Evaluation of Analgesic Patches in Cynomolgus Macaques (*Macaca fascicularis*)

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Opioids are widely used in veterinary and human medicine to manage pain. However, there is a paucity of information in the literature regarding the pharmacokinetics of opioid transdermal patches (TDP) in NHP. Therefore, to determine whether opioid TDP attain therapeutic concentrations in NHP, the pharmacokinetics of fentanyl (25 µg/h) and buprenorphine (10 and 20 µg/h) TDP were evaluated in naïve, adult, male cynomolgus macaques ($n = 4$) in a crossover study. Plasma opioid levels were determined by tandem liquid chromatography–mass spectrometry. The $AUC_{0-\infty}$ for fentanyl and the low and high dose buprenorphine patches were 115 ± 14 , 462 ± 74 , and 778 ± 344 ng×h/mL, and the plasma half-lives were 22 ± 4 , 77 ± 27 , and 42 ± 11 h, respectively. No adverse effects were noted throughout the study. Minimal therapeutic concentrations for fentanyl (0.2 ng/mL) and buprenorphine (0.1 ng/mL) were achieved in all macaques within 8 h of fentanyl and 24 h of buprenorphine TDP application. Therapeutic levels for the fentanyl and low- and high-dose buprenorphine patches were maintained for 96, 120, and 144 h, respectively. These findings suggest that 25-µg/h fentanyl patches should be replaced every 4 d, and the low- and high-dose buprenorphine patches should be replaced every 5 and 6 d, respectively. The results of this study show that fentanyl and buprenorphine patches achieve minimal therapeutic levels for clinically relevant periods of time and should be considered viable options for pain management in cynomolgus macaques.

Abbreviation: TDP, transdermal patches

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The principles of the ‘3 Rs’—replace, refine, and reduce—are universal standards for the humane use of animals in research.⁴⁶ Specifically, the principle of refinement is at the core of improving animal welfare. One example of refinement is through the administration of appropriate anesthesia and analgesia to ensure animal pain and distress are minimized.⁹ Opioids are commonly used in veterinary medicine in perioperative multimodal analgesia protocols. However, for some applications, such as transdermal opioid patches in NHP, efficacy is often extrapolated from other animal species or humans.

Cynomolgus macaques are valuable animal models for pharmaceutical development, organ transplant medicine, and neuroscience.²⁹ The nature of NHP research often requires major surgery; therefore, postoperative analgesia is a cornerstone of the successful recovery of these animals. Both fentanyl and buprenorphine are frequently used opioids in laboratory animal medicine, including for perioperative pain management in NHP.

Fentanyl is a pure μ -opioid receptor agonist that is indicated for the control of moderate to severe pain.³⁹ This drug has a rapid onset of action (less than 5 min) and a duration of action of 15 to 30 min when administered intravenously.^{17,18} Fentanyl is formulated as an injectable solution, transdermal solution, transmucosal lozenge, and transdermal patch.^{20,30} The transdermal patch is described to deliver fentanyl to cats and dogs at a controlled rate over 72 h.^{5,12,42} However, information regarding the pharmacokinetics and doses of the various formulations of fentanyl in NHP is sparse in the literature. One study that evaluated the use of the transdermal fentanyl solution in ma-

caques⁴⁷ found that this dosage had the potential to provide adequate analgesia for 7 d. However, the fentanyl solution is currently commercially unavailable, requiring clinicians to use other fentanyl formulations. Despite the routine use of fentanyl patches in NHP medicine, only one study⁶ is available that evaluated their pharmacokinetics; the authors described high interanimal variability and concluded that transdermal fentanyl patches could not be recommended in macaques without further investigation. We selected the patch used in the current study for direct comparison with these previous results⁶ and because this dose is the dose of choice for dogs weighing less than 10 kg¹⁹ and cats.⁵ The minimal therapeutic plasma concentration for fentanyl in NHP (0.2 ng/mL) was inferred from postoperative pain studies in humans^{22,32,39} and dogs.^{4,19,44}

