

Short-term Ocular Toxicity and Eye Irritation Tests Following Application of Sufentanil in Rabbits

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Abstract

Purpose: To test the safe clinical application of sufentanil as topical ophthalmic drops by examining treated rabbit eyes for ophthalmic irritation signs or short-time toxic reactions.

Methods: Twenty-four rabbits were randomly divided into 8 groups ($n=3$): The ocular toxicity at 14 d after eye drop administration was evaluated in groups 1 to 4, and at 30 d post-administration in groups 5 to 8. Groups 1 and 5 were treated with blank vehicle and served as normal controls. The left eyes of rabbits in groups 2 and 6 were exposed to low-dose sufentanil (5 μg , 2 drops within 5 min), groups 3 and 7 received moderate-dose sufentanil (7.5 μg , 3 drops within 10 min), and groups 4 and 8 received high-dose sufentanil (10 μg , 4 drops within 15 min). As self-controls, the right eyes of each rabbit were administered an equivalent amount of sodium chloride (9 g/L) at the same drop intervals. At 14 and 30 d after exposure to sufentanil, ophthalmic irritation signs were evaluated and corneas were stained with fluorescein and observed by slit-lamp microscopy. Corneal endothelial counts were performed and toxic reactions were evaluated.

Results: Multiple parameters were compared in the control and experimental groups by visual inspection and slit-lamp examination at 14 and 30 d after sufentanil administration. No evidence of irritation signs (including corneal opacity, conjunctival congestion, or edema), eye secretions, iris abnormalities, or temporal eye closure were noted. Corneal endothelial cell counts did not significantly differ between the control and experimental groups. Light microscopy revealed no pathological or morphological injury to the cornea, conjunctiva, iris, ciliary body, retina, or optic nerve in either group. The same observation outcomes were noted at 14 and 30 d after administration.

Conclusion: Single ocular administration of sufentanil at a dose of 5–10 μg in rabbits yields no ocular irritation or toxic responses at 14 or 30 d following eye drop delivery. (*Eye Science* 2014; 29:193–197)

Keywords: sufentanil; ophthalmic administration; short-term toxicity

Introduction

Sufentanil is a potent synthetic opioid analgesic drug. The main use of this medication is to act on central nervous system receptor, so it has a wide range of applications. It also offers properties of sedation and anesthesia induction (for example, during tracheal intubation), making it a good analgesic component of anesthetic regimen before and during an operation^{1–5}. It is approximately 5 to 10 times more potent than its parent drug, fentanyl, and 500 times as potent as morphine. In addition, its effects have a longer duration and the incidence of respiratory depression is lower compared with fentanyl^{1–5}. Sufentanil is commonly administered via intravenous, intrathecal, nerve retardance, subcutaneous⁶, or intranasal routes^{7,8}. However, the topical application of sufentanil in ocular surgery is rare.

The analgesia effect via intravenous administration can also be accompanied by side effects including respiratory depression, addiction, and tolerance. Peripheral topical administration by intrathecal, subcutaneous, or mucosal routes is therefore superior to intravenous administration. Animal and clinical experiments have demonstrated that opioid medication may prevent injury or exert analgesic effects through peripheral interaction⁹. A smaller dosage of opioid medication is needed for peripheral administration than for the intravenous route to yield the same analgesic effect, thereby decreasing or averting adverse events induced by opioid medicine. The peripheral route represents a novel alternative for administration of opioid drugs.

Studies on the topical ocular application of sufentanil

tanil in ocular surgery and relevant ocular irritation and toxicity are lacking at present, and sufentanil eye drop formulations have yet to be developed. Consequently, studies on potential toxic reactions induced by topical administration of sufentanil will determine the feasibility of using sufentanil in ocular surgery. Preliminary studies have indicated that no topical toxic reaction was caused by ocular application of sufentanil for short periods. However, identification of slight lesions to delicate eye tissues is critical, as these may evolve into substantive lesions with time. The present study therefore examined eye irritation and pathological changes after short-term ocular use of sufentanil in rabbit models.

