

Title: ENHANCED CARDIOVASCULAR EFFECTS OF MORPHINE DURING HYPOTHERMIA

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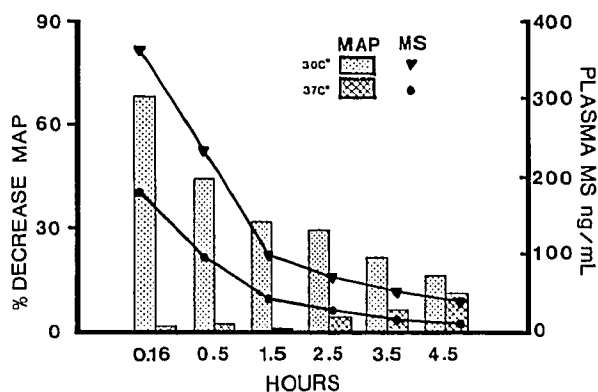
Introduction. Although temperature affects both the MAC of inhalation anesthetics and the action of non-depolarizing muscle relaxants, the effects of hypo and hyperthermia on the potency and dose requirements of opiates are not well defined. The effects of body temperature (BT) changes on plasma and cerebrospinal fluid (CSF) morphine levels, as well as on cardiovascular response, were studied after bolus intravenous (iv) administration of morphine in dogs with BT maintained at 30, 37, or 40°C.

Methods: Twenty mongrel dogs (wt 18.3 ± 5 kg) were used. Anesthesia was induced with iv pentothal and after endotracheal intubation, maintained with isoflurane-O₂. Dogs were mechanically ventilated and end-tidal CO₂ monitored. An arterial line, a Swan-Ganz catheter and a cisternal CSF drain were placed after induction. Hyperthermia (40°C) was induced and normothermia (37°C) was maintained by insulating the animals with heating blankets, while hypothermia (30°C) was induced by surface cooling with ice. After temperature was stabilized, 1 mg/kg of morphine (MS) was administered iv. Blood and CSF samples were taken and cardiovascular response measured before and at different time intervals after MS administration for a period of 4.5 hrs. MS concentration was determined by RIA. The estimates of pharmacokinetic variables were calculated using a curve stripping program (STRIFE). Differences between groups were compared by ANOVA followed by Student's t-test.

Results. MAP and mean PAP were not different among groups after the desired BT was stabilized. However, when compared to the normothermic 37°C group, the 40°C group had higher HR and CO, while the 30°C group had lower HR but normal CO. MS produced a significant decrease over starting values in MAP, mean PAP, CO and TVR only at 30°C. No such changes after MS administration were observed at 37°C or 40°C. While MS concentrations in the 30°C group were significantly higher both in plasma and CSF when compared to the normothermic 37°C, no differences were observed in the 40°C group. The concentration time points of MS were best fitted to a 2 compartment model. Decay curves were bi-exponential with t_{1/2} alpha of 0.19 ± 0.02 hrs at 37°C, 0.22 ± 0.01 at 30°C and 0.20 ± 0.03 at 40°C; indicating that the temperature induced changes in kinetics, were not due to changes in

distribution of MS. The t_{1/2} beta was 2.22 ± 0.24 hrs at 30°C, 1.59 ± 0.18 at 37°C and 1.37 ± 0.06 at 40°C; The 30°C value was significantly higher (p < 0.05). To determine the fraction of MS that could be available to bind to CNS opioid receptors, the plasma/CSF ratio for each dog at 10 min. after MS was determined. The ratios were 1.43 ± 0.2 at 30°C, 2.24 ± 0.3 at 37°C and 2.74 ± 1.1 at 40°C; indicating that the relative fraction of MS that crossed the blood-brain barrier (BBB) was decreased during hypothermia. The % decrease in MAP at 30°C and 37°C as well as the mean plasma concentration of MS for the same groups and time points are summarized in the Figure. The correlation coefficient between percent decrease in MAP and MS plasma levels in the 30°C group was 0.995.

Conclusions. 1) MS (1 mg/kg iv bolus) significantly decreases MAP, mean PAP, TVR and CO only in the hypothermic (30°C) group. 2) MS concentrations in plasma and CSF are significantly higher at 30°C, but are not affected by hyperthermia (40°C), when compared to the normothermic (37°C) controls. 3) Net transport of MS across BBB is lower at 30°C despite the higher concentrations observed in plasma and CSF. In summary, our results show that hypothermia increases plasma and CSF levels of MS and enhances its cardiovascular effects, suggesting that lower doses of morphine should be used in hypothermic patients with compromised cardiovascular function.



Plasma concentration and % decrease in MAP after MS administration at 30 and 37°C (n=7 for each group)