Buprenorphine is a semisynthetic, partial μ -opioid receptor agonist indicated for treatment of mild to moderate pain.^{16,25,53} The drug's onset of action is 30 to 60 min, and its duration of action is 8 to 12 h. Buprenorphine is formulated as an injectable, sustained release injectable, transmucosal solution, and a transdermal patch.^{25,53} Buprenorphine transdermal patches (TDP) are primarily used in human medicine for the treatment of osteoarthritis and cancer pain and have controlled drug delivery for 7 d.^{21,23,24,48,52} To date, animal studies evaluating buprenorphine patches are limited to swine, dogs, and cats.^{33,34,51} In the current study, the doses we selected reflect the lower and upper doses of the injectable sustained-release buprenorphine suggested for use in NHP.³⁶ The minimal therapeutic plasma concentration for buprenorphine in NHP was extrapolated from analgesic levels for humans, which range from 0.1 to 0.5 ng/mL,^{14,50} and for canines and swine, which range from 0.1 to 0.6 ng/mL.^{28,37,41,51}

Given the continued use of transdermal opioid patches in NHP in laboratory animal medicine and because of the success

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of this formulation for pain management in other species, it is essential to determine the pharmacokinetics of fentanyl and buprenorphine transdermal patches in cynomolgus macaques. Opioid TDP have the potential to refine analgesia, because they provide prolonged drug delivery with a single application and cause minimal stress to the animals. Through the current study, we aim to support the use of opioid transdermal patches in macaques by comparing the pharmacokinetics of 25- $\mu\text{g}/\text{h}$ fentanyl patches and 10- and 20- $\mu\text{g}/\text{h}$ buprenorphine patches. In light of the literature,^{32,43} we hypothesized that the fentanyl patch would achieve the therapeutic plasma concentration of 0.2 ng/mL within 8 h and that plasma drug levels would remain above this threshold for 3 d. In addition, we hypothesized that both the low- and high-dose buprenorphine patches would achieve the therapeutic plasma concentration of 0.1 ng/mL within 12 h and that plasma drug levels would remain above this threshold for 7 d.

Materials and Methods

Animals. The study population comprised 4 experimentally naïve, Mauritian-origin, male cynomolgus macaques (age, 5 to 7 y; weight, 5.5 ± 0.6 kg). All procedures were performed after approval was obtained from the University of Illinois at Chicago Animal Care Committee. The cynomolgus were housed in accordance with the *Guide for the Care and Use of Laboratory Animals*,²⁴ Public Health Service Policy,³⁵ and Animal Welfare Act and Regulations⁵⁴ in an AAALAC-accredited facility. Macaques were pair-housed and had visual and auditory contact with conspecifics. They received 15% Monkey Diet (no. 8714, Envigo-Teklad, Madison, WI) once daily and municipal tap water without restriction. The diet was supplemented with fresh produce or foraging mix once daily. Manipulable enrichment items were placed directly in the cages and rotated every 2 wk. In addition, speakers in the animal rooms provided auditory enrichment. The macaques were tuberculosis-free as determined by skin tests and considered healthy after assessment by physical examination, CBC analysis, serum chemistry analysis, and fecal flotation evaluation conducted during quarantine and then prior to the start of the study.

Drugs and materials. The macaques were acclimated to primate jackets (Lomir Biomedical, Malone, NY) for 24 h prior to the initiation of this study. Fentanyl (25 $\mu\text{g}/\text{h}$; Duragesic, Janseen Pharmaceutical, Titusville, NJ) and buprenorphine (10 $\mu\text{g}/\text{h}$ [low dose] and 20 $\mu\text{g}/\text{h}$ [high dose]; Butrans, Purdue Pharma LP, Stamford, CT) were placed individually in 3 locations on the ventral thorax of the macaques. The first patch was placed cranial to the nipples, the second was between the nipples, and the final patch was placed caudal to the nipples; a 14-d washout period was provided between patch applications, in a crossover study design. The ventral thorax was chosen because it is an area of low motion, the skin is taut, and it allowed for visual assessment during sedated exams to ensure that the patches had not become displaced. The macaques were sedated with ketamine (7 mg/kg IM), and the skin was shaved free of hair, cleaned thoroughly, and allowed to dry completely before each patch was applied. The patches were secured in place by using transparent adhesive bandage (Tegaderm, 3M, St Paul, MN), which was applied directly over the patches. The macaques wore primate jackets throughout the study to protect the patches from removal.

Health assessment. The macaques were weighed at the start of the study and at each sample collection time point to ensure that body weight was maintained. Cageside assessments were conducted daily throughout the study to monitor food

consumption, fecal and urinary outputs, activity level, respiratory depression, presence of vomit, and general attitude.⁷ At each blood collection time point, while the macaques were under ketamine sedation, the skin surrounding the patch was evaluated for irritation. In addition, rectal temperature, heart rate, and respiratory rate were measured and recorded at each sedation event.

