Title: DOES CLONIDINE POTENTIATE MORPHINE?

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Introduction. Opiates, such as morphine and the alpha 2 agonist, clonidine, have been shown to have anesthetic and analgesic effects.[1] Both drugs have a central effect decreasing sympathetic outflow and have a spinal dorsal horn effect increasing nociceptive pain threshold. These similarities suggest a potential overlapping of opiate and alpha adrenergic receptors. Data supporting the interaction of opiates with clonidine is limited. At the spinal cord level, enhancement of spinal opiate analgesia by the coadministration of intrathecal or systemic clonidine has been used clinically to reduce the intrathecal opiate dose and to prolong opiate analgesia. Centrally, opiates such as morphine have been shown to reduce anesthetic requirements in a dose-dependent manner over a wide dosage range. In contrast, in limited studies, 5 and 20 µg/kg doses of clonidine have been shown to decrease halothane anesthetic requirement in dogs 42 and 48%, respectively,[2] and to reduce fentanyl requirement 45% with a 5 µg/kg dose of clonidine in man. Dose response data for the anesthetic interaction of clonidine with opiates has not been established and is evaluated in this study.

Methods. Twenty-six male Sprague-Dawley rats having a mean weight of 295 g were anesthetized with halothane, intubated, and ventilated with a Harvard animal respirator. The femoral artery and vein were cannulated with PE-50 tubing and arterial blood gases were maintained within physiologic range. Arterial pressure, heart rate, and temperature were monitored. Alveolar concentrations of halothane, were assayed by gas chromatography. Halothane MAC was determined before, and one hour following, an intravenous dose of 6, 15, 30 and 60 µg/kg IV of clonidine. After observing the clonidine effect on MAC, a 2 mg/kg SC dose of morphine was given to the animals and MAC was redetermined 45 minutes later. Upon completion of this MAC determination, blood was collected and assayed for morphine content by HPLC.

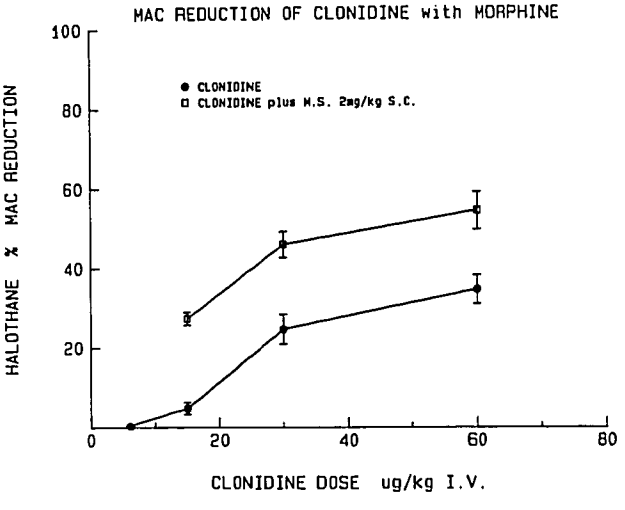
Results. The anesthetic effect of clonidine appears to have several dose-related components (Fig. 1). An initial threshold is noted and is evident by little to no anesthetic effects of clonidine with doses of 6 µg/kg. However, as the dose of the drug is increased, a significant anesthetic effect occurs. Doses of 30 µg/kg result in a 25% MAC reduction. A further increase in clonidine dose is associated with a minor increase in anesthetic effect so that a 60 µg/kg dose causes an apparent plateau with a 35% MAC reduction.

Combining this dose of morphine with clonidine produces a purely additive anesthetic effect at all doses of clonidine tested (Fig. 1). Morphine blood levels measured were unaffected by clonidine administration and were similar to those previously measured with the same morphine dose: 64-67 ng/ml.

Discussion. The results of this study suggest that the anesthetic effect of clonidine results from a reduction in sympathetic outflow. This effect is similar to that previously seen with CNS monoamine depletion by drugs such as reserpine.[5] In both cases, reduced monoamine transmitter release occurs. In the case of reserpine, decreased transmitter release is secondary to depletion of the transmitter. In contrast, clonidine decreases monoamine release by an alpha 2 agonist effect of the drug.

The combination of morphine and clonidine resulted in an additive anesthetic effect with no evidence of potentiation. This study suggests that adding clonidine to narcotic anesthetic techniques could be a useful approach to increasing anesthetic effectiveness of the narcotic while limiting hypertensive responses to surgical stimulation.

Figure 1



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