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Prophylactic treatment of episodic cluster headache with intravenous bolus of methylprednisolone

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Abstract We evaluated the efficacy of intravenous boluses of methylprednisolone followed by prednisone as a prophylactic treatment for episodic cluster headache. Fourteen male patients (mean age, 42.54 years) with episodic cluster headache were treated with 250-mg boluses of methylprednisolone on 3 consecutive days, followed by prednisone (90 mg/day orally) with gradual tapering in four weeks. Headache parameters of the active phases treated with methylprednisolone were compared with those of previous active phases in the same patients treated with other prophylactic medications. The primary efficacy criterion was decrease in the frequency of attacks during the first month of treatment. The statistical differences were calculated using Wilcoxon's test. The attacks were significantly less frequent in the active phases treated with methylprednisolone boluses than those treated with other medications ($p<0.05$). This treatment seems to be more effective than the usual prophylactic treatments for episodic cluster headache.

Key words Cluster headache • Steroids • Methylprednisolone • Prophylactic treatment

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Introduction

Cluster headache causes daily bouts of periocular pain of short duration but great intensity during the active phases. The preferred symptomatic treatment is sumatriptan administered subcutaneously, as this eliminates the pain in just a few minutes. However, when daily attacks of pain are frequent the tendency is to attempt their prevention. The ideal preventive treatment is still open to discussion, but one of the most frequently used is steroid therapy. Rationale for their use is their anti-inflammatory action, since it has been suggested that cluster headache is caused by an inflammatory process near the cavernous sinus [1], responsible for activation of the trigeminal vascular system [2].

Unfortunately, there is no generally accepted standard for the administration of steroids, even if the European Headache Federation has published consensus recommendations and guidelines [3]. On various occasions, we have administered prednisone orally at 80 mg/day for ten days, tapered down in 3 weeks; results were compared to those obtained with methysergide given at 6 mg/day [4]. The active phase was immediately stopped in only 2 of 50 cases, in spite of the late introduction of the treatment (on the twenty-third day on average). We later treated patients with episodic cluster headache with methylprednisolone (MP) or dexamethasone by either oral or parenteral route in higher doses, and obtained results similar to those of Cianchetti et al. [5], who suggested in a case report that the efficacy of steroids was greater when administered in high doses by parenteral route, even if this has never been demonstrated in a head to head comparison of prednisone and steroids.

To further investigate the prophylactic treatment of episodic cluster headache, we studied the efficacy of 250-mg boluses of methylprednisolone administered by intravenous route followed by a month course of prednisone by oral route.

Patients and methods

We studied 14 patients with diagnosis of cluster headache based on criteria of the International Headache Society (IHS) [6]. The patients were selected on the basis of fulfilling the following conditions: (1) data were available on previous cluster headaches treated with other prophylactic medication; and (2) they did not come under any of the exclusion criteria usually recommended in this type of study: addiction to substances, medications, drugs or alcohol, allergy to any of the components of the medication to be administered, current antidepressant or antipsychotic treatment, or neurological or general diseases that could interfere with steroid therapy. Patients gave informed consent to receive methylprednisolone after a full discussion of possible risk and benefits. We followed international guidelines regarding clinical research.

The patients had been instructed to register the date on which the active phase started. This was recorded together with the date of the visit and the date of administration of the first bolus, if these were not the same. On three consecutive days the patients received a daily bolus of 250 mg MP by intravenous route dissolved in 100 ml isotonic saline solution, together with a gastric protector. During the following ten days they were administered 90 mg prednisone per day by oral route, tapered down over four weeks.

The patients kept a diary recording the date of each episode of pain, the time at which the attack began, its duration in minutes (0–14 minutes, 1 point; 15–29 minutes, 2 points; and so on in 15-minute intervals) and its intensity (mild, 1 point; moderate, 2 points; severe, 3 points). This enabled the following data to be established: (1) date of the beginning of the active phase; (2) first day of treatment; (3) patients in which the attacks of pain had totally disappeared after the first bolus; (4) daily headache index, i.e. the mean of the sum of the frequency x duration x intensity of the daily attacks of pain after initiation of the prophylactic treatment; (5) headache index in the first month, i.e. the mean of the daily indexes since the start of treatment; and (6) number of headache days in the first month after treatment.

