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Correlation between body weight changes and postoperative pain in rats treated with meloxicam or buprenorphine

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Abstract

It is essential to identify objective and efficient methods of evaluating postoperative pain in rodents. The authors investigated whether postoperative changes in rates of body weight gain could serve as a measure of the efficacy of meloxicam or buprenorphine analgesia in growing rats. Young adult male Lewis rats underwent general endotracheal anesthesia and thoracotomy and were treated postoperatively for 3 d with saline (no analgesia), buprenorphine (six doses of 0.1 mg per kg) or meloxicam (three doses of 1 mg per kg). The authors evaluated rats' daily growth rates for 5 d after surgery and compared them with baseline (preoperative) growth rates. To discriminate between the effects of postoperative pain and other concurrent physiologic effects associated with anesthesia, thoracotomy or analgesia, the authors evaluated weight changes in multiple control groups. Treatment with buprenorphine in the absence of any other procedure or with anesthesia alone significantly affected rats' body weight. Notably, growth rate was maintained at near normal levels in rats treated postoperatively with meloxicam. These findings suggest that growth rate might serve as an efficient index of postoperative pain after major surgical procedures in young adult rats treated with meloxicam but not in rats treated with buprenorphine.

The clinical assessment and treatment of pain in the laboratory animal present unique challenges for scientific investigators, IACUCs, institutional veterinarians and regulatory agencies. Evaluation of pain in the ubiquitous laboratory rodent is especially challenging. Several studies suggest that clinical parameters such as change in body weight and daily oral fluid intake correlate with postoperative pain in rodents [1–4]. Although such parameters provide appropriate indications of rodent well-being during routine clinical care and maintenance, these objective measurements fail to account for typical factors operant during the postoperative period, such as the effect of narcotic analgesic medications on volition and the physiologic stress response to surgery. Recently, Flecknell and colleagues pioneered a method of postoperative behavioral monitoring in rats as an objective means to determine pain and analgesic efficacy [3,5,6]. With this scoring method, trained personnel observe rats for 5 –10 min relatively soon after surgery and document behavioral indicators of pain. We sought to investigate whether daily assessment of body weights could be an alternative or adjunct to the proposed behavioral scoring paradigm. Body weight can be accurately measured, and the timing of evaluation is flexible. This method is also objective and efficient, particularly for evaluating pain in group-housed rodents. Furthermore, a standardized, simple evaluation

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COMPETING INTERESTS STATEMENT

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method would ensure personnel compliance, and inexperienced personnel or those unaware of a particular treatment group assignment could reliably infer or predict pain states.

The American College for Laboratory Animal Medicine (ACLAM) Analgesia Task Force defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, and should be expected in an animal subjected to any procedure or disease model that would be likely to cause pain in a human"[7]. Analgesia is defined as freedom from or a complete loss of sensitivity to pain. Animals do not perceive pain in situations of neural blockade, which is produced with local, regional or spinal anesthesia, or during profound cerebral depression, which occurs during general anesthesia 8. Alternatively, pain perception can be altered such that pain is perceived yet is tolerable. Opioids and α_2-adrenergic agonists are examples of drugs known to alter pain perception in this manner. Finally, substances such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids accomplish analgesia by reducing both inflammation and the production of algogenic substances in damaged and inflamed tissues [9].

Prevention of pain in laboratory animals is a moral imperative for investigators, animal caretakers and veterinarians alike. It is also encouraged by the public, whose support for animal research declines as the pain experienced by animals increases [10]. ACLAM mandates that procedures expected to cause more than slight or momentary pain (for example, more than that caused by a needle prick or injection) require the appropriate use of pain-relieving measures, unless the withholding of analgesia is scientifically justified in an approved animal care and use protocol [11]. Moreover, pain elicits an endocrine response cascade, including release of cortisol, catecholamines and other stress hormones that cause a variety of physiologic and metabolic changes 12 that may confound the research protocol.

