Effective Searching for Category E Proposals

Callinectes sapidus
According to the Paperwork Reduction Act of 1995, an agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0579-0036. The time required to complete this information collection is estimated to average 2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

This report is required by law (7 U.S.C. 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2146.

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

1. REGISTRATION NUMBER

2. HEADQUARTERS RESEARCH FACILITY (Name, address, and telephone number as registered with USDA, include ZIP Code)

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets, if necessary.)

FACILITY LOCATIONS (Sites)

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets, if necessary, or use APHIS FORM 7023A)

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<th>Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes</th>
<th>Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs</th>
<th>Number of animals upon which teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs were used</th>
<th>Number of animals upon which teaching, research, experiments, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress on these animals and the reasons such drugs were not used must be attached to this report)</th>
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Animal Care Policy #12
Written Narrative for Alternatives to Painful/Distressful Procedures: March 25, 2011

• “..APHIS continues to recommend a database search as the most effective and efficient method for demonstrating compliance with the requirement to consider alternatives to painful/distressful procedures.”

• The Animal Welfare Act (AWA) regulations require principal investigators... to provide a written narrative of the methods used and sources consulted to determine the availability of alternatives, including refinements, reductions, and replacements.

• The database search narrative must, at a minimum, include
  – Names of the databases searched (“one database is seldom adequate”)
  – Date the search was performed
  – Time period covered by the search
  – The search strategy (including scientifically relevant terminology) used.

Tips for IACUCs

• Don’t arbitrarily require certain terms in the search

  The IACUC expects the following specific terms be included in a search of each painful or distressful procedure: “refine” or “refinement”, “analgesia”, “alternative”, “pain”, “distress”, “humane endpoints.”

• If you give an example of a search, make sure it works

  cecal ligation and puncture model pain severity ---no items found in PubMed

• Make your scientists aware of in-house information resources and how to access them

• Put an information specialist on your IACUC
AWIC’s Approach to Meeting the Information Requirements

• Approach the search in two phases.
• Analyze the protocol to determine where alternatives might be used and for terminology.
• Decide where to go for the information.
  – Databases
  – Websites
• Link terminology appropriately for best search results.
• Evaluate the search results.
Searching for Alternatives
Search Strategy

Two Phases

• *Phase I*: Reduction and refinement of citations pertinent to PI’s field of study.

• *Phase II*: Replacement or use of nonanimal or alternative animal models.
Do NSAIDs, opioids, or other analgesics lead to different outcomes for spared nerve models of neuropathic pain?
Search Strategy using Scopus

• #1 “SPARED NERVE INJURY” AND NEUROPATH* 995

• #2 PAIN? (W/8) (SURG* OR POSTSURG* OR POSTOPER* OR POST(PRE/1)SURG? OR POST (PRE/1)OPER* OR INCISION*) 24858

• #3 #1 AND #2 39
Influence of postoperative analgesics on the development of neuropathic pain in rats.
Stewart LS, Martin WJ.

Rodent models of neuropathic pain require extensive tissue manipulation to induce the lesion of interest which results in inflammation and postoperative pain that is unrelated to nerve injury per se. We sought to determine whether acute postoperative pain management affects the development of hallmark signs of neuropathic pain. Analgesic regimens (q 24 h x 3 days) were buprenorphine (0.05 and 0.1 mg/kg of body weight, s.c.), flunixin meglumine (1.1 and 2.5 mg/kg, s.c.), and fentanyl citrate (0.01 and 0.1 mg/kg, i.p.). The spared nerve injury model of neuropathic pain was used, and mechanical and cold allodynia as well as body weight gain were measured for 28 days. Buprenorphine and fentanyl alleviated mechanical sensitivity and prevented weight loss associated with the surgery (0 to 3 days), but opioid-related adverse effects were observed. Flunixin reduced wound inflammation and improved weight gain, but had no effect on nociceptive thresholds. Cold allodynia was unaltered by any treatment. By postoperative day 7, control and treatment groups did not differ with respect to weight gain or nociceptive thresholds. **Our findings suggest that postsurgical inflammation and pain behavior can be ameliorated without substantially altering the long-term development of neuropathic pain, provided that the selection of agent(s) and treatment regimen(s) is appropriate and the neuropathic pain of interest is evaluated seven days after surgery.**

