TITLE: NALMEFENE FOR REVERSAL OF RESPIRATORY DEPRESSION SECONDARY TO INTRATHECAL MORPHINE

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Nalmefene (NALM) is a pure opioid antagonist and an analog of naltrexone (1,2) with a duration of action at least 4 times longer than naloxone (3). We report the first clinical study using NALM to reverse the respiratory depression associated with the administration of intrathecal morphine (ITM).

After institutional approval, 24 consenting patients, ASA I-IV, undergoing elective abdominal surgery were enrolled. Following diazepam 0.1 mg/kg po, patients were given ITM 0.75 mg. Anesthesia was then induced with sufentanil (0.5-1.5 mcg/kg), thiopental (1-4 mg/kg), and vecuronium (100 mcg/kg) and maintained with sufentanil (0.3-0.6 mcg/kg/hr), air, oxygen, and low-dose isoflurane (<1%). Upon emergence from anesthesia, NALM (1 mcg/kg, n=16, Group 1 or 0.5 mcg/kg, n=8, Group 2) was administered IV for respiratory depression (pH < 7.30 and/or Pco_2 > 55 mm Hg) with repeat doses (1.0 or 0.5 mcg/kg, respectively) as necessary for recurrent respiratory depression. Vital signs, and ABG's were obtained at frequent intervals for 24 hours after NALM. Laboratory profiles were performed before surgery and 24 hours after dosing.

In all patients, NALM caused an increase in respiratory rate and a decrease in Pco_2. The table below illustrates the number of patients that required either additional NALM for respiratory depression compared to additional analgesia at some time after NALM administration.

GROUP	INITIAL NALM	ADDITIONAL NALM		SUPPLEMENTAL ANALGESIA	
		n	min after 1st NALM	n	min after 1st NALM
1 (n=16)	1 mcg/kg	5/16	124 (5-256)	7/16	424 (33-1346)
2 (n=8)	0.5 mcg/kg	3/8	49 (21-96)	4/8	386 (5-1280)

None of the 5 patients in Group 1 who received additional NALM required supplemental analgesia. One of the 3 patients in Group 2 did require supplemental analgesia after additional NALM.

NALM is a safe, effective opioid antagonist which reliably reverses respiratory depression without reversing the analgesic effects of ITM. The advantage of NALM rests in its long duration of action. A single NALM dose of 0.5-1.0 mcg/kg antagonizes respiratory depression with little additional NALM required and allows pain relief to be maintained with minimal additional opioid.

References:
1. J Medicinal Chem, 1975, p. 259.
2. J Pharm Expt Therap, 1977, p. 496.
3. Anesthesiology, V 64, 1986, p. 175.

A386

TITLE: USE OF DRONABINOL FOR PREANESTHETIC MEDICATION

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Dronabinol (Marinol™), delta-9-tetrahydrocannabinol, is a centrally-active antiemetic which is currently used for treating chemotherapy-induced nausea and vomiting. It is alleged to have sedative, antisialagogue, and bronchodilatory properties. This study was designed to examine the safety and efficacy of dronabinol when used as an oral preanesthetic medication.

25 consenting ASA I-II patients, ages 18-64 yrs, undergoing elective general surgical procedures were divided into five groups according to an IRB-approved protocol. Five patients in each group received dronabinol 2.5, 5, 10, 15, or 20 mg po, 60-90 min prior to induction of anesthesia. Patients were evaluated at the time of drug administration and at 30 and 60 min using visual analog scales (0 = minimal to 100 = maximal) to assess anxiety, somnolence, confusion, nausea, and comfort. Cardiorespiratory measurements (MAP, HR, RR, Sa02) were performed at 15 min. intervals. Upon entering the operating room, the analog scales were repeated and patients were asked to describe the overall effect of the premedicant (i.e., pleasant, unpleasant, or no change). They were also shown a picture to assess amnesia. Induction of anesthesia consisted of fentanyl 2 ug/kg iv, thiopental 4 mg/kg iv, and a muscle relaxant. During laryngoscopy, the degree of salivation (1 = mild to 3 = marked) was noted. Anesthesia was maintained with 1-2% isoflurane and 67% N_2O. A 24h follow-up questionnaire was used to assess patient acceptance and side effects.

Dronabinol produced dose-dependent sedation and confusion (figs. A and B). There were no significant changes in any of the cardiorespiratory variables. Overall, 56% of the patients reported feeling "more relaxed" (only one patient felt more anxious), 40% felt the premedicant was pleasant, and 36% stated that they would like to receive dronabinol in the future. All patients were able to recall the picture at the time of induction. Finally, there was a similar incidence of postoperative nausea (20%) in all five groups.

In conclusion, dronabinol 2.5-20 mg po, produced variable degrees of sedation and anxiolysis when administered 60-90 min prior to elective surgery. However, increased confusion was noted after higher doses. Controlled studies comparing dronabinol to commonly used premedicants are clearly needed.