

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

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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

from sensory fibres. Prevention of its effects by idazoxan supported the view that cizolirtine activated descending inhibitory noradrenergic systems in spinal cord^[1]. Like cizolirtine, there is evidence that analgesia due to opioids and

nicotine is partly mediated through *alpha*₂-adrenergic receptor spinal cord mechanisms^[2-5]. However, in contrast to morphine^[6], cizolirtine also exerted an effect against cold stimuli (Kayser V,

Christensen D, Farré A, unpublished observations).

Cizolirtine was well tolerated in a study in patients with pain following third molar tooth extraction^[7], and in a phase II dose-escalating pilot study in patients with mixed neuropathic pain syndromes, where a dose of 400 mg was found to be most effective (our unpublished data). The present double-blind, placebo-controlled trial was conducted to evaluate further the efficacy and safety of oral cizolirtine citrate in chronic neuropathic pain.

Methods

Study Population

The study, approved by the local ethics committee, was conducted at the Peripheral Neuropathy Unit, Imperial College School of Medicine, Hammersmith Hospital, London, UK. All patients provided written informed consent in accordance with the Declaration of Helsinki.

Patients aged ≥ 18 years, with neuropathic pain for at least three months, and a pain intensity score of ≥ 30 mm on a 100 mm Visual Analogue Scale (VAS), on the three baseline days (at 3 p.m.), were included.

Exclusion criteria included: pregnancy, lactation or women with child-bearing potential and inadequate contraception; abnormal electrocardiogram (ECG) or laboratory tests at screening; and a history of epilepsy, psychiatric disorders, drug or alcohol abuse.

Previously prescribed medications (anticonvulsants, tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics) could be used concomitantly provided that they were stabilised before inclusion, and remained unchanged throughout the study. If analgesia from the study medication was inadequate, patients were allowed paracetamol tablets to a maximum of 8 X 500 mg in a 24 h period, as 'rescue medication'.

Of 28 patients (16 males and 12 females; 26-84 years) enrolled, 25 completed the study (Table 1). Three patients withdrew during period I: one due to a possible adverse event (skin rash) after placebo treatment, and two for personal reasons unrelated to the medication.

Study Design

This was a randomised, double-blind, placebo-controlled, two-way crossover phase II study. Cizolirtine citrate (200 mg twice daily) or matching placebo capsules were administered in two treatment periods of 21 days each, separated by at least a 7-day washout period. Laboratories Dr Esteve provided randomisation codes in ten blocks of four, which ensured that all patients received the active treatment throughout all days in either study period. Each patient attended the clinic during baseline, and on days 1, 7, 14 and 21 of each treatment period, and for follow-up evaluation after the second period. Patients were given a diary to maintain during the study period, and a week's supply of medicines on day 1, 7 and 14 visits.

Screening Phase

At this visit, medical history was noted, and after physical and neurological examinations, patients completed a McGill Pain Questionnaire (MPQ)^[6] revised extended version including VAS and Beck Depression Inventory (BDI)^[9]. Mechanical hypersensitivity was determined using graded monofilaments (von Frey hairs). Standard pre-study examinations included: 12-lead ECG, blood sampling for haematology, biochemistry and for pregnancy testing in women with childbearing potential. Patients meeting the inclusion criteria were given a daily pain diary and were asked to score pain intensity with VAS at rest and on movement, and pain relief (0 = no relief; 4 = complete relief), three times a day for the following three days (days -2 to 0), with instructions to return on study day 1. Similar recordings were kept daily by the patients throughout both treatment periods.

Day 1, 7, 14 and 21 Visits

Patients were allotted randomisation numbers on the day 1 visit. The assigned trial medication was administered at 0900 (\pm 30 min). Mechanical hypersensitivity, MPQ-short form, BDI and ECG were recorded prior to dosing, while blood pressure was measured prior to, and 75 min after, the dose. At subsequent visits, these procedures were repeated and blood samples to determine plasma levels of cizolirine were collected prior to dosing. The second dose of study medication was self-administered at 2100 (\pm 30 min). Patients were instructed to record in the diary any adverse events, changes in the regular medication and intake of rescue medication during the periods in between hospital visits. Four to eight days after the end of the second period, patients underwent follow-up examination including ECG, blood tests (haematology and biochemistry) and urinalysis.

