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Using the Mouse Grimace Scale to Reevaluate the Efficacy of Postoperative Analgesics in Laboratory Mice

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Postoperative pain management in animals is complicated greatly by the inability to recognize pain. As a result, the choice of analgesics and their doses has been based on extrapolation from greatly differing pain models or the use of measures with unclear relevance to pain. We recently developed the Mouse Grimace Scale (MGS), a facial-expression–based pain coding system adapted directly from scales used in nonverbal human populations. The MGS has shown to be a reliable, highly accurate measure of spontaneous pain of moderate duration, and therefore is particularly useful in the quantification of postoperative pain. In the present study, we quantified the relative intensity and duration of postoperative pain after a sham ventral ovariectomy (laparotomy) in outbred mice. In addition, we compiled dose–response data for 4 commonly used analgesics: buprenorphine, carprofen, ketoprofen, and acetaminophen. We found that postoperative pain in mice, as defined by facial grimacing, lasts for 36 to 48 h, and appears to show relative exacerbation during the early dark (active) photophase. We find that buprenorphine was highly effective in inhibiting postoperative pain-induced facial grimacing in mice at doses equal to or lower than current recommendations, that carprofen and ketoprofen are effective only at doses markedly higher than those currently recommended, and that acetaminophen was ineffective at any dose used. We suggest the revision of practices for postoperative pain management in mice in light of these findings.

Abbreviations: AD_{50}, half-maximal analgesic dose; MGS, Mouse Grimace Scale; NSAID, nonsteroidal antiinflammatory drug; PEG, polyethylene glycol.

The management of pain is of the highest importance in laboratory animal welfare but is complicated greatly by the inability to recognize pain and dissociate it from other sources of distress. The ILAR *Guide for the Care and Use of Experimental Animals* mandates that "…unless the contrary is known or established, it should be assumed that procedures that cause pain in humans also cause pain in animals."[33] Many research protocols involve surgical procedures, which accordingly are believed to produce postoperative pain, and veterinary staff and research personnel have an ethical obligation to minimize or alleviate that pain unless postoperative pain is itself the topic of study. Administration of analgesics to relieve postoperative pain therefore remains a cornerstone of experimental animal welfare. The lack of obvious signs of pain in laboratory animals (especially in prey species) almost certainly contributes to the underuse of postoperative analgesics.[54] Even when analgesics are used, without valid measures of postoperative pain, whether current recommendations regarding analgesic choices and doses are appropriate is uncertain.

In addition, difficulties in measuring pain in laboratory animals present challenges to preclinical pain research. Most current studies involve tonic or chronic inflammatory and experimental nerve-injury assays.[42] In short-lasting (less than 90 min) inflammatory pain assays, like the abdominal constriction or formalin tests, reflexive writhing or squashing and licking or grooming behavior, respectively, associated with the inflamed body part provides an obvious and empirically valid measure of pain intensity. By contrast, in assays featuring presumably longer-lasting pain (hours to weeks), rodents display few if any overt behaviors indicative of ongoing pain[44] or obvious 'quality-of-life' changes that might be used as pain proxies.[68] As a result, pain researchers have focused almost exclusively on measuring thermal and mechanical hypersensitivity states (allodynia and hyperalgesia),[43] which are real but not particularly prevalent symptoms of human chronic pain states.[4,60]

Therefore, much existing research into the efficacy of postoperative analgesics in laboratory rodents has used either assays of questionable relevance to postoperative pain (for examples, see references 16, 25, 65, and 69); hypersensitivity measures instead of spontaneous pain measures (for examples, see references 8, 53, 63, and 75); nonselective proxy measures (for example, cardiovascular changes, food and water intake, locomotor activity, corticosterone levels, nest construction) featuring large intersubject variability (for examples, see references 1, 2, 14, 28, and 30); or subjectively scored ethograms of unclear validity, sensitivity, or specificity (for examples, see references 1, 14, and 46). To our knowledge, only one laboratory has taken a systematic and unbiased approach, using advanced statistical techniques to identify relevant behaviors from a large number of scorable alternatives, many of which can be automated.[20,57,58,74] But even this approach is hampered by high variability and low sensitivity, and its complexity renders it useful primarily for research purposes.

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We recently developed the Mouse Grimace Scale (MGS)[35] whereby spontaneous pain in mice is quantified according to objective and blinded scoring of facial expressions (using the facial action coding system[21]), as is done routinely for the measurement of pain in nonverbal humans.[73] We find that mice (and rats[62]) display stereotypical changes in facial musculature across a wide variety of pain states of moderate duration (including postoperative pain from ventral abdominal incisions), and these changes can be scored with remarkably high reliability and accuracy. In the current study using the MGS, we examined the apparent time course of postoperative pain after laparotomy and evaluated the efficacy against spontaneous pain of the 4 most commonly used rodent analgesics: the μ-opioid partial agonist buprenorphine; the nonsteroidal antiinflammatory drugs (NSAID) carprofen and ketoprofen; and the cyclooxygenase inhibitor acetaminophen.

