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ORIGINAL COMMUNICATION

The DMKG study group*

Misoprostol in the treatment of trigeminal neuralgia associated with multiple sclerosis

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(The members of the study group contributing to this work are listed in the appendix.)

Abstract Multiple sclerosis can be associated with trigeminal neuralgia which is often difficult to treat in this specific condition. We performed an open prospective trial on the efficacy and safety of the prostaglandin-E_1-analogue misoprostol (600 µg per day) in the reduction of attack frequency and pain intensity in patients with refractory trigeminal neuralgia associated with multiple sclerosis. Eighteen patients completed the study period and 14 of them showed a reduction of more than 50 % in attack frequency and intensity beginning five days after treatment onset. There were only mild and transient drug related side effects in three patients. One patient stopped taking misoprostol after the study period because of severe menorrhagia. Our results suggest that misoprostol is effective and safe in the treatment of this specific type of refractory trigeminal neuralgia.

Key words trigeminal neuralgia · misoprostol · multiple sclerosis

Introduction

Trigeminal neuralgia is a rare although typical brainstem symptom of multiple sclerosis (MS) occurring in about 2 % of all MS patients [5]. On the other hand, about 2 % of all patients with trigeminal neuralgia have MS [6]. In most cases, the semiology of this type of trigeminal neuralgia cannot be differentiated from the idiopathic form of trigeminal neuralgia and the principles of treatment are similar for both types [16]. However, specific open trials on the treatment of symptomatic trigeminal neuralgia have been performed suggesting an efficacy of lamotrigine [9], gabapentin [8, 15], and topiramate [17].

The pathophysiology of trigeminal neuralgia associated with MS is not fully understood. It has been suggested that demyelinating plaques in the entry zones of the trigeminal roots are responsible for the lancinating pain by ephaptic conduction [3, 10]. Inhibition of T-cell functions by prostaglandins could be a mechanism to decrease their inflammatory activity in the plaques and thus could be a specific therapy of this type of trigeminal neuralgia [13].

Misoprostol is a prostaglandin-E_1-analogue substance which has been approved for the treatment of drug induced gastritis and duodenitis and of gastric and duodenal ulcer [1]. In 1995, misoprostol was investigated in the treatment of trigeminal neuralgia associated with multiple sclerosis [14]. These patients did not respond to the conventional therapy such as carbamazepine and other anticonvulsants or baclofen. In six out of seven patients, misoprostol showed a good efficacy with complete or nearly complete abortion of the lancinating pain. This study has been reproduced in a small case series with three patients [11]. In refractory chronic cluster headache, however, misoprostol was not effective [2].

Since drug alternatives for the treatment of refractory trigeminal neuralgia in MS are lacking but urgently needed, we designed an open multi-centre study on the efficacy of misoprostol in this specific condition. In particular for those patients, who do not respond to anticonvulsants, antidepressants, or baclofen, a reliable and

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safe drug alternative would be extremely helpful to improve their quality of life. Furthermore, the efficacy of a substance with prostaglandine-E_1-analogue pharmacological properties would give an interesting insight into the pathophysiology of trigeminal neuralgia in MS.

Methods

We enrolled 18 consecutive patients with a diagnosis of trigeminal neuralgia (diagnosis 12.2.1 or 12.2.2) according to the criteria of the International Headache Society (IHS) [4] and with probable or definite MS according to the criteria by Poser et al. [12]. The clinical and demographic features were recorded based on the patients' history.

We included only patients who did not respond to conventional treatment with at least one anticonvulsant drug in a usual dose (e. g. at least 1,200 mg carbamazepine) or who could not tolerate treatment with anticonvulsant drugs. Patients gave informed consent to participate in this study. They were treated with 3 x 200 µg misoprostol per day for 14 days and were asked to record the number of neuralgic attacks per day, the average pain intensity of these attacks per day (visual analogue scale from 1 [= very mild pain] to 10 [= most intense pain]), and all adverse events in a diary for the time period of 14 days. Then, the patients came back to the hospital and the diaries were analysed. Four weeks after treatment onset, the patients were contacted again and asked about their current state. We also analysed adverse events in relation to the study drug. Concomitant medication for the treatment of MS (e. g., interferon therapy) was allowed but had to be constant during the study period. Analgesic, anticonvulsant, and antidepressive therapy had also to be unchanged during the study period.

