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Title : MORPHINE EFFECT AS A FUNCTION OF pH VARIATIONS

Authors : M.M. Eisenstein, D.S. Schulman, J.J. Kaufman, Ph.D. and M.C. Rogers, M.D.

Affiliation: Department of Anesthesiology/Critical Care Medicine and the Anesthesiology/Critical Care Research Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Introduction. In our earlier physicochemical studies on narcotics and narcotic antagonists[1] we observed a striking dependence of their lipophilicities (the tendancy to partition from aqueous to lipid) on pH even in the range of attainable human physiologic pH. The present studies on the relationship of variations in pH on the analgesic effect of narcotics in the rat demonstrate this effect physiologically.

Methods. Indwelling venous and arterial catheters, jugular and carotid, are implanted surgically into male Osburne-Mendell rats. Both prior to surgery and after postoperative recovery, baseline hot plate responses are determined. The response times for both are less than five seconds and do not differ statistically. In this present study 32 rats were used.

The hot plate test is the standard test used by NIH on narcotic analgesic studies. A hot plate is set to 55° C. Rats are placed on the hot plate and the test consists of waiting for a response to the heat. The response is determined subjectively by the investigator. If a rat remains on the plate for more than 5 sec during the baseline trial he is not used. Baseline response time is determined in two trials so that rats do not learn to jump off the plate on contact. After the drug has been injected into the rats they are placed on the hot plate at intervals at 2, 4,6,8,10,12,14,16,18,20,25,30,35 and 40 minutes. The rats are considered to be affected, anesthetized, by the drug if they remain on the hot plate without reacting to the hear for more than 5 sec longer than their baseline response. Also, their reaction time must be 5 secs above their baseline response for a minimum period covering 4 consecutive trials or 5 min. For example, if a rat's baseline time is 2.5 sec, it is considered anesthetized by the morphine if its response time to the heat is > 7.5 sec for the trials during period 2,4,6 and 8 min. Rats are not left on the plate more than 30 sec. ED_{50}'s are determined from this information.

The ED_{50} is the dose of a drug required to produce a specific response in 50% of the subjects to whom the drug is given (in this case, the response to the hot plate test). It is the standard used in narcotic analgesic research done by NIH.

Acute blood plasma pH changes are induced, after recovery from the operation to implant the catheters, by using either intraperitoneal injection or a continuous intravenous infusion at a rate of 0.0206 cc/min. of $NaHCO_3$ or NH_4Cl respectively. Doses are 1 mg/kg at a concentration of 100 mg/ml of $NaHCO_3$ or 10 meq/kg at a concentration of 100 meq/ml of NH_4Cl. Control rats received equal amounts, IP or IV, of normal saline. The rats are allowed to stabilize 1 hour after initial injection of $NaHCO_3$ or NH_4Cl, then morphine - 6 mg/kg to 12 mg/kg are given intravenously.

Results. The acidotic rats had an average blood pH of 7.15 (s.d. ± 0.06). The alkalotic rats had an average blood pH of 7.63 (s.d. ± 0.08) and control rats had an average blood pH of 7.42 (s.d. ± 0.06).

To show that less morphine is needed to anesthetize alkalotic rats than acidotic rats, it is necessary to show that the ED_{50} of morphine for alkalotic rats is less than the ED_{50} for acidotic rats. The ED_{50} of morphine for the control rats should lie in between. Our present data indicates that the ED_{50} for alkalotic rats ≈ 7 mg/kg, the ED_{50} for control rats ≈ 9 mg/kg and the ED_{50} for acidotic rats is above 11 mg/kg.

Discussion. These indicate that there are significant differences in the effects of morphine in the physiologic pH range observed in patients. Situations where this may turn out to be most important include post-operative patient care when rapid shifts in modes of ventilation may be associated with shifts in pH and with changes in analgesic effects of narcotics.

References.

1. Kaufman JJ, Semo NM, Koski WS: Microelectrometric Titration Measurement of the pK_a's and Partition and Drug Distribution Coefficients of Narcotics and Narcotic Antagonists and Their pH and Temperature Dependence. J Med Chem 18: 647-655, 1975