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Prolonged Corneal Analgesia Without Impairing Wound Healing Using a Novel Quaternary Ammonium N-Propylamiodarone Bromide

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ABSTRACT

Pain originating from corneal epithelial damage is a prevalent and distressing symptom caused by factors such as mechanical trauma, chemical exposure, ulceration, UV irradiation, or infection. Despite its frequency, effective and long-lasting treatments remain limited. This study evaluated a newly synthesized quaternary ammonium compound, N-propylamiodarone bromide (NPA), for its ability to provide prolonged corneal analgesia via selective entry through transient receptor potential vanilloid 1 (TRPV1) channels, while ensuring normal epithelial repair. Corneal injury was induced in 24 adult Wistar rats, which then received topical applications of saline, oxybuprocaine, or NPA (n = 8 per group). Pain responses were quantified using the von Frey filament assay. In a separate experiment, 32 rats with intact corneas were treated with oxybuprocaine, capsaicin (TRPV1 agonist), or NPA alone or in combination with capsaicin (n = 8 per group) to assess effects on mechanical sensitivity. Corneal epithelial recovery following injury and treatment was evaluated using fluorescence microscopy and hematoxylin–eosin staining in an additional 8 rats.

NPA produced markedly prolonged analgesia compared to oxybuprocaine in injured corneas (maximum effect duration: 215 ± 11 vs 25 ± 2 min, $P < 0.001$) without causing ocular irritation. In normal corneas, NPA did not affect baseline sensitivity; however, when co-administered with capsaicin, it induced significantly extended anesthesia relative to oxybuprocaine (165 ± 15 vs 31 ± 2 min, $P < 0.001$). Importantly, NPA treatment did not impede epithelial wound healing. The novel compound NPA provides durable corneal analgesia without interfering with tissue repair, representing a promising candidate for the management of pain associated with corneal injury.

Keywords: Corneal pain, Quaternary ammonium, N-propylamiodarone bromide, TRPV1, Analge

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Introduction

The cornea is among the most densely innervated tissues in the human body, containing sensory neurons that are highly sensitive to external stimuli [1–4]. Because of this, even mild stimuli that are typically non-painful elsewhere can induce significant discomfort in the cornea [3–7]. Common corneal injuries—including mechanical abrasions, chemical burns, ulceration, ultraviolet damage, or infections—often lead to acute and intense pain.

Currently available topical anesthetics, such as oxybuprocaine, are commonly applied to alleviate corneal pain in clinical settings. However, their analgesic effects are short-lived, generally lasting only 10–30 minutes, which necessitates repeated application and increases the risk of misuse [8–12]. Prolonged or frequent use of these drugs can compromise corneal integrity and delay epithelial healing. Alternative approaches—including NSAIDs, acetaminophen, corticosteroids, opioids, cycloplegics, cooling, patching, and bandage contact lenses—often provide incomplete pain relief and may carry systemic risks, such as kidney or respiratory complications [13–15].

Traditional local anesthetics are tertiary amines that exist in equilibrium between uncharged and charged states in the extracellular space [16, 17]. The uncharged form can cross neuronal membranes and, once protonated inside the cell, inhibit sodium channels to block nerve conduction [16, 17]. Recent advances have shown that

permanently charged quaternary ammonium compounds can selectively enter nociceptors through large-pore channels, such as TRPV1, and block sodium currents without affecting other cell types [18, 19]. This mechanism provides highly selective analgesia and longer-lasting effects because the compounds remain extracellular in non-target cells, reducing off-target interactions [16, 20, 21].

Based on this rationale, we synthesized a permanently charged quaternary ammonium derivative, N-propylamiodarone bromide (NPA), as a potential novel ophthalmic analgesic. We hypothesized that NPA would produce long-lasting corneal analgesia through TRPV1-mediated selective uptake in nociceptors, without interfering with corneal epithelial repair.

Materials and Methods

Ethical compliance

All experimental procedures adhered to the guidelines of the National Institutes of Health, the National Academy of Science, the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and the International Association for the Study of Pain. Animal protocols were approved by the University of Yamanashi Animal Care Committee (Approval Code: A4-6).