The primary efficacy measure was the reduction of the number of neuralgic attacks per day by more than 50 % (responders). We also calculated the average number of attacks and the average pain intensity per day for the total study period and the possibly or probably drug related adverse events.

Results

All patients completed the study period. The main demographic and clinical data of the patients are presented in Table 1. Most of the patients were female with the relapsing-remitting subtype of MS. The right trigeminal nerve was significantly more often affected than the left one. We did not observe any affection of the first branch, and most of the patients were affected in their second branch. In three patients, the second and the third branch were affected together (with the second branch being more painful). The previous drugs which had no effect on the trigeminal neuralgia were carbamazepine (12 cases), gabapentin (10 cases), amitriptyline (2 cases), oxcarbazepine (1 case), phenytoin (1 case), and sirdalud (1 case).

Table 2 shows the pain features of the patients before treatment onset and at day 14. In Fig. 1, the results of the diary analysis over the total study period are presented. The mean number of neuralgic attacks per day and the main intensity of pain continuously decreased during the first six days of the study period and then remained constant. At the end of the study period of two weeks, 14 patients (78 %) were responders as defined in the methods section; eight of them showed complete relief of pain. The decrease of the number of neuralgic attacks per day and of pain intensity compared between baseline and the last day of the study period was significant ($p < 0.001$ for both comparisons; Wilcoxon test). A sta-

Table 1 Demographic and clinical data of the patients participating in this study presented as arithmetic means with standard deviations (range in brackets) or as percentage

age (years)	50.3 ± 10.4 (34–70)
duration of MS (years)	12.2 ± 8.4 (1–27)
duration of trigeminal neuralgia (weeks)	66 ± 89 (1–300)
EDSS	4.2 ± 3.5 (0–9.5)
sex:	
male	5 (28 %)
female	13 (72 %)
type of MS:	
relapsing remitting	8 (44 %)
primary chronic progressive	3 (17 %)
secondary chronic progressive	5 (28 %)
undetermined	2 (11 %)
side of trigeminal neuralgia:	
right	12 (67 %)
left	6 (33 %)
most affected branch of trigeminal nerve:	
branch 1	–
branch 2	12 (67 %)
branch 3	6 (33 %)

Table 2 Pain features of the patients participating in this study before treatment onset (day 0) and on day 14. The data are presented as arithmetic mean with standard deviation (median and range in brackets). Statistical comparison by Wilcoxon-test

	day 0	day 14	significance
attacks per day	13.5 ± 7.5 (12; 3–30)	3.3 ± 5.6 (1; 0–10)	$p < 0.001$
pain intensity (VAS 1–10)	7.1 ± 2.1 (7; 3–10)	2.2 ± 3.0 (1; 0–10)	$p < 0.001$

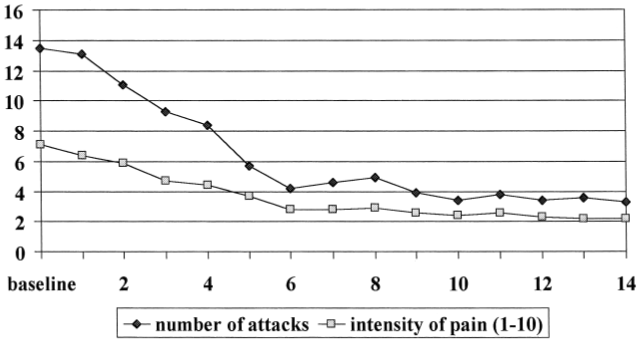

Fig. 1 Mean number of attacks per day and mean intensity of pain (on a visual analogue scale from 1 to 10) during a day for the study period from baseline to day 14. Both number and mean intensity of attacks is given on the y-axis.

tistical comparison between the responders and the nonresponders with respect to age, sex, duration of both MS and trigeminal neuralgia, and EDSS did not reveal any significant differences.