Materials and methods

Animal and grouping

Twenty-four healthy adult New Zealand rabbits (average body weight 2.3 ± 0.4 kg) with intact corneal epithelia and no signs of eye irritation or alternative structural abnormalities were provided by the animal laboratory of Zhongshan Ophthalmic Center. All animals were randomly divided into eight groups ($n=3$ for each group). Groups 1-4 were evaluated for ocular irritation and toxic reactions at 14 d after drug administration while groups 5-8 were evaluated at 30 d. The experimental procedures were approved by the Animal Use and Care Committee.

Medication

Sufentanil injection, 1 ml per animal, 50 μ g (Zeneca Corporation, batch number: 100878)

Experimental methods

Groups 1 and 5 were treated with blank vehicle and served as normal controls. The left eyes of the rabbits in groups 2 and 6 were treated with low-dose sufentanil (5 μ g, 2 drops within 5 min), groups 3 and 7 received moderate-dose sufentanil (7.5 μ g, 3 drops within 10 min), and groups 4 and 8 received high-dose sufentanil (10 μ g, 4 drops within 15 min). The right eyes of the rabbits served as self controls and were administered an equivalent amount of sodium chloride (9 g/L) at the same drop intervals. At 14 and 30 d after exposure to sufentanil, ophthalmic irritation signs were evaluated and corneas were stained with fluorescein and observed by slit-lamp microscopy. Corneal endothelial counts

were performed and toxic reactions were evaluated. The rabbits were then sacrificed under anesthesia and ocular tissues were collected and prepared for pathological examination and toxicity analysis.

Observational index

Grading of eye irritation reactions before and after eye drop administration¹⁰; anterior chamber inflammation and lens opacity by slit-lamp examination; corneal endothelial counting; pathological examination; changes in cornea, ciliary body, iris, retina, and optic papilla.

Results

Grading of eye irritation

The grading criteria used for the eye irritation test indicated no eye irritation reactions, including corneal opacity, conjunctival hyperemia, and edema, or eye secretions occurred at 14 d after drug administration in the control and experimental groups (Table 1). The same experimental outcomes were obtained at 30 d after sufentanil administration in the control and experimental groups (Table 2). No statistical significance was observed by a paired t-test for the grade of eye irritation between the control and experimental groups at 14 and 30 d after drug administration (Table 2).

Table 1 Comparison of eye irritation in the control and experimental groups at 14 d after drug administration

Group	Score	Evaluation	P value
Group 1 (control group)	0	No irritation	$P=0.147$
Group 2 (5 μ g sufentanil)	0	No irritation	$P=0.147$
Group 3 (7.5 μ g sufentanil)	0	No irritation	$P=0.147$
Group 4 (10 μ g sufentanil)	0	No irritation	$P=0.147$

Table 2 Comparison of eye irritation in the control and experimental groups at 30 d after drug administration

Group	Score	Evaluation	P value
Group 1 (control group)	0	No irritation	$P = 0.149$
Group 2 (5 μ g sufentanil)	0	No irritation	$P = 0.149$
Group 3 (7.5 μ g sufentanil)	0	No irritation	$P = 0.149$
Group 4 (10 μ g sufentanil)	0	No irritation	$P = 0.149$

Slit-lamp examination

At 14 d following sufentanil administration, the treated eyes showed no signs of temporal eye closure or negative aqueous scintillation in the anterior chamber and no lens opacity was noted in either the

control or the experimental groups when examined by slit-lamp examination (Figure 1). The same comparison outcomes were found 30 d after drug administration (Figure 2).

Corneal endothelial counting

A paired t-test revealed no effect of the different concentrations of sufentanil on corneal endothelial cells at either 14 d ($P=0.430$, Figure 3) or 30 d ($P=0.449$; Figure 4) after drug delivery.

