Title: REVERSAL OF MORPHINE-INDUCED RESPIRATORY DEPRESSION DURING FOURTH VENTRICULAR ADMINISTRATION OF BUTORPHANOL OR NALBUPHINE IN AWAKE DOGS: A COMPARISON.

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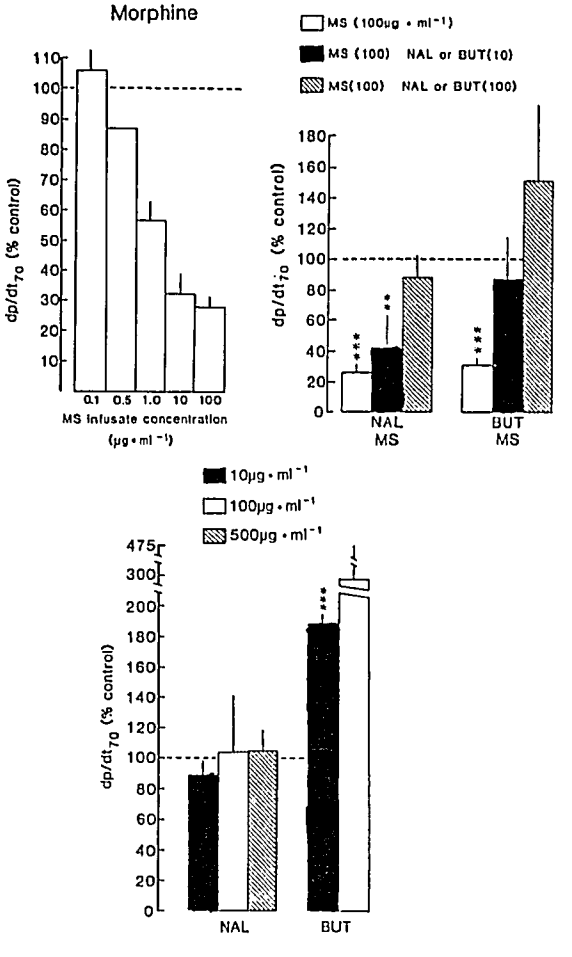
Introduction: An undesirable side effect of morphine administration is respiratory depression, a response presumably mediated through opiate receptors located in the vicinity of brainstem respiratory centers.[1] Recently, interest has focused on opiate agonist/antagonist drugs as an alternative to morphine administration. Two of the most popular of these are butorphanol (BUT) and nalbuphine (NAL). Both BUT and NAL provide analgesia and limited respiratory depression,[2] and NAL has been reported to be useful in reversing respiratory depression while maintaining analgesia following morphine.[3] However, no information is presently available on the ability of BUT to reverse morphine-induced respiratory depression, nor on the comparative influences of BUT versus NAL in this regard. In this study, we tested the comparative effects of intracerebroventricularly (ICV) administered BUT versus NAL in reversing morphine-induced respiratory depression, and the effect of each agent alone on ventilatory drive in the conscious dog.

Methods Adult dogs were surgically prepared 7-14 days prior to study with femoral artery and vein catheters, tracheostomy, and guide cannulae for the insertion of spinal needles into the fourth ventricle and cisterna magna.[4] The test drugs were prepared in an artificial CSF solution and delivered through a ventricle-to-cisterna magna perfusion (VCP) system. The CSF solution was controlled for temperature, pCO_2, and pH. During the studies, the dogs were awake and unanesthetized, and placed in a restraining stanchion. Spinal needles were placed through the guide cannulae at depths previously established during surgery. All drug perfusions were preceded by a one hour period of VCP with drug-free CSF (control). The protocol for drug studies was to perfuse with morphine sulfate (MS) at 0.1 to 100 $ug.ml^{-1}$ CSF for 1 h, then MS at 100 $ug.ml^{-1}$ CSF (1 h) followed by perfusion of MS (100 $ug.ml^{-1}$ CSF) plus either BUT (10 $ug.ml^{-1}$ or 100 $ug.ml^{-1}$ CSF) or NAL (10 $ug.ml^{-1}$ or 100 $ug.ml^{-1}$ CSF) for up to 1 h. BUT or NAL alone was also perfused at 10,100 and 500 $ug.ml^{-1}$ CSF. End-tidal CO_2 was continuously monitored. Arterial blood was sampled every ten minutes for pCO_2, pO_2, and pH. During each perfusion period, one or two CO_2 response evaluations were performed using a modification of a CO_2 rebreathing method. Analysis was based on arterial pCO_2 versus airway occlusion pressure.

Results The experimental results are summarized in the accompanying graphs. We found that VCP delivery of 100 $ug.ml^{-1}$ MS causes a depression of ventilation and ventilatory drive as evidenced by a reduction to 23-31% of control in the 1 sec airway occlusion pressure changes at $PaCO_2$ = 70 mmHg (dp/dt_{70}) during rebreathing. Inclusion of either 100 $ug.ml^{-1}$ NAL or BUT with 100 $ug.ml^{-1}$ MS resulted in a complete return of dp/dt_{70} to control levels. When NAL was administered alone in 10,100 and 500 $ug.ml^{-1}$ concentrations, ventilatory drive (dp/dt_{70}) was not affected. BUT, however, increased ventilatory drive to 180% of control levels when given at 10 $ug.ml^{-1}$. The 100 $ug.ml^{-1}$ BUT concentration caused increases in ventilatory drive and severe agitation in all the dogs tested.

Discussion The findings that ICV-infused NAL and BUT reverse morphine-induced respiratory depression confirm the results of previous studies using systemic drug administration. Our data supports the reversal of morphine-induced respiratory depression to be a mu-receptor anatagonist effect mediated at brain-stem sites. NAL alone did not affect pCO_2 or ventilatory drive, while BUT alone increased ventilatory drive. BUT is a known sigma receptor agonist, unlike NAL, which has no effect at the sigma receptor. These results suggest that sigma receptor stimulation may explain the increase in ventilatory drive caused by BUT.



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