

**Pharmacy & Therapeutics Committee  
Review of Narcotic Agonist-Antagonist  
7/98**

**Recommendations: MEC Approved**

Dezocine is not recommended for formulary addition. The formulary alternative, Nubain, has a wider range of indications (L&D, post MI), is less expensive, and has a superior pharmacokinetic profile (longer half life and quicker onset). Nubain may also be given subcutaneously in contrast to dezocine.

**Dosage Equivalences & Pharmacokinetics**

	Onset (min)	Time to Peak (min)	Duration (hr)	T <sub>1/2</sub> Hours	Dose (mg) Equivalent To 10 mg Morphine	Relative Antagonist Activity
<b>Buprenorphine (Buprenex)</b> IM 0.3 mg q6h IV 0.3 mg q6h	15	60	6	2-3	0.3	Equal to Naloxone
<b>Butorphenol (Stadol)</b> IM 1-4 mg q3-4h IV 1-2 mg q3-4h	<10 Rapid	30-60	3-4	2.5-4	2-3	30x Pentazocine 1/40 Naloxone
<b>Dezocine (Dalgan)</b> IM 5-20 mg q3-6 h IV 2.5-10mg q2-4h <b>Not Subcutaneous</b>	≤ 30 ≤ 15	30-150	2-4	2.4 (Dose Dependent > 10 mg)	10	Greater than Pentazocine
<b>Nalbuphine ( Nubain )</b> IM 10 q3-6h IV 10 q3-6h SC 10 q3-6h	< 15 2-3	60 30	3-6	5	10	10X Pentazocine 1/120 Naloxone
<b>Pentazocine (Talwin)</b> IM 30-60 mg q3-4h IV 30 mg q3-4h Oral	15-20 2-3 15-30	15-60 nd 60-180	3	2-3	30	Weak

**Cost Analysis**

Drug	IV Dose	Cost/Dose	Potential Cost/Day
Buprenorphine	0.3 mg q6h	\$2.21	\$8.84
Butrophanol	1-2 mg q4h	\$5.16-5.39	\$31.65
Dezocine	5-10 mg q4h	\$3.60-3.48	<b>\$21.24</b>
Nalbuphine	5-10 mg q 4h	\$0.378	<b>\$2.26</b>
Pentazocine	30 mg q4h	\$3.44	\$20.64

Usage For Last 12 months

Nalbuphine 2700 doses at \$0.378 / dose= \$1,020.6

Cost of equivalent doses of Dalgan

2700 doses at \$3.48/ dose = \$9,396

Cost Difference (\$8,375.40)

**Findings:**

- Nalbuphine has similar effects when compared to meperidine in L&D uses, causing little effect on fetal heart rate.
- Nalbuphine has similar cardiovascular effects when compared to morphine in post MI patients and is widely used for these patients. Dezocine increases cardiac index, stroke volume index, left ventricular stroke work index and pulmonary vascular resistance and is not suggested for use post MI.

	<b>Narcotic Agonist-Antagonists: Package Insert Side Effects</b>				
	<b>Buprenorphine</b>	<b>Butorphanol</b>	<b>Dezocine</b>	<b>Nalbuphine</b>	<b>Pentazocine</b>
<b>Respiratory Depression</b>	Equivalent to Morphine	Equivalent to Morphine	Equivalent to Morphine	Equivalent to Morphine	Equivalent to Morphine
<b>N/V</b>	1-5%/5-10%	13%	3-9%	6%	> 10%
<b>Sedation</b>	66%	43%	3-9%	36%	> 10%
<b>Confusion</b>	<1%	3-9%	<1%		< 1%
<b>Dizziness/Vert</b>	5-10%	19%	1-3%	5%	
<b>Inj. Site Rxn</b>	<1%		3-9%		
<b>Cardiovascular System</b>	Equivalent to Morphine	to Do not use post MI (Similar to Pentazocine)	Not Significant	Not Significant	Do not use post MI*

\*Pentazocine: Elevates systemic and pulmonary arterial pressure, systemic vascular resistance and left ventricular end-diastolic pressure, causing increased cardiac workload.  
 Nalbuphine does not significantly increase pulmonary artery pressure or systemic vascular resistance or cardiac work.

## L&D Use

Three studies on the effects of nalbuphine during labor, two compared effects to meperidine, see conclusion below. Dezocin use in L&D has not been studied.

AU - Poehlmann S, Pinette M, Stubblefield P

TI - Effect of labor analgesia with **nalbuphine hydrochloride** on fetal response to vibroacoustic stimulation.

AD - Department of Obstetrics and Gynecology, Maine Medical Center, Portland, USA.

AB - OBJECTIVE: To evaluate the effect of labor analgesia with nalbuphine hydrochloride on the fetal response to vibroacoustic stimulation. STUDY DESIGN: The response to fetal acoustic stimulation (FAS) was recorded in 27 laboring patients before analgesia. After analgesia with 5 mg nalbuphine hydrochloride administered subcutaneously, the response to FAS was again recorded. RESULTS: No ominous fetal heart rate (FHR) patterns were observed. FAS reliably increased FHR baseline and long-term FHR variability and produced FHR accelerations. Nalbuphine hydrochloride analgesia did not produce a significant decrease in long-term FHR variability or alter FHR baseline but did reduce the number of FHR accelerations recorded. **CONCLUSION: FAS-induced FHR accelerations did not differ from those observed before analgesia. Analgesia with low doses of nalbuphine did not alter fetal response to FAS, which therefore offers a means of assessing fetal well-being even in the narcotized fetus.**

SO - J Reprod Med 1995 Oct;40(10):707-10

AU - Giannina G, Guzman ER, Lai YL, Lake MF, Cernadas M, Vintzileos AM

TI - Comparison of the effects of **meperidine and nalbuphine** on intrapartum fetal heart rate tracings [see comments]

CM - Comment in: Obstet Gynecol 1996 Jan;87(1):158-9

AD - Department of Obstetrics, Gynecology, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, St. Peter's Medical Center, New Brunswick, USA.

AB - OBJECTIVE: To examine the effects of meperidine and nalbuphine on intrapartum fetal heart rate (FHR) tracings using computer analysis. METHODS: We studied 28 women with uncomplicated pregnancies in early labor at term with reactive FHR tracings. The women were randomized to receive either meperidine 50 mg or nalbuphine 10 mg intravenously on request. One-hour FHR recordings were obtained before and immediately after administration of the medications. RESULTS: There were no significant differences in the FHR characteristics of the two groups during the pre-treatment period. Nalbuphine significantly decreased the number of accelerations of 10 beats per minute (17 versus 4,  $P = .003$ ) and 15 beats per minute (10 versus 1.5,  $P = .001$ ), time spent in episodes of high variation (35.5 versus 10 minutes,  $P = .004$ ), long-term variation (47 versus 29.8 milliseconds,  $P = .002$ ), and short-term variation (8.4 versus 6.4 milliseconds,  $P = .03$ ). Meperidine had no significant effect on any FHR characteristic. **CONCLUSION: In the early intrapartum period of normal term pregnancies and at commonly used dosages, nalbuphine had a significant effect on FHR tracings, whereas meperidine had no effect, as determined by computer analysis.**

SO - Obstet Gynecol 1995 Sep;86(3):441-5

3

AU - Dan U, Rabinovici Y, Barkai G, Modan M, Etchin A, Mashiach S

TI - Intravenous **pethidine and nalbuphine** during labor: a prospective double-blind comparative study.

AD - Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel.

AB - The perfect analgesic regimen is constantly sought, no matter how labor is conducted. The quest for an effective drug that will afford maximum relaxation and pain relief with minimum interruption of any natural homeostatic mechanism is a foremost subject in present obstetric analgesics research. Synthetic alternatives are being offered, promising perfect compatibility with the clinician's demands. Nalbuphine, a semisynthetic narcotic agonist-antagonist analgesic of the penanthren series, is supposed not to be liable to cause respiratory depression and is expected to have fewer side effects. A double-blind, randomised prospective study of 137 patients who received 10 mg nalbuphine or 50 mg pethidine i.v. during the active phase of labor in term was carried out. Maternal cardiovascular variables, pain intensity, progress of labor and fetal heart rate during labor were related to side effect and neonatal outcome (1- and 5-min Apgar scores and umbilical venous pH). **Neither regimen showed an advantage over the other. Data analysis points to a possible transient depressive effect induced by nalbuphine on the fetal or neonatal central nervous system.**

SO - Gynecol Obstet Invest 1991;32(1):39-43

## Acute MI

Two studies of nalbuphine use in AMI were found. Dezocine has not be studied in AMI.

1

AU - Roth A, Keren G, Gluck A, Braun S, Laniado S

TI - Comparison of **nalbuphine hydrochloride versus morphine** sulfate for acute myocardial infarction with elevated pulmonary artery wedge pressure.

AD - Department of Cardiology, Tel-Aviv Medical Center, Israel.