Pathological examination

No significant inflammatory cell infiltration or necrotic hemorrhage were observed in the conjunctiva, cornea, corneoscleral limbus, iris, ciliary body, retina, or optic nerve at 14 d (Figure 5) or 30 d (Figure 6) after drug administration. Fisher's exact

test revealed no statistically significant difference between the left eyes in the control group at 14 d ($P=0.310$) or at 30 d ($P=0.440$). Figure 5 shows images of the conjunctival tissue, where A is the conjunctival tissue before drug administration and B is the conjunctival tissue after drug administration. A slight increase in lymphocyte number was observed, but no significant pathological changes were seen before or after drug administration.

Discussion

Sufentanil is a potent synthetic opioid analgesic drug that exerts a rapid effect (1–3 min) due to its lipid solubility. It has a wide range of applications in clinical settings. Like other opioid medications, it

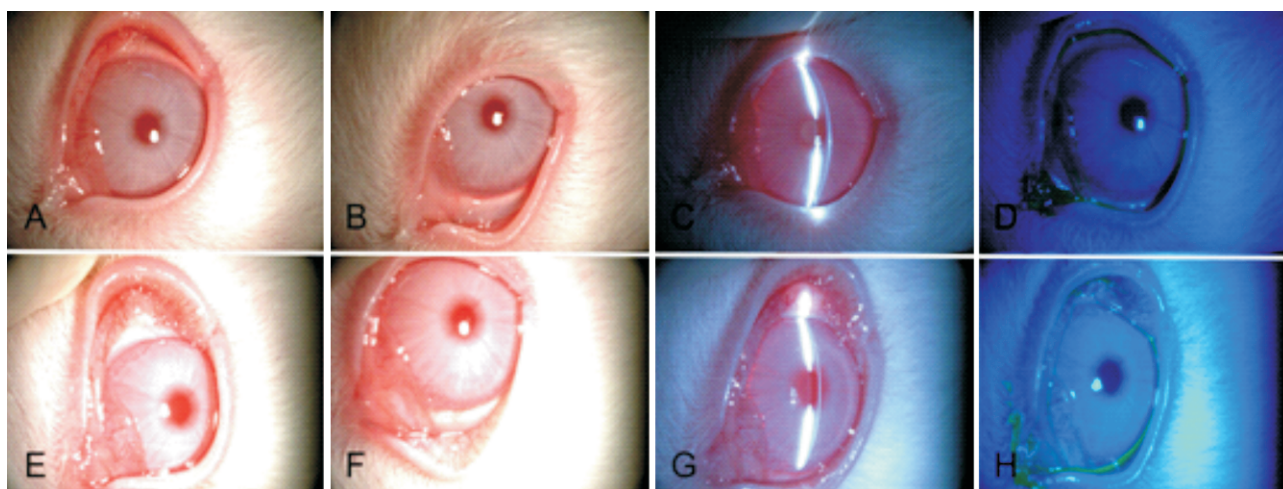


Figure 1 Comparison of anterior segment parameters in the control (vehicle only) and experimental (10 µg sufentanil) groups at 14 d after sufentanil administration.