Sample collection. Cynomolgus were sedated by using ketamine (7 mg/kg IM) at blood collection time points that were selected according to pharmacokinetic data from studies in other species. Blood was collected from alternating femoral veins and into 3-mL EDTA-treated vacuum phlebotomy tubes. An initial blood sample was collected prior to each patch application for baseline measurements (time 0). Blood collection time points for the fentanyl TDP were at 4, 8, 12, 24, 36, 48, 60, 72, 80, and 96 h after the patch was applied. Collection time points for both the low- and high-dose buprenorphine TDP were at 4, 8, 12, 24, 36, 48, 60, 72, 80, 96, 120, 144, and 168 h after the patches were applied. A final blood sample was collected at 24 h after the patches were removed. Within 15 min of sample collection, blood tubes were centrifuged at $1000 \times g$ for 10 min. Aliquots of plasma (1 mL) were frozen at -80°C until shipped on dry ice for analysis.

Sample analysis. Fentanyl plasma sample analysis was conducted by using UPLC with single-quadrupole MS detection. The chromatography system consisted of an Acquity I-Class UPLC with an Acquity QD mass spectrometer (Waters, Milford, MA). Calibration curves and quality controls were prepared by fortifying blank macaque plasma with stock solutions of fentanyl (Sigma-Aldrich, St Louis, MO) dissolved in 100% methanol. Plasma samples, standards, and quality controls were then prepared by adding 200 μL of sample to 400 μL of acetonitrile in a 16 $\times$ 100-mm glass tube. The tubes were vortexed for 15 s to mix solutions, sonicated for 5 min, and centrifuged at $1690 \times g$ for 10 min. The supernatant was transferred into clean glass tubes and dried under a stream of air at 40°C for 20 min. Samples were reconstituted in 250 μL of acetonitrile:water (50:50). Samples were vortexed for 15 s and then filtered through a 0.2- μm filter prior to injection onto the UPLC. Volumes of 8 μL for plasma samples, standards, and quality controls were injected onto the chromatography system at a flow rate of 0.4 mL/min, and the total run time was 5 min. Separation was achieved by using Waters Acquity UPLC BEH C18 (1.7 μm) sorbent and Vanguard column (Waters). A gradient mobile phase was used, consisting of 70:30 0.1% formic acid in water:0.1% formic acid in acetonitrile for 2.5 min, 10:90 water:acetonitrile for 1 min, and 70:30 0.1% formic acid in water:0.1% formic acid in acetonitrile for the final 1.5 min. All mobile phases were filtered through a 0.22- μm filter. The column temperature was maintained at 40°C , and the sample temperature was 20°C . Quantification was performed by using an electrospray ionization source operated in positive ion mode. The retention time for fentanyl was 1 min. Calibration curves were linear over a concentration range of 0.1 to 20 ng/mL, with an $r^2 \geq 0.99$. The lower limits of detection and quantification were 0.05 and 0.1 ng/mL, respectively. Accuracy (percentage deviation of measured concentrations from nominal concentrations) and precision (relative standard deviation) were determined from replicate quality-control samples of blank macaque plasma fortified with fentanyl at concentrations of 0.3 and 3 ng/mL. Because the volume of macaque plasma available was limited, only 2 quality-control concentrations were used during method validation and spanning the expected concentrations of the samples. Accuracy ranged from 87% to 98%, whereas precision ranged from 2% to 4% over the concentrations tested.

Plasma sample analysis for buprenorphine concentration was determined by using an automated liquid handling workstation (Microlab Star, Hamilton Robotics, Reno, NV). Samples (25 μ L) were placed in the wells of a 2-mL, 96-well plate. The plasma was extracted by using 275 μ L of acetonitrile containing stable label internal standard. The samples were vortexed for 1 min, centrifuged at $3200 \times g$ for 5 min, and then returned to the workstation. A 100- μ L sample of the supernatant was transferred to a well of a clean 96-well plate containing 200 μ L of 0.1% formic acid in water. Each sample was injected onto a 30 $\times$ 2.1-mm, 5 μ m Pace C18 (Fortis, Cheshire, England) column for analysis by LC–tandem MS (1290 Infinity HPLC, Agilent Technologies, Santa Clara, CA; Leap Autosampler, CTC Analytics, Zwingen, Switzerland; Sciex 6500+ Triple Quad Mass Spectrometer, Framingham, MA). The buprenorphine concentration in each sample was determined by using calibration curves with known peak:area ratios. The lower limit of quantitation for a 25- μ L plasma sample was 0.80 ng/mL.