AB - The hemodynamic and respiratory effects of intravenous nalbuphine hydrochloride and morphine sulfate were compared in a randomized fashion in 20 patients (age 65 +/- 11 years) with acute myocardial infarction and elevated pulmonary artery wedge pressure. Titration of the nalbuphine dose to lower pulmonary artery wedge pressure by greater than or equal to 25% resulted in a decrease of this parameter from 22 +/- 3 to 15 +/- 4 mm Hg, and was associated with a reduction in heart rate from 106 +/- 20 to 96 +/- 19 beats/min (p less than 0.05) and decreases in mean blood pressure (78 +/- 8 to 70 +/- 12 mm Hg, p less than 0.05) and mean pulmonary artery pressure (31 +/- 4 to 22 +/- 5 mm Hg, p less than 0.05), without any remarkable change seen in cardiac index (2.21 +/- 0.43 to 2.22 +/- 0.50 liter/min/m<sup>2</sup>, difference not significant), stroke volume index (22 +/- 7 to 23 +/- 4 ml/m<sup>2</sup>, difference not significant), stroke work index (17 +/- 7 to 18 +/- 7 g.m/m<sup>2</sup>), or systemic and pulmonary vascular resistances (1,675 +/- 333 to 1,513 +/- 508 and 191 +/- 78 to 170 +/- 109 dynes.s.cm<sup>-5</sup> respectively, all differences not significant). Nalbuphine also significantly reduced respiratory rate (32 +/- 8 to 26 +/- 8 resp/min, p less than 0.05) and pH (7.45 +/- 0.04 to 7.41 +/- 0.03, p less than 0.05) and increased arterial PCO<sub>2</sub> (32 +/- 6 to 35 +/- 6 mm Hg, p less than 0.05) without any major change in arterial PO<sub>2</sub> (63 +/- 13 to 66 +/- 17 mm Hg, difference not significant). **All these changes were coparable with morphine sulfate and no statistical difference was noted between the effects in duced by both drugs. Nalbuphines's dosage ranged from 5-30 mg (mean± SD 17 ± 8 mg) and could not be predicted from baseline hemodynamic and respiratory values.**

SO - Am J Cardiol 1988 Sep 15;62(9):551-5

4

AU - Greenbaum RA, Kaye G, Mason PD

TI - Experience with nalbuphine, a new opioid analgesic, in acute myocardial infarction.

AD - Royal Free Hospital and School of Medicine, London.

AB - A total of 141 patients admitted to hospital with a diagnosis of suspected myocardial infarction were randomized to treatment with intravenous diamorphine (71) or nalbuphine (70). Myocardial infarction was subsequently confirmed in 109 patients. Both drugs provided good analgesia. Heart rate, blood pressure, respiratory rate, peak flow and minute volume were measured over a three-hour study period. Except for a slight fall in systolic blood pressure in the nalbuphine-treated group, there were no statistically significant differences between the groups. The nalbuphine-treated group had higher levels of aspartate aminotransferase and hydroxybutyric acid dehydrogenase but not creatine phosphokinase. **The haemodynamic outcome and mortality at three months of the two groups were similar. It is concluded that nalbuphine provides effective analgesia coupled with few adverse circulatory or respiratory effects.**

SO - J R Soc Med 1987 Jul;80(7):418-21

## PostOperative Pain

9

AU - Finucane BT, Floyd JB, Petro DJ

TI - Postoperative pain relief: a double-blind comparison of **dezocine, butorphanol**, and placebo.

AB - The safety and efficacy of single intramuscular doses of dezocine (10 or 15 mg) were compared with butorphanol (2 mg) and placebo in 157 patients with moderate to severe postoperative pain. A verbal pain intensity scale, an analog pain intensity scale, and a verbal pain relief scale were used to record the patients' subjective assessments. The results of this study indicate that a single 10 or 15 mg intramuscular injection of dezocine is safe and more effective than placebo for four to six hours, respectively, in the treatment of moderate to severe postoperative pain (P less than .05). During the first hour of treatment the pain relief afforded by 2 mg of butorphanol was significantly greater than that afforded by 10 mg of dezocine (P less than .05), but both doses of dezocine provided long-lasting relief. The scores on all three efficacy scales were highest with the 15 mg dose of dezocine after the first hour, while the 10 mg dose of dezocine and butorphanol were compared during this period. Nausea and vomiting were the most commonly reported side effects (8% and 5% for dezocine versus 3% and 3% for butorphanol); injection site reactions were reported more frequently in the butorphanol group.

4

UI - 86156867

AU - Galloway FM

AU - Varma S

TI - Double-blind comparison of intravenous doses of dezocine, butorphanol, and placebo for relief of postoperative pain.

AB - The safety and efficacy of intravenous doses **of dezocine (5 or 10 mg), butorphanol (1 mg)**, and placebo were compared in a double-blind study in 160 patients with moderate to severe postoperative pain. Analgesic efficacy was assessed for 6 hours after each dose. Mean pain relief scores were consistently higher, indicating greater pain relief, for the three active treatment groups than for the placebo group. The 10-mg dezocine dose was the most effective treatment, and 5 mg of dezocine was comparable to 1 mg of butorphanol. In the 2 hours after the first dose, 32% of the 10-mg dezocine group, 53% of the 5-mg dezocine group, 65% of the butorphanol group, and 88% of the placebo group withdrew from the study because of unsatisfactory pain relief. The differences in these percentages were statistically significant ( $P$  less than 0.05) between each active therapy group and the placebo group, and between the 10-mg dezocine group and the butorphanol group. Changes in degree of sedation were similar in the three active therapy groups. Adverse reactions were rare, mild, and equally distributed among the four treatment groups. Nausea and vomiting occurred in 19% and 13% of dezocine and butorphanol patients respectively. We conclude that 10 mg of dezocine is superior to 1 mg of butorphanol, and that 5 mg of dezocine is as effective as 1 mg of butorphanol for the relief of moderate to severe postoperative pain.

SO - Anesth Analg 1986 Mar;65(3):283-7

1

UI - 98088432

AU - Gray A

AU - Johnson G

AU - Goodacre S

TI - Paramedic use of nalbuphine in major injury.

AD - Accident and Emergency Department, St James's University Hospital, Leeds, UK.

AB - Paramedic training and skills have been introduced in the United Kingdom in an attempt to improve prehospital patient care. There is presently little control and quality assurance in this potentially difficult environment and paramedic protocols have not been validated. We studied the use of nalbuphine by paramedics for patients with major injury in West Yorkshire. A case-control study was carried out using two cohorts of patients from the regional Major Trauma Outcome Study (MTOS) database; one group had received prehospital nalbuphine by paramedics (the intervention) and a matched group who had not (the control). Both groups of patients were reviewed by a panel of three consultants and a paramedic to assess which patients received or could have received nalbuphine appropriately. Only 85 patients from a database of 4170 patients received nalbuphine. Fifty-two (61%) patients were thought by the panel to have been given nalbuphine appropriately. The panel also concluded that 21 (18%) of the 115 patient control group could have been administered nalbuphine but did not receive the drug. This study demonstrates inadequate and sometimes inappropriate use of nalbuphine in prehospital trauma care. Quality assurance and audit systems should be implemented to identify and correct these deficiencies.

JOURNAL ARTICLE

LA - Eng

SO - Eur J Emerg Med 1997 Sep;4(3):136-9

2

UI - 98067986

AU - Khan FA

AU - Zaidi A

AU - Kamal RS

TI - Comparison of nalbuphine and buprenorphine in total intravenous anaesthesia.

AD - Department of Anaesthesia, Aga Khan University Hospital, Karachi, Pakistan.

AB - Nalbuphine (0.3 mg.kg<sup>-1</sup>) and buprenorphine (2.5 micrograms.kg<sup>-1</sup>) were compared as part of a total intravenous anaesthesia regimen using a propofol infusion in 60 patients undergoing laparoscopic cholecystectomy in a randomised double-blind study. Changes in haemodynamic variables greater than 20% from the baseline were noted. No difference was observed in blood pressure but the heart rate was significantly lower in the buprenorphine group. Intra-operative bradycardia (heart rate < 60 beat.min<sup>-1</sup>) occurred more often in the buprenorphine group. Recovery was fast and comparable with both drugs and no patient reported awareness. Quality of analgesia was similar in both groups. Both drugs provide suitable analgesic supplementation to total intravenous anaesthesia.

LA - Eng

SO - Anaesthesia 1997 Nov;52(11):1095-101

3

UI - 97219924

AU - Zacny JP

AU - Conley K

AU - Marks S

TI - Comparing the subjective, psychomotor and physiological effects of intravenous nalbuphine and morphine in healthy volunteers.

AD - Department of Anesthesia and Critical Care, The Pritzker School of Medicine, The University of Chicago, Illinois 60637, USA.

