Date :

Title : THE INFLUENCE OF DIAZEPAM AND DROPERIDOL ON CNS RECEPTOR BINDING.

Authors : Theodore H. Stanley, M.D., Josee Leysen, Ph.D., Carlos Niemegers, Ph.D.

Affiliation: Departments of anesthesiology, university of Utah Medical Center, 50 North Medical dr. Salt Lake City, Utah 84132 and University Hospital Leiden, Rijnsburgerweg 10, Leiden, The Netherlands and Janssen Pharmaceutical Laboratories, Beerse, Belgium.

It has been demonstrated that increasing doses of intravenous lofentanil, a potent (100 x as potent as fentanyl) long acting narcotic produce increasing analgesia and increasing central nervous system (CNS) opiate receptor binding in rats. It has also been shown that lofentanil (1.25 μg/kg, IV) is anesthetic in rats (totally blocks tail withdrawal (TWR) and righting reflexes (RR), causes non-responsiveness to abdominal incision and bone crush and produces rigidity in 100% of animals) but results in only 35% of binding in available opiate receptors in subcortical brain areas and 25% of binding in cortical receptors. Diazepam and droperidol are often given with narcotics in anesthesia to potentiate and/or prolong narcotic action. In this investigation increasing doses of intravenous lofentanil were given to rats with and without diazepam or droperidol in order to determine if the latter two compounds influenced the in vivo responses of the rats or their CNS opiate receptor binding.

Methods. One hundred forty seven rats were given 0.08, 0.16, 0.31, 0.63, 1.25 or 2.50 μg/kg of lofentanil IV. Thirty-six of these animals also received 25, 50, 100 or 200 μg/kg of diazepam and another 36 received 15.6, 31.2, 62.5 or 125 μg/kg of droperidol intravenously along with lofentanil. Thirty minutes following drug injection TWR, RR, rigidity and responsiveness to abdominal incision were evaluated in all animals. Immediately after scoring of the in vivo effect the animals were killed by decapitation. The cerebral cortex and subcortical areas were evaluated for degree of opiate receptor occupation using ^{3}H fentanyl in an ex-vivo fentanyl binding assay. This assay measures the inhibition of ^{3}H fentanyl binding by lofentanil. Lofentanyl is suitable for this kind of experiment because its in vitro measured dissociation time from the receptors is greater than 3 hours.

Results. Prolongation of TWR was observed with 0.31 μg/kg of lofentanil (alone) and gradually increased to complete non-responsiveness at 1.25 μg/kg. Muscle rigidity, loss of RR and non-responsiveness to abdominal incision started at 0.63 μg/kg of lofentanil and occurred in all animals at 1.25 μg/kg. Administration of diazepam or droperidol (in any dosage) did not change (potentiate or reduce) in vivo responses to any form of stimulation. Lofentanil alone (0.08 μg/kg) resulted in 10% of opiate CNS receptor occupation. At the point of complete anesthesia (1.25 μg/kg of lofentanil) 41% of cortical and 21% of subcortical opiate receptors were occupied. When lofentanil dosage was increased to 2.5 μg/kg cortical and subcortical opiate receptor binding increased to 63 and 54%. Although there was a tendency towards reduced opiate receptor binding when compared to lofentanil alone, combination of lofentanil with diazepam or droperidol (in any dosage or dosage combination) did not significantly alter the percentage of cortical or subcortical opiate receptors occupied.

Discussion and conclusion. The results of this study demonstrate that, when administered simultaneously with a narcotic compound, diazepam and droperidol do not significantly alter CNS opiate receptor binding. The data also indicate that in vivo responses of rats to various forms of stimulation during administration of sub-analgesic, analgesic and anesthetic doses of lofentanil are not changed by diazepam and droperidol. Our findings suggest that whatever potentiating effects deazepam or droperidol produce during narcotic analgesia or anesthesia are not due to the action of these compounds on the percentage of CNS opiate receptors occupied by narcotics.