MeSH Terms

- Analgesics/therapeutic use*
- Animals
- Cold Temperature
- Male
- Pain/drug therapy*
- Peripheral Nervous System Diseases/drug therapy*
- Postoperative Period
- Rats
- Rats, Sprague-Dawley
- Weight Gain
**A single subanesthetic dose of ketamine relieves depression-like behaviors induced by neuropathic pain in rats.**

Wang Jing; Goffer Yossef; Xu Duo; Tukey David S; Shamir D B; Eberle Sarah E; Zou Anthony H; Blanck Thomas J J; Ziff Edward B
Anesthesiology *(*) United States *) Oct 2011, 115 (4) p812-21,

BACKGROUND: Chronic pain is associated with depression. In rodents, pain is often assessed by sensory hypersensitivity, which does not sufficiently measure affective responses. Low-dose ketamine has been used to treat both pain and depression, but it is not clear whether ketamine can relieve depression associated with chronic pain and whether this antidepressant effect depends on its antinociceptive properties.

METHODS: The authors examined whether the spared nerve injury model of neuropathic pain induces depressive behavior in rats, using sucrose preference test and forced swim test, and tested whether a subanesthetic dose of ketamine treats spared nerve injury-induced depression.

RESULTS: Spared nerve injury-treated rats, compared with control rats, showed decreased sucrose preference (0.719 +/- 0.068 (mean +/- SEM) vs. 0.946 +/- 0.010) and enhanced immobility in the forced swim test (107.3 +/- 14.6s vs. 56.2 +/- 12.5s). Further, sham-operated rats demonstrated depressive behaviors in the acute postoperative period (0.790 +/- 0.062 on postoperative day 2).

A single subanesthetic dose of ketamine (10 mg/kg) did not alter spared nerve injury-induced hypersensitivity; however, it treated spared nerve injury-associated depression-like behaviors (0.896 +/- 0.020 for ketamine vs. 0.663 +/- 0.080 for control rats 1 day after administration; 0.858 +/- 0.017 for ketamine vs. 0.683 +/- 0.077 for control rats 5 days after administration).

CONCLUSIONS: Chronic neuropathic pain leads to depression-like behaviors. The postoperative period also confers vulnerability to depression, possibly due to acute pain. Sucrose preference test and forced swim test may be used to compliment sensory tests for assessment of pain in animal studies. Low-dose ketamine can treat depression-like behaviors induced by chronic neuropathic pain.

*Tags: * Male
*Descriptors: * *Anesthetics, Dissociative--pharmacology--PD; *Antidepressive Agents; *Depression--etiology--ET; *Depression--psychology--PX; *Ketamine--pharmacology--PD; *Neuralgia--drug therapy--DT; *Neuralgia--psychology--PX *; *Animals; Behavior, Animal--drug effects--DE; Cold Temperature--diagnostic use--DU; Corticosterone--blood--BL; Dose-Response Relationship, Drug; Hyperalgesia--psychology--PX; Neuralgia--complications--CO; Pain Measurement--drug effects--DE; Physical Stimulation; Rats; Rats, Sprague-Dawley; Sucrose--diagnostic use--DU; Swimming--psychology--PX; Taste--drug effects--DE

*CAS Registry No.: * 0 (Anesthetics, Dissociative); 0 (Antidepressive Agents); 50-22-6 (Corticosterone); 57-50-1 (Sucrose); 6740-88-1 (Ketamine)
Effect of post operative drug treatment on the development of mechano-cold allodynia in rats following spared nerve injury (SNI)

Oerther S.; Stenfors C.
<http://dx.doi.org/10.1016/S1754-3207(11)70756-8>

Background and Aims: Spared nerve injury (SNI) is a traumatic nerve-injury model used in rat to mimic chronic neuropathic pain condition in man. The response to mechano-cold stimuli after nerve injury in Lewis rats (LEW/HanHsd) is used to measure development of hypersensitivity in these rats. Acute pain is linked to the post operative phase. In this study we investigated the effect of post-operative pain medication on the long term development of mechano-cold allodynia.

