peak	Final
A	91.5 (0.5)	11.40 (2.72)	14.19* (4.54)	13.70* (4.37)
B	87.2 (0.6)	12.00 (2.69)	17.38* (5.87)	13.83#* (5.33)
C	83.0 (0.9)	12.64 (2.81)	22.37* (9.88)	18.14#* (10.1)
D	79.0 (1.0)	12.30 (3.54)	27.82* (13.8)	21.26#* (12.4)

\* different from baseline value, p<0.05.  
 # different from peak value, p<0.05.



1. J Appl Physiol, 52:1030, 1982
2. J Appl Physiol, 64:521, 1988
3. Anesthesiology, 67:551, 1987

\*Foundation for Anesthesia Education and Research/Association of University Anesthesiologists Anesthesia Research Fellow