Four weeks after onset of treatment, eight patients (44 %) were still under misoprostol, five patients (28 %) discontinued the study medication because of inefficacy, and one patient (6 %) stopped the medication because of severe menorrhagia. In four patients (22 %), the trigeminal neuralgia had stopped spontaneously at that time.

In four patients, all from one centre and with complete relief of trigeminal neuralgia by misoprostol, we stopped the treatment for two weeks and then started it again. All these patients reported recurrence of trigeminal pain attacks after stopping the medication. The neuralgic attacks vanished after again starting the misoprostol medication.

In total, four patients complained of drug related side effects. These were diarrhoea and gastrointestinal discomfort in three cases and menorrhagia in two cases.

Discussion

The most important finding in our sample is that the majority of patients with refractory trigeminal neuralgia associated with MS showed a remarkable benefit from the treatment with misoprostol. We, thus, could confirm previously reported observations [11, 14] with our larger case series. Misoprostol can be regarded as an alternative drug if anticonvulsants are not effective or not tolerated. Unfortunately, we could not detect any factors predicting the therapeutic response of the patients.

The sample of our study shows the typical features of trigeminal neuralgia associated with MS such as predominance of the right side and of the second branch, higher frequency in older patients, occurrence about 12 years after onset of MS and more often in the relapsing types of MS [5–7]. Therefore, we believe that our sample is representative for the clinical phenomenon of trigeminal neuralgia in MS patients.

There were only mild and transient adverse events in the total sample. One patient, however, could not take misoprostol longer than the study period, although it gave her complete relief from the pain, because of menorrhagia. This is a typical and well known side effect of misoprostol [1].

We cannot conclude from our data what is the mechanism of action responsible for the efficacy of misoprostol. However, in experimental models of MS it has been shown that prostaglandins of different types are able to suppress the inflammatory activity, in particular of T-cells [13]. This might lead to a decrease of demyelination in the MS plaques and, thus, to a reduction of the ephaptic nerve conduction which is responsible for the pain in MS associated trigeminal neuralgia although the inflammation in the region of demyelination in the nerve root entry zone is very limited [10]. However, this hypothesis is very preliminary and the data of our study do not allow any further speculations.

There are some limitations in our study. First, we did not perform a placebo-controlled trial. The efficacy of misoprostol, however, was so remarkable in the majority of patients that we do not believe there could have been a placebo effect. Furthermore, in four patients we stopped misoprostol resulting in a new onset of neuralgic attacks; these attacks stopped again by another treatment with misoprostol. Second, we only included patients with refractory trigeminal neuralgia. We cannot draw conclusions from our trial about the efficacy of misoprostol in all patients with trigeminal neuralgia. Third, the observation period of two weeks with a follow-up after four weeks is too short for any conclusion on the long term efficacy. Anecdotally, five patients out of our sample are known to have been taking misoprostol for months with continuous benefit while two patients partly lost the benefit over a period of months.

In conclusion, our data suggest that treatment with misoprostol 600 μg per day is a treatment option in refractory trigeminal neuralgia associated with MS. It is safe and effective in the majority of patients but not in all.

Appendix

Members of the German Migraine and Headache Study Group who contributed to this study: Stefan Evers, MD, corresponding author (University of Münster, Germany); Stefanie Förderreuther, MD (University of Munich, Germany); Karsten Henkel, MD (University of Ulm, Germany); Andrea Kraft, MD (University of Halle, Germany); Martin Marziniak, MD (University of Würzburg, Germany); Arne May, MD (University of Regensburg, Germany); Erwin Kunesch, MD (University of Rostock, Germany); Rainer Jens Lüttmann, MD (University of Münster, Germany)

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