Animals

Adult male and female Wistar rats (10–12 weeks old) were obtained from Japan SLC (Tokyo, Japan). Animals were housed in groups at 23 ± 2 °C under a 12-hour light/dark cycle with free access to food and water. Behavioral experiments were conducted between 9:00 and 18:00 by a single observer blinded to the experimental groups. Rats were acclimated to the testing environment for one hour on each of two consecutive days prior to experimentation.

Chemical synthesis and preparation

NPA (N-[2-[4-(2-Butylbenzofuran-3-carbonyl)-2,6-diiodophenoxy]ethyl]-N,N-diethylpropan-1-aminium bromide) was synthesized as a permanently charged quaternary ammonium derivative via alkylation of amiodarone with propyl trifluoromethanesulfonate in 1,2-dichloroethane at room temperature over 5.5 days. The reaction mixture was concentrated under reduced pressure, and the intermediate triflate salt was converted to the bromide form via anion exchange resin (Dowex 21K) and isolated as a white solid. Purity (>98%) and molecular identity were verified by HPLC-MS and NMR.

For in vivo studies, NPA was dissolved in water at 80 °C, cooled to 20 °C, and diluted with saline containing 5% DMSO and 5% Tween [20]. Oxybuprocaine, capsaicin (Fujifilm Wako Pure Chemical, Osaka, Japan), and ruthenium red (Sigma-Aldrich Japan, Tokyo, Japan) were prepared in the same solvent. All solutions were freshly prepared prior to use. Drug preparation and dosing were performed by personnel separate from those conducting behavioral assessments to maintain experimental blinding.

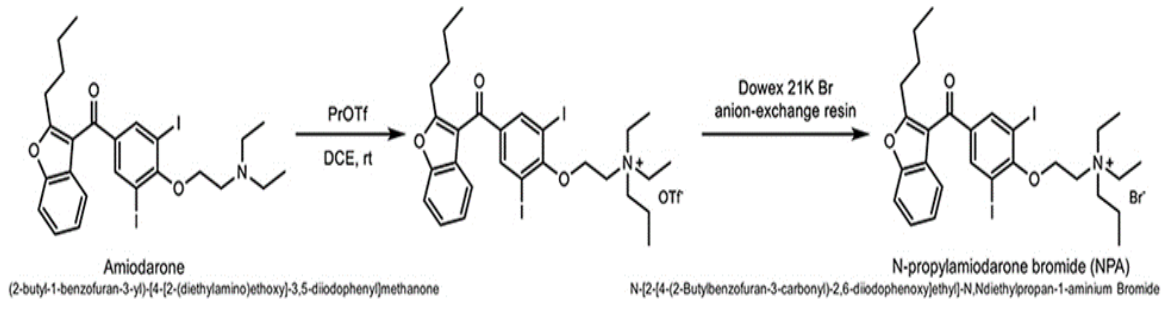


Figure 1. A novel quaternary ammonium N-propylamiodarone bromide was custom-synthesized using amiodarone as a parent compound.

Abbreviations: DCE, 1,2-dichlo roethane; PrOTf, propyl trifluoromethanesulfonate.

Corneal epithelial injury model and analgesic treatment

Corneal epithelial damage was generated following previously established protocols [22]. Briefly, under anesthesia with 2% isoflurane and using 10× magnification, a 4-mm trephine was used to mark the central region of the left cornea in 24 rats, after which a rotating burr (Ideal Microdrill; BioResearch, Nagoya, Japan) was used

to remove the epithelium. Upon recovery from anesthesia, rats received topical application of either normal saline, 12 mM oxybuprocaine, or 12 mM NPA (n = 8 per group, balanced for sex with 4 males and 4 females), in 50 µL volumes. The chosen concentration of oxybuprocaine corresponded to standard clinical dosing (0.4%, ~12 mM).

Assessment of corneal pain sensitivity

Mechanical sensitivity of the cornea was measured using the von Frey filament technique [23]. Measurements were obtained at baseline and at multiple intervals post-drug administration (5, 10, 20, 30, 45 min; 1, 2, 3, 4, 5, and 6 h). Rats were placed in individual observation chambers, and five calibrated filaments (0.04, 0.07, 0.16, 0.4, and 0.6 g bending forces) were applied perpendicular to the corneal center for 1 s. The minimal filament force eliciting a response—blinking, wiping, or escape—was recorded as the pain threshold. If no response occurred with the heaviest filament (0.6 g), a threshold of 1.0 g was assigned to prevent injury from repeated testing.