In several studies, weight loss in adult animals and alterations in normal growth rates in young animals have been used as indicators of postoperative pain [1–4,13]. None of those studies, however, distinguished between weight alterations caused by postoperative pain and those caused by physiologic effects of anesthesia or analgesic drugs. To determine whether weight alterations can indicate postoperative pain after an invasive surgical procedure, we investigated changes in weight gain patterns in analgesic-treated and in untreated growing young adult rats that underwent thoracotomy. We included numerous control groups to determine the extent of growth rate perturbations attributable to treatment with anesthesia or analgesia. We studied both a common opioid (buprenorphine) and an NSAID (meloxicam) to dissect any drug-specific effects.

METHODS

Rats

All procedures were approved by the Yale IACUC. Rats were singly housed in approved facilities in the Yale Animal Resources Center and were maintained under routine husbandry practices. We used male Lewis rats (n = 44; Charles River, Wilmington, MA) that weighed 205.9 g on average (± 3.7 g s.d.) and were approximately 56 d old at the start of the study. Rats had free access to standard rat chow (Harlan, Madison, WI) and to autoclaved, hyperchlorinated water.

Experimental design

We weighed rats and then assigned them to one of nine experimental groups (Table 1). Rats acclimated to their environmental conditions for 2 d (study days −4 to −2). On study day −2, we began pre-surgery handling and weighing procedures. On day 0, each rat underwent one of the following procedures: no operative procedure (groups A, B and C), general endotracheal

anesthesia (GETA) alone (groups D, E and F) or GETA plus thoracotomy (groups G, H and I). Immediately after extubation, rats received subcutaneous (s.c.) injections of saline ('mock' injections; groups A, D and G), buprenorphine (0.1 mg per kg body weight; groups B, E and H) or meloxicam (1.0 mg per kg body weight; groups C, F and I). Throughout study days 0, 1 and 2, additional buprenorphine and matched mock injections were administered once every 12 h, and on days 1 and 2, additional meloxicam and matched mock injections were administered every 24 h. We weighed rats on study days −2 through 5, between 8 and 10 AM each day (before surgery on day 0). We normalized the measurements to represent weight change over the course of exactly 24 h.

Anesthesia (GETA) and surgical procedures

We carried out all surgical manipulations on study day 0. Separate rooms were used for operative procedures and for housing. We divided rats in groups D– I into pairs; one rat in each pair was subjected to GETA only, and the second rat in the pair underwent GETA plus thoracotomy. We sequentially anesthetized rats in each pair in an induction chamber and then immediately intubated each rat with a 14-gauge vascular catheter endotracheal tube. We connected each rat to a ventilator (Model 683, Harvard Apparatus, Holliston, MA) and administered 1.5–3% isoflurane and 0.4 l oxygen per min (tidal volume: 2.5 ml per kg; respiratory rate: 80 breaths per min). Rats were maintained under deep plane anesthesia during the procedure. In particular, we confirmed the absence of response to noxious stimuli (paw pinch) and ensured that rats ' heart rates did not exceed 350 beats per min during surgery. We carried out surgery on an operating table that was equipped with electrocardiogram electrodes, which we used to record rats' electrocardiograms and to measure their heart rates. The table also contained an automated electronic heater (Model THM-100, Indus Instruments, Houston, TX), which we set to maintain a core temperature of 37 °C to guard against hypothermia. Both rats in each pair were maintained under anesthesia for the same amount of time.

Thoracotomy—We prepared the surgical field by first removing the rat's fur with depilatory cream (Nair, Church & Dwight, North Brunswick, NJ) and then disinfecting the area with betadine and 70% ethanol. We made a 3-cm incision from the left sternal border to the left anterior axillary line overlying the fifth interspace. We gently undermined the dermis in all directions and bluntly dissected a plane beneath the pectoralis major muscle. The pectoralis major muscle was reflected superomedially, and the pectoralis minor muscle was reflected laterally and stabilized using a single spring retractor. We used tenotomy scissors to make a 2-cm incision in the left fourth interspace, taking care to avoid injury to the heart, lung and vascular structures. We used gauze moistened with saline to retract the left lung superiorly and then placed a second spring retractor in the fourth interspace and expanded it to 1 cm. We then removed the intercostal retractor and gauze and reapproximated the ribs with four interrupted 3-0 chromic sutures passed with a tapered needle. We closed the skin using a single running 4-0 polypropylene suture. We then removed the isoflurane component of the inhaled gas and, upon the return of spontaneous respiration, extubated the rat.

