The (R)-isomer of isometheptene*, decreases trigeminal sensitivity in the Inflammatory Soup and Spontaneous Trigeminal Allodynia rat models.

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**Abstract**

Background:

Isometheptene, a racemic mixture of (R)- and (S)-enantiomers, is an active ingredient of the commonly known headache medication, Midrin. Although a previously assumed mechanism of action relied on the vascular hypothesis of migraine, the (R)- and (S)-enantiomers remain elusive. Assessing the effect of each isomer individually in headache is essential in developing more efficacious treatment options for migraine patients. Two rat models of trigeminal pain which feature aspects of the inflammatory cascade and that have been developed to study the effects of therapeutic compounds and interaction of the mechanisms behind migraine. The inflammatory soup (IS) model is developed by repeated dural infusion of an inflammatory soup for a month which results in chronic trigeminal sensitivity that outlasts the initial infusion for months. Both models experience similar symptoms to human migraine such as an increased sensory sensitivity, photophobia, responsiveness to nociceptive and nociceptive plus inflammatory stimuli, and sensitivity to dural nociceptors.

Objective

The aim of this study was to test the effects of the (R)- and (S)-isomers of isometheptene on trigeminal sensitivity in the inflammatory soup and spontaneous trigeminal allodynia rat models.

Methods:

The pharmacokinetics (PK) of racemic and (R)/isometheptene were studied in rats using isomer-specific LC/MS. The effects of the (R)- and (S)-isometheptene on trigeminal sensitivity/allodynia in the IS and STA rats were assessed. Animals for this study represent the 17th generation of an STA rat colony. Periorbital thresholds, as measured with von Frey filament(s) was determined to test trigeminal sensitivity prior to and 0.5, 1.5, 2.5, and 3.5 hr- and 24 hr-post treatment with (S)-isometheptene, (R)-isometheptene, or saline vehicle. All treatments were administered intraperitoneally.

Results:

Rats were treated by intraperitoneal (i.p.) infusion of saline (n=10), IS, (R)-, and (S)-isometheptene (n=8 each). These rats exhibited episodic threshold decreases that were similar between the IS and STA models (Fig. 3). Treatment with 30 mg/kg of the (R)- and (S)-isometheptene mucate significantly increased trigeminal thresholds at the 0.5 hr (2.3-fold), 1.5 hr (3.0-fold), 2.5 hr (2.9-fold), and 3.5 hr (3.1-fold) time points in IS rats (Fig. 2). Treatment with 30 mg/kg of the (R)-isomer of isometheptene mucate significantly increased trigeminal thresholds at the 0.5 hr (7.6-fold), 1.5 hr (8.4-fold), 3.5 hr (5.5-fold), and 24 hr (8.2-fold) time points in STA rats (Fig. 1). In contrast, treatment with 30 mg/kg of the (S)-isomer had no effect on trigeminal sensitivity in either the IS or STA models (Fig. 2.5). Treatment with 30 mg/kg of the (R)- or (S)-isomer had no effect on trigeminal sensitivity or allodynia (Fig. 2.5).

Conclusions:

These data show that (R)-isometheptene treatment relieved trigeminal sensitivity in the inflammatory soup and spontaneous trigeminal allodynia rat models, two models representative of the chronic nature of migraine. Additional dosing experiments are warranted to determine the dose response of this effect. These findings support development of the (R)-isomer of isometheptene as an abortive therapeutic for primary headache and other chronic pain indications.

* (R)-isometheptene is being investigated in the US for tension-type headache under a US IND and is not approved for any indication.

**Introduction**

Migraine, containing isometricheptene Mucate (65 mg), Dihydrochlorphenam (100 mg) and Astatinoprin (252 mg), is indicated for relief of migraine headache. It was initially believed that isometricheptene’s vasoactive effects were responsible for Midrin’s efficacy in migraine. Isometricheptene, however, is a racemic mixture of (R)- and (S)-enantiomers, each with its own very distinct receptor-interaction profile. The (R)-isomer has high specificity as an agonist for imidazoline receptor type 1 (11) while the (S)-isomer has no affinity for this receptor. (11) An agonist knock-out mouse feature reduced pain phenotypes, suggesting that this receptor may be involved in pain and that the (R)-isomer could be the effective component to isometricheptene’s role in migraine headache treatment through its receptor (Zhang, 2013).

**Chronic Migraine Model**

Rats were fitted with a cannula for inflammatory soup infusions (Bradley, PSG/2, SHT, Hamilton). Von Frey testing was done in a plastic tube restraint in the periorbital region of the rat above the rostral part of the eye. Threshold was noted when rats quickly retracted their head away from the bending von Frey monofilament or performed a long touch of its face with the ipsilateral paw. Infusions were performed 3x/wk to simulate episodic activation of dural nociceptors in chronic migraine (Fig. 1) (Dohshan, 2007).

**Spontaneous Trigeminal Allodynia Model**

Most animal headache models require manipulation of the animal, often with a stimulus to activate dural nociceptors or the trigeminal nerve. Using behavioral methods of monitoring trigeminal pain in rats, our group discovered a rat with spontaneous episodic trigeminal allodynia. Subsequent mating showed that the strain is inher-ited in 40-50% of offspring from affected animals crossed to unaffected animals, and in ~60–70% of offspring from crosses with 2 affected animals. A stable colony has been established through 18 generations of inbreeding. These rats exhibit episodic threshold decreases that are responsive to treatment by the NSAC, TRPA1, and DHE. They also experience photophobia (Dohshan, 2012).

**Results - Inflammatory Soup Model**

To assess trigeminal allodynia, pororibol Von Frey threshold measurements were performed throughout the treatment period in rats receiving infusions of saline (n=10) or IS (n=10) 3 days/week. Rats receiving infusions of IS transitioned to a more sensitive state, as seen in a decrease in their periorbital thresholds, whereas rats receiving saline infusions did not transition to a more sensitive state. Rats that have transitioned to chronic periorbital sensitivity have thresholds of < 2.0 g. Naive or non-transitioned rats do not respond to any pressure less than 8.10 g.

**Results - STA Model**

The (R)-isomer of isometheptene*, decreases trigeminal sensitivity in the STA model. No significant changes in trigeminal sensitivity were seen when IS rats were treated with 1mg/kg R- or S- isometheptene (i.p.) and 0.5 hr (p<0.05). 30mg/kg of IS isometheptene decreased trigeminal sensitivity while 300mg/kg had no effect on sensory thresholds. Rats receiving saline treatment had no change in sensory thresholds over the course of the experimental timeline. (n=8 rats/group, *P<0.01, **P<0.001).

**Citations**


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**Poster Citation**