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Evaluation of Liposome-Encapsulated Oxymorphone Hydrochloride in Mice after Splenectomy

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The use of mice in biomedical research is increasing, largely due to the production and use of genetically engineered animals. Providing postoperative pain control in mice presents many challenges, and long-acting analgesic preparations would be advantageous for this species. A single subcutaneous injection of a liposome-encapsulated (LE) preparation of oxymorphone was compared with multiple injections of buprenorphine or saline in outbred mice undergoing splenectomy. Control groups were given isoflurane alone or isoflurane and an injection of LE oxymorphone but did not undergo surgery. The following parameters were evaluated for 5 days after surgery and were compared with presurgical baseline data for each group: food and water consumption, body weight, ethographic score, and voluntary exercise on a running wheel. Ethographic scores indicated less postsurgical pain in both groups of mice that received either analgesic preparation compared with mice that received only saline. However, mice given LE oxymorphone had superior postoperative recovery, as measured by wheel-running distance and body weight gain, compared with mice given buprenorphine or saline. Mice undergoing splenectomy had significant decreases in body weight, food and water consumption, voluntary exercise, and other normal behaviors. Administration of liposomal oxymorphone at the time of surgery improved postsurgical recovery as measured by these parameters compared with multiple injections of buprenorphine or saline alone. Administration of LE oxymorphone at the time of surgery improved postsurgical recovery, as measured by these parameters.

The availability of genetically engineered mice as models of human disease has vastly increased the number of mice used in biomedical research over the past 20 years. Law and Public Health Service policy mandate provision of adequate analgesia for animals undergoing surgical procedures (11, 24). The evaluation of analgesic drugs to alleviate pain due to a major surgical procedure in mice is complex. Mice do not display many of the typical animal pain behaviors, making evaluation by use of an ethogram less effective. Mice have small body size and high metabolic rate, necessitating higher dosages of most drugs on a per kilogram basis than those for larger animals (9). At the same time, it is also necessary to avoid repeated restraint and handling of the animals, especially after surgery. This is particularly true of immunodeficient mice or mice with genetic alterations that make them intolerant of stress. There also are financial implications. A unique strain or genetically engineered mouse may cost hundreds of dollars, or be difficult to obtain. Therefore, losing animals to postsurgical complications has a negative impact on research budgets.

Little has been published on the assessment and treatment of pain in laboratory mice. Running wheels have been used to assess voluntary exercise of mice in a wide variety of experiments (3, 17, 23, 29, 30). The study reported here was designed to evaluate the effectiveness of liposome-encapsulated (LE) oxymorphone or buprenorphine in controlling postoperative pain, using the running wheel as a means of measuring locomotor activity, indicative of the willingness/ability of mice to engage in voluntary exercise.

Several classes of drugs are routinely administered to rodents, including mice, for relief of postsurgical pain. These include nonsteroidal anti-inflammatory drugs (NSAIDs) such as flunixin, carprofen, or ketoprofen, and opioid analgesics, especially buprenorphine (19-21, 31). Despite recent improvements in NSAIDs, opioid analgesics are still the most effective drugs for controlling moderate to severe acute pain. Buprenorphine is the most widely used opioid analgesic in mice and rats because it has longer duration of action (6 to 12 h) compared with standard pharmaceutical preparations of drugs such as morphine sulfate, butorphanol tartrate, or oxymorphone (25, 31). Nonsteroidal anti-inflammatory drugs can have serious adverse gastrointestinal tract effects in rodents, especially if they are administered orally (31). Buprenorphine as an analgesic for rodents also has several disadvantages. Even with administration every 12 h, timely and efficient dosing of animals is difficult and time consuming, especially when large numbers of animals undergo experimental surgical procedures on the same day. Buprenorphine is a partial agonist opioid drug, and there is a ceiling effect on the analgesia it provides. Results of a previous study in our laboratory (7) indicated that buprenorphine was not an effective analgesic drug in rats undergoing intestinal resection, a procedure associated with moderate to severe visceral pain.