Analgesia treatments

Rats received six doses of buprenorphine (0.1 mg per kg body weight; Buprenex, Abbott Animal Health, Chicago, IL), three doses of meloxicam (1 mg per kg; Metacam, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO) or equivalent injections of physiologic saline. For all rats that underwent surgery, the initial dose was administered s.c. immediately after extubation. Rats in groups A, B and C received their initial injection at the same time as did rats in their matched GETA alone and GETA –thoracotomy cohorts. Remaining meloxicam and matched saline doses were administered at 8 AM on days 1 and 2, and remaining buprenorphine and matched saline doses were administered at 8 PM and at 8 AM on days 0–2. In rats that underwent surgery, we prevented dehydration by diluting initial analgesic doses

in physiologic saline at a total volume of 3 ml. All other injections had a total volume of 0.5 ml each.

Data and statistical analyses

We evaluated rats' daily growth rates by calculating the percentage of body weight change during a 24-h period. We first weighed rats on day −2. Growth rate change reported for day −1 represents the 24-h period between day −2 and day −1. Within each group, we determined statistical significance of differences between mean daily growth rates using a one-way ANOVA with a Bonferroni correction (Prism 4.0 software, Graphpad Software, Inc., San Diego, CA).

RESULTS

The mean baseline daily growth rate (measured between study days − 2 and 0) of the young adult rats used in this study was 3.58% (± 1.0% s.d.), which is considered a normal growth rate for male Lewis rats that are 5–9 weeks of age [14]. We noted that on day − 1, growth rates in buprenorphine, meloxicam and saline treatment groups were significantly different from one another ($P < 0.05$). By day 0, there were no significant differences in growth rates among the various groups.

Analgesic drug (or saline) alone (groups A, B and C)

Rats that received saline or meloxicam injections showed post-injection growth rates that were slightly lower than baseline (Fig. 1a); this reduction was insignificant, however. In contrast, in rats that were treated with buprenorphine, we noted a significant reduction in growth rates by study day 2 ($P < 0.05$). Weight gain continued to be significantly depressed in these rats until study day 4.

GETA with no surgery (groups D, E and F)

For rats that received saline injections after GETA alone, growth rate on day 1 was significantly lower than baseline (difference of about 3 % between growth rates on day − 1 and day 1; $P < 0.05$; Fig. 1b). For rats that were treated with meloxicam, the growth rate on study day 2 was significantly higher than that on day 0 ($P < 0.05$). For rats that received buprenorphine after GETA, we observed a statistically significant reduction in post-procedure growth rates. In particular, growth rates on each of study days 1 through 4 were significantly lower than baseline values (P ranged from < 0.001 to < 0.05; Fig. 1b). The growth rate of these rats showed significant recovery after analgesia was discontinued (growth rate on day 5 was significantly higher than that on day 4; $P < 0.05$).

GETA plus thoracotomy (groups G, H and I)

In rats that underwent thoracotomy and did not receive analgesics, we observed a significant postoperative reduction in growth rate (growth rate on day 1 was 5% lower than that on day − 1; $P < 0.01$; Fig. 1c). Growth rate in these rats returned to a nearly normal level by postoperative day 2. We also observed significant reductions in growth rate in rats that were treated with buprenorphine. These rats, unlike the rats that underwent thoracotomy without receiving analgesia, showed a growth rate that was significantly lower than baseline until postoperative day 5 ($P < 0.05$; Fig. 1c). Furthermore, in contrast to rats that received buprenorphine with GETA alone, the growth rate of these rats did not recover significantly after analgesia was discontinued. In rats that underwent thoracotomy and were treated with meloxicam, we observed no significant changes in growth rate.

DISCUSSION

We investigated whether changes in normal body weight gain could be used as a simple and objective measure of pain in growing young adult rats that were subjected to an operative procedure. Further investigation will determine whether our observations in this study extend to rats of different ages and strains and to female rats.