Materials and Methods

Subjects. All subjects were CD1 (ICR:Crl) mice (age, 6 to 8 wk) that were bred in our vivarium from mice obtained from Charles River Laboratories (Boucherville, Quebec, Canada). Mice were housed in standard 7.5 in. × 11.5 in. × 5 in. polycarbonate caging (with 1/4-in. corncob bedding; Harlan Teklad, Madison, WI) in groups of 2 to 5 with same-sex littermates, under a 12:12-h light:dark cycle (lights on at 0700), in a temperature-controlled environment (20 ± 1 °C), and with ad libitum access to food (diet 8604, Harlan Teklad) and tap water. No pathogens other than mouse norovirus were present in the vivarium. Mice each underwent only one surgery (or drug or anesthesia exposure), and roughly equal numbers of male and female mice were tested in each cohort. Neither main effects of sex nor interactions with sex were noted, so collapsed data are reported. All experiments were approved by the McGill Downtown Animal Care and Use committee and were consistent with Canadian Council on Animal Care guidelines.[11]

Digital video. Mice were placed individually on a tabletop in cubicles (9 × 5 × 5 cm high) with 2 walls of transparent acrylic glass and 2 side walls of removable stainless steel. Two high-resolution (1920 × 1080) digital video cameras (High-Definition Handycam Camcorder, model HDR-CX100, Sony, San Jose, CA) were placed immediately outside both acrylic glass walls to maximize the opportunity for clear head shots. Video was taken for 30-min immediately before surgery, and for 30-min periods centered around the postsurgical time points considered (1, 2, 4, 6, 8 12, 16, 24, 36, and 48 h). For practical reasons, separate cohorts of mice were tested from 1 to 8 h (n = 8) and from 12 to 48 h (n = 16) after surgery. An increased sample size was used in the 12- to 48-h group to obtain a more accurate conclusion regarding the duration of postoperative pain. In drug (and control) experiments (n = 4 to 8 per group, except for the laparotomy plus no treatment group, with n = 16), video was taken from 60 to 90 min after surgery or treatment.

Surgery. A laparotomy, designed to mimic a ventral ovariectomy, was performed in isoflurane–oxygen-anesthetized mice by a single surgeon. After shaving and disinfection of the surgical site, a 1-cm midline incision was made by using a scalpel. Muscle layers and skin edges were closed with 5-0 polydioxanone suture and skin edges apposed by using tissue glue. Once recovered from anesthesia, mice were housed individually in clean cages and then reintroduced to video cubicles at the appropriate time point after surgery. In one experiment, mice were anesthetized with isoflurane for the same amount of time as an average surgery (10 min), but no incisions were made. All surgeries were performed at 0900 ± 1 h, except in a single circadian experiment, during which some surgeries were performed at 2100 ± 1 h.

Figure 1. Representative photographs of a mouse at baseline (facial grimacing not present; 0), a mouse with moderate facial grimacing (1) and a mouse with obvious facial grimacing (2). For a graphic representation of individual action units, see reference 35.

Drugs. Buprenorphine, carprofen, and ketoprofen were dissolved in physiologic saline, and acetaminophen was dissolved in 30% polyethylene glycol. These drugs (volume, 10 mL/kg) were injected at the following doses subcutaneously in the flank immediately after surgery and before the mice had recovered from anesthesia: buprenorphine, 0.001, 0.01, 0.05, and 0.1 mg/kg; carprofen, 5, 10, 15, 20, and 25 mg/kg; ketoprofen, 1, 5, 10, 15, and 20 mg/kg; and acetaminophen, 100, 300, and 450 mg/kg. Drugs were obtained from CDMV (St Hyacinthe, Quebec, Canada) and Abbeyvet Export (Hartford, England). In one experiment, mice were injected with saline, polyethylene glycol, 0.1 mg/kg buprenorphine, 20 mg/kg carprofen, 15 mg/kg ketoprofen, or 300 mg/kg acetaminophen (because 450 mg/kg acetaminophen approaches toxic doses in mice[27]) but did not receive anesthesia or surgery.

