

Cizolirtine Citrate (E-4018) in the Treatment of Chronic Neuropathic Pain

P. Shembalkar¹, J. Täubel², M. Abadias³, R. Arezina², K. Hammond² and P. Anand¹

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Summary and Introduction

Summary

This study was performed to determine the efficacy and safety of oral cizolirtine citrate, a novel agent, in the treatment of chronic neuropathic pain. Cizolirtine was tested in a double-blind, placebo-controlled, two-way crossover study, having previously been shown to have significant analgesic and anti-hyperalgesic action in neuropathic pain models and preliminary human studies.

Twenty-five patients with neuropathic pain, which was persistent for at least three months, and scored > 30 mm on a 100 mm visual analogue scale (VAS), were included. A subgroup of five patients had primary skin allodynia, i.e. pain evoked by non-noxious stimuli in the territory of the injured nerve. Cizolirtine 200 mg or placebo was administered twice daily for a treatment period of 21 days, each separated by a washout interval of 7 days. Assessments of skin allodynia were performed using the graded monofilaments (von Frey hairs) on days 1 (predose), 14 and 21 (90 min postdose). All patients were instructed to maintain a daily pain diary throughout the study.

Results showed that the differences in VAS and allodynia scores between cizolirtine and placebo treatments were not significant in the overall analysis ($p \geq 0.05$); cizolirtine was well tolerated. In a subgroup of five patients with primary allodynia, a 53% reduction in VAS score from baseline at rest ($p = 0.007$) and 55% on movement ($p = 0.0002$) at day 21 was observed with cizolirtine, as compared to 8% at rest ($p = 0.5215$) and 13% on movement ($p = 0.4187$) with placebo. Similarly, allodynia improved with cizolirtine ($p = 0.03$) but not with placebo ($p = 0.9$) in this subgroup. Cizolirtine may be effective in primary allodynia after peripheral nerve injury, and a further trial in a larger number of such subjects is warranted.

Introduction

Current analgesic therapies have limited effect and usefulness in chronic neurogenic pain. The pharmacological agents most often used in neuropathic pain, such as the anti-depressant, anti-arrhythmic and anti-epileptic drugs, were not discovered or designed for this condition, and may have side-effects. Cizolirtine citrate (E-4018), a novel non-opioid analgesic (Laboratories Dr Esteve, Spain), has shown efficacy in animal models of chronic neuropathic pain, with few side-effects. In the rat nerve loose-ligation model, cizolirtine showed significant analgesic activity against thermal stimulus-induced pain (ED_{50} 4.8 mg/kg) and mechanical hyperalgesia

(data source: Laboratories Dr Esteve). A clinical trial of cizolirtine citrate was therefore undertaken in patients with chronic neuropathic pain syndromes.

Pre-clinical studies indicated the mechanisms of action of cizolirtine. Systemic administration of cizolirtine significantly reduced the spontaneous outflow of substance P from spinal cord in control and polyarthritic rats^[1]. In view of the well-established role of substance P in spinal nociception, the effect of cizolirtine may result, at least partly, from its inhibitory influence on spinal release of substance P