Methods: The surgery was conducted under isoflurane anaesthesia in male rats (n = 7-8 per group). Prior to surgery, one group of rats were given s.c. doses of Temgesic (buprenorphine) (0.05 mg/kg) and Rimadyl (carprofen)(5 mg/kg), diluted in saline followed by a second dose of Temgesic 6-8 hours post surgically. Another group of SNI rats were given saline injections as control. All animals were tested for their response to cold stimuli applied to the plantar surface of the injured paw using a modified ethyl chloride spray can. Both SNI groups were tested if a single dose of morphine (6.25 mumol/kg, sc) could reverse the response to ethyl chloride 30 minutes post drug administration. Results: The SNI-operated rats showed consistent aversive reactions in response to mechano-cold stimuli applied to the injured paw. Post operative Temgesic/Rimadyl treatment did not affect the response to mechano-cold stimuli. Morphine decreased the response in all rats whether post operative pain management was applied or not. Conclusions: Post operative pain management did not influence the response to mechano-cold stimuli in SNI rats.

*Drug Descriptors: *buprenorphine; sodium chloride; chloroethane; morphine; carprofen; isoflurane

*Medical Descriptors: *rat; *pain; *drug therapy; *nerve injury; *alldynia; *Europe stimulus; male; surgery; single drug dose; drug administration; aerosol; neuropathic pain; human; Lewis rat; hypersensitivity; model; anesthesia; injection
Neuropathic pain, a chronic and debilitating condition in humans, is often modeled in animals by inducing nerve injury. Pain-related sensory changes studied in these models include hypersensitivity to thermal stimuli (hyperalgesia), light touch (mechanical allodynia), and the injection of painful chemicals (chemogenic hypersensitivity). In modeling neuropathic pain, it is important to closely replicate the clinical condition to improve translatability. The current study explored preventive analgesia for postoperative neuropathic pain. Since human patients routinely receive postoperative morphine as part of their analgesic regime, the impact of postoperative morphine on the preventive effects of drugs being studied needed to be determined. Previous research using the spared nerve injury (SNI) model of neuropathic pain demonstrated that amitriptyline has preventive anti-hyperalgesic effects that are not significantly altered by postoperative morphine administration. In this study, propentofylline (1 h preoperatively and then daily for 7 days) alleviated long-term mechanical allodynia in the SNI model. This was not affected by morphine administration (postoperatively and daily for 3 days). When given in combination, propentofylline and amitriptyline maintain their individual long-term effects in the presence of postoperative morphine. Many nerve injury models, including the SNI model, involve extensive tissue manipulation to produce physical injury to a nerve(s), causing pain and inflammation that may not be related to the long-term sensory changes of interest. Here the exploration of postoperative morphine, to improve translatability, likely provided the rats with relief from pain which was not necessary for the study outcomes, and represents a potential refinement for further studies using this model.

Drug Descriptors: *morphine; amitriptyline; propentofylline; analgesic agent
Medical Descriptors: *pain; *biomedicine; *animal use model; neuropathic pain; nerve injury; human; hypersensitivity; allodynia; patient; tissues; rat; injury; nerve; inflammation; analgesia; injection; stimulus; hyperalgesia
Evaluation of Post-operative Analgesics in a Model of Neuropathic Pain

Authors: Simkins, Mikele D.; Shadiack, Annette M.; Burns, Carol A.; Molino, Lory J.; Amaratunga, Dhammika; Hall, Jeffery; Rogers, Kathryn E.; Clark, Laura P.

Source: Journal of the American Association for Laboratory Animal Science, Volume 37, Number 6, November 1998, pp. 61-63(3)

Abstract:
Chung model-operated animals received analgesic doses of oxymorphone, buprenorphine, carprofen, and EMLA cream (2.5% lidocaine and 2.5% prilocaine) on days 0-4 post-operatively to examine their effects on the development of neuropathic pain in the rat. Although the animals receiving oxymorphone and buprenorphine showed signs of marked sedation, 67% and 60% respectively had developed mechanical allodynia (a form of neuropathic pain) on day 8 post-operatively. The carprofen treated group showed none of the signs of sedation, and on day 14 post-operatively 60% of the animals had developed mechanical allodynia. The EMLA cream-treated group did not show overt signs of post-operative pain or sedation, and 50% developed mechanical allodynia on day 3 post-operatively. Although the time course of development of mechanical allodynia differed between treatment groups, we find that post-operative analgesics can be delivered to rats during the immediate postoperative period without inhibiting the eventual development of neuropathic pain in this animal model.
Cecal Ligation and Puncture

NIH Public Access
Nat Protoc. Author manuscript; available in PMC 2009 September 29.
Published in final edited form as:
PMCID: PMC2754226
Cecal Ligation and Puncture

• Withholding analgesics for animals undergoing CLP is sometimes requested by investigators out of concern for immunomodulatory effects of analgesics interfering with scientific outcomes.