Frame 'grabbing' and scoring. Individual frames from AVCHD (Advanced Video Coding High-Definition) video files were 'grabbed' automatically by using Rodent Face Finder software, developed by one of the authors.[62] This software detects frames, in an unbiased fashion, in which eyes and ears are visible and image quality is not compromised by motion blurring. Image files thus identified were cropped and then copied into PowerPoint (Microsoft, Redmond, WA), one image per slide. A PowerPoint macro (http://www.tushar-mehta.com/powerpoint/randomslideshow/index.htm) was used to randomize the slide order. Identifications were removed to ensure that subsequent coding was performed blind by a single, experienced experimenter (SGS).

Randomized and unlabeled photos were presented sequentially on a large, high-resolution computer monitor. For each photo, the scorer assigned a value of 0, 1, or 2 for each of the 5 MGS action units: orbital tightening, nose bulge, cheek bulge, ear position, and whisker change.[35] In every case, a score of 0 indicated high confidence of the scorer that the action unit was absent. A score of 1 indicated either high confidence of a moderate appearance of the action unit or equivocation over its presence or absence. A score of 2 indicated high confidence of a marked appearance of the action unit. The final MGS score was the average score across the 5 action units, and mean difference scores were obtained by subtracting baseline (presurgery, predrug, or preanesthesia) MGS scores from those after surgery, treatment, or anesthesia. Using all 5 action units for scoring is crucial, because orbital tightening alone is produced by sedation. See Figure 1 for prototypical photographs consistent with average MGS scores of 0, 1, and 2.

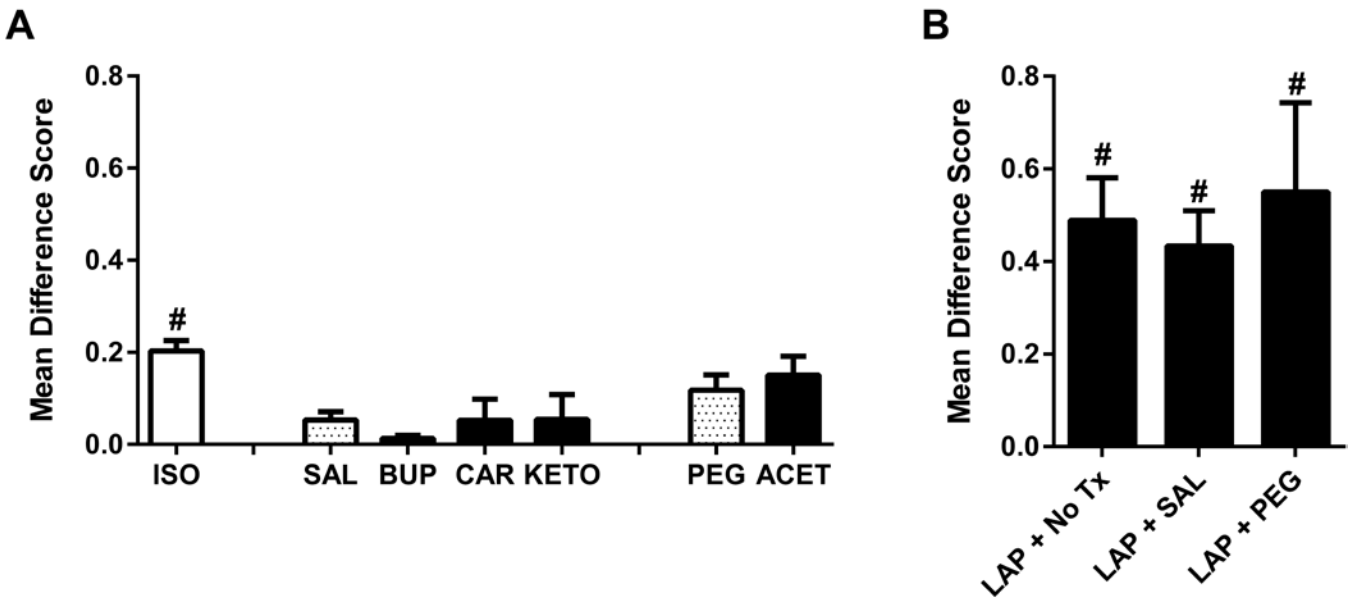

Figure 2. Effects of control conditions on MGS scores (1 h after surgery or treatment), either (A) in the absence of pain or (B) after laparotomy. Bars represent mean ± SEM mean difference scores (see text); open bars indicate anesthesia only; stippled bars are vehicle control groups; and black bars are drug groups. ISO, isoflurane; SAL, saline; BUP, buprenorphine; CAR, carprofen; KETO, ketoprofen; PEG, polyethylene glycol; ACET, acetaminophen. #, Value significantly ($P < 0.001$) different from 0 (no change from baseline) according to 1-sample *t* test.

