Title: VENTILATORY SENSITIVITY TO HYPOXIA AFTER ADMINISTRATION OF AN AGONIST/ANTAGONIST.

Authors: E.M. Camporesi, M.D., P. Glass, M.D., R.E. Moon, M.D., E. Steinhaus and R. Wagoner, B.S.

Affiliation: Departments of Anesthesiology, Physiology and Medicine, Duke University Medical Center, Durham, N.C. 27710

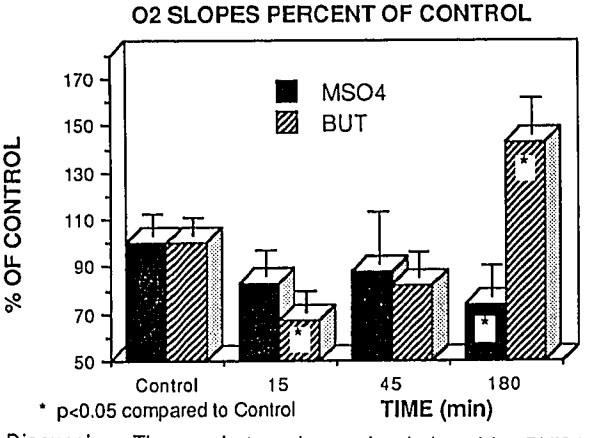
A reduction in ventilatory sensitivity to CO2 has been traditionally used to quantify respiratory depression induced by narcotics. Among the opiates, the agonist/antagonist (a/a) group has been characterized by the display of a "ceiling effect" for respiratory depression tested by CO2 rebreathing during administration of progressive doses [1]. Blunting of ventilatory response to hypoxia has also been demonstrated after administration of morphine sulphate (MSO4) in volunteers [2], but hypoxia has rarely been utilized to characterize respiratory depression by narcotics. The aim of our study was to compare ventilatory responses both to hypoxia and hypercapnia after IV administration of an a/a opiate (Butorphanol bitartrate, BUT) and of MSO4, at equianalgesic dose.

Methods. Data were obtained from eight healthy volunteers (weight range 55-107 kg; age range 24-36 years) giving informed consent. This study was approved by the Institutional Revue Board. The study design consisted of double-blinded, cross-over, randomized IV administration of BUT (0.02 mg/kg) and MSO4 (0.1 mg/kg). These doses are considered equianalgesic by common clinical standards. The two study periods were separated by at least 7 days. Respiratory studies were obtained before drug administration (Control). After the IV injection the first CO2 rebreathing test was obtained at 10 min and the first hypoxic study at 20 min: these studies are expressed as 15 min post injection. Similarly,ventilatory responses were obtained at 45 min and at 180 min. Ventilatory responses to increasing CO2 levels and to progressive hypoxia were obtained by rebreathing from a bag-in-the-box semiclosed breathing circuit. For CO2 rebreathing, ventilation (VI) and end-tidal CO2 (PetCO2) were measured for each 30 sec period while CO2 increased from 5% to 10%. Inspired O2 was closely controlled at FIO2=0.21 by a sensor in the inspiratory limb of the circuit and an O2 injection system adding the required O2 to the bag. Therefore hypercapnic responses were obtained during normoxia. For the hypoxic responses, VI and SO2 (Saturation, from finger pulse oximeter) were measured every 30 sec while inspired O2 in the rebreathing system was linearly reduced over 7 min from 0.21 to 0.10. Lower safety limits of inspired O2 were set in order to terminate the rebreathing study when SO2 was reduced below 70%, or the inspired PO2 was less than 45 mm Hg, or the subject felt distress and would remove the mouthpiece and breathe air. A by-pass circuit powered by a low pressure turbine diverted part of the rebreathing volume through a CO2 scrubber: this manually controlled system maintained PetCO2 constant during the hypoxic trial. Therefore the hypoxic ventilatory responses were obtained during normocapnia. After BTPS correction all VI values were linearly regressed vs. PetCO2 or (100-SO2) values to yield slopes (slCO2, and slO2, in l/min/mmHg, or l/min/(100-SO2) respectively), intercepts calculated at PetCO2 values of 55 mmHg, or at SO2 values of 80%, respectively (VI55 and VI80, l/min) and correlation coefficients. Statistical analysis was performed by ANOVA for repeated measures. The BMDP2V program for interactions of the main effects was utilized, as well as paired-t test for differences between the two drugs.P< 0.05 was considered significant.

Results All subjects tolerated the narcotic administration with only minor complaints: of the 64 ventilatory curves collected, only one (15 min BUT) was not completed by a subject due to persistant nausea. Control values for the 8 subjects were within accepted ranges (slCO2= 3.17 ± .5 l/min/mmHg,; slO2= 1.15 ± .12 l/min/(100-SO2); mean of all Controls, ± SE) The following Table and Figure summarize the changes observed at different times.

Table: Mean values (8 subjects) for all respiratory parameters **as % of Control** after MSO4 or BUT (* significantly different from Control).

MSO4	15 min	45 min	180 min
slCO2	63 *	60 *	68 *
VI55	81 *	77 *	78 *
slO2	78	74	67 *
VI80	89	84	85 *
BUT			
slCO2	76 *	69 *	92
VI55	63 *	81	96
slO2	62 *	79	145 *
VI80	72 *	84	122 *



Discussion. The respiratory depression induced by BUT is short lived. Both indices of hypoxic ventilatory sensitivity are still depressed at 180 min after MSO4, but they are significantly increased above Control for BUT. Overall, no significant correlation was found between the indices of CO2 sensitivity and of sensitivity to hypoxia, suggesting that in healthy volunteers reduction of ventilatory sensitivity to hypoxia after opiates cannot be adequately predicted from the blunting of CO2 responsiveness.

References:

1. Kallos T and FS Caruso Anaesthesia 1979,34:633.
2.Weil JV et Al New Eng J Med 1975, 292:1103.