Title: EFFECTS OF NALBUPHINE ON NORMAL AND OXYMORPHONE-DEPRESSED VENTILATORY RESPONSES TO CARBON DIOXIDE CHALLENGE

Authors: R.M. Julien, M.D., Ph.D.

Affiliation: Department of Anesthesia, Oregon Health Sciences University, Portland, Oregon 97201

Introduction. The usefulness of narcotic analgesics in anesthesia is limited by drug-induced respiratory depression. Recently, nalbuphine (Nubain), a mixed agonist-antagonist narcotic, has been reported to possess a ceiling effect on respiratory depression and to be effective in reversing respiratory depression induced by oxy- morphine (Numorphan) or hydromorphone (Dilaudid). The present experiments were designed to evaluate the effect of nalbuphine on the ventilatory response to increasing levels of inspired CO₂ both in normal volunteers and in volunteers with oxy Morphine-induced respiratory depression.

Methods. Experiments were conducted in 18 subjects, aged 24 to 61. All studies were approved by the Human Research Committee. An intravenous line was established and each subject, breathed a mixture of 95% O₂ and 5% CO₂ from a 13 liter Collins respirometer connected to a closed anes thea circle without absorbing gases. The gas flow was controlled by a 1-way Rudolph breathing valve. End-tidal CO₂ and O₂ were analyzed by a Perkin-Elmer model 1100 medical gas analyzer. Tidal volume and cumulative minute ventilation were continuously recorded on a chart recorder.

The gas mixture was rebreathed until end-tidal CO₂ reached 8% to 10% (Paco₂ = 58-73 torr). For data analysis, minute ventilation was plotted against end-tidal CO₂. In 9 subjects, CO₂ response curves were obtained before drug administration and after oxy Morphine (1.5 mg), nalbuphine (0.1 mg/kg), and nalo xone (0.4 mg), all doses administered i.v. In 9 additional subjects, CO₂ response curves were obtained before drug administration and after sequential doses of nalbuphine (0.1 mg/kg to 1.0 mg/kg). Following each experiment, each subject was observed for at least 6 hours.

Results. Curve A, Fig. 1, is the averaged control CO₂ response curve for 9 subjects. Curve B illustrates the depression of the response by 1.5 mg oxy Morphine. Such respiratory depression was greatly reduced by nalbuphine (0.1 mg/kg, Curve C), with modest additional reduction by nalo xone (0.4 mg).

Curve A, Fig. 2, is the averaged control CO₂ response curve for 9 additional subjects. Following nalbuphine, 0.1 mg/kg, there is a right shift (Curve B) indicative of modest respiratory depression which is not potentiated by additional doses of nalbuphine (0.5 and 1.0 mg/kg), curves C and D.

Discussion. Oxy Morphine, a pure narcotic agonist approximately 10X more potent than morphine, was chosen for the present experiments because of its relative lack of sedative effects; a factor of significance when reversing narcotic-induced respiratory depression with nalbuphine. While nalbuphine effectively reverses fentanyl-induced respiratory depression, (unpublished observations), it does not reverse narcotic-induced sedation. The present results quantitate the reduction of oxy Morphine-induced respiratory depression by low doses of nalbuphine and demonstrate that additional reversal if desired, can be obtained with nalo xone. No evidence of renarcotization was observed.

The respiratory depression produced by the "reversal" dose of nalbuphine was presented in Fig. 2, which also demonstrated that additional doses of 1.0 mg/kg did not produce further respiratory depression. These results confirm the clinical observations that nalbuphine will effectively antagonize narcotic-induced respiratory depression and that there is a "ceiling effect" for the modest degree of respiratory depression produced by the drug.

References.

Figure legends.
Fig. 1. (left) Ventilatory response to CO₂ in 9 subjects; Control (A) and after sequential administration of oxy Morphine (B), nalbuphine (C), and nalo xone (D).
Fig. 2. (right) Ventilatory response to CO₂ in 9 subjects; Control (A) and after sequential doses of nalbuphine, 0.1 mg/kg (B), 0.5 mg/kg (C), and 1.0 mg/kg (D).