Evaluation of eye irritability

To monitor potential ocular irritation, the number of wiping responses within 1 min after drug application was counted. Additionally, the eyes were observed for hyperemia, chemosis, corneal opacity, or excessive tearing, and scored as absent (0), mild (1), or severe (2).

Analgesic testing in naïve corneas

An additional cohort of 32 rats with uninjured corneas was randomly assigned to four groups: 12 mM oxybuprocaine, 12 mM NPA alone, 12 mM NPA combined with 1% capsaicin (a TRPV1 agonist), or 1% capsaicin alone (n = 8 per group, balanced for sex). Corneal mechanical sensitivity and ocular irritability were assessed using the same von Frey and observational protocols described above, at baseline and multiple time points up to 6 h post-treatment.

Dose-response study and EC50 determination

To evaluate the dose-response relationship of NPA relative to oxybuprocaine, male rats with corneal injury were treated with varying concentrations of NPA (0.12, 0.36, 1.2 mM) or oxybuprocaine (0.36, 1.2, 3.6 mM) in 50 µL volumes (n = 5 per concentration). A vehicle control group (normal saline with 5% DMSO and 5% Tween20, n = 3) was included. Analgesic efficacy was determined using a 0.6-g von Frey filament as previously described, with effectiveness defined as the absence of any nociceptive response. EC50 values—the concentration at which 50% of animals displayed complete analgesia—were calculated (see Statistics). Subsequently, analgesic duration at the EC50 was evaluated over 360 min in a separate cohort of 12 male rats (6 per group).

TRP channel involvement in NPA analgesia

To investigate whether TRP channels mediate NPA-induced analgesia, a subset of rats received pre-treatment with ruthenium red (50 µL, 100 mM) 15 s prior to NPA administration at its EC50 (1.0 mM). Mechanical sensitivity was compared with animals treated with NPA alone. Control data from the EC50 NPA group were reused to minimize animal use.

Corneal healing assessment

Epithelial injury and drug administration

Corneal epithelial defects were induced in both eyes of 8 additional rats (4 males, 4 females). Following anesthesia, 50 µL of either 12 mM NPA or saline was applied. Wound healing was evaluated over 48 h using fluorescein staining and hematoxylin–eosin histology. An additional study assessed the effect of repeated NPA dosing (50 µL, 12 mM at 0, 6, 12, 24, 30, and 36 h post-injury) on epithelial recovery.

Fluorescence imaging

Under anesthesia, fluorescein was applied to the corneal surface, and images were captured at 0, 24, and 48 h using blue-light microscopy. Defect areas were quantified using ImageJ, with relative wound area calculated as the proportion of the initial defect remaining.

Histological analysis

Following the final imaging session, rats were euthanized and eyes were fixed in methanol and paraformaldehyde (Superfix KY-500, Kurabo Industries, Osaka, Japan) for 2 h at 23 °C, then overnight at 4 °C. Central corneas were

dissected, embedded in paraffin, and sectioned. Sections were deparaffinized, stained with hematoxylin for 5 min and eosin for 10 min, and central epithelial thickness was measured under microscopy.

Statistical analysis

Data were analyzed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). Changes in corneal mechanical sensitivity over 6 hours and epithelial wound areas over 48 hours were evaluated using two-way repeated measures ANOVA with subsequent Sidak's or Dunnett's post hoc tests, as appropriate. The frequency of eye-wiping responses was compared via either one-way ANOVA or a two-tailed t-test, depending on the dataset. The maximum analgesic effect duration (mechanical threshold = 1.0 g) between two groups was analyzed using a two-tailed t-test. Drug dose-response curves were fitted with a four-parameter logistic model, and statistical differences between curves were determined using an F-test. Corneal epithelial thickness was analyzed using the Wilcoxon signed-rank test. Sample sizes were determined a priori with G*Power 3.1.9.3 to detect a 15% difference between groups, achieving 80% power at a 0.05 significance level. All results are presented as mean ± SEM, with $P < 0.05$ considered statistically significant.

