Date :

Title : ANTAGONISM OF KETAMINE INDUCED NARCOSIS BY NALOXONE

Authors : L.L. Kraynack, R.N., J. Gintautas, M.D., B.J. Kraynack, M.D., G. Racz, M.D.

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

Introduction. Ketamine hydrochloride, a cyclohexanone derivative, rapidly induces a cataleptic state of anesthesia characterized by an altered state of consciousness with profound somatic analgesia.[1] During recovery from anesthesia, patients exhibit prolonged awakening time, vivid dreaming and increased psychomotor activity manifested by confusion, disorientation, and irrational behavior. The intravenous administration of naloxone after ketamine anesthesia significantly reduces recovery room time, reverses disorientation, nystagmus, and analgesia in patients (Racz, unpublished observation). We investigated the interaction of naloxone on the duration of ketamine-induced sleeping time in the rat.

Methods. Sprague-Dawley male rats (100-125g) were used. Each rat was weighed and given an intraperitoneal (IP) injection of ketamine hydrochloride (175 mg/kg). Immediately after the loss of the righting reflex (LRR), rats were given an IP injection of naloxone hydrochloride (1, 10 or 50 mg/kg) or 0.9% saline. A second group received intracerebroventricular (ICV) injections after LRR of 15 microliters of naloxone (120 or 240 micrograms) or 0.9% saline, as previously described.[2] A third group was injected with atropine 2.5 mg/kg IP 30 minutes prior to ketamine injection; which was followed by ICV naloxone (240 µg). There were six animals in each group. Naloxone was dissolved in 0.9% saline. Awakening was defined as regaining the righting reflex (RRR). Sleeping time (ST), defined as the period between LRR and RRR, was recorded for all experimental groups. All rats given ICV injections were decapitated at the time of RRR and the needle tract was examined. Rats which did not show a definitive needle tract or had evidence of intracerebral hemorrhage were excluded from the study.

Results. In the dose range tested, IP naloxone did not alter ketamine ST. Dose related antagonism of ketamine narcosis in rats by ICV naloxone was observed. The mean control ST value ± SEM, was 98.67 ± 8.94 minutes. ICV naloxone doses of 120 and 240 micrograms significantly reduced the mean ST values (± SEM) to 71.67 ± 2.53 and 47.67 ± 4.11 minutes respectively (statistically significant difference from control and each test group at 0.05 level according to Duncan's Multiple Range Test). Thus ST was shortened to 73 and 48% of control. The antianesthetic action of naloxone was abolished by pretreatment of the animal by atropine. Atropine by itself did not affect the duration of ketamine-induced narcosis.

Discussion. We have demonstrated the ability of ICV administered naloxone to dose-relatedly shorten ST in rats anesthetized with ketamine, while IP naloxone had no effect. We have observed similar differences in antianesthetic action, dependent on route of administration, for other analeptic agents. The data suggest the possibility that naloxone may act directly by affecting arousal center(s) in the brain. This finding supports our previously reported contention that antianesthetic agents do not arouse by stimulating the respiratory, cardiovascular or temperature centers, but by directly affecting arousal systems in the brain.[2] The naloxone concentrations tested were far above that needed to effectively antagonize opiate drugs, and may suggest that it is unlikely that the antianesthetic effect of ICV naloxone is mediated via its opiate antagonist action. Antagonism by naloxone of a physiologic response is a necessary, but insufficient criterion to implicate endogenous opiate mediation.[3] Horita and Carino observed that a cholinergic mechanism may be responsible for the analeptic action of naloxone in pentobarbital anesthesia.[4] Similarly, our results suggest that a central cholinergic mechanism may be involved in naloxone antagonism of ketamine-induced narcosis. Our findings, and others, suggest that naloxone may possess other important pharmacologic properties not related to opiate receptor binding.

This research was supported by the American Society of Anesthesiologists and Parker B. Francis Foundation.

References.

1. Pryor, W.J. and Bush, D.C.T.: In A Manual of Anesthetic Techniques, Year Book Medical Publishers, Inc., Chicago, 1973, p. 84.
2. Kraynack, B.J., Cohn, M.L., Cohn, M., et al: Comparisons between the Antianesthetic Action of Dibutyryl Cyclic AMP and Analeptic Drugs on Amobarbital-Induced Narcosis in the Rat. Pharmacology 14:39-46, 1976.
3. Sawynok, J., Pinsky, C. and LaBella, F.S.: Minireview on the Specificity of Naloxone as an opiate antagonist. Life Sciences 25:1621-1632, 1979.
4. Horita, A. and Carino, M.A.: Analeptic and Antianaleptic Effects of Naloxone and Naltrexone in Rabbits. Life Sciences 23: 1681-1686, 1978.

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/53/3 Suppl/S59/627455/0000542-198009001-00059.pdf by guest on 11 November 2024