Title: FAILURE OF INTRATHECALLY ADMINISTERED NALBUPHINE TO SUPPRESS VISCERAL PAIN IN PREGNANT RATS

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Introduction. It has been suggested, and recently challenged, that a unique form of naloxone-reversible analgesia becomes activated during pregnancy in experimental animals. Those studies, however, only assessed somatic stimuli. Since a major portion of labor pain involves non-somatic nociceptive input, a visceral writhing stimulus has been utilized in our laboratory to evaluate pregnancy-induced analgesia. In our previous study,[1] a trend suggestive of enhanced visceral pain tolerance was noted at term pregnancy; however, additive spinal analgesia following intrathecal administration of a mu receptor agonist (fentanyl) could not be demonstrated. Since intrathecally administered nalbuphine suppressed rat responses to visceral pain,[2] we hypothesized that this kappa agonist/mu antagonist might have added effectiveness in pregnant animals. The following abstract summarizes a reassessment of endogenous visceral analgesia, the establishment of an intrathecal nalbuphine dose response, and our attempt to demonstrate enhanced spinal efficacy at term pregnancy.

Methods. A. Catheter Implantation. The technique for catheter placement is similar to the method previously reported[1] with two exceptions: 1) a more extensive laminectomy involving the spinous processes of T13, L1 and L2 to obtain better visualization of the catheter; and 2) rostral subdural insertion of the catheter enabling the catheter to lie at the lumbar enlargement. B. Nociceptive Responses. Visceral pain assessment was performed by analyzing writhing reactivity over a two-minute observation period following an I.P. injection of 1.5 ml of 4% saline. A dose response analysis was done in nonpregnant rats to determine an effective intrathecal nalbuphine dose that could reduce the baseline writhing by 20 percent (ED20). Catheterized rats were tested just before intrathecal saline/drug treatment (baseline scoring) and 60 minutes later. Following the dose response testing, the catheterized rats were mated and retested at term pregnancy (day 21 of gestation) and two days post-partum after receiving intrathecal administration of either saline or ED-20 dose of nalbuphine. The data are presented as mean values, and the statistical analysis involved the use of one way analysis of variance (ANOVA) and the Wilcoxon sign rank test.

Results. Nalbuphine's effect in blocking the writhing response was assessed by calculating the percent writhing score change between the pretreated baseline score and the sixty minute drug treated score. The results of the dose response analysis showed that nalbuphine was able to exert a writhing suppression effect in the 60 mcg, 90 mcg and 120 mcg nalbuphine treated groups (Table 1). The ED20 was determined to be 60 mcg. Decreased mean baseline writhing scores (analgesia) were observed in the pregnant rat groups, but statistical significance using one way ANOVA could not be appreciated (Table 2). The addition of 60 mcg of intrathecal nalbuphine was shown to have a writhing suppression (analgesic) effect in the nonpregnant and postpartum rats but was ineffective in the pregnant rats (Table 2).

Table 1

Dose:	Naive	Saline	30 mcg	60 mcg	90 mcg	120 mcg
% Writhing Score Change:	-4.1	-8.5	-4.3	-20.1	-47.4	-26.9
Wilcoxon P value:	0.25	0.17	0.25	0.02	0.015	0.01

Table 2

Rat Group:	Nonpregnant (60 mcg)	Pregnant (60 mcg)	Postpartum (60 mcg)
Baseline Writhing Score:	25.2	21.3	27.7
% Writhing Score Change:	-20.1	-5.6	-22.9
Wilcoxon P value:	0.02	0.20	0.005

Discussion. A chronic spinal catheter is a useful tool to assess the efficacy of intrathecal narcotics in non-pregnant, pregnant, and post-partum states. A trend showing decreased mean baseline writhing scores in term pregnant rats was suggestive but not conclusive in demonstrating endogenous analgesia in pregnancy. Preliminary dose response analysis demonstrated effective blunting of 4% saline writhing with peak effects noted at 90 mcg. This result is in agreement with the known plateau effect of a mixed agonist/antagonist agent. The failure of nalbuphine to provide effective spinal analgesia was disappointing since its safety profile suggests clinical usefulness as a regional analgesic for labor and delivery. We have been able to demonstrate that, in some animals within a study group, a naloxone-reversible form of analgesia becomes evident at term pregnancy (unpublished observations). Since visceral analgesia is known to be mediated by both mu and kappa receptor systems, nalbuphine's antagonism of the former may have reduced endogenous suppression of visceral nociception to a degree that offset its relatively weak kappa analgesic effects. While enhancement of endogenous analgesia remains unclear in humans, this possibility may have implications during labor and delivery. In this setting, more optimal visceral analgesia may be provided by a potent yet selective kappa agonist (i.e. dynorphin).

References.

1. Sinatra RS, Marando R, Ngeow JYF, Collins JG. Visceral pain tolerance in pregnant rats following intrathecal administration of fentanyl. Anesthesiology 65:A370, 1986

2. Schmauss C, Doherty C, Yaksh TL: The analgetic effects of an intrathecally administered partial opiate agonist nalbuphine hydrochloride. Eur J Pharmacol 86:1-7, 1983.