Analgesic effects of NPA in a corneal injury model

Topical application of N-propylamiodarone bromide (NPA) on injured corneas provided substantially prolonged analgesia relative to oxybuprocaine. The mean duration of peak analgesic effect for NPA was 215 ± 11 minutes, compared to 25 ± 2 minutes for oxybuprocaine (n = 8 per group; $P < 0.001$; **(Figure 2)**). Analgesic efficacy was not influenced by the sex of the animals (oxybupracaine: P = 0.837; NPA: P = 0.761; **(Figure 3c)**). No statistically significant differences were observed in the number of wiping bouts within the first minute after drug administration across the treatment groups (saline: 4.3 ± 0.7; oxybuprocaine: 5.1 ± 0.8; NPA: 5.25 ± 0.9; F [2, 21] = 0.348; P = 0.710). Importantly, none of the rats showed evidence of ocular irritation, including hyperemia, chemosis, lacrimation, or corneal opacity, indicating that all treatments were well-tolerated.

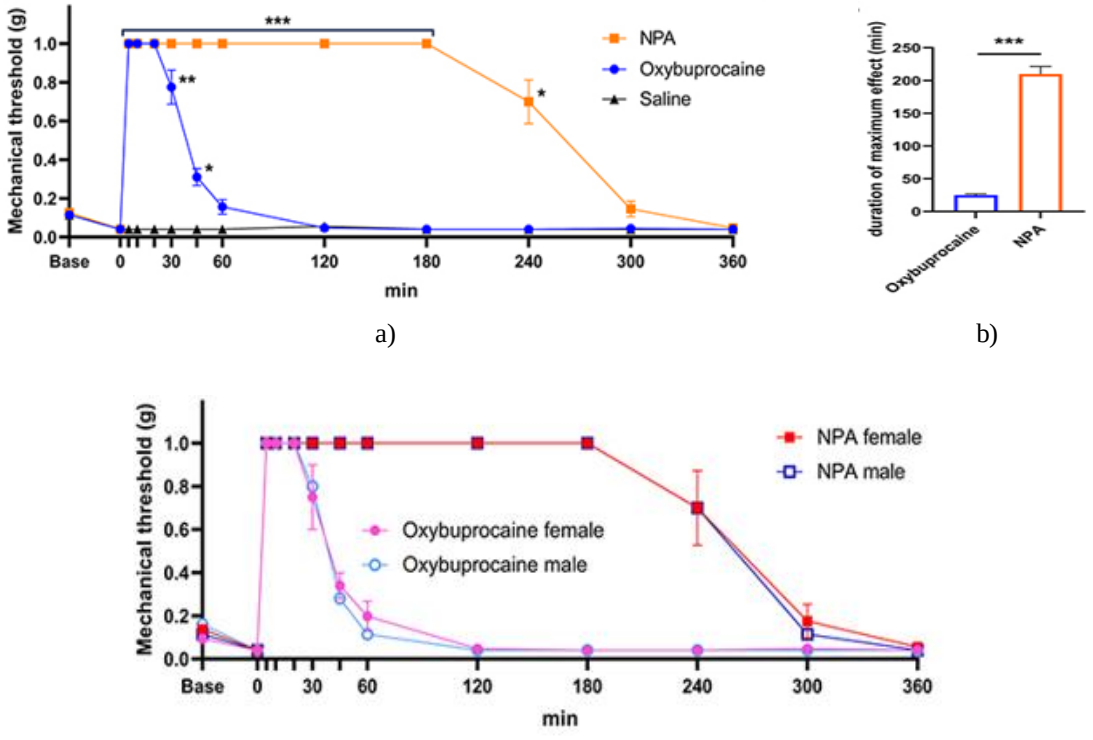
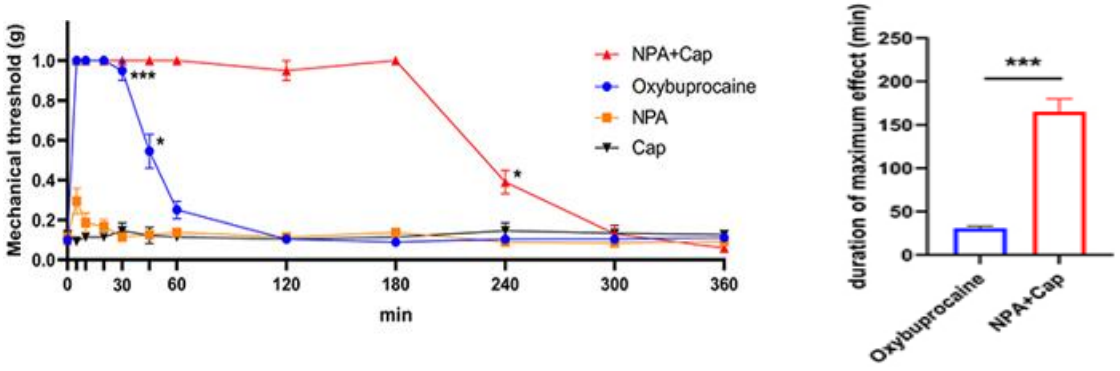