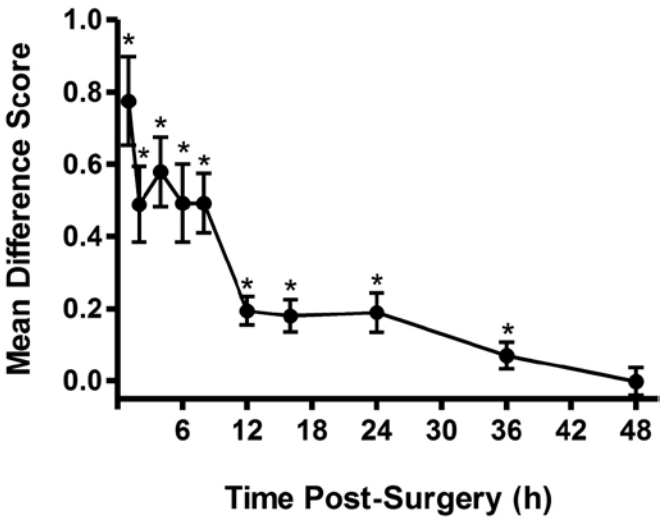

Figure 3. Time course of postoperative pain after surgery in mice as revealed by facial grimacing. Bars represent mean ± SEM mean difference scores. *, $P < 0.05$ compared with 0 (no change from baseline) according to 1-sample *t* test.

Statistical analyses. All statistical analyses were performed by using Systat version 11 (SPSS, Chicago, IL), with a criterion of $\alpha = 0.05$. Normality and homoscedasticity of all data sets were confirmed by using the Shapiro–Wilk and Levene tests, respectively, and thus parametric statistics were used in all cases. Control group data were analyzed by one-sample Student *t* test, comparing with 0, or compared with their appropriate vehicle by ANOVA. Time-course and circadian data were analyzed by using repeated-measures ANOVA, followed where appropriate by posthoc testing for repeated measures with Sidak correction for multiple comparisons. Drug efficacy data were analyzed by one-way ANOVA followed by the Dunnett case-comparison posthoc test (one-sided, comparing with the combined vehicle group). Half-maximal analgesic doses (AD_{50}) and 95% confidence intervals were estimated as described previously[66] and implemented by the FlashCalc 40.1 Pharmacological and Statistical Calculations Excel macro (M Ossipov, University of Arizona).

Results

Control conditions. First we wished to determine whether facial grimacing as a measure of pain and analgesia might be confounded by effects of anesthesia, vehicle injection, or analgesics in the absence of pain. Figure 2 A illustrates the effects on facial grimacing of isoflurane exposure, saline and PEG vehicle injection, and drug injection at high doses, all measured approximately 1 h after exposure. Only isoflurane significantly ($t_7 = 8.8$, $P < 0.001$) affected MGS scores. This effect, however, was small (less than 0.2) and accounted for entirely by increases in orbital tightening (data not shown), suggesting that many mice had not returned to full alertness after anesthesia at this time point. Importantly, no drugs produced any effects on MGS scores relative to their vehicles.

Figure 2 B illustrates the effects of treatment with vehicle (saline or polyethylene glycol) only on facial grimacing 1 h after laparotomy. As expected, all groups showed highly significant increases in MGS scores (all $P < 0.001$), but there were no intergroup differences ($F_{2,24} = 0.2$, $P = 0.86$). Because of this, we combined the groups into a mean vehicle group ($n = 27$) so that analgesic effects would be compared with the most accurate baseline possible.

Time course of postoperative pain. Figure 3 shows the time course of MGS score increases after laparotomy. Highly significant repeated-measures effects were seen in both the 1- to 8-h and 12- to 48-h cohorts compared with their own baselines (both $P < 0.001$), and scores at all time points except 48 h after surgery were significantly higher than 0 ($P < 0.05$). No significant effects of weight (as a proxy for age) were noted.

Circadian effects. Half of the mice in the 12- to 48-h cohort underwent laparotomy in the morning (0900) and half in the evening (2100), and these groups had baseline and 12- and 24-h postsurgery time points in common. Figure 4 reveals that although there was no significant circadian effect on baseline MGS scores ($F_{2,15} = 3.2$, $P = 0.07$; Figure 4 A), mice operated on in the