Pharmacokinetic analysis. Pharmacokinetic analysis of plasma concentration data was performed by using the validated Phoenix WinNonlin suite, Version 6.3 (Pharsight, Cary, NC). Plasma concentration–time data was obtained after analysis of the plasma samples collected from the macaques and were analyzed by using a noncompartmental pharmacokinetic model. The peak plasma concentration (C_{max}) and the time to C_{max} were determined directly by inspection of the concentration–time data; C_{max} was defined as the highest concentration observed. The parameter t_{max} was estimated as the corresponding time point at which C_{max} occurred. The AUC was calculated according to the linear and logarithmic trapezoidal rule and standard extrapolation techniques with the terminal elimination rate constant for AUC_{0-inf} . Corresponding rate constants, plasma clearance, half-life, and apparent volume of distribution were calculated.

Results

Pharmacokinetics. The plasma concentration of fentanyl achieved by using a 25- μ g/h TDP exceeded the minimal therapeutic level of 0.2 ng/mL in 3 cynomolgus macaques by 4 h after patch application and by 8 h afterward in the 4th animal. The plasma concentrations remained above the minimal therapeutic level for 96 h (4 d), and 3 of the animals' plasma levels dropped below the minimal threshold by 24 h after the patch was removed. The maximal concentration of 2 ± 0.4 ng/mL occurred at 14 ± 7 h, and the AUC_{0-inf} was 115 ± 14 ng $\times$ h/mL (Figures 1 and 2, Table 1).

The plasma concentration of buprenorphine achieved by using the 10- μ g/h TDP exceeded the minimal therapeutic level of 0.1 ng/mL in 2 macaques within 8 h, by 12 h in a 3rd animal, and by 24 h in the remaining animal. Plasma buprenorphine concentrations remained well above the therapeutic level for 120 h (5 d) for all animals. The plasma concentration of buprenorphine was below the minimal therapeutic level by 144 h in 1 animal and 168 h after patch application in a 2nd animal; the remaining 2 macaques maintained therapeutic concentrations until 24 h after the patch was removed. In addition, buprenorphine C_{max} was 3 ± 1 ng/mL and occurred at 57 ± 15 h. The AUC_{0-inf} was 462 ± 73 ng $\times$ h/mL (Figure 3, Table 1).

The buprenorphine plasma concentration from the 20- μ g/h TDP achieved the minimal therapeutic level of 0.1 ng/mL within 8 h after application for 3 of the 4 macaques and by 24 h in the remaining animal. Plasma buprenorphine concentration for the high-dose patch remained above the minimal therapeutic level for 144 h (6 d) in all 4 animals, and 2 had plasma buprenorphine

Figure 1. Plasma concentration (ng/mL) of fentanyl (25- μ g/h patch) in 4 cynomolgus macaques over 96 h (4 d) and at 24 h after the patch was removed (–24 h). The minimal therapeutic plasma concentration of fentanyl in NHP is 0.2 ng/mL.

Figure 2. Plasma concentration (ng/mL; mean $\pm$ 1 SD, $n = 4$) of fentanyl (25- μ g/h patch) in cynomolgus macaques over 96 h (4 d) and at 24 h after the patch was removed (–24 h). The minimal therapeutic plasma concentration of fentanyl in NHP is 0.2 ng/mL.

concentrations that remained above the minimal threshold for 168 h after patch application; in all cases, plasma concentrations fell below the minimum by 24 h after the patch was removed. In addition, C_{max} (8 ± 4 ng/mL) occurred at 45 ± 6 h, and the AUC_{0-inf} was 778 ± 344 ng $\times$ h/mL (Figures 4 and 5, Table 1).

Clinical assessment. Regardless of the apparently high opioid plasma concentrations across all 3 treatment groups, none of the macaques presented with adverse events. Daily cageside health assessments throughout the study revealed no dyspnea, respiratory depression, emesis, or sedation and no change in appetite or fecal or urinary output. Heart rate, respiratory rate, and rectal temperature remained within normal limits when measured during sedated physical exams at each blood collection time point. Body weight remained stable throughout the study, and skin around and under the patches showed no irritation or abnormality. All opioid TDP remained intact and in place throughout each application period.