AB - The purposes of this study were to characterize the subjective, psychomotor and physiological effects of nalbuphine in healthy non-drug abusing volunteers and to compare and contrast the effects of equianalgesic doses of nalbuphine and morphine. Subjects (12 males, 4 females) without histories of opiate dependence were injected in an upper extremity vein with 0, 2.5, 5.0 or 10 mg/70 kg nalbuphine, or with 10 mg/70 kg morphine, using a randomized, double-blind, crossover design. The 10-mg doses of nalbuphine and morphine are considered equianalgesic and are doses commonly given for relief of postoperative pain. Subjective effects of nalbuphine included increased scores on the Pentobarbital-Chlorpromazine-Alcohol Group scale and the Lysergic Acid Diethylamide scale of the Addiction Research Center Inventory; increased adjective checklist ratings of "nodding," "numb" and "sweating"; increased visual analog scale ratings of "coasting or spaced out," "high" and "sleepy" and increased "feel drug effect" and drug-liking ratings. Ten milligrams of nalbuphine had subjective effects similar, and similar in magnitude, to those of 10 mg of morphine. Nalbuphine produced exophoria and

impairment on the Digit Symbol Substitution Test in a dose-related fashion. Ten milligrams of morphine produced euphoria but did not affect performance on the Digit Symbol Substitution Test. Both nalbuphine and morphine induced miosis and decreases in respiration rate. The results of the present study demonstrate that 2.5 to 10 mg nalbuphine had orderly, dose-related effects on subjective, psychomotor and physiological variables. The results also indicate that 10 mg of nalbuphine produces a profile of subjective, psychomotor and physiological effects similar to that of an equianalgesic dose of morphine (10 mg). The similarity in profiles between drugs at this dose is consistent with both infrahuman studies, which suggests that nalbuphine is a mu agonist, and studies with nondependent opioid abusers, in which relatively low doses of nalbuphine (such as 10 mg) produce morphine-like effects.

LA - Eng

SO - J Pharmacol Exp Ther 1997 Mar;280(3):1159-69

4

UI - 96130415

AU - Poehlmann S

AU - Pinette M

AU - Stubblefield P

TI - Effect of labor analgesia with nalbuphine hydrochloride on fetal response to vibroacoustic stimulation.

AD - Department of Obstetrics and Gynecology, Maine Medical Center, Portland, USA.

AB - OBJECTIVE: To evaluate the effect of labor analgesia with nalbuphine hydrochloride on the fetal response to vibroacoustic stimulation. STUDY DESIGN: The response to fetal acoustic stimulation (FAS) was recorded in 27 laboring patients before analgesia. After analgesia with 5 mg nalbuphine hydrochloride administered subcutaneously, the response to FAS was again recorded. RESULTS: No ominous fetal heart rate (FHR) patterns were observed. FAS reliably increased FHR baseline and long-term FHR variability and produced FHR accelerations. Nalbuphine hydrochloride analgesia did not produce a significant decrease in long-term FHR variability or alter FHR baseline but did reduce the number of FHR accelerations recorded. CONCLUSION: FAS-induced FHR accelerations did not differ from those observed before analgesia. Analgesia with low doses of nalbuphine did not alter fetal response to FAS, which therefore offers a means of assessing fetal well-being even in the narcotized fetus.

SO - J Reprod Med 1995 Oct;40(10):707-10

5

UI - 96123220

AU - Dawes GS

TI - Comparison of the effects of meperidine and nalbuphine on intrapartum fetal heart rate tracings [letter; comment]

CM - Comment on: Obstet Gynecol 1995 Sep;86(3):441-5

MH - Analgesics, Opioid/\*PHARMACOLOGY

MH - Comparative Study

MH - Female

MH - Heart Rate, Fetal/\*DRUG EFFECTS

MH - Human

MH - Labor

MH - Meperidine/\*PHARMACOLOGY

MH - Nalbuphine/\*PHARMACOLOGY

MH - Pregnancy

PT - COMMENT

PT - LETTER

LA - Eng

SO - Obstet Gynecol 1996 Jan;87(1):158-9

6

UI - 95354392

AU - Doenicke A

AU - Moss J

AU - Lorenz W

AU - Hoerneck R

TI - Intravenous morphine and nalbuphine increase histamine and catecholamine release without accompanying hemodynamic changes.

AD - University of Munich, Germany.

AB - Patients receiving intravenous morphine at doses of 0.3 and 1.0 mg/kg for general anesthesia have been reported to show significant elevations in plasma histamine that are associated with hemodynamic changes. We

undertook a prospective, randomized, double-blind trial in which 0.15 mg/kg morphine or 0.3 mg/kg nalbuphine was administered intravenously to normal volunteers. Thirteen of 15 subjects receiving morphine and 10 of 14 subjects receiving nalbuphine had elevations in plasma histamine levels and symptoms of histamine release within 5 minutes of drug administration. Six subjects in the morphine group and five in the nalbuphine group exhibited levels of plasma histamine > 2.0 ng/ml, but these levels were not associated with hemodynamic changes and occurred 10 to 15 minutes after drug administration. Our study suggests that the opiate-induced elevation of plasma histamine derives from cutaneous mast cells.

MH - Adolescence

MH - Adult

SO - Clin Pharmacol Ther 1995 Jul;58(1):81-9

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7

UI - 95380100

AU - Giannina G

AU - Guzman ER

AU - Lai YL

AU - Lake MF

AU - Cernadas M

AU - Vintzileos AM

TI - Comparison of the effects of meperidine and nalbuphine on intrapartum fetal heart rate tracings [see comments]

CM - Comment in: Obstet Gynecol 1996 Jan;87(1):158-9

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SO - Obstet Gynecol 1995 Sep;86(3):441-5

1

UI - 93049581

AU - Benzer A

AU - Hussler R

AU - Russegger L

AU - Faserl A

AU - Balogh D

TI - Increase in cerebrospinal fluid pressure in normocapnic volunteers in response to nalbuphine.

AD - Department of Anaesthesia, University of Innsbruck, Austria.

AB - We have carried out a double-blind randomized study of the effect of nalbuphine (0.2 mg.kg<sup>-1</sup> i.v.) or placebo on mean lumbar cerebrospinal fluid (CSF) pressure, mean cerebral perfusion pressure (CPP), transcutaneous PCO<sub>2</sub> (tcPCO<sub>2</sub>), mean arterial blood pressure (MAP), and heart rate (HR) in 10 spontaneously breathing volunteers using invasive CSF pressure measurement. Nalbuphine increased CSF pressure from 9.2 mmHg to 16.4 mmHg and decreased CPP from 83.6 mmHg to 74.4 mmHg without significantly changing tcPCO<sub>2</sub>, MAP, or heart rate. In the placebo group there were no significant changes in CSF pressure, CPP, tcPCO<sub>2</sub>, MAP, or heart rate. These findings suggest that nalbuphine should be used with caution in patients at risk of intracranial hypertension.

SO - Eur J Clin Pharmacol 1992;43(2):193-5

2

UI - 91204720

AU - Preston KL

AU - Bigelow GE

AU - Liebson IA

TI - Discrimination of butorphanol and nalbuphine in opioid-dependent humans.

AD - Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Francis Scott Key Medical Center, Baltimore, MD 21224.

AB - The purpose of the study was to evaluate the agonist and antagonist stimulus properties of the mixed opioid agonist antagonists butorphanol and nalbuphine in opioid-dependent subjects. Opioid-dependent volunteers (methadone 30 mg/day, PO) were trained in a three-choice drug discrimination procedure to discriminate between the effects of saline (2 ml), hydromorphone (10 mg/70 kg) and naloxone (0.15 mg/70 kg) administered IM.

Subjects earned monetary reinforcement for correctly identifying the training drugs by letter code. Other subjective, behavioral and physiological measures were also collected. Hydromorphone and naloxone increased drug-appropriate responses and other characteristic subjective effects measures. Butorphanol and nalbuphine produced increases in naloxone-appropriate discrimination responding and in those subjective effect measures increased by naloxone. Butorphanol produced greater than 80% naloxone-appropriate responding at 1.05 mg/70 kg; nalbuphine produced 100% naloxone-appropriate responding at 2.1 mg/70 kg. Neither butorphanol nor nalbuphine showed opioid agonist-like effects in these subjects maintained at moderate levels of physical dependence. In opioid-dependent subjects, the stimulus effects of butorphanol and nalbuphine are antagonist-like.

SO - Pharmacol Biochem Behav 1990 Nov;37(3):511-22

3

UI - 92112132

AU - Dan U

AU - Rabinovici Y

AU - Barkai G

AU - Modan M

AU - Etchin A

AU - Mashiach S

TI - Intravenous pethidine and nalbuphine during labor: a prospective double-blind comparative study.

AD - Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel.

AB - The perfect analgesic regimen is constantly sought, no matter how labor is conducted. The quest for an effective drug that will afford maximum relaxation and pain relief with minimum interruption of any natural homeostatic mechanism is a foremost subject in present obstetric analgesics research. Synthetic alternatives are being offered, promising perfect compatibility with the clinician's demands. Nalbuphine, a semisynthetic narcotic agonist-antagonist analgesic of the penanthren series, is supposed not to be liable to cause respiratory depression and is expected to have fewer side effects. A double-blind, randomised prospective study of 137 patients who received 10 mg nalbuphine or 50 mg pethidine i.v. during the active phase of labor in term was carried out. Maternal cardiovascular variables, pain intensity, progress of labor and fetal heart rate during labor were related to side effect and neonatal outcome (1- and 5-min Apgar scores and umbilical venous pH). Neither regimen

showed an advantage over the other. Data analysis points to a possible transient depressive effect induced by nalbuphine on the fetal or neonatal central nervous system.

SO - Gynecol Obstet Invest 1991;32(1):39-43

4

UI - 92059986

AU - Weiss BM

AU - Schmid ER

AU - Gattiker RI

TI - Comparison of nalbuphine and fentanyl anesthesia for coronary artery bypass surgery. Hemodynamics, hormonal response, and postoperative respiratory depression.