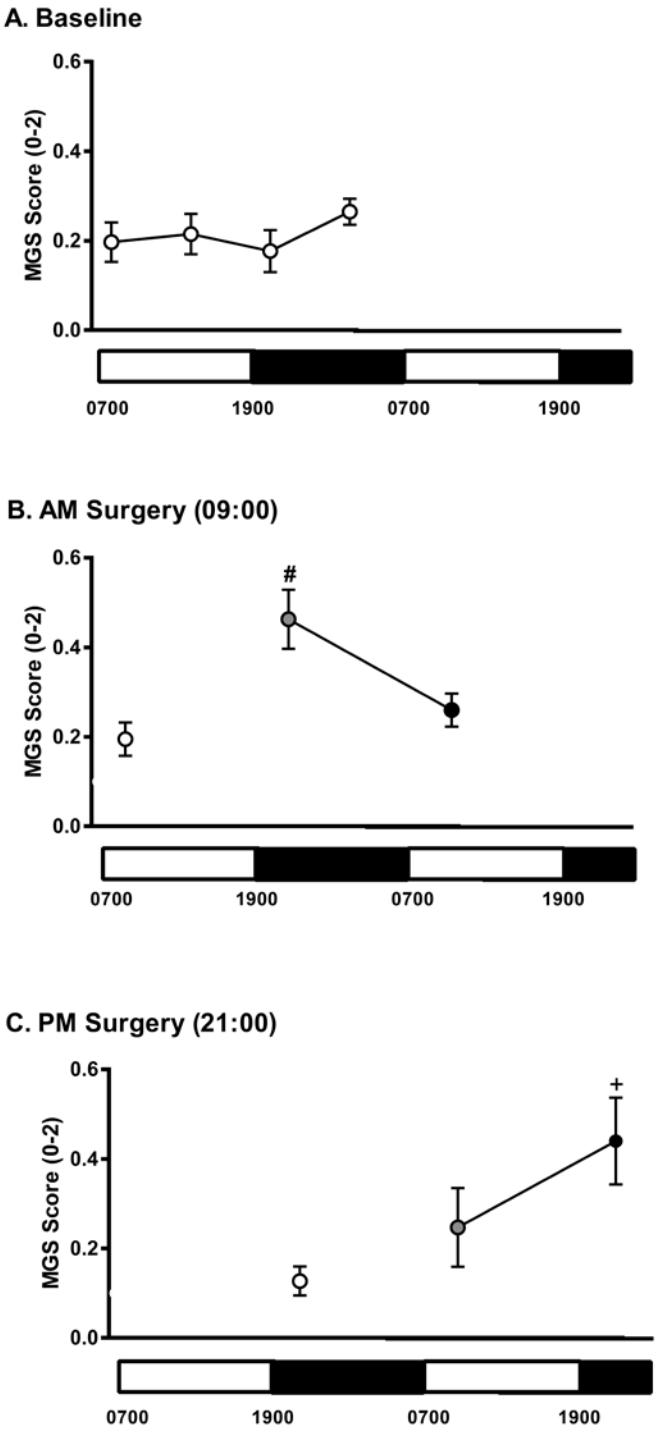

Figure 4. Circadian effects on postoperative pain. Symbols represent mean ± SEM of raw MGS scores (scale, 0 to 2). In all graphs, open circles are baseline measurements, gray circles are measurements 12 h after surgery; and black circles are measurements at 24 h after surgery. Timelines below graphs indicate 12:12-h photoperiod (lights on, 0700). (A) There is no effect of time of day on baseline MGS scores. The temporal pattern of increases in MGS scores after surgery differ between (B) mice that received surgery in the morning (0900) and (C) those that underwent surgery in the evening (2100). Because MGS scores at 12 and 24 h after surgery (see Figure 2) did not differ significantly, these data indicate increased postoperative pain levels during the dark photophase. +, $P < 0.01$; #, $P < 0.001$ compared with baseline value.

morning displayed larger increases at 12 h after surgery than at 24 h after surgery (Figure 4 B), whereas mice operated on in the evening displayed smaller increases at these time points (Figure 4 C). This conclusion is supported by a significant interaction between surgery time and repeated measures ($F_{2,28} = 9.1$, $P = 0.001$) and can be most simply interpreted as revealing higher levels of postoperative pain at night (that is, in the active [dark] photophase of the mouse), given that overall MGS scores were equivalent at the 12- and 24-h time points (Figure 3).

Drug inhibition of postoperative pain. Dose–response curves illustrating the effects of various doses of the 4 commonly used analgesics studied are shown in Figure 5. ANOVA revealed significant main effects of dose for buprenorphine ($F_{4,45} = 2.7$, $P < 0.05$), carprofen ($F_{5,58} = 3.0$, $P < 0.05$), and ketoprofen ($F_{5,56} = 2.6$, $P < 0.05$) but not acetaminophen ($F_{3,39} = 0.6$, $P = 0.65$). Separate ANOVA were performed for each individual action unit for acetaminophen, and none of the action units displayed significant inhibition compared with vehicle levels. AD_{50} (and 95% confidence intervals, when appropriate) of the 4 drugs are as follows: buprenorphine (0.01 mg/kg; 0.0013 to 0.10 mg/kg), carprofen (29 mg/kg; 18 to 48 mg/kg), ketoprofen (65 mg/kg; 19 to 233 mg/kg), and acetaminophen (greater than 1000 mg/kg).