Opioid drugs have been produced as long-acting formulations

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Table 1. Ethogram for mice

Score	Coat	Eyes	Coordination/posture	Overall condition
0	Normal, well groomed, smooth sleek hair coat	Open, alert	Normal	Normal
1	Not well groomed	Squinted eyes	Walk awkward or slightly hunched; still runs or moves about	Rough appearance but acts fairly normal
2	Rough hair coat, dirty incision	Closed	Walk hunched, walking on eggshells, doesn't run, walks slowly	Slightly depressed, rough appearance or slightly agitated
3	Very rough hair coat, hair loss, dirty incision		Walks slowly with effort or only by tapping on cage	Very rough or very agitated
4			Hunched, stumbles or must be pushed to get to move	
5			Hunched, won't walk even when pushed	

that can be given by the oral (2, 8, 10), transdermal (4, 5, 13), or injectable (14, 15, 32, 33) route. Long-acting oral or transdermal preparations made for human beings can be used for larger animals such as dogs and pigs, but are not suited to animals the size of common laboratory rodents because most of the dosage formulations are too large for animals with small body size. Also, long-acting oral opioid medications, such as Oxycontin or MS Contin, must be swallowed intact to be effective as a time-release preparation, and it would be difficult to impossible to induce rodents to consume the pills intact. Therefore, injectable formulations of long-acting opioids would be optimal for mice.

Oxymorphone is an opioid drug that is ten times more potent than morphine sulfate and has been used in a wide variety of animal species, including rodents (9, 31). We have developed a long-acting formulation of oxymorphone hydrochloride (Douglas Pharmaceuticals Ltd., Auckland, New Zealand) by encapsulating it into liposomes. Liposome-encapsulated oxymorphone was tested in a rat model and was found to provide prolonged relief of postsurgical visceral pain (16, 28). Results of our previous study indicated that a single injection of LE oxymorphone relieved postoperative visceral pain for at least 48 h in rats (16). This is in contrast to standard oxymorphone, which must be administered every 4 to 8 h. Additionally, LE oxymorphone was an effective analgesic for up to 7 days in rats with chronic constrictive injury of the sciatic nerve (28). The advantages of this preparation over standard opioid formulations include a logistically easy dosing regimen for treating postoperative pain and fewer adverse effects (16, 28).

The purpose of the study reported here was to assess the analgesic effectiveness of LE oxymorphone in mice after splenectomy in comparison with that in mice given a placebo or buprenorphine twice daily after splenectomy. A second purpose of this study was to incorporate voluntary wheel-running as a measure of postoperative recovery quality and analgesia, in concert with determination of a behavioral ethogram, food intake, and changes in body weight.

Materials and Methods

Animals. All procedures involving animals were approved by the animal care and use committee of the University of South Dakota in accordance with the *Guide for the Care and Use of Laboratory Animals*. Six-week-old male ICR mice were purchased from Harlan Sprague Dawley (Madison, Wis.) and were designated specific pathogen free by the supplier on the basis of results of: serologic testing for *Mycoplasma pulmonis*, Sendai virus, mouse hepatitis virus, pneumonia virus of mice, minute virus of mice, mouse parvovirus, Theiler's murine encephalomyelitis virus, reovirus 3, rotavirus, ectromelia virus, lymphocytic choriomeningitis virus, mouse adenovirus (strain 1 & 2), polyoma virus, mouse cytomegalovirus, Hantaan virus, mouse thymic virus, mouse pneumonitis virus, lactate dehydrogenase-elevating virus, *Encephalitozoon cuniculi*, and *Clostridium piliforme*); polymerase chain reaction analysis for *Helicobacter* spp., *Mycoplasma pulmonis*, *Corynebacterium bovis*, and *Pneumocystis carinii*; and microscopic examination for endo- and ectoparasites. Animals were singly housed conventionally in static Micro-Isolator™ cages (Lab Products Inc., Seaford, Del.) with Harlan Sani-Chip bedding (Harlan, Madison, Wis.) that was changed once a week, were fed Harlan Teklad rodent diet 8604 (Harlan, Madison, Wis.), and were provided tap water. Mice were acclimated for 5 days prior to experimentation and were maintained throughout acclimation and experimentation at 22°C and approximately 40% humidity on a 12/12-h light/dark photoperiod. Male ICR mice were used to test the analgesic efficacy of LE oxymorphone after splenectomy. Food and water intake, body temperature, body weight, and locomotor activity were recorded every 24 h for 5 days from the onset of the experiment. Mice were randomly assigned to five experimental groups.