AD - Institute of Anesthesiology, University Hospital Zurich, Switzerland.

AB - To determine whether nalbuphine might replace fentanyl as the principal opioid for anesthesia during coronary artery bypass surgery, 20 patients undergoing myocardial revascularization were anesthetized with flunitrazepam and with a continuous infusion of either nalbuphine (an opioid agonist-antagonist) or fentanyl (a pure opioid agonist) in equipotent dosage ratio of 333:1. During endotracheal intubation, all patients given nalbuphine, but only one given fentanyl (P less than 0.05), required nitroglycerin to control arterial blood pressure. Two minutes after tracheal intubation, plasma values of epinephrine, norepinephrine, vasopressin, and cortisol did not change in the fentanyl group compared with the awake (baseline) levels, whereas catecholamines and vasopressin significantly increased with nalbuphine compared with the baseline and with the values in the fentanyl group. A steady state of anesthesia (30 min after intubation), when compared with the

baseline, was characterized by unchanged systemic and pulmonary blood pressures and increased systemic vascular resistance with nalbuphine, by decreased systemic and pulmonary pressures and resistances with fentanyl, and by comparably decreased cardiac index with both opioids. Hormone values returned to baseline levels but norepinephrine remained significantly higher in the nalbuphine than in the fentanyl group. A bolus injection of either nalbuphine (2.5 mg/kg) or fentanyl (7.5 micrograms/kg) given during the steady-state period of anesthesia provoked only minimal hemodynamic changes. Before skin incision, 7 of 10 patients receiving nalbuphine required nitroglycerin to control arterial blood pressure. After sternotomy, both groups required nitroglycerin, but additional antihypertensive drugs were necessary mainly in the nalbuphine group.(ABSTRACT TRUNCATED AT 250 WORDS)

SO - Anesth Analg 1991 Nov;73(5):521-9

5

UI - 92025360

AU - Zeller W

AU - Kueck J

AU - Tennis G

TI - Sinusoidal fetal heart rate pattern after administration of nalbuphine.

AD - Department of Obstetrics and Family Practice, Skaggs Community Hospital, Branson, MO 65616.

SO - J Am Board Fam Pract 1991 Jul-Aug;4(4):261-2

6

UI - 90261438

AU - Rawal N

AU - Wennhager M

TI - Influence of perioperative nalbuphine and fentanyl on postoperative respiration and analgesia.

AD - Department of Anesthesiology and Intensive Care, Orebro Medical Center Hospital, Sweden.

AB - In a double-blind study the relative postoperative respiratory and analgesic effects of perioperatively administered nalbuphine and fentanyl were compared in 60 females undergoing gynecological surgery under i.v. anesthesia. One milliliter (10 mg) nalbuphine was considered equipotent to 1 ml (100 micrograms) fentanyl. In the recovery period pain was assessed by visual analog score (VAS) and recovery by Pegboard scoring. Respiratory function was evaluated by continuous monitoring of respiratory frequency and end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) and by frequent arterial blood gas analyses. The total volume of analgesic required for surgical analgesia was similar in the two groups. Patients in the nalbuphine group showed mild to moderate increases in pulse rate during the intubation phase and in blood pressure during surgery. Fentanyl was more effective in suppressing these cardiovascular responses. Within the first 15 min following recovery, increasing PaCO<sub>2</sub> and ETCO<sub>2</sub> as well as respiratory rates below 10/min were noted in 8 patients, who all belonged to the fentanyl group; in 4 of these patients i.v. naloxone had to be administered to reverse respiratory depression. Prolonged sedation was a common feature in patients receiving nalbuphine. It was concluded that fentanyl was superior to nalbuphine in attenuating the pressor responses to intubation and surgery. However, fentanyl was associated with respiratory depression in a considerable number of patients. The quality and duration of postoperative analgesia were similar in the two groups.

SO - Acta Anaesthesiol Scand 1990 Apr;34(3):197-202

7

UI - 91082634

+AU - Crul JF

AU - Smets MJ

AU - van Egmond J

TI - The efficacy and safety of nalbuphine (NUBAIN) in balanced anesthesia. A double blind comparison with fentanyl in gynecological and urological surgery.

AD - Medical Faculty University of Nijmegen, The Netherlands.

AB - In a prospective double blind study the efficacy and safety of nalbuphine as an analgesic in balanced anesthesia has been compared to fentanyl. In 63 patients, ASA class I-III, major gynecological or urological surgical procedures were performed under balanced anesthesia. Analgesia could be satisfactory maintained in all cases, but in cases of nalbuphine more hypnotics were necessary to keep the patients unconscious. The ratio of fentanyl and nalbuphine consumption was 1:200 (by weight). The nalbuphine cases can be distinguished by: more stable but higher arterial pressures and absence of arrhythmia; lower incidence of nausea and vomiting in the postoperative period; less respiratory depression at the end of anesthesia, not needing antagonists, as compared to 11 patients needing antagonization in the fentanyl group; and a larger incidence of minor local allergic reactions at the injection site. Awareness was not observed in any patient of either group. Although nalbuphine has a weaker analgesic and hypnotic effect, it is perfectly possible to provide balanced anesthesia in combination with

a hypnotic and a muscle relaxant. Advantages are the absence of respiratory depression as well as nausea and vomiting in the postoperative period.

SO - Acta Anaesthesiol Belg 1990;41(3):261-7

8

UI - 91029794

AU - Blaise GA

AU - Nugent M

AU - McMichan JC

AU - Durant PA

TI - Side effects of nalbuphine while reversing opioid-induced respiratory depression: report of four cases [see comments]

CM - Comment in: Can J Anaesth 1991 Sep;38(6):800-1

AD - Department of Anesthesia, Notre Dame Hospital, University of Montreal, Quebec, Canada.

AB - Nalbuphine hydrochloride, an agonist-antagonist opioid, is

reported to reverse the respiratory depression of moderate doses of fentanyl (20 micrograms.kg<sup>-1</sup>) and still provide good analgesia. We report four patients having abdominal aortic aneurysm repair in which we attempted to reverse the respiratory depression of large doses of fentanyl (50-75 micrograms.kg<sup>-1</sup>) with nalbuphine (0.3 mg.kg<sup>-1</sup>, 0.1 mg.kg<sup>-1</sup> or 0.05 mg.kg<sup>-1</sup>). Nalbuphine reversed respiratory depression in all four patients and the respiratory rate increased from 10 to 23 breaths per minute, end-tidal CO<sub>2</sub> decreased from 7.0 +/- 0.3 per cent to 5.6 +/- 0.7 per cent, and peak inspiratory pressure after 0.1 seconds increased from 4 +/- 1.4 to 13 +/- 2.6 mmHg. However, hypertension, increased heart rate, and significant increase in analogue pain scores accompanied reversal of respiratory depression. Agitation, nausea, vomiting, and cardiac dysrhythmias also were observed frequently. We do not recommend the use of nalbuphine to facilitate early extubation of the trachea after large doses of fentanyl for abdominal aortic surgery.

SO - Can J Anaesth 1990 Oct;37(7):794-7

1

UI - 88324169

AU - Roth A

AU - Keren G

AU - Gluck A

AU - Braun S

AU - Laniado S

TI - Comparison of nalbuphine hydrochloride versus morphine sulfate for acute myocardial infarction with elevated pulmonary artery wedge pressure.

AD - Department of Cardiology, Tel-Aviv Medical Center, Israel.

AB - The hemodynamic and respiratory effects of intravenous nalbuphine hydrochloride and morphine sulfate were compared in a randomized fashion in 20 patients (age 65 +/- 11 years) with acute myocardial infarction and elevated pulmonary artery wedge pressure. Titration of the nalbuphine dose to lower pulmonary artery wedge pressure by greater than or equal to 25% resulted in a decrease of this parameter from 22 +/- 3 to 15 +/- 4 mm Hg, and was associated with a reduction in heart rate from 106 +/- 20 to 96 +/- 19 beats/min (p less than 0.05) and decreases in mean blood pressure (78 +/- 8 to 70 +/- 12 mm Hg, p less than 0.05) and mean pulmonary artery pressure (31 +/- 4 to 22 +/- 5 mm Hg, p less than 0.05), without any remarkable change seen in cardiac index (2.21 +/- 0.43 to 2.22 +/- 0.50 liter/min/m<sup>2</sup>, difference not significant), stroke volume index (22 +/- 7 to 23 +/- 4 ml/m<sup>2</sup>, difference not significant), stroke work index (17 +/- 7 to 18 +/- 7 g.m/m<sup>2</sup>), or systemic and pulmonary vascular resistances (1,675 +/- 333 to 1,513 +/- 508 and 191 +/- 78 to 170 +/- 109 dynes.s.cm<sup>-5</sup> respectively, all differences not significant). Nalbuphine also significantly reduced respiratory rate (32 +/- 8 to 26 +/- 8 resp/min, p less than 0.05) and pH (7.45 +/- 0.04 to 7.41 +/- 0.03, p less than 0.05) and increased arterial PCO<sub>2</sub> (32 +/- 6 to 35 +/- 6 mm Hg, p less than 0.05) without any major change in arterial PO<sub>2</sub> (63 +/- 13 to 66 +/- 17 mm Hg, difference not significant).(ABSTRACT TRUNCATED AT 250 WORDS)

SO - Am J Cardiol 1988 Sep 15;62(9):551-5

2

UI - 88238961

AU - Sury MR

AU - Cole PV

TI - Nalbuphine combined with midazolam for outpatient sedation. An assessment in fiberoptic bronchoscopy patients.