Discussion

Using the MGS, a newly developed measure of spontaneous pain based on a well-validated procedure in humans, we provide evidence herein for the duration of spontaneous pain after laparotomy and the efficacy (or lack thereof) of 4 commonly used postoperative analgesics. We observed that statistically significant spontaneous pain is present for 36 to 48 h after surgery (and at relatively high levels for 8 to 12 h) and that this pain may be more intense in the evening. In addition, we found that buprenorphine is fully efficacious at recommended doses against early postoperative pain, that carprofen and ketoprofen are efficacious only at doses much higher than those currently recommended, and that acetaminophen is not efficacious.

The validity of our conclusions is enhanced greatly by the fact that no other nociceptive assay was substituted for postoperative pain—instead, pain from laparotomy was studied directly. This feature is crucial because nociceptive assays differ from one another in terms of both their intensity and duration and their underlying physiology. For example, compared with wildtype mice, those deficient in interleukin 1 and PICK1 (protein interacting with C kinase 1) display reduced sensitivity to mechanical and thermal hypersensitivity produced by multiple assays of inflammatory and neuropathic pain but are equisensitive after skin incision.[3,32] In addition, we show that the dependent measure used here is not affected by analgesic administration itself, and therefore our quantification of pain inhibition by those analgesics is unconfounded. By contrast, many of the behaviors previously considered[56] were altered by buprenorphine itself, as of course are locomotor activity and food and water intake.[37] In addition, behavioral changes are produced by transportation, anesthesia, and the surgery itself (which may or may not be directly related to pain).[56] Furthermore, we here demonstrate a slight but significant change in MGS scores produced by isoflurane exposure but in a direction that would not obscure the observation of analgesia.

Of course, the present conclusions are valid only to the extent that the MGS itself is a valid measure of spontaneous pain. That the MGS measures spontaneous pain seems obvious, given that no evoking stimuli were applied. Our previous experiments with the MGS established the method's high inter- and intrarater reliability, high accuracy in making pain–no-pain determinations, stimulus intensity-dependence, and sensitivity to detect the analgesic effects of both opioid and nonopioid drugs.[35] In subsequent experiments, we established that coding of facial