Drug preparation. Liposome-encapsulated oxymorphone was prepared by use of a described method (16, 28).

Outcome measures. All mice were singly housed, and each was provided with identical running wheels 7 days prior to the experiment. Running wheels were equipped with an odometer (Velo 2, model CC-VL200 CatEye, Osaka, Japan) to record wheel revolutions, and calculations were adjusted to accommodate running wheel size. Running distances were recorded every 24 h. We also evaluated behavior using an ethogram. Behavior was observed, and results were recorded at postoperative hour (POH) 12, 24, 48, and 72. Coat, eyes, coordination/posture, and overall physical condition were evaluated and scored using this ethogram (Table 1). A pain index score was achieved by adding together the scores for coat, eyes, coordination/posture, and overall condition, then calculating the average for each group at each time point. Persons scoring mice for behavioral parameters were not blinded to the experimental condition, but were well trained in the assessment of normal and abnormal murine behaviors.

In conjunction with recording running distances and behavior, food and water intake as well as body weight were recorded. Each animal was given five pieces of standard laboratory rodent diet with a combined weight of approximately 25 g. Every 24 h, the pieces of diet were collected and weighed. The consumption rate was determined by subtracting the total weight of the remaining pieces from the total weight of the five pieces at administration. After being weighed, small pieces of diet were discarded and replaced with fresh pieces as needed to aid in recovery. A minimal amount of bedding was used in the cage

Table 2. Experimental groups

Group 1 n = 10	Group 2 n = 10	Group 3 n = 6	Group 4 n = 8	Group 5 n = 6
Isoflurane	Isoflurane	Isoflurane	Isoflurane	Isoflurane
Splenectomy	Splenectomy	Splenectomy	No surgery	No surgery
LE oxymorphone	Buprenorphine	No analgesia	LE oxymorphone	No analgesia

to aid in recovering all diet pieces. Water bottles were filled with fresh tap water and weighed. Every 24 h, the bottle was removed and its weight was recorded.

Surgical procedure. Splenectomy was used to induce postoperative pain. Mice of groups 1, 2, and 3 were anesthetized with isoflurane (Baxter Healthcare Corp, Deerfield, Ill.) and were prepared for surgery in aseptic manner. A ventral midline incision was made, and the spleen was removed using electrocautery of major vessels. The abdominal incision was closed with continuous 5-0 Vicryl (Ethicon, Inc., New Brunswick, N.J.) sutures in the body wall and Nexaband (Veterinary Laboratory Products, Phoenix, Ariz.) tissue adhesive on the skin.

Experimental groups. After recording baseline measurement of running distances, food and water intake, and body weight, mice were randomly allotted to five groups (Table 2). Group 1 mice received 2 mg of LE oxymorphone/kg of body weight, s.c., immediately after surgery. Mice of this group also received a sham injection of 0.2 ml of sterile saline, s.c., every 12 h after surgery for 24 h. Group 2 mice received 0.2 mg of buprenorphine/kg, s.c., immediately after surgery and every 12 h for 24 h. Mice of the remaining three groups served as controls. Group 3 mice served as a non-analgesic surgical control. This group was given 0.2 ml of sterile saline immediately after surgery and every 12 h for 24 h. Mice of group 4 served as a non-surgical positive control; they were anesthetized with isoflurane until a surgical depth of anesthesia was reached. This anesthesia depth was maintained in these mice for 10 min, then they were allowed to recover. This group was then given 2 mg of LE oxymorphone/kg, s.c., immediately after anesthetic administration ended and 0.2 ml of sterile saline, s.c., every 12 h for 24 h. Group 5 mice served as a non-surgical negative control and did not undergo surgery or receive any analgesic, but instead were only anesthetized. Mice were anesthetized using isoflurane until a surgical depth of anesthesia was reached. This anesthesia depth was maintained in these mice for 10 min, then they were allowed to recover. Analgesics were not given, but animals received 0.2 ml of sterile saline, s.c., immediately after anesthetic administration ended and every 12 h for 24 h.