Figure 2. N-propylamiodarone produced long-lasting analgesia against corneal injury pain (n = 8/group). (**a**) Threshold for mechanical stimuli assessed using von Frey technique. (**b**) Duration of maximum effect (mechanical threshold = 1.0 g). (**c**) Sex difference in the threshold for mechanical stimuli assessed using von Frey technique.

Abbreviation: NPA, N-propylamiodarone bromide.

Notes: *P < 0.05, **P < 0.01, ***P < 0.001 vs Saline. ***P < 0.001 vs Oxybuprocaine.



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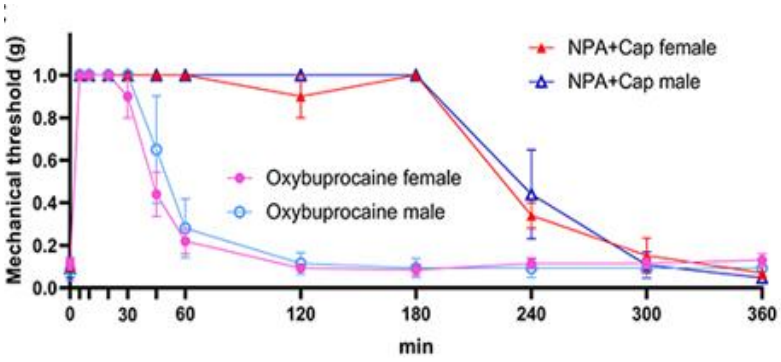

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Figure 3. The co-administration of N-propylamiodarone bromide and capsaicin produced long-lasting anesthesia in naïve corneas (n = 8/group). (a) Threshold for mechanical stimuli assessed using von Frey technique. (b) Duration of maximum effect (mechanical threshold = 1.0 g). (c) Sex difference in the threshold for mechanical stimuli assessed using von Frey technique.

Notes: *P < 0.05, ***P < 0.001 vs baseline of the same group. ***P < 0.001 vs Oxybuprocaine.

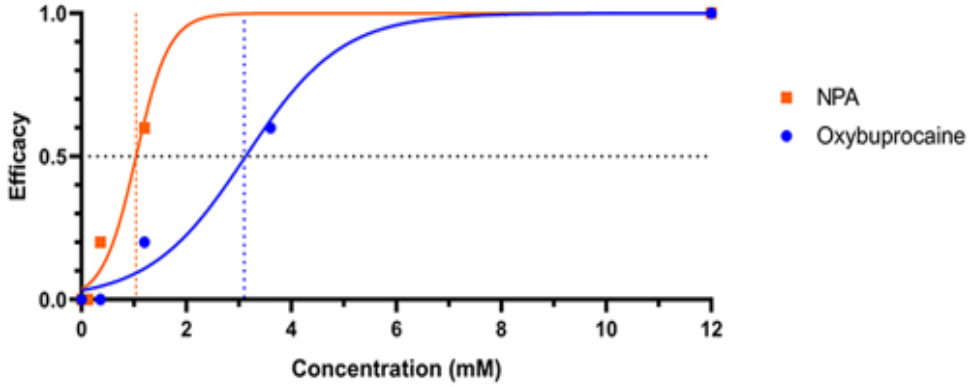
Abbreviations: Cap, capsaicin; NPA, N-propylamiodarone bromide.