AD - Anaesthetics Laboratory, St Bartholomew's Hospital, West Smithfield, London.

AB - Forty patients who required day case fiberoptic bronchoscopy were sedated with either nalbuphine 0.2 mg/kg and midazolam 0.05 mg/kg (n = 20), or midazolam 0.05 mg/kg alone (n = 20). Extra midazolam was administered when required. The degree of respiratory depression measured by arterialised venous carbon dioxide levels was recorded together with heart rate, arterial blood pressure, respiratory rate and sedation score, before

administration of the drugs and at regular intervals thereafter. Patients who received nalbuphine had slightly higher carbon dioxide levels but respiratory rate and cardiovascular changes were similar in both groups. The addition of nalbuphine to midazolam improves the quality of sedation but prolongs the recovery time and increases the incidence of side effects.

SO - Anaesthesia 1988 Apr;43(4):285-8

3

UI - 89269490

AU - Admiraal PV

AU - Wozniak S

TI - Comparison of intramuscular nalbuphine and nicomorphine in the treatment of post-operative pain.

AD - Dept. of Anesthesiology, Reinier de Graaf Gasthuis, Delft.

AB - Nalbuphine and nicomorphine were administered intramuscularly in single doses for the relief of moderate to severe pain after abdominal surgery in a group of 40 patients to compare the analgesic effect and clinical tolerance during a 2 hour period. There was no statistically significant difference of the analgesic effect. In both groups SBP, DBP and RR decreased and HR increased significantly after injection but the tolerance of nalbuphine seems to be better. Nalbuphine is a good choice for postoperative pain.

SO - Acta Anaesthesiol Belg 1989;40(1):59-64

4

UI - 88011029

AU - Greenbaum RA

AU - Kaye G

AU - Mason PD

TI - Experience with nalbuphine, a new opioid analgesic, in acute myocardial infarction.

AD - Royal Free Hospital and School of Medicine, London.

AB - A total of 141 patients admitted to hospital with a diagnosis of suspected myocardial infarction were randomized to treatment with intravenous diamorphine (71) or nalbuphine (70). Myocardial infarction was subsequently confirmed in 109 patients. Both drugs provided good analgesia. Heart rate, blood pressure, respiratory rate, peak flow and minute volume were measured over a three-hour study period. Except for a slight fall in systolic blood pressure in the nalbuphine-treated group, there were no statistically significant differences between the groups. The nalbuphine-treated group had higher levels of aspartate aminotransferase and hydroxybutyric acid dehydrogenase but not creatine phosphokinase. The haemodynamic outcome and mortality at three months of the two groups were similar. It is concluded that nalbuphine provides effective analgesia coupled with few adverse circulatory or respiratory effects.

SO - J R Soc Med 1987 Jul;80(7):418-21

5

UI - 88021873

AU - Zsigmond EK

AU - Winnie AP

AU - Raza SM

AU - Wang XY

AU - Barabas E

TI - Nalbuphine as an analgesic component in balanced anesthesia for cardiac surgery.

AD - Department of Anesthesiology, University of Illinois Medical Center, Chicago.

AB - The efficacy and safety of nalbuphine hydrochloride as an IV analgesic used in combination with pretreatment and supplemental doses of diazepam with and without N<sub>2</sub>O were assessed in 15 patients scheduled to undergo aortocoronary bypass (n = 11) or valve replacement surgery (n = 4). The loading infusion of 3.0 mg/kg nalbuphine given in 20 min 5 min after conclusion of IV injection of 0.4 mg/kg/5 min diazepam caused no significant changes in systolic or diastolic systemic and pulmonary arterial blood pressures or in heart rate, cardiac index, stroke index, systemic and pulmonary vascular resistance, or right and left ventricular stroke work index. After the initial 1-hr loading infusion of 6.66 +/- 0.89 mg/kg nalbuphine (mean +/- SE), additional nalbuphine infusion maintenance doses of 4.73 +/- 0.77, 1.87 +/- 0.31, 2.16 +/- 0.23, 1.65 +/- 0.22, and 2.35 +/- 0.44 were used in the subsequent hourly periods to maintain a pain-free state throughout surgery. Hemodynamic changes during the three most stressful periods, tracheal intubation, skin incision, and sternotomy, were not statistically significant. Normal plasma catecholamine and cortisol levels indicate that these patients experienced neither stress nor pain during the maintenance of anesthesia. Nalbuphine caused no significant histamine release. All patients had uncomplicated maintenance of and emergence from anesthesia.

SO - Anesth Analg 1987 Nov;66(11):1155-64

6

UI - 87225387

AU - Scott RF

TI - A double-blind comparison of nalbuphine and meperidine hydrochloride as intravenous analgesics in combination with diazepam for oral surgery outpatients.

AB - This study compared the analgesic efficacy, sedative, and amnesic properties, and side effects of nalbuphine versus meperidine as intravenous premedicants in combination with intravenous diazepam for the treatment of outpatients undergoing the removal of impacted third molars with alveolar nerve block anesthesia. Forty patients were evaluated in this double-blind crossover study. Nalbuphine was shown to have analgesic, sedative, and amnesic properties similar to meperidine. Nalbuphine, when compared to meperidine, produced significantly lower intraoperative systolic and diastolic blood pressures. Because of this cardiovascular stability, nalbuphine should be considered over meperidine for use in the cardiovascularly compromised patient undergoing oral surgery.

SO - J Oral Maxillofac Surg 1987 Jun;45(6):473-6

7

UI - 88054114

AU - Hew EM

AU - Sang EH

AU - Gordon RG

TI - Nalbuphine: a supplement to isoflurane and enflurane anaesthesia. AD - Department of Anaesthesia, Mount Sinai Hospital, Toronto, Ontario, Canada.

AB - A retrospective study was carried out to review the intra-operative use of nalbuphine at the average dose of 1.5 mg/kg as a supplement to isoflurane and enflurane in balanced anaesthesia in 108 surgical patients. Intra-operative cardiovascular stability and the quality of emergence were examined. The amount of halogenated anaesthetic used was compared to the theoretical amount that would have been needed in the absence of nalbuphine. In 90% to 95% of patients, blood pressures remained within 20% of baseline for the duration of anaesthesia. At emergence, 80% of patients had no pain. Nalbuphine appeared to reduce halogenated anaesthetic requirements by approximately 50%. These promising results for the intraoperative use of nalbuphine need to be confirmed by controlled prospective studies.

SO - Curr Med Res Opin 1987;10(8):531-9

8

UI - 87211130

AU - Zsigmond EK

AU - Durrani Z

AU - Barabas E

AU - Wang XY

AU - Tran L

TI - Endocrine and hemodynamic effects of antagonism of fentanyl-induced respiratory depression by nalbuphine.

AB - Endocrine and hemodynamic changes associated with the antagonism of fentanyl by nalbuphine have not been reported. Therefore, the authors studied ten patients after anesthetic induction with thiopental, fentanyl, tracheal intubation aided by succinylcholine and maintenance with diazepam, pancuronium, N<sub>2</sub>O, and further doses of fentanyl. Eight of the patients underwent cholecystectomy, one had a hysterectomy, and another had an abdominoplasty. After reversal of neuromuscular block at the conclusion of surgery, normal ventilation was restored by 0.22 +/- 0.02 mg/kg intravenous nalbuphine (mean +/- SEM). Plasma levels of free norepinephrine, histamine, and cortisol did not increase after antagonism of the fentanyl-induced respiratory depression, but plasma concentration of epinephrine increased significantly but without significant hemodynamic changes. Minute ventilation was 1.5 +/- 0.4 L/min before and 11 +/- 1, 10 +/- 1, 11 +/- 1, and 10 +/- 1 L/min at 15, 30, 45, and 60 min after antagonism; corresponding PaCO<sub>2</sub> levels were 56 +/- 2, 44 +/- 1, 49 +/- 7, 49 +/- 1, 42 +/- 1 mm Hg. The mean analogue pain score remained below 1.5. We conclude that nalbuphine effectively antagonizes fentanyl-induced respiratory depression without adverse endocrine and circulatory changes or loss of analgesia.

SO - Anesth Analg 1987 May;66(5):421-6

9

UI - 86252982

AU - Kururattapun SA

AU - Prakanrattana U

TI - Nalbuphine versus morphine for postoperative analgesia in critically ill patients.

SO - J Med Assoc Thai 1986 Apr;69(4):210-5

10

UI - 86127484

AU - Feinstein SJ

AU - Lodeiro JG

AU - Vintzileos AM

AU - Campbell WA

AU - Montgomery JT

AU - Nochimson DJ

TI - Sinusoidal fetal heart rate pattern after administration of nalbuphine hydrochloride: a case report.