We chose to carry out the thoracotomy procedure because it involves the manipulation of bone and is therefore considered to be severely painful to both humans and animals. To ensure adequate analgesia in rats that underwent thoracotomy, we administered high doses of buprenorphine (0.1 mg per kg) and meloxicam (1.0 mg per kg); these doses fall within the range of traditionally proposed doses [15,16]. To discriminate between perturbations in normal weight gain caused by postoperative pain and changes associated with the physiological effects of animal handling, GETA or thoracotomy, we included many single-intervention control groups. We expected that the two analgesia regimens we chose would completely mitigate pain as well as pain-related disruptions to body weight gain.

We found that GETA alone caused a reduction of up to 3% in normal weight gain; this would seem to suggest that more severe changes in weight gain can be attributed to postoperative pain. However, we observed that buprenorphine treatment alone or in combination with GETA caused prolonged weight loss independent of any surgical intervention. Therefore, alterations in body weight cannot definitively be attributed to postoperative pain if rats receive postoperative buprenorphine injections twice daily at a dose of 0.1 mg per kg. Notably, treatment with meloxicam at a daily dose of 1 mg per kg s.c. was not associated with growth rate alterations in any experimental group, indicating that meloxicam does not produce confounding weight disturbances with this particular treatment schedule. Therefore, for a growing young adult rat that has undergone surgery and has been treated with a non-steroidal analgesic, a reduction of more than 3% in postoperative daily weight gain might indicate that the rat is experiencing pain. In these situations, veterinarians should consider increasing the analgesic dose and its intended duration. An additional practical advantage of NSAID analgesics over opioids is their approved use outside of Drug Enforcement Agency regulations (http://www.usdoj.gov/dea/pubs/scheduling.html).

Buprenorphine is a partial agonist of μ receptors, which are found mainly at supraspinal sites. Even though the serum half-life for buprenorphine is 2.8 h in rats, the drug undergoes extensive enterohepatic circulation, which may extend the duration of its effects [17]. In rats, buprenorphine's effective duration of action is believed to range from 6 to 8 h after s.c. injection, according to the spinal reflex arc [18]. Questions remain, however, regarding the dosing interval and duration of treatment needed to relieve pain in rodents after common surgical procedures [13]. Variations in analgesic efficacy, evaluated according to tail withdrawal latencies, have been noted among various strains of adult male rats [19]. Intriguingly, repeated injected doses of 0.1 mg buprenorphine per kg body weight can elicit antinociceptive tolerance in male rats [20]. In our study, we chose to administer buprenorphine s.c. every 12 h, as this administration frequency and route are common in US laboratory animal research protocols that use buprenorphine. Oral dosing of buprenorphine is complicated by changes in water consumption in the absence of operative procedures [20].

Many extra-analgesic effects have been reported after buprenorphine administration in rats. Notably, this was also the case in studies that used lower doses of buprenorphine than the dose we administered in this study (0.1 mg per kg). For example, dose-dependent changes in body temperature, heart rate and blood pressure were noted in female Wistar rats that received a single dose (0.006–0.15 mg per kg) of s.c. buprenorphine [21]. In rats that received the highest dose, alterations in blood pressure failed to normalize even by 24 h post-injection. Stewart *et*

al. showed that rats that underwent surgery (hind paw incisional model of pain) and then received daily s.c. doses of buprenorphine at doses of 0.025, 0.05 or 0.1 mg per kg had lower body weights than did rats that underwent the same surgery and were treated with vehicle alone 22. Hayes and Flecknell 23 observed decreases in body weight, food and water intake and activity during the dark period (compared with preoperative values) in rats that underwent laparotomy and received a single postoperative dose of s.c. buprenorphine (0.05 mg per kg). Furthermore, Cooper and colleagues 13 noted reductions in postoperative body weight and food consumption (compared with preoperative values) in rats that underwent laparotomy and received two daily doses of buprenorphine (either 0.01 mg per kg or 0.1 mg per kg). Another study showed that in rats that did not undergo surgery, a single dose of 0.05 mg buprenorphine per kg altered behaviors that were evaluated in a clinical scoring paradigm 24. We therefore anticipate that the growth rate alterations we observed in subjects that did not undergo surgery and were treated with a relatively high dose of parenteral buprenorphine would also occur in rats treated with lower doses. Buprenorphine might directly affect appetence or metabolism, which would account for the postoperative reductions in weight gain and other systemic changes that have been observed in rats that were treated with buprenorphine across the full spectrum of recommended doses.