Analgesic effects of NPA in naïve corneas

In eyes without injury, topical application of N-propylamiodarone bromide (NPA) alone did not produce a significant change in mechanical sensitivity **(Figure 3a)**. However, when co-applied with capsaicin, NPA generated markedly prolonged corneal anesthesia compared with oxybuprocaine, with the duration of maximal effect measuring 165 ± 15 minutes versus 31 ± 2 minutes for oxybuprocaine (n = 8 per group; P < 0.001; **(Figure 3b)**). No differences in analgesic response were detected between male and female rats for either oxybuprocaine or the NPA–capsaicin combination (P = 0.381 and 0.644, respectively; **(Figure 3c)**). Capsaicin administered alone failed to induce corneal anesthesia. Additionally, the frequency of eye-wiping behaviors within one minute after administration did not differ significantly between the oxybuprocaine and NPA groups (3.4 ± 1.4 vs 4.3 ± 1.4, n = 8 each; P = 0.658), and no ocular irritation—including hyperemia, lacrimation, or corneal opacity—was observed in either group.

Dose-response analysis and EC50 comparison

Dose-response experiments revealed that NPA exhibited greater analgesic potency than oxybuprocaine, with EC50 values of 1.0 mM and 3.1 mM, respectively (P = 0.002; **(Figure 4a)**). When administered at their respective EC50 concentrations, NPA produced significantly longer-lasting analgesia in the corneal injury model compared to oxybuprocaine (F [1, 10] = 9.840, n = 6 per group; P = 0.011; **(Figure 4b)**). These findings highlight both the enhanced potency and the extended duration of action of NPA relative to conventional local anesthetics.



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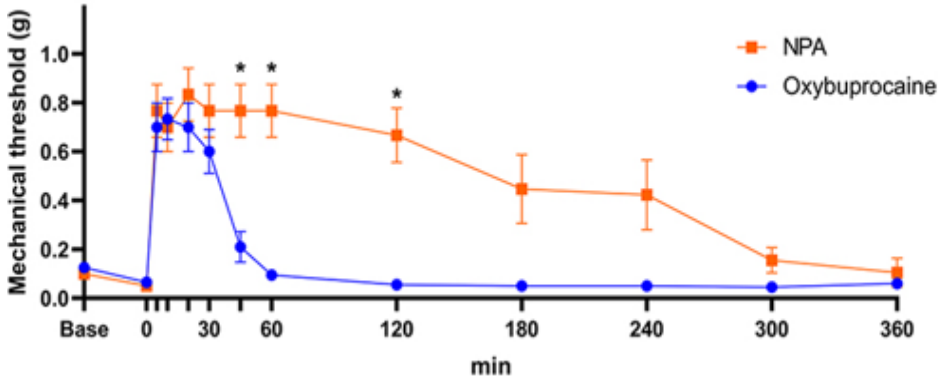

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Figure 4. The potency of NPA was significantly greater than that of oxybuprocaine. (a) Dose-response relationship of NPA and oxybuprocaine on corneal pain. (b) Threshold for mechanical stimuli assessed using von Frey technique.

Note: *P < 0.05 vs Oxybuprocaine.

Abbreviation: NPA, N-propylamiodarone bromide.

