

Title: ANALEPTIC ACTION OF NALOXONE ABOLISHED BY ATROPINE PRETREATMENT

Authors: B. J. Kraynack, M.D., J. Gintautas, M.D. Ph.D., and L. L. Kraynack, R.N.

Affiliation: Texas Tech University Health Sciences Center, Anesthesiology Research Laboratories, Department of Anesthesiology, 3601 4th Street, Lubbock, Texas 79430

Introduction. There is no compelling *in vivo* evidence to indicate that the predominant effects of general anesthetics are mediated by an action on or through an opiate receptor. We previously reported that intracerebroventricularly (ICV) administered naloxone but not naltrexone shortened, in a dose-related manner, the duration of sleeping time (ST) in rats anesthetized by intraperitoneal (IP) injection of pentobarbital, ketamine or halothane.² The evidence supports the hypothesis that naloxone may govern the duration of narcosis through the activation of an opposing, physiologic arousal system on the CNS, unrelated to pharmacologic competition for opiate receptors. A study was designed to investigate the role of the cholinergic system on the modification of the duration of narcosis.

Methods. Four groups of male Sprague-Dawley rats (125-150 g) received an intraperitoneal (IP) injection of atropine sulfate (ATR) (1 mg/kg) or 0.9% saline (1 cc/kg) (NSS). Thirty minutes later, the rats received an intraperitoneal injection of naloxone (0.66 μ M in 15 μ l) or 15 μ l of NSS according to a method previously described.² (N=10 rats per group). Awakening was defined as regaining the righting reflex (RRR). Sleeping time (ST), defined as the period between LRR and RRR, was recorded for all groups.

Results. The results are shown in Table 1. Group I (control), which received IP saline pretreatment and ICV saline, had a mean sleeping time \pm SEM of 131.1 \pm 6.0 minutes. Centrally administered naloxone shortened the duration of sleeping time by 40% (Group II). Pretreatment with IP atropine (Group III) did not alter duration of ST from control. However, pretreatment with atropine abolished the analeptic action of centrally administered naloxone (Group IV).

Discussion. Multiple lines of evidence suggest that the analeptic effect of naloxone is not mediated by an opiate receptor mechanism.^{1,2} This study clearly demonstrates that a cholinergic system may be related to the analeptic action of naloxone. Naloxone may govern the duration of barbiturate narcosis through the activation of an opposing cholinergic arousal system in the CNS. Barbiturates and other general anesthetics may affect, by activation or depression,

one or more unrelated CNS systems. Naloxone, acting through a physiologically opposed cholinergic system, may facilitate arousal. In further agreement with this view are our findings that atropine pretreatment of rats anesthetized with ketamine or halothane, also abolished the anti-anesthetic action of naloxone. Consequently, the analeptic action of naloxone may be linked to a cholinergic effect. The role of acetylcholine and other transmitter systems in this model awaits further investigation.

Table 1

Treatment	Duration of Sleeping Time as Percent of Control
Group I (Control) (IP=NSS; ICV=NSS)	100%
Group II (Naloxone) (IP=NSS; ICV=Naloxone)	60% ¹
Group III (Atropine Control) (IP=ATR; ICV=NSS)	NC ²
Group IV (Atropine-Naloxone) (IP=ATR; ICV=Naloxone)	NC ²

1. Significantly different from control and other treatment groups at 0.05 level (Duncan's Multiple Range Test).
2. NC = no change from control; not significantly different from control or each other at 0.05 level.

References.

1. Yaksh TL, Howe JR: Opiate receptors and their definition by antagonists. *Anesthesiology* 56: 246-249, 1982
2. Kraynack, BJ, Gintautas J: Naloxone: Analeptic action unrelated to opiate receptor antagonism? *Anesthesiology* 56: 251-253, 1982