Efficacy Measurements and Statistical Analysis

The primary efficacy parameter was the change in the pain intensity (VAS score) from baseline (day 0, 1500) to day 21 of each treatment period. A percentage reduction in the VAS score from baseline (i.e. analgesic effect) was also calculated. For the purpose of this study, a 30% reduction was considered meaningful and the chi-square test was used in statistical testing.

Secondary efficacy parameters were pain relief, changes in mechanical hypersensitivity, MPQ and BDI scores. Univariate statistics by time and treatment were calculated for all parameters. Based on the distributions of the two parameters, the ANOVA technique was utilised to analyse the pain intensity differences between treatment groups and by days 7, 14 and 21 after treatment. A two-sided statistical test was used whenever significance was tested.

Results

Primary Outcome

The mean pain intensity relative to baseline was generally lower after both cizolirine and placebo treatment. There was significant reduction (compared to baseline) in mean \pm SD VAS score at 1500 on day 21 with cizolirine at rest (39.7 ± 22.3 mm, $p = 0.04$), and on movement (46.4 ± 24.9 mm, $p=0.02$). The corresponding values with placebo were not significantly different from baseline (rest: 40.0 ± 22.9 mm, $p>0.22$; movement: 47.2 ± 25.2 mm, $p > 0.48$), respectively. Although the mean VAS changes from baseline were statistically significant with cizolirine, the differences between cizolirine and placebo treatment were not significant.

A 30% reduction in pain intensity was achieved by \geq 40% of patients receiving both cizolirine and placebo by day 7. Slightly more patients achieved analgesic effect on day 14 with cizolirine.

Secondary Efficacy Parameters

With cizolirtine, 56% of patients reported some form of pain relief as reported using a verbal rating scale (VRS) on day 21 as compared to 48% with placebo; however, no statistical significance was achieved between the treatments.

Both cizolirtine citrate and placebo resulted in similar reductions in various types of pain on the short form MPQ; the reductions were generally of a one-step decrease. Subjectively, a more positive response was elicited in the second study period regardless of the treatment administered.

The mean BDI scores on study days 14 and 21 (as compared to day 1) were generally similar with cizolirtine (7.6 and 7.3, respectively) and placebo treatment (8.7 and 8.1), suggesting that the magnitudes of changes in depressive symptoms were not influenced by cizolirtine treatment.

Graded monofilament (von Frey hair) values, which measure mechanical sensitivity, were converted into gram force in 24 patients (data were not available for one patient), and baseline (day 0) values were compared with day 21 of both treatment periods. There was a statistically significant reduction in hypersensitivity (characterised by applying different monofilaments of varying pressure to the skin) with cizolirtine from baseline ($p = 0.004$) as compared to placebo ($p = 0.196$), which was more pronounced in a subgroup of five primary skin allodynia patients. The differences between cizolirtine and placebo treatments were, however, not significant in the overall analysis ($p > 0.05$).

Efficacy in a Subgroup of Responders

A subgroup of five patients with primary allodynia and hyperalgesia (i.e. hypersensitivity restricted to the territory of the injured nerve) responded excellently to cizolirtine treatment. There was a 52.6% ($p = 0.007$) reduction in the mean VAS score from baseline at rest and 54.7% ($p = 0.0002$) on movement on day 21 with cizolirtine as compared to 8.1% at rest ($p = 0.52$) and 13.2% on movement ($p=0.42$) with placebo. Similarly, hypersensitivity was remarkably decreased in these patients with cizolirtine ($p=0.03$) but not with placebo ($p=0.86$). Although both VAS scores and hypersensitivity were improved from baseline with cizolirtine, differences between cizolirtine and placebo treatment did not reach statistical significance.

Cizolirtine was generally well tolerated and there were no serious adverse events. One patient developed mild skin rash after placebo treatment and was withdrawn from the study during first period. Only five adverse events were considered as possibly treatment-related.