Data for each patient referred to one active phase treated with MP and another previous one treated with different prophylactic medications. Therefore, data were available for 14 active phases treated with MP and 14 other active phases treated with different prophylactic medications.

The results were assessed according to the efficacy criteria recommended by Lipton et al. [8]. The primary efficacy criterion was any decrease in the frequency of attacks during the first month after the beginning of the treatment, comparing the active phases treated with MP and the previous phases in the same patients treated with other prophylactic medications. Other efficacy criteria were: (1) percentage of patients completely free of pain after the first bolus of MP; (2) reduction of the frequency, duration and intensity of the attacks of pain, expressed by the monthly headache index; (3) reduction in the number of days with attacks after the third bolus of MP; and (4) duration of the active phase after beginning treatment.

Statistical differences in the comparative study between the active phases treated with boluses and the previous phases in the same patients treated with other prophylactic medications were calculated using a non-parametric test (Wilcoxon's test).

Results

All 14 patients included in this study were men (Table 1). The mean age at onset of cluster headache was about 25 years. The follow-up of the patients was on average about 7 years. The boluses were administered, on average, 17 years after the onset of the complaint.

In previous active phases, the patients had received different prophylactic treatments (Table 2). Frequently it consisted of 120 mg verapamil three times a day by oral route, with or without 1–4 mg ergotamine tartrate daily by rectal or oral route. Symptomatic treatment included the use of oxygen according to normal standards [7] and analgesics. The data referring to these active phases were collected in the same way as during treatment with steroids.

As a mean, there were no significant differences in the first day of treatment when using MP (21.86±10.79 days) or other prophylactic treatments (21.07±23.36 days) (Table 3). The patients treated with MP had a mean of about 6 days with pain during the month following initiation of the treatment, whereas the active phases treated with other medica-

Table 1 Characteristics of the 14 male patients with cluster headache. Values are mean (SD)

Age at onset on cluster headache, years	25.08	(11.39)
Age at the date of administration of the first bolus of methylprednisolone, years	42.54	(10.05)
Follow-up period	7.07	(4.92)

Table 2 Prophylactic treatments used in the active phases prior to the one treated with high doses of methylprednisolone

	Patient													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Verapamil	X	X		X			X		X					X
Ergotamine	X	X	X		X	X	X	X	X				X	
Lithium										X	X			
Nimodipine	X		X								X			
Indomethacin				X										
Prednisone						X						X		
Methysergide					X									

Table 3 Headache parameters during active phase in 14 male patients with cluster headache, according to type of prophylactic treatment

	Methylprednisolone[a]				Other medications[b]			
	Mean (SD)		Median (IRQ)		Mean (SD)		Median (IRQ)	
Start of treatment (day of the active phase)	21.86	(10.79)	22.50	(11.75–28.50)	21.07	(23.36)	10.50	(7.00–26.75)
Remission of the pain (days after the bolus)*	9.86	(14.26)	7.00	(0–12.50)	38.79	(41.66)	26.50	(12.50–41.75)
Days with pain[c]*	5.86	(7.78)	4.00	(0–7.25)	15.29	(10.07)	12.50	(7.75–28.50)
Headache index[c]*	32.57	(43.16)	8.00	(0–54.00)	325.36	(656.02)	92.00	(44.00–339.00)

IRQ, interquartile range

[a] 250 mg intravenous boluses on 3 consecutive days; [b] retrospective data; [c] during the first month of treatment

*$p<0.05$ methylprednisolone vs. other medications; Wilcoxon's test

tions had almost three times more days with pain ($p<0.05$). The monthly headache index was ten times lower for the active phases treated with MP ($p<0.05$). Equally, the active phases extended, on average, for about ten days after treatment with MP, whereas the active phases treated using other medications lasted four times longer ($p<0.05$). The attacks of pain completely disappeared after treatment with MP in almost one-third of the patients, but this did not occur in any of the active phases under other treatments (data not shown).

Two patients treated with MP mentioned digestive upsets; one patient reported acne and another insomnia. These slight adverse effects were well tolerated.

Discussion

The standard treatment for cluster headache is subcutaneous administration of sumatriptan, but in order to prevent recurrent attacks several drugs are used. This variability is related to the lack of a medication that is clearly more effective than the others; perhaps this is the reason why there are wide differences in the recommendations concerning prophylactic treatment for cluster headache [9–13].