AB - Nalbuphine hydrochloride (Nubain) is a synthetic analgesic available for use during labor. It is known to possibly cause respiratory depression in the neonate, but to date there are no published reports of any intrapartum alterations of fetal heart rate. A case presentation is given of a persistent sinusoidal pattern appearing after Nubain administration.

SO - Am J Obstet Gynecol 1986 Jan;154(1):159-60

11

UI - 85196947

AU - Moldenhauer CC

AU - Roach GW

AU - Finlayson DC

AU - Hug CC Jr

AU - Kopel ME

AU - Tobia V

AU - Kelly S

TI - Nalbuphine antagonism of ventilatory depression following high-dose fentanyl anesthesia.

SO - Anesthesiology 1985 May;62(5):647-50

12

UI - 85300907

AU - Brock-Utne JG

AU - Ritchie P

AU - Downing JW

TI - A comparison of nalbuphine and pethidine for postoperative pain relief after orthopaedic surgery.

AB - Nalbuphine hydrochloride (Nubain; Du Pont Pharmaceuticals), a synthetic agonist-antagonist analgesic, in a dose of 20 mg was compared with pethidine 100 mg in 60 patients after elective surgery in a random double-blind study. Both drugs were given intramuscularly on the first day after surgery. The pain intensity and visual analogue scales would seem to indicate that nalbuphine has a longer duration of action than pethidine (P less than 0,05). The respiration rates in the pethidine group were significantly more depressed 30 minutes after the injection than in the nalbuphine group (P less than 0,05). Nalbuphine caused less depression of both systolic and diastolic blood pressure at both 30 and 60 minutes (P less than 0,001). The results of the study show that nalbuphine, in the dose used here, may prove to be a useful substitute for pethidine.

SO - S Afr Med J 1985 Sep 14;68(6):391-3

13

UI - 86048506

AU - Kay B

AU - Healy TEAU - Bolder PM

TI - Blocking the circulatory responses to tracheal intubation. A comparison of fentanyl and nalbuphine.

AB - The effects of three drug administration programmes on the haemodynamic responses to tracheal intubation have been compared. Thirty patients received thiopentone 4 mg/kg. Ninety seconds later, following the injection of either saline, nalbuphine 0.3 mg/kg or fentanyl 5 micrograms/kg, suxamethonium 1.5 mg/kg was given. The pressor response to tracheal intubation which occurred after saline was reduced after nalbuphine (p less than 0.05) but a tachycardia still occurred. In contrast, neither an increase in blood pressure nor heart rate occurred in those patients given fentanyl. It is concluded that nalbuphine 0.3 mg/kg is only partially effective in reducing the cardiovascular responses to laryngoscopy and tracheal intubation.

SO - Anaesthesia 1985 Oct;40(10):960-3

1

UI - 92411463

AU - Ding Y

AU - White PF

TI - Comparative effects of ketorolac, dezocine, and fentanyl as adjuvants during outpatient anesthesia [see comments]

CM - Comment in: Anesth Analg 1993 May;76(5):1170-1

AD - Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas 75235-9068.

AB - The comparative effects of ketorolac, dezocine, and fentanyl were evaluated in 136 healthy female patients undergoing outpatient laparoscopic procedures according to a randomized, double-blind protocol. Patients received ketorolac (60 mg) or dezocine (6 mg) or fentanyl (100 micrograms, control group) before the start of the operation. A standardized general anesthetic technique consisting of midazolam (2 mg), fentanyl (50 micrograms), and propofol (2 mg/kg) for induction of anesthesia followed by propofol (120 micrograms.kg-1.min-1), vecuronium (1-2 mg), and 67% nitrous oxide in oxygen for maintenance of anesthesia, was used. In the postanesthesia care unit, 61% of patients in the fentanyl group received analgesic drugs for persistent pain, compared with 34% and 25% in the ketorolac and dezocine groups, respectively. Similarly, less postoperative fentanyl (mean +/-SD) was required in the ketorolac (22 +/- 33 micrograms) and dezocine (18 +/- 35 micrograms) groups, compared with the fentanyl (58 +/- 71 micrograms) group. However, 52% of the patients receiving dezocine required antiemetic therapy in the postanesthesia care unit, compared with 20% and 18% in the fentanyl and ketorolac groups, respectively. Finally, recovery times were significantly shorter in the ketorolac (vs dezocine) group. Although both ketorolac and dezocine were effective alternatives to fentanyl when administered during outpatient laparoscopy, dezocine was associated with an increased incidence of postoperative nausea and a delayed discharge time compared with ketorolac.

SO - Anesth Analg 1992 Oct;75(4):566-71

2

UI - 92206640

AU - Zacny JP

AU - Lichtor JL

AU - de Wit H

TI - Subjective, behavioral, and physiologic responses to intravenous dezocine in healthy volunteers.

AD - Department of Anesthesia and Critical Care, Pritzker School of Medicine, University of Chicago, IL 60637.

AB - Dezocine is an agonist-antagonist opiate that acts at the mu receptor, and is used for management of pain.

Monkeys will readily press a lever to receive an injection of dezocine, and in former opiate addicts dezocine produces positive subjective effects similar to those of morphine. It is not clear, however, what its subjective

effects are in people who do not have a history of opiate abuse. To answer this question, a within-subjects design was used in which 10 normal healthy volunteers (six men, four women) were injected with 0, 2.5, 5.0, and 10 mg/70 kg of dezocine in a double-blind fashion. Subjects completed several questionnaires (e.g., Addiction Research Center Inventory) commonly used in abuse liability testing before and at periodic intervals for up to 5 h after drug injection. We also assessed psychomotor performance (e.g., eye-hand coordination) and several physiologic measures (e.g., pupil size, respiration rate) at these times. Dezocine produced increases in ratings of drug liking (P less than 0.001), as well as other subjective effects that might be considered as pleasant ("good mood," "drunken," "coasting," "happy" ratings) (all P less than 0.05). At the same time, the drug had effects (increased dysphoria and sedation) that typically are not reported by addicts. Dezocine produced psychomotor impairment and miosis (constriction of the pupils) in a dose-dependent fashion. The observation that dezocine produces euphoria and increased drug-liking ratings in individuals without histories of drug abuse suggests that hospitals and surgicenters should have strict accountability procedures with this drug.

SO - Anesth Analg 1992 Apr;74(4):523-30

3

UI - 91042103

TI - Dezocine.

MH - Adult

MH - Analgesics, Opioid/\*ADMINISTRATION & DOSAGE/ADVERSE EFFECTS/ PHARMACOKINETICS

MH - Clinical Trials

MH - Cycloparaffins/\*ADMINISTRATION & DOSAGE/ADVERSE EFFECTS/ PHARMACOKINETICS

MH - Human

MH - Injections

MH - Substance-Related Disorders

PT - JOURNAL ARTICLE

LA - Eng

SO - Med Lett Drugs Ther 1990 Oct 19;32(829):95-6

4

UI - 93115919

AU - Jacobs AM

AU - Youngblood F

TI - Opioid receptor affinity for agonist-antagonist analgesics.

RF - REVIEW ARTICLE: 40 REFS.

AD - Reconstructive Surgery of the Foot and Ankle, Deaconess Hospital, St. Louis, MO.

AB - Analgesic medications are distributed to a variety of receptors within the central nervous system. Activity at these receptors ( $\mu$  1,  $\mu$ ,  $\sigma$ ,  $\delta$ ,  $\kappa$ ) results in both the beneficial pain-relieving effects of analgesics as well as undesirable side effects. The mixed agonist-antagonist class of analgesics offers the potential benefit of greater receptor site selectivity while diminishing the incidence of adverse sequelae, such as respiratory depression. Traditionally, it has been suggested that mixed agonist-antagonist medications may be associated with decreased analgesic effectiveness. However, newer agents of this mixed class may result in effective analgesia while diminishing the incidence of side effects.

SO - J Am Podiatr Med Assoc 1992 Oct;82(10):520-4

5

UI - 91275715

AU - Hoskin PJ

AU - Hanks GW

TI - Opioid agonist-antagonist drugs in acute and chronic pain states. RF - REVIEW ARTICLE: 118 REFS.

AD - Royal Marsden Hospital, London, England.