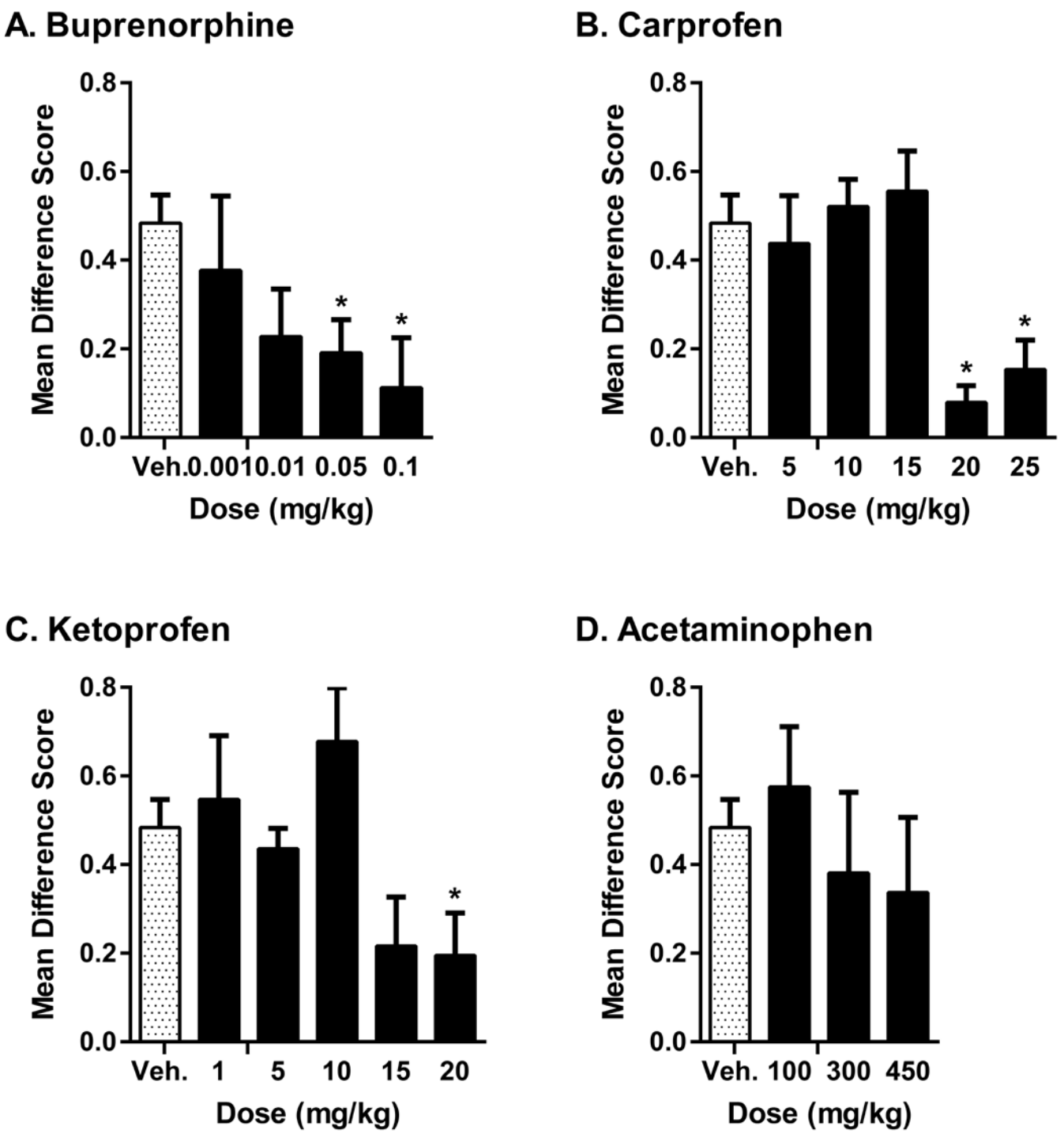

Figure 5. Dose–response relationships for 4 analgesics: (A) buprenorphine; (B) carprofen; (C) ketoprofen; and (D) acetaminophen in a mouse model of postoperative pain. Bars represent mean ± SEM mean difference scores (see text). *, Value significantly ($P < 0.05$) different from that for the vehicle only (Veh.; 0-mg/kg dose) by the Dunnett case-comparison posthoc test (1-way). These values were used to calculate AD_{50} values (see text).

expression is effective in laboratory rats as well.[62] Although for research purposes the MGS is used by scoring photographs taken from digital video, the system can also be used in real time by veterinarians, animal technicians, and experimenters.

Our current observations suggest that spontaneous postoperative pain lasts for 36 to 48 h after laparotomy, with a peak very soon after the surgery. In fact, the 1-h postsurgery peak (mean difference score, 0.78 ± 0.12; Figure 3) is quite a bit higher than the combined vehicle group mean at the same time point (0.48 ± 0.06; Figure 5). Given that the latter group has a much higher sample size than the former ($n = 27$ compared with $n = 8$), very early postoperative pain levels (Figure 3) likely are exaggerated, even though moderate levels of grimacing clearly persist until the 8-h time point before dropping considerably.

Estimates of pain duration after surgery vary widely in the literature. Pain-relevant behaviors (twitching, back arching, stagger or fall, and writhing) can be observed for 2 to 6 h after surgery.[57,59] Other investigators have observed changes

lasting several days in food intake,[1] locomotor or exploratory activity,[1,41] conditioned operant responding,[41] and ethogram scores.[14] In contrast, other experiments have noted impairments that persist as long as 14 d.[6,30,41]

Mechanical and thermal hypersensitivity after incision persists for anywhere from 1 to 22 d.[9,10,22,40,51,52,55,70,72,75,76] Decreased weight-bearing, alleged by some as a measure of spontaneous pain[15,45,61,63] but more likely representing the animal's desire to avoid mechanical allodynia resulting from touching the ground,[43] persists for 2 to 3 d.[9,71,72,76] Hypersensitivity likely lasts longer than does spontaneous pain from an inflammatory injury, as evidenced by a first-person account of a pain researcher who accidentally injected himself with complete Freund adjuvant.[29]

The use of the MGS might underestimate the true duration of spontaneous pain, because prey animals presumably are highly motivated not to display facial grimacing and may eventually learn to control their facial musculature even as pain persists, as do patients with chronic pain.[18] Of course, this masking of response is even more likely for behaviors such as twitching, back arching, stagger or fall, and writhing, which are almost certainly more visible to potential predators, even from a distance, than is facial expression.