NPA exhibits superior corneal analgesic potency

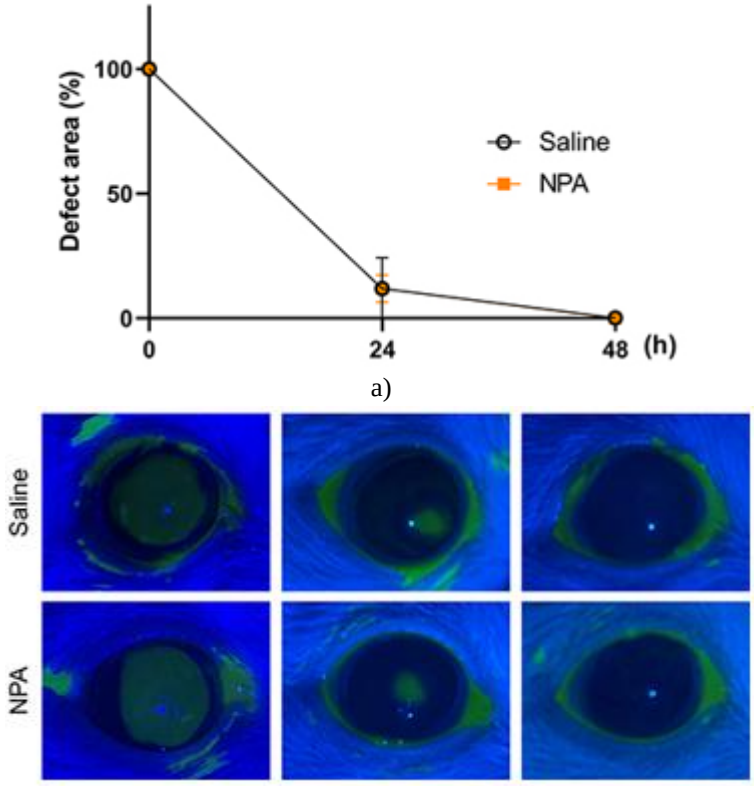
N-propylamiodarone bromide (NPA) demonstrated markedly stronger analgesic effects than oxybuprocaine in our corneal injury model. Analysis of dose-response relationships revealed that NPA achieved effective corneal anesthesia at lower concentrations and produced a longer duration of pain relief **(Figure 4a)**. Mechanical sensitivity thresholds, measured using von Frey filaments, were consistently higher for NPA-treated eyes relative to those treated with oxybuprocaine (*P < 0.05; **(Figure 4b)**), confirming its enhanced efficacy.

TRP channel contribution to NPA's analgesic action

To determine the involvement of transient receptor potential (TRP) channels in NPA-mediated analgesia, we pretreated animals with ruthenium red, a broad TRP blocker. This intervention partially diminished the pain-relieving effect of NPA ($F[1,10] = 5.69$, $n = 6$ per group; $P = 0.038$), supporting the notion that NPA's selective cellular entry and sustained anesthesia rely on TRP channel activity.

Corneal wound healing remains unaffected by NPA

The impact of NPA on epithelial repair was evaluated over 48 hours. Topical application of NPA did not delay wound closure compared with saline controls, as indicated by similar residual defect areas at 24 hours (11.2% ± 1.9% vs 11.2% ± 4.4%, P = 0.461) and 48 hours (0.14% ± 0.14% vs 0%, P > 0.999; **(Figure 5)**). Histological measurements showed comparable central epithelial thickness between groups (42.7 ± 2.9 μm vs 40.4 ± 3.3 μm; n = 8; P = 0.637; **(Figure 6)**). Moreover, repeated administration of NPA across multiple time points did not compromise corneal repair relative to controls (24 h: 17.0% ± 3.9% vs 16.2% ± 2.1%, P = 0.742; 48 h: 0.59% ± 0.21% vs 0.36% ± 0.30%, P = 0.563). These results indicate that NPA achieves extended analgesia without impairing epithelial regeneration, even with repeated dosing.



a)

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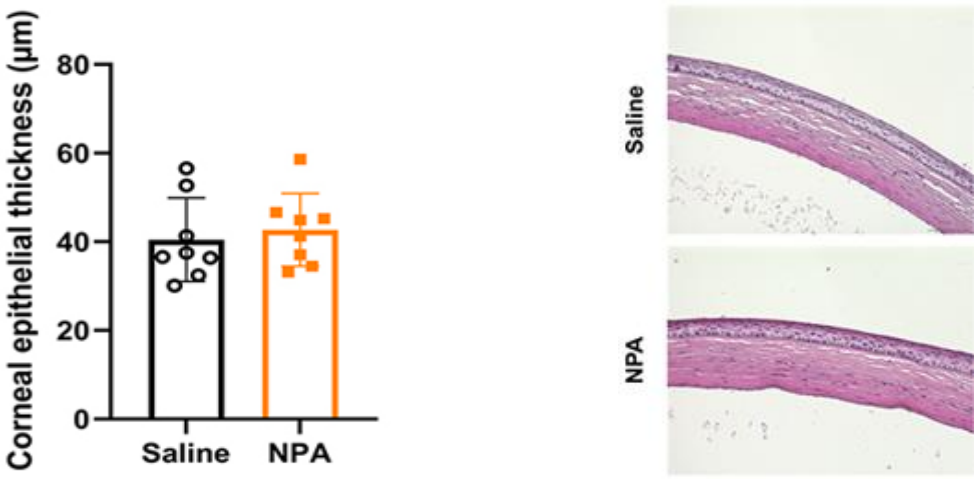
Figure 5. N-propylamiodarone did not hamper corneal wound healing (n = 8/group). (**a**) Corneal epithelial defect area after injury. (**b**) Representative images of corneal epithelial surface stained with fluorescein.
Abbreviation: NPA, N-propylamiodarone bromide.



