The (R)-isomer of isometheptene decreases trigeminal sensitivity in a rat model of primary headache

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Introduction

Isometheptene is thought to be the active ingredient of the commonly known headache medication, Midrin. Previously, we found only the (R)-enantiomer to be effective in alleviating headache behavior in two models of headache compared to the (S) enantiomer. Experiments using electrical and mechanical stimulation of the dura in animals with no history of headache pain have been used to elucidate the mechanisms of the trigeminovascular system at the level of the trigeminal ganglion, trigeminal nucleus caudalis, periaqueductal gray, and thalamus. The limitation of these acute models is that electrical and mechanical stimulation of the dural blood vessels does not cause long lasting pain similar to recurrent headache pain in humans. Two animal models for the investigation of headache pathophysiology that include aspects of the chronic nature of headache were included in this study. These models provide a new approach to study the pathophysiology of recurrent headache and support validation of novel treatments.

Methods

Experimental Design

To determine the efficacy of the (R)-isomer of isometheptene in the two rat trigeminal headache models, a 4 point dose response curve was conducted. Periorbital thresholds, measured using von Frey filaments, were obtained to determine trigeminal sensitivity prior to and after treatment with either (R)-isometheptene (1, 10, 30, 60 mg/kg), or saline vehicle. A 100 mg/kg dose was omitted due to muscle related fatalities observed in the rat models, though it was well tolerated in human testing. All treatments were administered intraperitoneally. Von Frey data was analyzed using Prism, and a Two-Way ANOVA was performed to determine statistical significance with the factors group and time. Following the completion of the 24 hr-post treatment time point, animals were perfused with 4% PFA. Trigeminal ganglion and brainstem were collected and sectioned at 20 μm.

Results

Figure 1: R-isomer of the isometheptene (ISO) dose response in the STA Model. STA rats showed a significant increase in trigeminal threshold in the 1 mg/kg of ISO treated at the 0.5 hr (***P<0.001), 1 hr (**P<0.01), 1.5 hr (**P<0.01), 2 hr (**P<0.01), and 2.5 hr (**P<0.01). Testing of 10 mg of ISO showed increases in thresholds at 1.5 hr (**P<0.01) and 2.5 hr (**P<0.01). Testing of 30 mg of ISO showed increases in trigeminal thresholds at the 0.5 hr (**P<0.01), 1 hr (**P<0.01), 1.5 hr (**P<0.01), 2 hr (**P<0.01), and 2.5 hr (**P<0.01). Testing of 60 mg of ISO showed increases in trigeminal thresholds at the 1.5 hr (**P<0.01), 2 hr (**P<0.01), and 2.5 hr (**P<0.01).

Figure 2: R-isomer of the isometheptene (ISO) dose response in the IS Model. Treatment with 10 mg/kg of ISO showed increases in trigeminal thresholds at the 1.5 hr (***P<0.001) and 2.5 hr (***P<0.001). Administration of 30 mg/kg of ISO resulted in increases in trigeminal thresholds at the 1.5 hr (***P<0.001) and 2.5 hr (***P<0.001). Testing of 60 mg/kg of ISO showed increases in trigeminal thresholds at the 1.5 hr (***P<0.001), 2.5 hr (***P<0.001) and 24 hr (***P<0.001).

Discussion & Conclusions

• Findings show differential dose-response effects of (R)-isometheptene treatment on trigeminal sensitivity that are dependent on the headache model.
• Treatment with (R)-isometheptene showed better efficacy for the IS model at a lower dose compared to the STA model.
• Treatment with (R)-isometheptene in the STA model resulted in a significant improvement in trigeminal thresholds that persisted for 24 hours.
• Side effects at the 60 mg/kg dose included seizures in a subset of animals, possibly affecting the thresholds in this treatment group for both models.
• Treatment with (R)-isometheptene reduced the number of nNOS and CGRP positive trigeminal ganglia neurons and slightly reduced CGRP immunoreactivity in the TNC for both STA and IS models.
• Findings supports the (R)-isomer of isometheptene as a therapeutic for chronic spontaneous type headaches such as migraine, as well as for inflammatory pain conditions.

References:


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