

## K14 Longitudinal Transdermal Fentanyl Compared With Morphine Sulfate Treatments in a Rabbit (*Oryctolagus cuniculus*) Model System: Impacts on Behavior and Health

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**Learning Overview:** The goals of this presentation are to: (1) describe the longitudinal effects of systemic opioids, particularly fentanyl and morphine sulfate, on behavioral and physiologic parameters; and (2) demonstrate the long-term use of transdermal fentanyl patches in the management of analgesia in a rabbit model system.

**Impact on the Forensic Science Community:** This presentation will impact the forensic science community by providing novel longitudinal data regarding the behavior and physiologic effects of prolonged opioid use in a rabbit model system. With the current trend of opioid overdoses poised to expand its impact further, forensic scientists will learn an empirical methodology for evaluating soft and hard tissue responses, behavioral changes, and physiological effects associated with prolonged opioid use in a live animal proxy.

Transdermal fentanyl patch systems have been applied to various animal species, including dogs, cats, swine, rabbits, and non-human primates.<sup>1-6</sup> However, in rabbits, the transdermal fentanyl patch literature remains sparse and its application has been investigated in a segmented manner.<sup>4,5</sup> Given the limited data available, an opportunity exists to improve understandings of the longitudinal effects of opioids on rabbit behavior and physiology. This is critical given that rabbits remain a popular laboratory animal for research activities. For example, in 2017, more than 54,000 rabbits were reportedly involved in animal research involving pain and received a pain-relieving drug as a result. Thus, the primary purpose of the current research was to develop a longitudinal model for studying the effects of prolonged opioid exposure, specifically fentanyl and morphine sulfate, in a rabbit model system.

Skeletally mature, 6-month old (2.3-3.0kg), male New Zealand White rabbits (*Oryctolagus cuniculus*;  $n=21$ ) were sourced from Covance Research Products Inc. Rabbits were individually housed in stainless steel rabbit batteries that allowed for some interaction, while keeping the animals lodged separately. The rabbits were quarantined and habituated to the testing conditions for a two-week period. Animals were randomly divided into three groups of seven animals each: morphine, fentanyl, and controls. The control group was further randomly divided into saline vehicle ( $n=3$ ) and transdermal patch groups ( $n=4$ ). Following the acclimation period, the experimental treatments for the opioid groups (morphine and fentanyl) were initiated and continued for eight weeks. The morphine sulfate group received a dose of 3mg/kg/day via subcutaneous injection. The control group was administered saline at a dose of 3mg/kg/day. A 25- $\mu$ g/h slow release transdermal fentanyl patch was placed on the interscapular region of rabbits in the fentanyl group every third day, following shaving of the hair. Patches were secured by an overlying Tegaderm™ transparent film dressing. A placebo patch (Tegaderm™) was placed on each control patch animal comparable to the experimental animals. Rabbit jackets from Lomir Biomedical were applied to all experimental patch (fentanyl) and control animals (Tegaderm™) in order to prevent the animals from chewing the dressings.

Daily observations were recorded at consistent time points. Classifications for fecal output and food consumption were assigned values of 1 (normal), 2 (moderate), and 3 (low), and compared among the treatment groups and controls using one-way Analysis of Covariance (ANCOVA) tests with jacketing as a co-variate. Fecal output was not significantly impacted by drug treatment ( $F_{(2, 17)}=0.286$ ,  $p=0.755$ ,  $\eta^2=0.033$ , power=0.095). Food consumption was significantly impacted ( $F_{(2, 17)}=5.44$ ,  $p=0.015$ ,  $\eta^2=0.390$ , power=0.841), and a Tukey's Honest Significant Difference (HSD) post-hoc test indicated that morphine rabbits were significantly depressed in food consumption compared to controls ( $p=0.012$ ).

Qualitatively, all fentanyl patch rabbits consistently displayed skin irritation and erythema, abnormal stress behaviors (e.g., acute anorexia), respiratory depression, ocular proptosis, and poor overall health compared to the morphine and control groups. While the morphine injections did not result in notable changes in outward appearance, these animals demonstrated consistently lower food consumption throughout the experiment and heavy sedation following treatments. Despite its prevalence in short-term studies in the literature, these findings suggest that long-term experimental use of transdermal fentanyl patches results in behavioral changes that may confound the effects caused solely by the narcotic in question.

This report is the first documented data characterizing longitudinal transdermal fentanyl patches as a route for administration of analgesia in rabbits. The documented adverse effects associated with such longitudinal treatments addresses an evident literature gap that will inform future forensic, biomedical, and veterinary medicine research.

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### Fentanyl, Rabbits, Morphine

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