Statistics. Statistical analysis was performed using StatMost (Dataxiom Software Inc., Los Angeles, Calif.). Comparisons between groups at a particular time point were done using a non-parametric Mann-Whitney test. Analysis of variance (ANOVA) within groups and across time was done using one-way ANOVA with repeated measures and the Newman-Keuls' test. If variance was not equal, a non-parametric analysis was done using the Kruskal-Wallis test. A value of $P < 0.05$ was considered significant.

Results

Behavior. At POH 12, there was a significant difference between group 3 mice (surgery/no postoperative analgesia), and those of the two surgical groups given postoperative analgesics (groups 1 and 2; Fig. 1). The mice that were not given postoperative analgesics had mean (± SEM) pain index score of 3.33 ± 0.45.

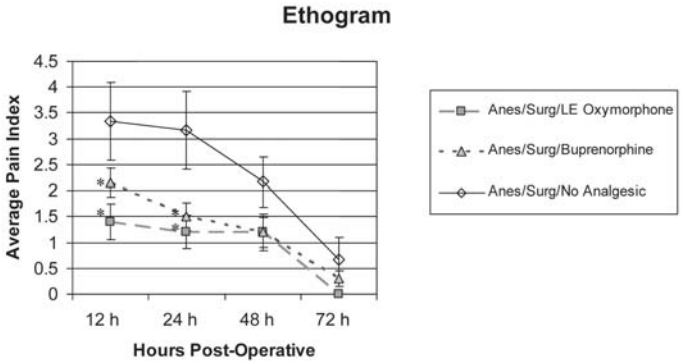

Figure 1. Ethographic assessment of male ICR mice after splenectomy using the ethogram in Table 1. Mice receiving opioid analgesics, either liposome-encapsulated (LE) oxymorphone (Anes/Surg/LE Oxymorphone) or buprenorphine (Anes/Surg/Buprenorphine), have significantly lower pain scores at 12 and 24 h than do mice not receiving analgesics (Anes/Surg/No Analgesic).

This was significantly higher than pain scores for mice that were given postoperative LE oxymorphone (1.4 ± 0.34; $P = 0.03$). Mice given postoperative buprenorphine (group 2) also had significantly lower mean pain index score at 12 h (2.15 ± 0.28; $P = 0.03$). There was, however, no significant difference in pain score between groups 1 and 2 at POH 12. At POH 24, mice of group 3 had significantly higher pain score than did mice of group 1 or 2 ($P = 0.01$, both groups). There was not a significant difference between groups 1 and 2 at this time point. By POH 48 and 72, there were no significant differences in pain scores between any of the groups. The two control groups that did not receive surgery (groups 4 and 5) had a constant pain index of zero at all time points, so their data are not included in Fig. 1.

Voluntary exercise. All groups were affected by their treatment on the day of surgery (day 0). All mice that underwent splenectomy decreased the distance run compared with their presurgical average ($P < 0.00001$). Even group 5 mice (anesthesia only) ran an average of 32% less than the distance they ran prior to the procedure (Fig. 2). Group 3 mice (surgery/no analgesia) had the greatest reduction in average distance run: only 26% of their average distance prior to surgery. Mice administered LE oxymorphone (group 1) after surgery had average running distances that were significantly higher than those of mice that did not receive analgesics after surgery (group 3) ($P = 0.004$). Mice administered buprenorphine after surgery (group 2) also had running distances that were significantly higher than those of mice that did not receive analgesics after surgery (group 3) ($P = 0.007$).