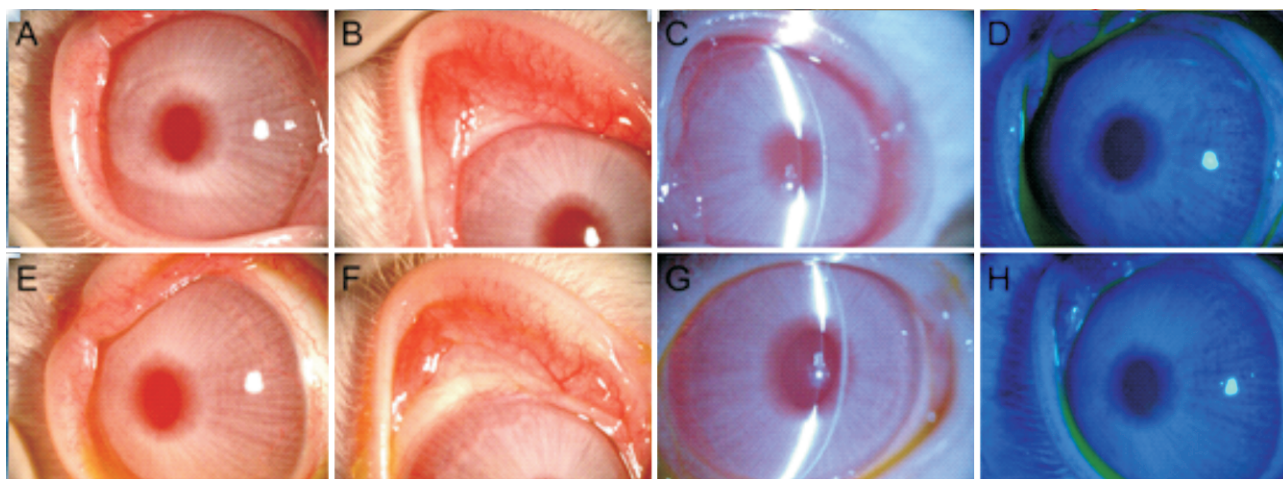


Figure 2 Comparison of anterior segment parameters in the control (vehicle only) and experimental (10 µg sufentanil) groups at 30 d after sufentanil administration. Control: A-D; Experimental: E-H.

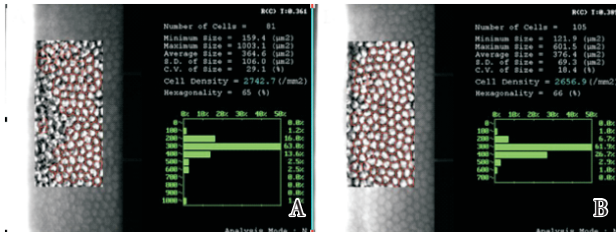


Figure 3 Comparison of corneal endothelial counts in the control (vehicle only) and the experimental (10 µg sufentanil) groups at 14 d after sufentanil administration. Control; A; Experimental; B.

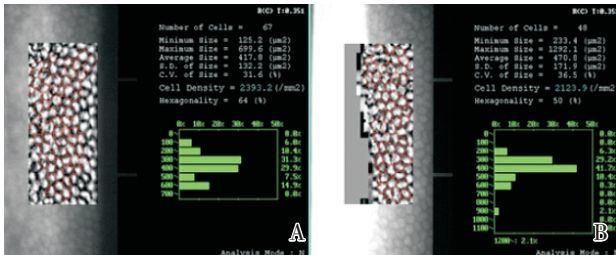


Figure 4 Comparison of corneal endothelial counts in the control (vehicle only) and the experimental (10 µg sufentanil) groups at 30 d after sufentanil administration. Control; A; Experimental; B.

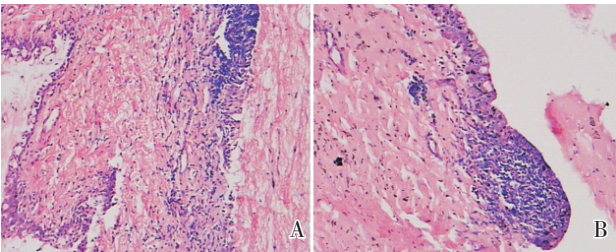


Figure 5 Comparison of pathological parameters in the control (vehicle only) and the experimental (10 µg sufentanil) groups at 14 d after sufentanil administration.