Discussion

Despite commonplace use of opioid TDP in laboratory animal medicine, this study is the first to demonstrate that they are a viable option for clinical use in NHP. These data establish that fentanyl patches maintain adequate and consistent therapeutic plasma levels in NHP, contrary to a previous investigation.⁶ Furthermore, the current research shows that buprenorphine patches similarly maintain therapeutic plasma concentrations in cynomolgus macaques for a clinically significant duration.

In contrast to a previous study,⁶ the results of the current study confirm our hypothesis that the 25- μ g/h fentanyl TDP

Table 1. Pharmacokinetic parameters for fentanyl and low- and high-dose buprenorphine transdermal patches in cynomolgus macaques

	Fentanyl	Low-dose buprenorphine	High-dose buprenorphine
Elimination half-life (h)	16.57 ± 10.06	64.20 ± 13.52	42.40 ± 10.62
Maximal plasma concentration (ng/mL)	2.23 ± 0.39	3.43 ± 1.18	8.07 ± 3.85
Time to maximal plasma concentration (h)	14.00 ± 6.93	57.00 ± 15.10	45.00 ± 6.00
AUC _{0-inf} (ng×h/mL)	114.56 ± 13.56	462.39 ± 73.53	777.63 ± 343.81
AUC _{0-last} (ng×h/mL)	110.25 ± 10.77	300.79 ± 102.22	678.51 ± 295.86

For all parameters, $n = 4$, except elimination half-life for the low-dose buprenorphine group ($n = 3$), where data from macaque CN8911 were excluded due to a low confidence coefficient.

would achieve and maintain plasma concentration levels above the minimal therapeutic level of 0.2 ng/mL, which is inferred from the human¹⁴ and canine literature.¹⁹ The maximal plasma concentration of 2.0 ± 0.4 ng/mL, achieved at 14 ± 7 h, is well above the minimal threshold but no dyspnea, bradycardia, sedation, emesis, skin irritation, or other adverse events were observed. All 4 macaques had plasma fentanyl concentrations that exceeded the minimal therapeutic level for 96 h after patch application, and by 24 h after patch removal, plasma fentanyl concentrations had dropped below this threshold in 3 of the 4 animals. According to our results, fentanyl TDP can be applied at the time of anesthetic induction in combination with perioperative analgesia, achieve the minimal therapeutic level by 8 h, and should be replaced after 4 d, if the need for analgesia persists.

Our study also determined that both the low- and high-dose formulations of buprenorphine TDP achieve the minimal therapeutic plasma level of 0.1 ng/mL within 24 h of patch application, consistent with findings in the human literature.²⁷ The therapeutic threshold for buprenorphine in NHP is hypothesized to be the same as the minimal effective concentration that controls mild to moderate pain in opioid-naïve humans.^{13,15,36,50} The NHP threshold also is consistent with minimal therapeutic plasma levels extrapolated from swine⁵¹ and canines.²⁸ Given that both patch doses exceeded the minimal therapeutic plasma concentration, we recommend using the 10- μ g/h TDP over the 20- μ g/h patch. Although the maximal concentrations of 3 ± 1 ng/mL and 8 ± 3 ng/mL for the low- and high-dose buprenorphine patches, respectively, are well above the therapeutic threshold of 0.1 ng/mL, we noted no dyspnea, bradycardia, sedation, emesis, skin irritation, or other adverse events in the animals. Furthermore, buprenorphine TDP can be applied during anesthetic induction for ease of application, as long as additional analgesia is administered for the initial 24 h postoperatively. We recommend the additional analgesic coverage during the immediate postoperative period because a single outlier in each of the dosage groups required 12 to 24 h to reach the therapeutic threshold. Alternatively, the buprenorphine TDP can be applied 24 h preoperatively, but this method would require additional animal manipulation. Residual buprenorphine plasma concentrations for both the low- and high-dose TDP groups fell below the minimal therapeutic level within 24 h after the patch was removed. Finally, low- and high-dose buprenorphine TDP should be replaced after 5 and 6 d, respectively, if signs of pain persist.

Transdermal drugs are absorbed along a concentration gradient through the epidermis and into the dermal layer, where large capillary beds take up the drug and distribute it to the systemic circulation.³¹ Several factors contribute to absorption variations between subjects and between drugs.² In humans, stratum corneum thickness, skin hydration, underlying skin disease or injuries, body temperature, and genetics all have the potential to cause variable drug absorption rates.^{31,38} These

Figure 3. Plasma concentration (ng/mL) of buprenorphine (10- μ g/h patch) in 4 cynomolgus macaques over 168 h (7 d) and at 24 h after patch removal (-24 h). The minimal therapeutic plasma concentration in NHP is 0.1 ng/mL.