At POH 24 (day 1), groups that did not undergo surgery (groups 4 and 5) and the group of mice that received LE oxymorphone at the time of surgery (group 1) increased the distance they were running to near or above pre-operative averages. The mice that received LE oxymorphone ran an average of only 7% less compared with that of group 5 mice that did not receive surgery or analgesics. The mice that received LE oxymorphone after surgery (group 1) also had significantly higher running distances compared with those for mice that did not receive analgesics after surgery (group

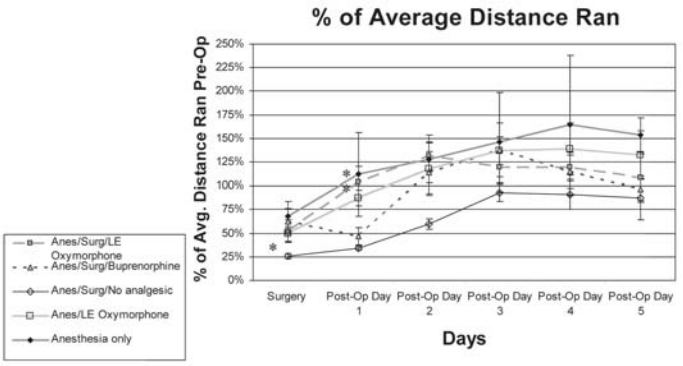

Figure 2. Assessment of voluntary wheel running as a measure of postoperative recovery quality in male ICR mice after splenectomy. The five groups are outlined in Table 2. There was a significant difference in the average distance run per group, compared with average pre-operative running distance. On the day of surgery, mice receiving LE oxymorphone (Anes/Surg/LE Oxymorphone) had average running distances significantly higher than did mice that did not receive analgesics after surgery (Anes/Surg/No analgesia). At 24 h after surgery, mice receiving LE oxymorphone (Anes/Surg/LE Oxymorphone) had average running distances significantly higher than did mice that did not receive analgesics (Anes/Surg/No analgesia) and mice administered buprenorphine (Anes/Surg/Buprenorphine). There was no significant difference in running distance between mice administered buprenorphine (Anes/Surg/Buprenorphine) and mice not receiving analgesics (Anes/Surg/No analgesia).

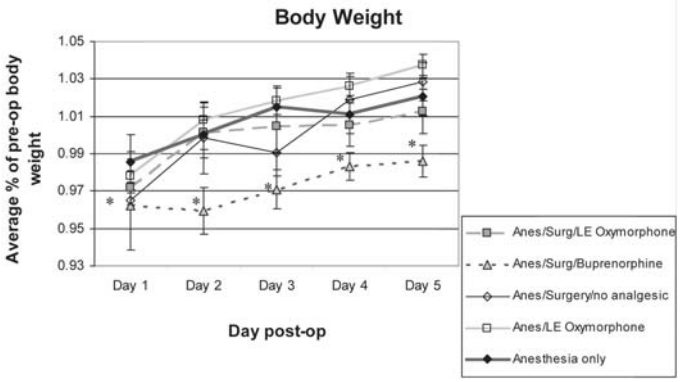

Figure 3. Assessment of the effect of treatment after splenectomy in male ICR mice. The five groups are outlined in Table 2. Mice that had received buprenorphine (Anes/Surg/Buprenorphine) had significant loss of body weight, compared with mice that received LE oxymorphone (Anes/Surg/LE Oxymorphone). Over the course of the study, mice administered buprenorphine (Anes/Surg/Buprenorphine) never regained to their pre-operative weight. *Denotes significant difference $P \leq 0.05$.

3) ($P = 0.004$) and for mice that were administered buprenorphine after surgery (group 2) ($P = 0.008$). The mice that were administered buprenorphine after surgery (group 2) had running distances that were only 47% of their pre-operative average. The average distance run by this group of mice was 58% less than the average distance run by mice that did not receive surgery or analgesics (group 5). In fact, at POH 24 (day 1), there was no significant difference in running distance between mice administered buprenorphine after surgery (group 2) and mice not receiving analgesics (group 3) ($P = 0.1$).

At POH 48 (day 2), average distance run by the mice administered buprenorphine (group 2) increased to 113% of the average distance run before surgery. The activity of mice of the group administered LE oxymorphone mice did not differ significantly at any time point from that of the anesthesia-only controls, and was significantly greater for at least 48 h (day 2) after surgery from that of surgical controls that did not receive analgesics. The average distance ran by mice administered buprenorphine (group 2) and mice administered LE oxymorphone (group 1) after surgery was significantly higher than that of mice that did not receive analgesics ($P = 0.004$, both groups).