Meloxicam is an oxicam type of NSAID, with antipyretic, analgesic and anti-inflammatory mechanisms of action that resemble those of aspirin. The antipyretic effects derive from the ability of oxicam compounds to prevent prostaglandin E_2 production in the hypothalamus. Meloxicam produces anti-inflammatory effects because it inhibits the cyclooxygenase pathway and therefore decreases the production of downstream mediators of inflammation, which include arachadonic acid, leukotrienes and prostaglandins. All agents in the NSAID group inhibit the cyclooxygenase (COX) enzymes COX-1 and COX-2. After laparotomy in rats, local inhibition of COX-1 by local infusion within the spinal cord abrogates reduction of normal behaviors such as rearing [25–27]. Spinal expression of COX-1 mRNA expression is markedly greater than spinal expression of COX-2 mRNA in models of postoperative pain but not in models of inflammatory pain 28. Highly invasive surgical procedures such as thoracotomy affect both local and peripheral pathways. Meloxicam and other NSAIDS in the oxicam subgroup are proposed to decrease local inflammation by preferentially inhibiting COX-2, thereby decreasing prostaglandin release in areas of active inflammation. Oxicams also have a longer duration of action than do other classes of NSAIDs 29, which permits daily administration as performed in this study. Meloxicam administered at 20 mg per kg, a dose substantially higher than that used in our current study, was recently shown to inhibit corticosteroid release and behaviors attributable to pain after vasectomy in mice [30].

A large meta-analysis of human trials showed that initiating either opioid or NSAID analgesia during the preoperative (preemptive) period was no more effective than initiating analgesia after surgery in patients undergoing a wide range of operative procedures [31]. To our knowledge, no controlled studies have indicated that this effect would be different in animals. Therefore, we adopted a more traditional postoperative medication scheme and administered the first dose of analgesic immediately after extubation. Rats that were not treated with postsurgical analgesia rebounded to normal weight gain by day 2 after thoracotomy, thus suggesting that pain subsided at some point between 24 and 48 h after surgery. This time frame is longer than that reported in other studies involving laparotomy [3,6,24,32]; thoracotomy probably causes a higher level of pain because of manipulation of the rib cage. Therefore, IACUCs and investigators must ensure that laboratory rodents receive 48 h of effective analgesia after highly invasive operative procedures that may cause moderate to severe pain (for example, those involving bone).

Studies have suggested evaluating post-laparotomy pain in rats by scoring specific pain-associated behaviors during an observation period of 5–10 min, beginning about 25 min after

surgery [16]. Because laboratory animals are often housed in groups, we propose that the daily weighing of animals may be a more efficient and objective method for monitoring large groups of rodents. Furthermore, with the latter method, social rodents such as rats and mice can continue to be co-housed after surgery, promoting their well-being throughout the operative period. This is in contrast to pain evaluation methods such as measurement of food and water consumption, in which animals must be singly housed to enable collection of data.

Physiological and behavioral changes associated with pain may vary, depending on the rat strain 14,33 and gender (male rats are more sensitive than females to opioids) 33–35, as well as the experimental procedure 36 and skill of the surgeon. In order to use weight gain alterations as a correlate of postoperative pain in any given procedure, we recommend evaluating weight change in response to anesthesia and NSAID analgesia (without surgery) in several controls of the same age, strain and sex as the experimental subjects. In the absence of such experiment-specific analyses, we suggest that a 3% reduction in growth rate in otherwise healthy young adult rats represents a humane cut-off that should prompt investigators, laboratory animal caregivers and veterinary staff to modify the administered analgesia regimen.