• Is there any literature available to support this concern or knock it down?
Search strategy

• S1 CELCAL LIGATION (2W) PUNCTURE  8280
• S2 ((PAIN (3N)(MANAGE? OR CONTROL? OR PREVENT? OR RELIEF OR RELIEV?) OR ANALGES? OR BUPRENORPHINE OR RIMADYL OR CARPROFEN OR KETOPROFEN OR ACETAMINOPHEN OR BUTORPHANOL)) 793475
• S3 S1 AND S2 38
• S4 RD (unique items)  22
Sepsis research relies heavily on animal models. **One of the most frequently used models, cecal ligation and puncture (CLP), involves surgery, and animal use committees may require the use of analgesics after CLP.** However, some analgesics are immunomodulatory and may affect research outcomes. In addition, both septic inflammation and responses to opioids may vary with the sex of the subject. Therefore, we investigated the effects of buprenorphine in inbred mice of both sexes undergoing CLP. We hypothesized that buprenorphine would not significantly change the outcome or patterns of inflammation in C57BL/6 mice after CLP. Male and female C57BL/6 mice underwent CLP surgery and were randomized into 2 groups to receive either buprenorphine or saline. Three-week survival studies were performed (n = 20 per group). Survival did not differ between groups of female mice, but male mice that received buprenorphine had decreased survival compared with that of controls. Reducing the dose of buprenorphine in male mice ameliorated the difference in survival. To examine inflammation, mice (n = 10 per group) were euthanized at 12, 24, or 48 h after CLP. Cell counts and cytokines were measured in the blood and peritoneal lavage fluid. In female and male C57BL/6 mice, buprenorphine treatment resulted in few differences in inflammatory parameters, although peripheral neutrophil counts were decreased transiently in male mice. **The findings suggest that the effects of buprenorphine on sepsis models in C57BL/6 mice may be sex-specific. Consequently the use of analgesics must be assessed on a study-by-study basis, and investigators should define analgesic regimens when publishing sepsis studies.**

*Tags: * Female; Male
*Descriptors: * *Analgesics, Opioid--administration and dosage--AD; *Buprenorphine --administration and dosage--AD; *Cecum--surgery--SU; *Sepsis--immunology --IM; *Sepsis--mortality--MO *; * Animal Welfare; Animals; Blood Chemical Analysis; Cecum--injuries--IN; Cell Count; Coinfection--blood--BL; Coinfection--immunology--IM; Coinfection --microbiology--MI; Coinfection--mortality--MO; Cytokines--analysis--AN; Cytokines--blood--BL; Disease Models, Animal; Dose-Response Relationship, Drug; Ligation; Mice; Mice, Inbred C57BL; Peritoneal Lavage; Punctures; Sepsis--blood--BL; Sepsis--microbiology--MI
*CAS Registry No.: * 0 (Analgesics, Opioid); 0 (Cytokines); 52485-79-7 (Buprenorphine)
Cecal ligation and puncture (CLP) is the sepsis model that more closely resembles the human pathology, but it is likely to cause suffering to experimental animals. However, it is not clear whether the use of analgesia may affect some parameters evaluated in experimental sepsis research. Therefore, we investigated the effects of fentanyl and tramadol in experimental sepsis in the rat. The following parameters were evaluated: body temperature, body weight, water and food ingestion, mortality, analgesia, blood leukocytes, mean arterial blood pressure, vascular reactivity to phenylephrine, lung myeloperoxidase activity, and plasma levels of IL1-β, glutamic-oxaloacetic, glutamic-pyruvic, lactate, creatinine and urea. While producing significant analgesia, the opioids modify minimally the parameters, with the exception of sepsis-induced hypotension and mortality. Although fentanyl and tramadol can minimize pain and the general suffering of animals submitted to CLP surgery, their effects on cardiovascular parameters as well as in the mortality indicate that their use in experimental sepsis must be done with caution and with all the proper control groups.
Effects of tramadol and buprenorphine on select immunologic factors in a cecal ligation and puncture model.