Water consumption. There were no significant differences between any of the groups at any time points with respect to water consumption. However, there was a trend toward decreased water consumption in mice administered buprenorphine (group 2) and mice not receiving analgesics (group 3) compared with that of the other groups.

Food consumption. All groups were affected by the treatments on the day of surgery. However, only the mice that received buprenorphine (group 2) had a significant decrease in food consumption compared with mice that were anesthetized only (group 5; $P = 0.01$). There were no significant differences between any of the groups at any other of the time points with respect to food consumption.

Body weight. Body weight decreased in all groups of mice at POH 24 (Fig. 3). By POH 48, mice of groups 1, 4, and 5 weighed 100% of their pre-procedure body weight. Mice administered LE oxymorphone (group 1), maintained their body weight compared with pre-operative values. However, mice that received buprenorphine (group 2) had significantly lower body weight for all five postoperative days compared with that for all other experimental groups including those given LE oxymorphone (group 1) ($P = 0.03$ to 0.05) Over the course of the experiment, the only group that did not regain or exceed their pre-operative weight was the group administered buprenorphine (group 2).

Discussion

Using the parameters evaluated in the study reported here, a single dose of LE oxymorphone administered to mice at the time of surgery resulted in superior analgesia and recovery quality compared with that associated with multiple doses of buprenorphine. Most interestingly, mice administered LE oxymorphone at the time of surgery returned to normal wheel-running activity as quickly as mice that were only anesthetized and did not receive analgesics. Mice administered buprenorphine had lower postoperative body weight gain than that of mice of all other groups, including mice which did not receive analgesics following surgery. Even at postoperative day 5, mice administered buprenorphine had not regained their pre-operative weight. Over five postoperative days and with regard to body weight or the average distance ran, there was no significant difference between mice that had been administered a single dose of LE oxymorphone and control animals that had been anesthetized only.

Buprenorphine is currently considered the standard opioid analgesic for use in rats and mice. The reasons for the widespread use of buprenorphine include convenience of administration, since the drug can be administered every 8 to 12 h compared with drugs such as the standard pharmaceutical preparations of oxymorphone or morphine sulfate, which must be given every 4 to 6 h (9, 31). Buprenorphine is a partial agonist drug. That means there is a ceiling effect on adverse effects of the drug such as respiratory depression. There is also a ceiling effect on the amount of analgesia possible using buprenorphine,

whereas pure agonist drugs such as oxymorphone do not have a ceiling effect and provide more analgesia in dose-dependent manner (12, 26).

The effects of buprenorphine in rats have been studied extensively. At clinically relevant dosages (0.01 and 0.05 mg/kg, s.c.), buprenorphine caused a reduction in food intake and an increase in home cage activity in rats that were not subjected to surgery (18). In a surgical model, however, buprenorphine administration resulted in less body weight loss and greater food and water consumption in rats after either laparotomy or bile duct ligation surgery (19, 20). Orally administered buprenorphine presented in gelatin was also superior to a single injection of morphine sulfate with respect to weight recovery and food and water intake in rats after laparotomy (21).

In our study, buprenorphine was superior to saline with respect to the quality of postoperative recovery, as measured by ethographic scores. There was a trend, however, for mice administered buprenorphine for postoperative analgesia to have lower food and water consumption than mice administered either saline or LE oxymorphone. Also, mice administered buprenorphine were the slowest to recover their body weight compared with mice given saline or LE oxymorphone. These data are in contrast to the data in rats, where administration of buprenorphine improved all outcome measures. There could be several reasons for this finding. The dosage of buprenorphine used in mice for this study (0.2 mg/kg) may not be as well matched to the postoperative needs of mice as the dosage cited in literature for use in rats. Also, the splenectomy model may have induced a different degree of pain than that associated with either simple laparotomy or bile duct ligation, as was done in the rat studies (19-21). Because of the ceiling effects on its analgesic properties, buprenorphine is more applicable to procedures that induce mild to moderate pain, whereas pure agonist opioids are recommended for alleviation of moderate to severe pain (12, 31). Also, results of algesiometric studies in mice indicate that buprenorphine may have an effective duration of only 3 to 5 h in this species (6). Results of a previous study (7) in our laboratory indicated that rats with intestinal resection had better postoperative ethographic scores when given oxymorphone for postoperative pain than did rats given buprenorphine. One of the principle disadvantages of pure agonist opioids such as oxymorphone, however, is their short duration of action, especially in small mammals such as mice. Liposomal preparation of oxymorphone to form a subcutaneous depot injection eliminates the necessity of giving repeated injections of drug at short intervals.