AB - The agonist-antagonist opioid analgesics are a heterogeneous group of drugs with moderate to strong analgesic activity comparable to that of the pure agonist opioids such as codeine and morphine but with a limited effective dose range. The group includes drugs which act as an agonist or partial agonist at one receptor and an antagonist at another (pentazocine, butorphanol, nalbuphine, dezocine) and drugs acting as a partial agonist at a single receptor (buprenorphine). These drugs can be classified as nalorphine-like or morphine-like. Meptazinol does not fit into either classification and occupies a separate category. Pentazocine, butorphanol and nalbuphine are weak  $\mu$ -antagonists and  $\kappa$ -partial-agonists. All three drugs are strong analgesics when given by injection: pentazocine is one-sixth to one-third as potent as morphine, nalbuphine is slightly less potent than morphine, and butorphanol is 3.5 to 7 times as potent. The duration of analgesia is similar to that of morphine (3 to 4 hours). Oral pentazocine is closer in analgesic efficacy to aspirin and paracetamol (acetaminophen) than the weak opioid analgesics such as codeine. Neither nalbuphine nor butorphanol is available as an oral formulation. At usual therapeutic doses nalbuphine and

butorphanol have respiratory depressant effects equivalent to that of morphine (though the duration of such effects with butorphanol may be longer). Unlike morphine there appears to be a ceiling to both the respiratory depression and the analgesic action. All of these 3 drugs have a lower abuse potential than the pure agonist opioid analgesics such as morphine. However, all have been subject to abuse and misuse, and pentazocine (but not the others) is subject to Controlled Drug restrictions. Buprenorphine is a potent partial agonist at the mu-receptor, and by intramuscular injection is 30 times as potent as morphine. A ceiling to the analgesic effect of buprenorphine has been demonstrated in animals and it is also claimed in humans. However, there are no reliable data available to define the maximal dose of buprenorphine in humans. A practical ceiling exists for sublingual use in that the only available formulation is a 2 micrograms tablet and few patients will accept more than 3 or 4 of these in a single dose. The duration of analgesia is longer than that of morphine, at 6 to 9 hours. There have been suggestions that buprenorphine causes less respiratory depression than morphine, but viewed overall it appears that in equianalgesic doses the 2 drugs have similar respiratory depressant effects.(ABSTRACT TRUNCATED AT 400 WORDS)

SO - Drugs 1991 Mar;41(3):326-44

1

UI - 86028886

AU - Jasinski DR

AU - Preston KL

TI - Assessment of dezocine for morphine-like subjective effects and miosis.

AB - Dezocine is an analgesic soon to be marketed in the United States. In this study we examined the abuse potential of dezocine. Subjective and miotic effects of single subcutaneous doses of dezocine, morphine, and placebo were assessed under double-blind conditions in 10 adult male nondependent drug abusers. Dezocine and morphine were equipotent in inducing a constellation of effects typical of opioid agonists, including miosis and increases in opioid signs and symptoms, liking, and euphoria. Both drugs were consistently identified by subjects as being "dope" (opiates). Thus the profile of effects of single doses of dezocine indicate that the drug has the potential to be abused. However, the agonist-antagonist activities of dezocine demonstrated by others suggest that its abuse potential is less than that of morphine.

SO - Clin Pharmacol Ther 1985 Nov;38(5):544-8

2

UI - 85293258

AU - Warren MM

AU - Boyce WH

AU - Evans JW

AU - Peters PC

TI - A double-blind comparison of dezocine and morphine in patients with acute renal and ureteral colic.

AB - The safety and analgesic efficacy of dezocine and morphine in the treatment of acute renal or ureteral colic due to calculi were evaluated in 2 multicenter, double-blind studies, comparing 10 mg. dezocine and 10 mg. morphine in 88 patients, and 15 mg. dezocine and 10 mg. morphine in 61 patients. All patients received an intramuscular injection of the test drug, and pain intensity and pain relief were evaluated through 4 hours after drug administration. Vital signs, degree of sedation and adverse effects also were recorded. Mean efficacy scores were virtually identical for 10 mg. dezocine and 10 mg. morphine but 15 mg. dezocine produced consistently better analgesia than 10 mg. morphine. This superiority of 15 mg. dezocine was statistically significant on the pain analogue scale at 1 to 4 hours. More morphine-treated than dezocine-treated patients withdrew from each study because of inadequate pain relief. The frequency of adverse effects was not significantly different between groups in either study and none of the patients had clinically significant changes in vital signs. These results indicate that dezocine is a safe and effective analgesic for the treatment of renal and ureteral colic due to calculi, and 15 mg. dezocine were more effective than 10 mg. morphine in this pain model.

SO - J Urol 1985 Sep;134(3):457-9

3

UI - 86196848

AU - Pandit UA

AU - Kothary SP

AU - Pandit SK

TI - Intravenous dezocine for postoperative pain: a double-blind, placebo-controlled comparison with morphine.

AB - Dezocine, a new mixed agonist-antagonist opioid analgesic, and morphine were compared in a double-blind study in 206 patients with postoperative pain. The analgesic efficacy of single intravenous injections of dezocine (2.5, 5.0, and 10.0 mg), morphine (5.0 mg), and placebo was assessed by verbal and visual scales at regular intervals for six hours after administration. All active treatments provided greater pain relief than placebo. Pain

relief with dezocine 5 and 10 mg was significantly greater (P less than .05) than with placebo for up to four and five hours, respectively, and with morphine up to one hour. Pain relief scores were significantly higher (P less than .05) with morphine than with placebo at all observations except that of the fifth hour, and higher with dezocine 2.5 mg than with placebo for the first 30 minutes. Doses of 5 and 10 mg of dezocine produced approximately the same peak analgesic effect, with the larger dose having a longer duration of effect. All active treatments produced mild to moderate sedation. Side effects were few and mild or moderate with all of the treatments. The physician's and the patients' evaluations favored dezocine in a dose-dependent order, with morphine 5 mg rated lower than dezocine 5 mg and higher than dezocine 2.5 mg.

SO - J Clin Pharmacol 1986 Apr;26(4):275-80

4

UI - 86156867

AU - Galloway FM

AU - Varma S

TI - Double-blind comparison of intravenous doses of dezocine, butorphanol, and placebo for relief of postoperative pain.

AB - The safety and efficacy of intravenous doses of dezocine (5 or 10 mg), butorphanol (1 mg), and placebo were compared in a double-blind study in 160 patients with moderate to severe postoperative pain. Analgesic efficacy was assessed for 6 hours after each dose. Mean pain relief scores were consistently higher, indicating greater pain relief, for the three active treatment groups than for the placebo group. The 10-mg dezocine dose was the most effective treatment, and 5 mg of dezocine was comparable to 1 mg of butorphanol. In the 2 hours after the first dose, 32% of the 10-mg dezocine group, 53% of the 5-mg dezocine group, 65% of the butorphanol group, and 88% of the placebo group withdrew from the study because of unsatisfactory pain relief. The differences in these percentages were statistically significant (P less than 0.05) between each active therapy group and the placebo group, and between the 10-mg dezocine group and the butorphanol group. Changes in degree of sedation were similar in the three active therapy groups. Adverse reactions were rare, mild, and equally distributed among the four treatment groups. We conclude that 10 mg of dezocine is superior to 1 mg of butorphanol, and that 5 mg of dezocine is as effective as 1 mg of butorphanol for the relief of moderate to severe postoperative pain.

SO - Anesth Analg 1986 Mar;65(3):283-7

5

UI - 86078835

AU - Pandit SK

AU - Kothary SP

AU - Pandit UA

AU - Kunz NR

TI - Double-blind placebo-controlled comparison of dezocine and morphine for post-operative pain relief.

AB - Dezocine, a new mixed agonist-antagonist-type opioid analgesic, was compared in a double-blind trial with placebo and 10 mg of morphine in 190 patients with acute postoperative pain. The medications were given intramuscularly. Dezocine was administered at three dose levels (5, 10, and 15 mg). Pain relief scores, sedation, and side effects were recorded at 15, 30, 60, 120 and 240 min after injection. Significantly higher pain relief scores (p less than 0.05) were reported for the groups receiving dezocine 10 and 15 mg than the placebo group at all observation times, except for dezocine 15 mg at four hours. Morphine produced significantly better pain relief than placebo only between the second and fourth hour after administration. Significantly better pain relief was obtained with dezocine (10 and 15 mg) than with morphine during the first hour. The mean four-hour cumulative pain relief scores (TOTPAR) were significantly (p less than 0.05) higher than placebo for all active treatment groups. Side effects were few with no significant differences between the treatment groups. Seventy-nine per cent of the patients in the dezocine 15 mg group, and 73, 68, 58 and 50 per cent respectively, of the patients in the dezocine 10 mg, dezocine 5 mg, morphine 10 mg and placebo group had a satisfactory clinical response. Significantly (p less than 0.05) more patients in the groups receiving dezocine 10 and 15 mg than in the placebo group had a satisfactory clinical response; the difference was not significant for the dezocine 5 mg and morphine 10 mg groups.(ABSTRACT TRUNCATED AT 250 WORDS)

SO - Can Anaesth Soc J 1985 Nov;32(6):583-91

6

UI - 87108062

AU - Romagnoli A

AU - Keats AS

TI - Low ceiling respiratory depression by ciramadol.

AB - Ciramadol, an agonist-antagonist analgesic of lesser milligram potency than morphine, given intravenously at 30 mg/70 kg produced respiratory depression equivalent to that observed with morphine 10 mg/70 kg. Respiratory

depression was measured in terms of drug induced displacement of the carbon dioxide response curve of healthy volunteers. In contrast to the progressive respiratory depression by each 10 mg/70 kg increment of morphine, further doses of ciramadol up to 90 mg/70 kg failed to increase respiratory depression. The ceiling of respiratory depression by ciramadol was half the ceiling previously demonstrated for nalbuphine and dezocine. Ceiling respiratory depression may be a general characteristic of agonist-antagonist type analgesics in contrast to pure agonist analgesics.

SO - Int J Clin Pharmacol Res 1986;6(6):451-5

7

UI - 89356331

AU - O'Brien JJ

AU - Benfield P

TI - Dezocine. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy.