Although numerous investigations of circadian effects on pain in laboratory animals and humans have been published, the literature is considerably contradictory (see references 13 and 48 for reviews). In the rodent literature, virtually all existing experiments have used acute, thermal assays; in the 5 studies of which we are aware that used tonic, inflammatory stimuli, our results appearing to show higher pain sensitivity in the active phase are broadly concordant with all.[19,47-50] In particular, circadian effects on postoperative pain in rodents have never been studied, to our knowledge. A recent study in humans directly addressed this issue and found higher resting, sitting, forced expiration and cough-evoked pain levels in posthysterectomy patients at 0800 h compared with 3 other time points.[7] This observation is also concordant with the current results, given that 0800 h represents the beginning of the active phase in humans in a hospital setting.

We noted dose-dependent buprenorphine analgesia, with essentially complete abolition of facial grimacing at the 0.05 and 0.1 mg/kg doses. These findings are entirely consistent with the range of buprenorphine doses that have been found to be effective against postoperative pain by using a variety of dependent measures.[1,6,28,37-39,59,64,67] The facts that the 0.01-mg/kg dose showed a strong trend toward significance (P = 0.12) and that the AD_{50} estimate was 0.01 mg/kg suggest that buprenorphine may be more potent in mice than is appreciated currently. Given that higher doses of buprenorphine can produce behavioral effects on their own,[17,30,56] perhaps lower doses should be considered. However, our conclusions only apply to pain relief at 1 h after surgery; higher doses might produce longer-lasting analgesia.

Because of the reluctance of many investigators to administer an opioid agonist that might interfere with their experiments and because of buprenorphine's status as a controlled drug, there is great demand to use long-acting NSAID like carprofen and ketoprofen for postoperative pain management in rodents. Our institution recommends dose ranges of 5 to 10 mg/kg for carprofen and 2 to 5 mg/kg for ketoprofen. Both drugs at 5 mg/kg reduced pain-relevant behaviors (twitching, back arching, stagger or fall, and writhing) after laparotomy,[57,59] and carprofen at 2.5-to 10-mg/kg doses were found to be effective in another study, although dose-dependency could not be demonstrated.[58] When food and water intakes and locomotor activity were used as measures, 5 mg/kg carprofen was found to be variously effective[12,23] or ineffective.[1] The same dose was effective at reinstating burrowing behavior after surgery.[2,34] By using mechanical or thermal hypersensitivity as the endpoint after hindpaw incision, ketoprofen at doses of 10 to 30 mg/kg was partially effective,[26,53] but in another similar study that used guarding as the endpoint, doses as low as 0.5 mg/kg ketoprofen were effective.[63]

Our current findings suggest that carprofen and ketoprofen can produce inhibition of spontaneous pain after laparotomy but only at doses considerably (2- to 4-fold) higher than those currently recommended. It is intriguing that the relative potency of carprofen and ketoprofen is preserved in the current study, with the estimated AD_{50} of carprofen (29 mg/kg) being approximately half that of ketoprofen (65 mg/kg). Revising the recommended doses of these NSAID upward to ensure adequate pain relief seems prudent, but note that these doses may exceed the threshold for gastrointestinal ulcerogenisis.[5,31]

The current findings reveal no evidence of analgesia from acetaminophen at doses ranging from 100 to 450 mg/kg; higher doses were not given because of concerns over hepatotoxicity. Acetaminophen's lack of efficacy is not all that surprising, given that all previous investigations of postoperative pain similarly failed to observe acetaminophen analgesia[20,30,64] except for an observation of reversal of thermal hyperalgesia by 100- and 300-mg/kg doses.[24] Acetaminophen can produce measurable analgesia against some pain states, and even using the MGS, we have previously shown partial efficacy of 300 mg/kg acetaminophen against inflammatory (zymosan-induced) pain.[35] Our current findings strongly suggest that acetaminophen should not be used for the management of postoperative pain in mice.

In conclusion, facial expression coding of pain in laboratory animals affords considerable advantages over existing methods. This method has been confirmed to be reliable, accurate, and sensitive in 3 species: humans, mice, and rats. Facial expressions in laboratory animals can be scored objectively, either in real time by veterinarians and animal care technicians or from digital images by blinded experimenters for research purposes. Of interest is a recent demonstration that observers asked to score postoperative pain in rabbits spent more time looking at the face than any other body part and were more likely to make incorrect assessments when doing so.[36] However, none of the participants in the cited study[36] had been trained to recognize key pain-related features in the rabbit's face. In our experience, once a scorer is trained, highly accurate pain–no-pain judgments are possible and can be made in mere seconds of observation. Because an MGS score is a singular measure, complex statistical procedures or transformations are not required.

We believe that the current findings—showing efficacy of buprenorphine, carprofen, and ketoprofen (but only at high doses), and not acetaminophen—likely represent the most relevant assessment conducted thus far of the true efficacy of these common analgesics for postoperative pain. We hope that others adopt the MGS to evaluate the efficacy of other compounds, in other species, and against a wider range of pain states.

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