Steroids are frequently used in daily clinical practice for the prevention of cluster headache pain attacks: a recent survey showed that a steroid drug was used by one-third of all patients [14]. Such a widespread use is better supported by clinical experience [3] because there are few clinical trials [9] in which the efficacy of steroids has only been investigated in simple, open studies [4, 14–22]. Admittedly, the results obtained in a double-blind, placebo-controlled study would be more scientific and easier to interpret. However, we agree with the opinion of Krabbe and Steiner [3] who consider unacceptable a long-lasting trial with placebo in episodic cluster headache with severe and frequent pains; in fact, we are not sure if a placebo-controlled study would have been, ethical or necessary in this particular situation, because our patients had several daily bouts of excruciating pain. It was also questionable to carry out an active-controlled study in this situation, as we knew that other prophylactic strategies were not clearly successful in our patients during the seven-year period (as a mean) of follow-up.

The type of steroid used, route of administration, daily dose, and duration of treatment have all been extremely variable in these studies [4, 14–22]. Therefore, it is not surprising that there is no generally accepted consensus for their administration. Sometimes the steroid by oral route seems to have a positive effect, but on other occasions it is apparently not effective or its efficacy disappears upon reducing the dose so that the bouts reappear in 80% of the patients when tapering off the treatment [17]. In our daily clinical experience and in agreement with other authors [5, 21], the higher the priming dose and the longer the period during which the steroid treatment is maintained, the greater the probability that the treatment will be effective, especially if high doses of dexamethasone or methylprednisolone are used by parenteral route [5]. Nevertheless, there is no head to head trial of oral prednisone vs. intravenous steroids that proves this hypothesis.

The first objective of any prophylactic treatment is to immediately abort the active phase, which seems to be extremely difficult in episodic cluster headache. In this sense, immediate and complete remission followed MP therapy in one-third of our patients. It is important to point out that MP boluses were started on the twenty-first day of the active phase as a mean. One could argue that the remission of the active phase after the administration of MP is related to the late introduction of the treatment. However, the absence of any remissions of the previous active phases treated with other medications (also introduced in our patients on the twenty-first day of previous cluster periods) goes against this opinion. Further proof of just how difficult it is to obtain an immediate interruption of the active phase is given by the results obtained in a previous open study by our group [4]: the only immediate remissions occurred in 4 of 50 active phases treated with either 6 mg methysergide or 80 mg prednisone by oral route. Undoubtedly the results obtained with MP plus oral prednisone should be considered acceptable for a complaint like cluster headache for which it is so difficult to achieve prophylactic treatment.

If the active phase does not disappear, other objectives should be sought after such as reducing and decreasing the frequency, intensity and duration of the attacks. In daily clinical practice it is usually difficult to be sure of reaching these objectives, since there is such a vast interindividual and intraindividual variability in the duration and in other characteristics of the active phases. However, in spite of these difficulties, data from our study support the fact that MP is highly effective in blocking this complaint. For example, the number of days with bouts of pain during the month immediately following initiation of treatment, which was our primary efficacy criterion, was much lower for the active phases treated with MP than with other prophylactic treatments. In the same way, the headache index was significantly lower and there were far fewer attacks during the month following the introduction of treatment with MP. It is interesting to highlight some of these figures: patients treated with MP had only about 6 days of pain during the following month and the active phases lasted about 10 days. This means that the total mean duration of the active phase treated with MP (days without treatment + days with treatment) was one month; this low figure contrasts with the mean duration of about two months in the previous active phases of these patients when they were treated using other prophylactic medications.

MP boluses were administered to rapidly stop the cluster period while prednisone was given to maintain the response once the remission was achieved. Accordingly, it is impossible to decide if the efficacy of the therapy at one month is due only to the effect of MP or to both medications: a study with a different design is needed to answer this question. Moreover, it would be advisable to clarify the best dose of MP as well as the number of days in which it is administered, since it is possible that the use of higher doses for shorter periods might be as effective as the regime used in this study. Further studies comparing different doses and treatment durations are required to address this question. In conclusion, the use of intravenous boluses of methylprednisolone seems to be more effective than the usual prophylactic treatments used in episodic cluster headache, although further studies are needed to find the most effective dose and treatment schedule.

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