Title: DISTRIBUTION OF ^{3}H-MORPHINE FOLLOWING LUMBAR EPIDURAL ADMINISTRATION IN RABBITS

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Introduction: Despite its popularity in pain management, Epidural (epi) morphine (M) still poses unanswered questions. The mechanism for its long duration of action and its spread and elimination after administration have not been clearly delineated. This abstract reports a study of the distribution of ^{3}H-Morphine (^{3}H-M) following lumbar epi injection in unanesthetized rabbits.

Method: Under N_2O + O_2 + Halothane endotracheal anesthesia, the cistern magna (CM) and epi space of 3-4kg New Zealand Albino rabbits were cannulated for sampling of cerebrospinal fluid (CSF) and administration of ^{3}H-M, respectively. One week after surgery, animals demonstrating intact neurological function were tested in 3 groups: Group 1 (n=3) received via the epi catheter (PE 10) 500ul of 1.3mM morphine containing 200 pM ^{3}H-M (specific activity = 24Ci/mmol). CSF (0.1ml) and arterial blood (0.1ml) were sampled at 0, 5, 15, 30, 45, 60, 90, 120 minutes. At the end of 2 hrs., following euthanasia with intravenous pentobarbital, the brain and spinal cord (SC) were removed in one piece and frozen at -70°C immediately. 2mm thick slices of (SC) were sampled at 1cm intervals. These SC sections and slices from various brain areas were solubilized individually in protosol and counted along with plasma, and urine in a Beckman liquid scintillation counter. Group 2 (n=3) underwent the same treatment as group 1, except blood and CSF were sampled for 6 hrs., followed by SC removal. Group 3 (n=3) received the same treatment as 1 & 2, however blood & CSF were sampled for 12 hrs.(n=2) and 16 hrs.(n=1); euthanasia ensued.

Results: Following epi injection of ^{3}M-H, radioactivity (RA) was barely detectable, i.e., 3-6 times background count of 25 cpm in plasma in 10 minutes and in CSF in 10-30 minutes. Cpm ranged between 54-174 for plasma and 42-173 for CSF; with the exception of one rabbit which had 902 and 379 cpm in CSF at 60 and 90 minutes, respectively. A significant amount of RA was recovered in the SC, post epi ^{3}H-M, predominantly around the injection site (Fig. 1). When expressed as percentage of the cpm injected, the results were: 4.2% ± 1.1% at 2 hrs. and 1.6% ± 0.66% at 6 hrs. (Fig. 2). A significant amount of RA was also detected in spinal roots (SR), urine and urinary bladder. The majority of RA recovery was in the urine with cpm ranging between 2916-16966. In 3 animals, RA was barely detectable in the kidneys. RA was not detected in the SC and SR between 12 & 16 hrs.(group 3). Only a small amount of RA was detectable in the urine at 16 hrs.

Discussion: Although epi M is known to act on spinal cord opioid receptors, while local anesthetics block at the axonal membrane,[1] both penetrate the dura into the SC and SR similarly following epi administration. Our finding of RA in the SC and SR predominantly around the injection site is consistent with Bromage's result of epi administration of ^{14}C lidocaine.[2] The low concentration of RA in the plasma was probably the result of dilution. Renal concentration made it possible to measure increased RA in urine. The fact that the bulk of RA was recovered from urine suggests that the kidneys are the main route of elimination after epi ^{3}H-M. Following IV or IM injection of ^{3}H-M in man and rat, the components of RA in urine have been reported to be 60-70% M glucuronate, 20% other metabolites of M, 5% free M and 0-0.5% tritiated water.[3] The ^{3}H-M we used was labelled at 1 position. Both 1 & 6 positions are stable. The persistence of RA in SC and SR following epi ^{3}H-M could explain the long duration of action of epi morphine.

Conclusion: ^{3}H-M persisted in the SC and SR for an extended period of time after epi injection, predominantly around the injection site. Urinary excretion seemed to be the main route of elimination.

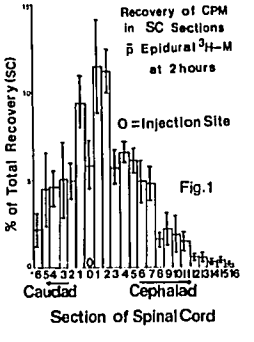

Fig.1

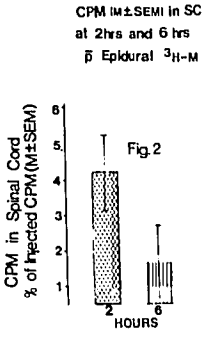

Fig.2

References: 1.Cousins M, et al: Intrathecal and epidural administration opioids. Anesthesiology 61:276-310,1984 2.Bromage PR, et al: Local anesthetic drugs: Penetration from the spinal extradural space into the neuraxis. Science 140:392-394,1963 3.Fishman J, et al: Preparation of Morphine 6-^{3}H and its isotopic stability in man and in rat. J Med Chem 17:778,1974