Discussion

Although cizolirtine caused a reduction in pain intensity and allodynia from baseline as compared to placebo, the benefit was not statistically significant in the patients overall, or in subgroups with major nerve trunk injuries. However, cizolirtine did appear remarkably effective in a subgroup of patients with primary local hypersensitivity caused by peripheral nerve and tissue trauma, as indicated by the VAS score and monofilament (von Frey hair) scores; however, the responses in these patients were not statistically significant, possibly due to the small sample size. The differential response in this subgroup may be explained by the different mechanisms underlying the pain symptoms in the other subgroups of patients.

In the subgroup of patients with primary allodynia, there was peripheral nerve and associated soft tissue and/or bone injury, and the local hypersensitivity developed in the region of the soft tissue injury weeks or months later. It may be proposed that in these patients injured nerve fibres regenerated to injured soft tissues and skin. These nerve fibre 'sprouts' were likely to

have increased expression of substance P, as a result of their contact with injured or inflamed tissues; the latter are known to have higher levels of nerve growth factor (NGF), which up-regulates substance P expression^[10,11]. The increased concentration of substance P and its release in the dorsal horn of the spinal cord may in turn contribute to the hypersensitivity. Cizolirtine, by blocking this release of substance P, may provide symptomatic relief of pain and allodynia. The animal model studies of substance P and its receptor in pain mechanisms would support the above proposed explanation^[1]. Substance P and its receptor play a role in the development of hyperalgesia, but not necessarily its maintenance^[12-14]. This may explain why cizolirtine was effective only in patients with primary allodynia - nerve fibres 'sprouts' may require persistent contact with excessive NGF levels, causing subsequent up-regulation of substance P and continuing spinal cord hypersensitivity, or 'wind-up', a phenomenon that is completely lost in the substance P receptor-deficient mouse model^[15].

Patients who responded poorly to cizolirtine have different underlying pain mechanisms, such as a major nerve trunk injury, where, in contrast to the patients described above, endogenous substance P is decreased^[16]. In these patients, ectopic neuronal impulses at the site of injury, mediated in part by sodium channel accumulation, may lead to pain and secondary hyperalgesia, i.e. hypersensitivity beyond the territory of the injured nerve^[17]. Similar mechanisms are likely to occur in spinal root injury (radiculopathy).

Efficacy of the commonly used drugs for pain following nerve injury like tricyclic antidepressants, carbamazepine and gabapentin, in the treatment of primary hyperalgesia and allodynia, has not been established^[18]. Although there is an open label study^[19] suggesting that gabapentin is effective in allodynia, there has been no double-blind study demonstrating this effect. Further, the double-blind studies with gabapentin have been in neuropathic pain due to diabetic neuropathy^[20] and post-herpetic neuralgia^[21], and not after nerve injury. We are not aware of any human studies demonstrating the effect of amitriptyline or carbamazepine in allodynia. The opioids, including morphine and fentanyl, were found to have no anti-allodynic action^[22,23]. Tramadol was reported to relieve pain and allodynia in painful polyneuropathy^[24], but the risk of dependence and abuse, even though reported to be low^[18,24], remains a matter of concern. Ketamine is effective in allodynia^[23], but needs to be administered parenterally. Intravenous lignocaine is highly effective in managing pain and hyperalgesia^[25], but there are severe limitations with regard to this mode of delivery.

In summary, cizolirtine may turn out to be the best tolerated and effective of available medications for primary hyperalgesia and allodynia: a further clinical trial with greater numbers of such cases is warranted. Cizolirtine also deserves investigation in other conditions where substance P-related mechanisms are involved, such as painful hypertrophic scars, inflammatory arthritis and urinary bladder pain^[11].

Tables

Table 1. Characteristics of 25 patients who completed the study, presented as the number or mean (range)

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Characteristic	Value
Gender (men/women)	13/12
Age (years)	49.5 (27-84)
Height (cm)	169.5 (141.12-186.25)
Weight (kg)	74.4 (50-99)
Clinical diagnosis:	Number of patients
primary skin allodynia with nerve injury	5
brachial plexus injury	5
major nerve trunk injury	9
radiculopathy	3
reflex sympathetic dystrophy	1
post-herpetic neuralgia	2
Concomitant medications:	Number of patients
opioid analgesics	8
tricyclic antidepressants	9
anticonvulsants	9
benzodiazepines	5
NSAIDs	14
muscle relaxants	2
others	22*

*Prescribed for secondary indications

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