Abstract
Sepsis research relies on animal models. The models that most closely resemble clinical disease, such as cecal ligation and puncture, require surgery. After surgery, analgesics may not be included in experimental protocols because of concern over effects on inflammatory responses. This often generates animal welfare controversies within institutions; however, there are no scientific studies directly addressing the effects of analgesics on surgical models of sepsis. The purpose of this study was to characterize the effects of opioids on key parameters used in sepsis research. Female ICR mice were divided into four treatment groups (Ringer's lactate solution, high- or low-dose tramadol, buprenorphine) for 3-week mortality studies (n = 12 per treatment). Experimental groups were then repeated, and mice were killed at 12, 24, and 48 h postsurgery for cell counts, differentials, and cytokine levels in blood, peritoneum, and airways. Mortality studies demonstrated no significant differences between controls and any treatment group. However, significant differences were noted between buprenorphine and high-dose tramadol, revealing more and later deaths with tramadol. For comparison of immune parameters, Mann-Whitney U or Student t test was performed, emphasizing comparisons between treatment and control. Although several results were significant, comparisons between control and any treatment group yielded no differences that remained consistently apparent during the observation period. Again, differences were observed between the treatments. The results suggest that judicious and limited use of some analgesics may not dramatically affect the outcome of similarly conducted cecal ligation and puncture studies when compared with those not using analgesics. However, when different analgesics are used, comparisons between studies may be complicated.

Publication Types
Comparative Study

Effects of buprenorphine on a cecal ligation and puncture model in C57BL/6J mice.
Related citations

Effects of tramadol and buprenorphine on select immunologic factors in a cecal ligation and puncture model.

Humane endpoints in shock research.

Six at six: interleukin-6 measured 8 h after the initiation of sepsis predicts mortality over 3 days.

Did you mean: cecal ligation puncture ("animal welfare" or endpoint? OR humane OR refine?) (243 items)
Six at six: interleukin-6 measured 6 h after the initiation of sepsis predicts mortality over 3 days.

Remick DG, Bolgos GR, Siddiqui J, Shin J, Nemzek JA
Shock. 2002 Jun;17(6):463-7

Abstract

Virtually all of the recent therapeutic interventions for treating sepsis have failed to improve survival. One potential explanation is that the heterogeneity of the immune response to the septic challenge is such that only a portion of the patients die as a result of excessive inflammation. The clinical trials lacked power because traditional measurements do not accurately identify these patients. Previous work has shown that higher levels of interleukin (IL)-6 are found in those mice that die from septic peritonitis; therefore, we sought to determine whether IL-6 measured 6 h after surgery could predict outcome. Adult, female BALB/c mice (n = 79) were subjected to cecal ligation and puncture with a 21-gauge needle and treated with imipenem in D5W every 12 h for 5 days, resulting in a homogenous population at the outset. Six hours after surgery, 20 microl of blood was obtained from the tail vein to measure IL-6. Mortality was followed for 21 days. Overall 3-day survival was 77%, and 21-day mortality was 56%. Plasma IL-6 levels >2,000 pg/mL were determined to predict mortality within the first 3 days with a sensitivity of 58% and specificity of 97%. To further refine the mortality prediction, body weight and a complete blood count were performed 24 hours after cecal ligation and puncture. Discriminate analysis indicated that a weighted formula combining body mass, lymphocyte, and platelet count would predict death with sensitivity of 83% and a specificity of 79%. We tested the value of the IL-6 prediction by surgically resecting the cecum in those animals with IL-6 > 2000 pg/mL, which resulted in a significant improvement in survival. These data demonstrate that IL-6 measured 6 h after injury accurately predicts mortality resulting from experimental sepsis. This measurement may be determined quickly so that therapy may be targeted only to those individuals at significant risk of dying and initiated within sufficient time to be effective.

MeSH Terms

Effects of no-analgesia-surgery vs. analgesia-surgery vs analgesia-no surgery on metastasis rates to the lungs

A Mouse Model of Pulmonary Metastasis from Spontaneous Osteosarcoma Monitored In Vivo by Luciferase Imaging
Published online 2008 March 19. doi: 10.1371/journal.pone.0001828
PMCID: PMC2265554
Search strategy

• S1  MOUSE OR MICE OR RAT OR RATS OR ANIMAL OR ANIMALS 34371662
• S2  (CANCER OR CARCINOMA OR TUMOR OR TUMOUR) AND (METASTAT? OR METASTA?) (4N) (LUNG OR LUNGS) 119259
• S3  SURGERY OR SURGICAL 9630727
• S5  ANALGES? OR BUPRENORPHINE OR RIMADYL OR CLONIDINE OR FENTANYL OR KETAMINE OR CARPROFEN OR KETOPROFEN OR ACETAMINOPHEN OR BUTORPHANOL 792352
• S6  AFFECT? OR EFFECT? OR INFLUENCE? OR CONFOUND? OR IMPACT? 33156499
• S7  S1 AND S2 AND S3 8150
• S8  S6 (6N) S5 177133
• S9  S7 AND S8 15
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The analgesic drug tramadol prevents the effect of surgery on natural killer cell activity and metastatic colonization in rats.