Figure 4. Plasma concentration (ng/mL) of buprenorphine (20- μ g/h patch) in 4 cynomolgus macaques over 168 h (7 d) and at 24 h after patch removal (-24 h). The minimal therapeutic plasma concentration in NHP is 0.1 ng/mL.

elements also apply to the use of TDP in animals and should be considered when the variation between subjects and across species is observed.

Transdermal opioid patches have the advantage of decreasing animal stress, because they require only a single application rather than repeated injections or continuous infusion. In addition, opioid TDP avoid the peaks and troughs caused by injectable formulations, which, in humans, are associated with increased incidence of side effects including nausea and vomiting, respiratory depression, and sedation.³¹ The continuous drug delivery of the TDP decreases the likelihood of intermittent lapses in analgesic coverage, and TDP—unlike topical solutions or sustained-release injectable formulations—can be removed quickly if adverse effects do occur.

Although our study emphasizes many benefits of fentanyl and buprenorphine TDP in NHP pain management, their use has some limitations. Sex-associated differences have been demonstrated with the use of opioids in other species, including humans and rodents,^{3,8} and with the transdermal fentanyl solution in rhesus macaques.⁴⁷ Therefore, both males and females should be included in future opioid TDP studies. Similarly, future investigations of the pharmacokinetics should be con-

Figure 5. Plasma concentration (ng/mL; mean $\pm$ 1 SD) of buprenorphine (10- and 20- μ g/h patches) over 168 h (7 d) and at 24 h after the patch was removed (-24 h). The minimal therapeutic plasma concentration of buprenorphine in NHP is 0.1 ng/mL.

ducted in additional NHP species and analyzed to understand interspecies variability.

Ideally, pharmacokinetic data are compared with assessments of analgesia to develop species-specific therapeutic thresholds. Analgesiometric tests are a potential method for assessing the efficacy of opioid TDP; however, these models evaluate different pain pathways than those involved in postsurgical pain,⁴⁵ thus complicating full analysis of analgesic coverage. Moreover, NHP generally hide signs of mild to moderate pain, making behavioral parameters difficult to characterize.^{1,34}

The use of ketamine sedation for the application and removal of the opioid patches and at each blood collection time point is a potential confounding factor in our study, given that both opioids and ketamine are metabolized through CYP450 enzyme pathways in the liver.¹¹ Although opioids and ketamine are metabolized primarily by CYP3A4,¹⁰ opioids can also be degraded by alternative CYP enzymes as well as through an entirely separate process, glucuronidation,⁴⁹ when the primary CYP pathway is saturated. In addition, in humans, ketamine can be metabolized by a secondary CYP enzyme when CYP3A4 is not abundant.^{10,11} Therefore, we consider that the effects of ketamine metabolism on the pharmacokinetics of opioid TDP are minimal at most.

The results of the current study support the use of fentanyl and buprenorphine TDP as feasible and practical analgesic options in NHP pain management protocols. The use of fentanyl TDP may be preferential in clinical setting, because they are more affordable (\$25.00 per patch) than buprenorphine patches (\$75.00 to \$150.00 per patch) and have a faster onset of action (8 h compared with 24 h). However, fentanyl TDP have a shorter duration of action (4 d) than either low- or high-dose buprenorphine TDP. With durations of action of 5 and 6 d, the low- and high-dose buprenorphine TDP, respectively, had longer periods of therapeutic efficacy than fentanyl TDP and therefore may be favored in clinical scenarios when analgesic coverage is required for an extended length of time. All 3 TDP consistently achieved and maintained plasma concentrations well above the minimal therapeutic levels for a clinically relevant postapplication period. However, regular assessment of patients for the presence of breakthrough pain is indicated, as with the use of all analgesics. In addition, despite the relatively high maximal concentration levels, neither fentanyl nor buprenorphine TDP resulted in the development of dyspnea, bradycardia, sedation, emesis, skin irritation, or other adverse events, thus confirming

the safety of both opioid TDP. Our current data support the use of fentanyl and buprenorphine TDP as viable and safe options for perioperative analgesia in cynomolgus macaques.

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