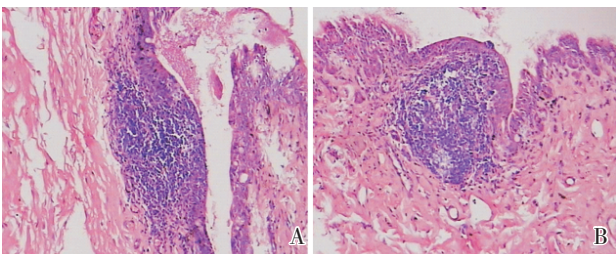


Figure 6 Comparison of pathological parameters in the control (vehicle only) and the experimental (10 µg sufentanil) groups at 30 d after sufentanil administration.

exerts an analgesic effect in central nervous system, but also has analgesic functions in the peripheral

system. The functional mechanism is that inflammation increases the density and activity of opioid receptors in peripheral nerve endings⁶.

Antonijevic et al. demonstrated that opioid medication can exert analgesic effects by interacting with opioid receptors in peripheral sensory neurons. Ritter et al. also reported that peripheral endogenous opioid peptides can also exert analgesic effects by interacting with opioid receptors in the peripheral sensory neurons. The peripheral analgesic function of opioid medications raises the possibility of developing analgesic drugs that do not cross the blood–brain barrier and avoid side effects on the central nervous system⁹. However, the clinical value of the peripheral function remains to be investigated.

The combination of peripheral and central nervous system analgesia probably reduces the required dose of these medications. Single intravenous administration of sufentanil is likely to cause respiratory depression and alternative adverse events. However, ocular application of the equivalent dose of medicine may decrease or avert the incidence of adverse events because the blood concentration of drugs is diluted by tear fluid and only slowly elevated. Ocular use of sufentanil is a convenient and reliable alternative for surface and general anesthetics. It not only has the desired target analgesic effect, but it also provides analgesia and sedation in the central nervous system. Therefore, ocular application of sufentanil can be of significant value in clinical practice.

The conjunctiva and cornea are the first line of defense of the eyes in contact with different eye drops. Strong drug irritation may arouse conjunctival inflammation and edema. The antiseptics contained in the eye drops can destroy the tiny structures of the corneal epithelial layer, cause epithelial barrier defects, and delay the healing of ocular wounds¹¹. Eye drops yield non-specific ocular surface manifestations, most commonly characterized as conjunctival reactions, such as papilla and follicle toxicity and delayed allergic responses, and even conjunctival scarring. Corneal toxicity includes superficial punctate corneal epithelial lesions and even corneal melting and perforation¹².

Schoenwald et al.¹³ suggested that eye drops are distributed on the eye surface via tear fluid and ab-

sorbed through corneal, conjunctival, and scleral pathways, and are removed along with tear fluid. The medication first enters the aqueous humor via the conjunctiva and then diffuses into surrounding tissues. It also enters into the uveal and vitreous body via conjunctival and scleral pathways. Only a slight amount of eye drop solution is distributed into posterior ocular tissues such as the lens, vitreous body, or retina, etc. Inappropriate ocular use of medication probably causes the observed incidences of glaucoma, cataract, optic nerve damage, and retinopathy. These issues should be prevented when administering drugs to the eyes.

The present study used a wide range of sufentanil doses (5, 7.5, and 10 μg) for administration to the rabbit eyes, but no acute toxic reactions were observed at any dose. However, the efficacy and safety of sufentanil administration at only two time points (approximately 2 and 4 weeks) have been investigated. The possibility that the medication can enter or accumulate in the eye tissues and cause delayed toxic reactions or pathological changes remains to be evaluated by long-term observational studies.

The experimental outcomes demonstrated that ocular use of sufentanil is a safe and reliable administering route in rabbits, providing fundamental supporting evidence for its subsequent application in clinical settings. Topical use of sufentanil is likely to integrate the central nervous system and peripheral analgesia and reduce or even eliminate opioid medication-induced side effects, making it a novel approach for analgesia medication in clinical practice. The underlying mechanism and further details about its efficacy remain to be elucidated by relevant investigations.

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