Gaspani Leda; Bianchi Mauro; Limiroli Elena; Panerai Alberto E; Sacerdote Paola

Surgery stress has been shown to be associated in rat with decreased natural killer (NK) cell activity and enhancement of tumor metastasis. We have previously shown that the analgesic drug tramadol stimulates NK activity both in the rodent and in the human. In the present study, we analyze, in the rat, tramadol ability to prevent the effect of experimental surgery on NK activity and on the enhancement of metastatic diffusion to the lung of the NK sensitive tumor model MADB106. The administration of tramadol (20 and 40 mg/kg) before and after laparotomy significantly blocked the enhancement of lung metastasis induced by surgery. In contrast, the administration of 10 mg/kg of morphine was not able to modify this enhancement. The modulation of NK activity seemed to play a central role in the effect of tramadol on MADB106 cells. In fact, both doses of tramadol were able to prevent surgery-induced NK activity suppression, while the drug significantly increased NK activity in normal non-operated animals. Morphine, that in normal rats significantly decreased NK cytotoxicity, did not prevent surgery-induced immunosuppression. The good analgesic efficacy of tramadol combined with its intrinsic immunostimulatory properties suggests that this analgesic drug can be particularly indicated in the control of peri-operative pain in cancer patients.

Tags: * Male

Descriptors: * *Analgesics, Opioid--pharmacology--PD; *Killer Cells, Natural--drug effects --DE; *Laparotomy--adverse effects--AE; *Neoplasm Metastasis--drug therapy --DT; *Neoplasm Metastasis--immunology--IM; *Stress, Physiological--immunology--IM; *Tramadol--pharmacology--PD *; * Adjuvants, Anesthesia--pharmacology--PD; Animals; Disease Models, Animal; Dose-Response Relationship, Drug; Down-Regulation—drug effects--DE; Down-Regulation--immunology--IM; Killer Cells, Natural--immunology--IM; Lung Neoplasms--drug therapy--DT; Lung Neoplasms--secondary--SC; Morphine--pharmacology--PD; Neoplasm Metastasis--prevention and control--PC; Pentobarbital--pharmacology--PD; Rats; Rats, Inbred F344; Spleen--cytology --CY; Spleen--drug effects--DE; Spleen--immunology--IM; Stress, Physiological--physiopathology--PP; Tumor Cells, Cultured
EMBASE

Does analgesia and condition influence immunity after surgery? Effects of fentanyl, ketamine and clonidine on natural killer activity at different ages

Forget P.; Collet V.; Lavand'homme P.; De Kock M. European Journal of Anaesthesiology (* United Kingdom ) March 1, 2010 , 27/3 (233-240)

Background and objective: Cellular immunity varies in the perioperative period. We evaluated the effects of fentanyl, clonidine and ketamine at different time points after surgery and in animals in different conditions (young vs. old).

Materials and methods: Rats undergoing laparotomy under sevoflurane anaesthesia were assigned to receive saline, fentanyl (40mugkg SUP -1 ), clonidine (10mugkg SUP -1 ) or ketamine (10mugkg SUP -1 ) 1 h before surgery. Natural killer (NK) activity was quantified at different time points (immediately or after 18, 24, 48, 72 h and 8 days) in vitro by the lysis of YAC-1 cells. In-vivo assessment included counting the number of lung metastases induced by the MADB-106 cells. Results: During the first 24 h after surgery, a rapid increase in NK activity was noted, followed by a significant depression returning to baseline at 8 days. Analgesics show specific effects: fentanyl depressed NK activity with or without surgery. Clonidine depressed NK activity in nonoperated animals and during the first 24 h after surgery. Ketamine depressed NK activity in nonoperated animals but, after surgery, this activity varied with the same time course as saline. Ketamine and clonidine significantly reduced the number of lung metastases in operated animals. Ketamine significantly reduced the number of metastases in old nonoperated animals. Finally, ageing has a significant negative influence. Conclusion: Surgery, analgesics and co-existing conditions significantly influence cellular immunity. The importance of these changes varies with time. Fentanyl had a worse influence than clonidine and ketamine, but seemed equally protective against the development of metastases. (c)