Voluntary exercise in mice given access to a running wheel has been used to study a large number of behavioral and physiologic parameters in this species (3, 17, 23, 29, 30). This includes evolution of behavioral traits such as hyperactivity (24), the effects of drugs on these hyperactive mice (27), as well as sleep, stress, circadian rhythms, and aging (3, 29, 30). Our study, however, represents the first use of voluntary activity measured by wheel-running as a measure of postsurgical outcome in mice. The running wheel was an effective tool in evaluating analgesia and proved to be more valuable than traditional methods. The ethogram used in the current study was not sensitive as an indication of postsurgical pain. At 48 h, ethographic pain scores in all groups were low, suggesting that the animals were not experiencing pain or were fully recovered. Data collected from the measurement of voluntary exercise using a running wheel, however, indicated that the animals were not fully recovered. Previous studies in rats have indicated that home cage locomotor behavior was decreased in animals undergoing surgical procedures, but total locomotor behavior alone was variable and was not a sufficiently sensitive indicator of postsurgical analgesic treatment outcome (19, 20). Focal sampling of a variety of behaviors by use of canonical discriminate analysis of the data was more sensitive in distinguishing differences in behavior between rats given different treatments after laparotomy, but this technique requires a considerable amount of time investment by human observers as well as sophisticated statistical analyses (21).

Measurement of analgesia in rodents generally is performed for one of two reasons, either to test novel preparations of drugs or to test treatment outcome to improve research practices and animal welfare. Testing for both objectives has traditionally relied heavily on algesiometric testing in otherwise healthy, nonpainful animals. Algesiometric methods designed for rodent testing generally have used a thermal stimulus applied to a tail or a paw with either dry heat or hot water (6). The advantages of this type of testing are that it is simple to perform, and large numbers of animals and test compounds or test formulations can be examined in a short period. Traditional algesiometric methods also provide an objective measurement of the animal's response to the thermal stimulus. Algesiometric testing generally only evaluates the response to high-intensity stimuli, and most postsurgical clinical pain is likely a combination of short-duration, high-intensity pain and longer duration of low-intensity pain. Differences in pain intensity may explain some of the differences in effective dosages reported in algesiometric (22) and postsurgical (21) studies. Drugs that cause sedation or loss of motor function that prolongs the time to withdrawal from a thermal stimulus without enhancement of analgesic effects per se can affect algesiometric tests.

Experiments that measure multiple postsurgical outcomes in rodents such as changes in body weight, food and water consumption, and measurements of behavior, are more difficult, expensive, and time consuming than is traditional algesiometry. Such studies also have largely been confined to those involved in determining appropriate treatments that enhance animal welfare and are not typically used for testing novel analgesic compounds or formulations (19-21). Measurement of behavior in rodents is becoming more sophisticated and more objective, driven by the need for behavioral phenotyping of transgenic animals (1). An argument may be made that postsurgical studies that measure multiple outcomes should be used to supplement traditional algesiometry, for assessment of animal welfare as well as for evaluation of novel compounds.

In conclusion, the study reported here, using wheel-running in combination with traditional behavioral ethograms for detection of pain in rodents, indicated that a single dose of LE oxymorphone administered to mice at the time of surgery resulted in superior recovery quality compared with multiple doses of buprenorphine. We also observed that voluntary wheel-running was a sensitive measure of the quality of recovery in mice after splenectomy. Further studies are warranted to test and refine the duration and degree of analgesic efficacy of liposomal oxymorphone in other surgical models in rodents and other species.

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