RF - REVIEW ARTICLE: 50 REFS.

AD - Adis Drug Information Services, Auckland, New Zealand.

AB - Dezocine is an analgesic agent with opioid agonist and antagonist activity. After parenteral administration of therapeutic doses it is approximately equipotent with morphine, and has proved at least as effective an analgesic as morphine, pethidine (meperidine) and butorphanol in moderate to severe postoperative pain. However, preliminary pharmacodynamic data indicate that the ceiling of analgesic activity of dezocine occurs at a higher level of analgesia than that of reference agonist/antagonist agents. Also, the drug exhibited a morphine-like degree of anaesthetic-sparing activity in animals. Although long term data are very limited, single doses of dezocine are well tolerated, with mild and transient sedation and gastrointestinal upset the principal adverse effects. As with some other agonist/antagonist analgesics, a 'ceiling' effect to dezocine-induced respiratory depression occurs with increasing dosage, beyond which further depression has not been observed. In single analgesic doses, however, dezocine is a slightly more potent respiratory depressant than morphine. Clinically important haemodynamic changes have not been observed with usual analgesic doses of dezocine. As an agonist/antagonist opioid, the dependence liability of dezocine would be expected to be lower than that of pure agonist opioids, but extended clinical use is required before more definitive conclusions can be drawn in this regard. Unlike older drugs of its type, dezocine produced opiate-like subjective effects and was identified as morphine-like by drug abusers. Thus, provided the promising conclusions of currently available clinical studies are confirmed with its wider use, dezocine should be a useful additional agent for the treatment of moderate to severe postoperative pain.

SO - Drugs 1989 Aug;38(2):226-48

8

UI - 87274551

AU - Stambaugh JE Jr

AU - McAdams J

TI - Comparison of intramuscular dezocine with butorphanol and placebo in chronic cancer pain: a method to evaluate analgesia after both single and repeated doses.

AB - Sixty hospitalized subjects with chronic moderate to severe pain as a result of advanced cancer were enrolled in a randomized, parallel, double-blind trial comparing single doses and multiple doses of intramuscular dezocine (10 mg) with butorphanol (2 mg) and placebo. During the initial 6-hour efficacy evaluation, analgesia was measured using verbal and visual scripts and vital signs, and acute toxicity information was recorded. Subjects with initial pain relief entered the 7-day multidose portion of the trial, and efficacy and toxicity data were recorded daily. After the initial dose the peak analgesia of the active agents was similar, but the duration of analgesia was longer with dezocine. After multiple doses, dezocine was superior to butorphanol in terms of length of treatment. Dezocine had less toxicity than had butorphanol after both single and repeated doses, further suggesting that dezocine may be beneficial in managing chronic cancer pain. The described study design is unique in that it compares the analgesic efficacy and toxicity of several analgesics with placebo after both single and multiple doses in the same subject. This method may prove to be an alternative pain model to evaluate chronic cancer pain.

SO - Clin Pharmacol Ther 1987 Aug;42(2):210-9

9

UI - 86208403

AU - Finucane BT

AU - Floyd JB

AU - Petro DJ

TI - Postoperative pain relief: a double-blind comparison of dezocine, butorphanol, and placebo.

AB - The safety and efficacy of single intramuscular doses of dezocine (10 or 15 mg) were compared with butorphanol (2 mg) and placebo in 157 patients with moderate to severe postoperative pain. A verbal pain intensity scale, an

analog pain intensity scale, and a verbal pain relief scale were used to record the patients' subjective assessments. The results of this study indicate that a single 10 or 15 mg intramuscular injection of dezocine is safe and more effective than placebo for four to six hours, respectively, in the treatment of moderate to severe postoperative pain (P less than .05). During the first hour of treatment the pain relief afforded by 2 mg of butorphanol was significantly greater than that afforded by 10 mg of dezocine (P less than .05), but both doses of dezocine provided long-lasting relief. The scores on all three efficacy scales were highest with the 15 mg dose of dezocine after the first hour, while the 10 mg dose of dezocine and butorphanol were compared during this period. Nausea and vomiting were the most commonly reported side effects; injection site reactions were reported more frequently in the butorphanol group.

SO - South Med J 1986 May;79(5):548-52

10

UI - 87023901

AU - Lippman M

TI - Analgesic potencies of dezocine and butorphanol [letter] MH - Analgesics/\*THERAPEUTIC USE

MH - Butorphanol/\*THERAPEUTIC USE

MH - Cycloparaffins/\*THERAPEUTIC USE

MH - Human

MH - Morphinans/\*THERAPEUTIC USE

MH - Pain, Postoperative/\*DRUG THERAPY

PT - LETTER

LA - Eng

SO - Anesth Analg 1986 Nov;65(11):1246

11

UI - 86140597

AU - Locniskar A

AU - Greenblatt DJ

TI - Determination of ciramadol and dezocine, two new analgesics, by high-performance liquid chromatography using electrochemical detection.

SO - J Chromatogr 1986 Jan 10;374(1):215-20

12

UI - 86220367

AU - Locniskar A

AU - Greenblatt DJ

AU - Zinny MA

TI - Pharmacokinetics of dezocine, a new analgesic: effect of dose and route of administration.

AB - The pharmacokinetics of intravenous (IV) dezocine, and bioavailability of intramuscular (IM) and subcutaneous (SQ) dezocine, were evaluated in healthy male volunteers. Elimination half-life following 5, 10, and 20 mg IV doses averaged 2.6-2.8 h, and was independent of dose. Clearance decreased slightly, although significantly, with dose. After Deltoid IM injection, dezocine was rapidly absorbed (peak level: 0.6 h after dose), with bioavailability 97%. Thus dezocine has extensive distribution, high clearance and short half-life over a range of IV doses. It is rapidly and completely absorbed following IM or SQ administration.

SO - Eur J Clin Pharmacol 1986;30(1):121-3

13

UI - 85229169

AU - Littman GS

AU - Walker BR

AU - Schneider BE

TI - Reassessment of verbal and visual analog ratings in analgesic studies.

AB - The relative performance of three analgesic rating scales--visual pain analog, verbal pain intensity, and verbal pain relief--was assessed in clinical trials with 1,497 patients and a variety of pain models. The scales correlated strongly with one another, with inconsistent and generally minimal differences in sensitivity. Overall, the verbal relief scale tended to be slightly more sensitive than the pain analog rating, which in turn showed a small advantage over the verbal pain intensity assessment. When the scores derived from the categorized ratings 1 hour after drug dosing (generally the time of peak effect) were analyzed, there was little difference whether a parametric or nonparametric approach was taken. When the cumulative measures of overall effect over 6 hours were considered, however, the nonparametric approach was decidedly more powerful. There was a similar pattern when the analog scores were analyzed. This unanticipated finding appears to be due to the cumulative measures (from all three scales) being more skewed toward the lower end of their respective ranges than are

the 1-hour scores. A composite efficacy variable was defined, incorporating data from the three primary scales; this measure was found to be generally comparable in sensitivity to the individual scales and may be useful as a global summary of response. While our investigation provides evidence that any of the ratings considered will accurately reflect analgesic response, the verbal relief scale was the most sensitive and might be the best choice if a single measure is desired.

SO - Clin Pharmacol Ther 1985 Jul;38(1):16-23

14

UI - 85229183

AU - Rothbard RL

AU - Schreiner BF

AU - Yu PN

TI - Hemodynamic and respiratory effects of dezocine, ciramadol, and morphine.

AB - The hemodynamic and respiratory effects of dezocine and ciramadol, two agonist-antagonist analgesics, were compared with those of morphine in 30 patients undergoing diagnostic cardiac catheterization. Each subject received a single intravenous dose of dezocine (0.125 mg/kg), ciramadol (0.6 mg/kg), or morphine (0.125 mg/kg) in a double-blind fashion. Hemodynamic and respiratory parameters were measured at baseline and 5, 10, and 20 minutes after dosing. Dezocine increased the cardiac index (CI; 2.67 to 2.92 L/min/m<sup>2</sup>), stroke volume index (SVI; 43.6 to 47.6 ml/beat/m<sup>2</sup>), left ventricular stroke work index (LVSWI; 57.4 to 64.7 gm-m/m<sup>2</sup>), and pulmonary vascular resistance (PVR; 105.6 to 154.0 dynes X sec/cm<sup>5</sup>). Ciramadol increased the CI (2.78 to 3.22 L/min/m<sup>2</sup>), SVI (40.9 to 48.2 ml/beat/m<sup>2</sup>), LVSWI (51.1 to 57.9 gm-m/m<sup>2</sup>), and mean pulmonary arterial pressure (PA; 14.7 to 18.9 mm Hg). Morphine had no effect on CI, SVI, LVSWI, PA, or PVR, but it significantly lowered systolic and diastolic blood pressures. There were no appreciable changes in heart rate, left ventricular end-diastolic pressure, mean arterial pressure, or mean pulmonary capillary wedge pressure after any of the drugs. All three drugs significantly decreased systemic vascular resistance. There were no clinically significant changes in respiratory parameters. We conclude that dezocine, ciramadol, and morphine have no clinically important adverse effects on cardiac performance.

SO - Clin Pharmacol Ther 1985 Jul;38(1):84-8