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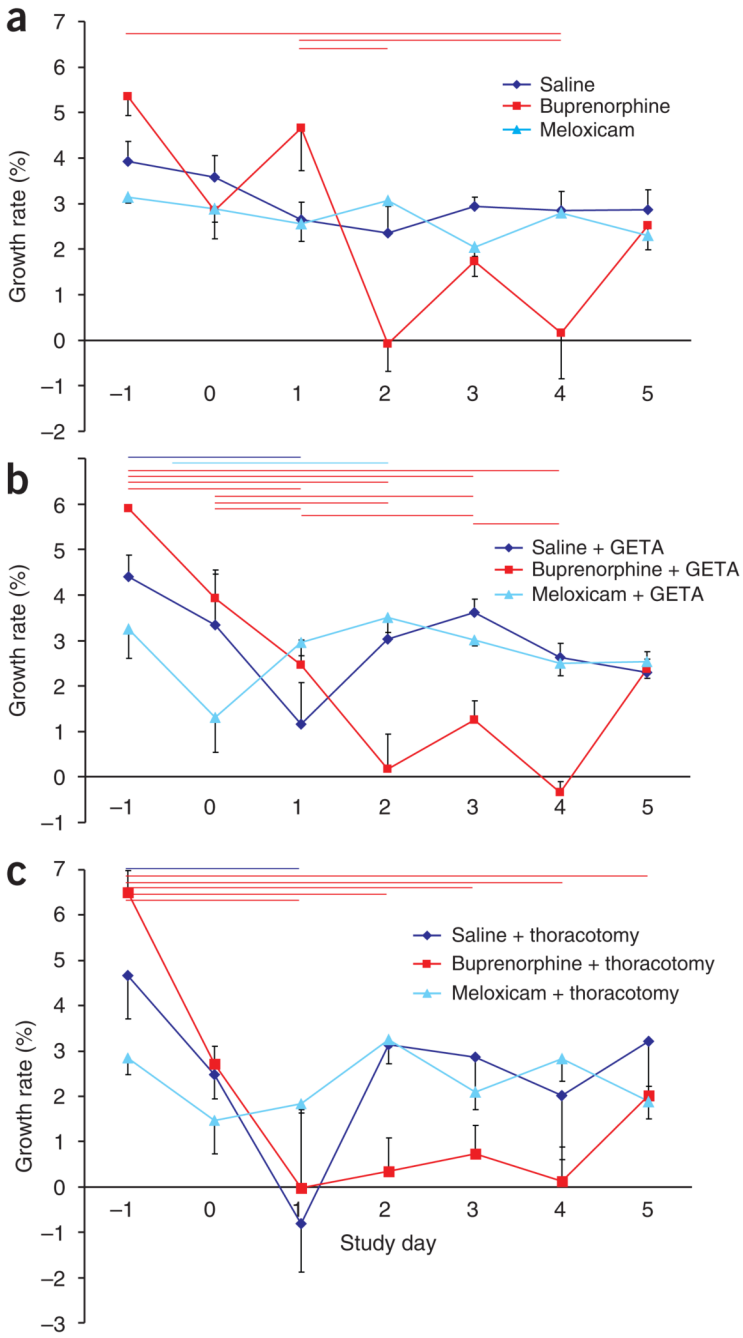

FIGURE 1.

Growth rates over 24-h periods in young adult rats that underwent various manipulations associated with a thoracotomy. For groups D–I, GETA and thoracotomy were carried out on day 0. On days 0 (post-procedure for groups D–I), 1 and 2, rats received injections of saline, buprenorphine or meloxicam. Error bars indicate s.e.m. Horizontal lines indicate a significant difference within a single group when comparing growth rates on two study days ($P < 0.05$; ANOVA with Bonferroni correction). (**a**) Rats that did not undergo anesthesia or surgery (groups A, B and C). (**b**) Rats that underwent GETA with no surgery (groups D, E and F). (**c**) Rats that underwent GETA and thoracotomy (groups G, H and I).

TABLE 1

Experimental groups

Group	*n*	Procedure	Analgesic
A	5	None	Saline
B	5	None	Buprenorphine
C	4	None	Meloxicam
D	5	GETA	Saline
E	5	GETA	Buprenorphine
F	5	GETA	Meloxicam
G	5	GETA + thoracotomy	Saline
H	5	GETA + thoracotomy	Buprenorphine
I	5	GETA + thoracotomy	Meloxicam