Medical Descriptors: *analgesia; *cellular immunity; *groups by age; *natural killer cell aging; analysis of variance; anesthesia; animal experiment; article; blood sampling; breast adenocarcinoma; cancer cell; cell activity; cell count; controlled study; cytolysis; drug effect; drug mechanism; in vitro study; in vivo study; laparotomy; lung metastasis; multivariate analysis of variance; nonhuman; peripheral blood mononuclear cell; rat
Buprenorphine ameliorates the effect of surgery on hypothalamus-pituitary-adrenal axis, natural killer cell activity and metastatic colonization in rats in comparison with morphine or fentanyl treatment.

Franchi S, Panerai AE, Sacerdote P.


Not all opioids employed in clinical practice share the same immunosuppressive properties. The potent partial micro-agonist buprenorphine appears to exhibit a neutral effect on the immune responses. **Surgery stress is associated with decreased natural killer cell activity (NK) and enhancement of tumor metastasis in rats.** We analyzed the ability of buprenorphine to prevent the effects of experimental surgery on HPA activation (plasma corticosterone levels), NK activity and lung diffusion of the NK sensitive tumor MADB106. Buprenorphine (0.1mg/kg) was compared with equianalgesic doses of fentanyl (0.1mg/kg) and morphine (10mg/kg) in this animal model. In normal animals morphine and fentanyl stimulate the HPA axis, decrease NK activity and augment tumor metastasis, while buprenorphine is devoid of these effects. Surgery significantly raised corticosterone levels, suppressed NK activity and increased MADB106 metastasis. **Only buprenorphine was able to prevent the neuroendocrine and immune system alterations and ameliorate the increase of tumor metastasis induced by surgical stress.** These preclinical findings suggest that an adequate treatment of surgically induced stress immunosuppression with an opioid drug devoid of immunosuppressive effects may also play a protective role against the metastatic diffusion following cancer surgery.


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Source
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Abstract

BACKGROUND/PURPOSE:
Mammalian target of rapamycin suppression by rapamycin inhibits tumor growth and neovascularization via cyclooxygenase-2 (COX-2) downregulation with no effect on lung metastases. We hypothesize that combining a selective COX-2 antagonist (celecoxib) with rapamycin would decrease lung metastases.

METHODS:
Ewing sarcoma cells (SK-NEP-1) were surgically implanted into the left kidney of athymic mice (n = 40). The mice were divided into 4 treatment groups (control, rapamycin only, celecoxib only, and combination) and then killed at 6 weeks. Primary tumors were weighed. Vasculature was examined using lectin angiography and immunohistochemistry, and lung metastases were examined using H&E and CD99 immunostaining. Tumor weight and lung metastases were analyzed.

RESULTS:
Mean primary tumor weights were significantly reduced in the rapamycin-treated groups but not in the celecoxib-only group. Lectin angiography and endothelial markers immunostaining showed markedly decreased vascularity in the rapamycin-treated groups but not in the celecoxib-only group. Celecoxib-treated groups showed significantly fewer mice with lung metastases than non-celecoxib-treated groups.

CONCLUSION:
Celecoxib prevents lung metastasis in a murine model of Ewing sarcoma with no effect on tumor size or neovascularization. Cyclooxygenase-2 may represent a future potential target for metastatic disease prevention.

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Anesthetic drugs accelerate the progression of postoperative metastases of mouse tumors.

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Abstract

Experiments were made to investigate the effect of four anesthetic drugs that are commonly used in surgical practice on the postoperative growth of mouse tumors in syngeneic recipients. These experiments revealed that some of the anesthetics when applied for surgical excision of the local tumor, strongly accelerated postoperative progression of spontaneous lung metastases produced by the 3LL Lewis lung carcinoma and by the B16 melanoma. Some of the drugs caused the appearance of metastases in organs, such as the liver, in which spontaneous metastases are not usually produced by these tumors. A T10 sarcoma clone that does not produce detectable metastases in immune intact mice even following intravenous injection, did produce metastases when injected into animals treated with pentothal sodium.

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Other things to consider

• Humane endpoints
  – Pain scoring
• Veterinary nursing care
  – Water gels
  – Nutrient gels
  – Heat