a) b)

Figure 6. N-propylamiodarone did not influence corneal wound healing (n = 8/group). (**a**) Epithelial thickness of the central cornea at 48 h after injury (n = 8/group). (**b**) Representative images of the central cornea stained with hematoxylin and eosin.
Abbreviation: NPA, N-propylamiodarone bromide.Discussion

Extensive research has focused on developing analgesics that selectively enter nociceptors through open-state large-pore channels, such as TRPV1 [19, 24, 25]. Prior studies have shown that quaternary derivatives of local anesthetics, including QX314, can provide prolonged analgesia when administered together with TRPV1 agonists [20]. However, the requirement for co-administration of TRPV1 agonists—which themselves trigger significant pain—has limited the clinical applicability of this approach. Interestingly, in injured or inflamed tissues, these

large-pore channels are often naturally activated, enabling permanently charged sodium channel blockers to access nociceptors directly and produce analgesic effects [26, 27]. Consistent with these observations, our study demonstrates that N-propylamiodarone bromide (NPA) alone achieves long-lasting corneal analgesia without the need for capsaicin co-administration in the setting of epithelial injury.

NPA is a quaternary derivative of amiodarone that preserves the parent compound's core chemical structure while acquiring a permanent positive charge. Although amiodarone is not conventionally classified as a sodium channel blocker, it exhibits inhibitory activity on voltage-gated sodium channels similar to lidocaine [28]. Its high plasma protein binding (~96%) and extended half-life (up to 80 h) further suggest its potential as a scaffold for potent, long-acting analgesics [29, 30]. Unlike systemic amiodarone, which can affect off-target cells and cause local tissue irritation [31], topical administration of NPA to the cornea targets the densely innervated ocular surface, thereby minimizing off-target effects. Moreover, the permanent positive charge of NPA enhances nociceptor selectivity, reducing the likelihood of undesirable interactions with other cell types.

In line with these properties, our findings indicate that topical NPA provides robust and sustained analgesia in injured corneas without interfering with epithelial recovery. Pain relief persisted for at least four hours, markedly exceeding that achieved with an equivalent concentration of oxybuprocaine. These results position NPA as a promising candidate for the development of novel, long-acting ophthalmic analgesics. Beyond corneal injury, NPA may be applicable to other ocular pain conditions, such as postoperative discomfort, dry eye, and allergic eye disease, where large-pore transducer channels are involved in nociceptive signaling [2, 32, 33]. Nonetheless, because NPA requires open-state large-pore channels for cellular entry, it is not suitable for conventional procedural anesthesia.

Several limitations should be considered. Although our results support the involvement of TRP channels in NPA-mediated analgesia, other pathways for cellular uptake cannot be excluded. Future studies utilizing advanced techniques, such as patch-clamp electrophysiology or high-resolution imaging, will be necessary to fully elucidate the underlying mechanisms. Additionally, although NPA did not induce ocular irritation in this study, comprehensive safety assessments are essential prior to clinical translation.

Conclusion

This study demonstrates that NPA, a novel quaternary ammonium compound, provides long-lasting analgesia for corneal injury without delaying epithelial repair. These findings support the potential of NPA as a candidate for the development of long-acting ophthalmic analgesics targeting corneal pain.

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Conflict of Interest: Masakazu Kotoda is named as the inventor on a patent pending covering the design and use of NPA (application number: 2023-146529). The other authors declare that no competing interests exist.

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Ethics Statement: None

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