Single high-dose steroid treatment in episodic cluster headache

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Corticosteroids appear to be the most rapid-acting of the prophylactic drugs used in the treatment of cluster headache (CH). These agents are frequently employed as a short-term regimen to induce clinical remission. In this study, we assessed in an open fashion the effect of high dose methylprednisolone (MPD) in a group of 13 patients with episodic CH (3 females and 10 males). On the 8th day of the active period, MPD was administered intravenously at the dose of 30 mg/kg body weight, as a 3-h infusion in saline. The attack frequency was followed for 7 days. The mean daily attack frequency before MPD administration was statistically different from that reported after treatment (respectively: 1.38 ± 0.42 and 0.83 ± 0.78; P = 0.05 Student’s t-test). The mean interval between MPD administration and the occurrence of the first subsequent attack was 3.8 ± 2.2 days (range: 2–7 days). Only 3 (23%) of 13 patients experienced a complete headache remission. No significant side-effects were noted after MPD administration. These data further demonstrate that in most patients with episodic CH, high-dose systemic steroid administration may invariably interrupt attack recurrence for a few days, but is ineffective in maintaining complete clinical remission. This study also suggests that MPD administered as a solitary dose does not provide any advantage above prednisone in CH treatment. □Cluster headache, steroid therapy, symptomatic treatment, transitional prophylaxis

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Introduction

Several drugs are commonly used in the short-lasting prophylactic treatment of episodic cluster headache (CH). The main aim of such an approach is to obtain a prompt interruption of the series of pain attacks. If this is not achieved, one can at least obtain a decrease in frequency, duration, and intensity of CH attacks. A secondary aim is to maintain remission for a period longer than that expected in the absence of treatment.

Among the prophylactic agents used in CH, corticosteroids, such as prednisone and dexamethasone, are the most rapid-acting ones (1). Due to their rapid setting-in efficacy and their potency, they are generally most useful during the time necessary for other prophylactic drugs to be started and become effective. There is clinical evidence at hand concerning the effectiveness of corticosteroids in CH, even though it mostly derives from studies performed according to uncontrolled experimental designs. The largest series (n = 77) is that by Kudrow (1), that showed that 60 mg prednisone was completely effective in inducing a persistent remission, in 77% and partially effective in another 12% of episodic CH patients. This efficacy appears to be strictly dose-dependent. Dexamethasone, at the dose of 4 mg b.i.d. for two weeks followed by 4 mg/day for one week, has also been shown to be beneficial (2).

Recently, a treatment with methylprednisolone (MPD) i.v. followed by prednisone orally has been
reported to be more effective than the usual prophylactic treatment (3).

Uncertainty exists as to the effectiveness of steroids in inducing a stable clinical remission. Several observations (4–6) as well as scattered clinical experience suggest that once the doses of dexamethasone or prednisone are tapered, pain attacks almost invariably tend to recur, and additional therapy must be given. This tendency probably depends upon dosage and duration of therapy (4). On the other hand, a steroid treatment course extended beyond a three week period may not be well tolerated by all patients.

Over the past years, it has become widely accepted that the use of high-dose steroids, such as MPD 0.5–1 g/day intravenously for a period of 3–10 days, is effective in various neurological diseases (i.e. demyelinating diseases, such as multiple sclerosis) and other immune disorders. In these cases, steroids have generally been found to be well tolerated, more effective than when administered at lower doses for longer periods, and devoid of major adverse effects. With this in mind, a study with a different design was carried out by Cianchetti et al. (7), who placed a single CH patient on a regimen of repeated administration of MPD 0.5–1 g/day i.v., and found a beneficial effect, lasting 4–5 days on each occasion.

The aim of the present study was therefore to evaluate in a sizeable group of episodic CH the effectiveness of a single, high-dose, parenteral steroid administration in inducing and maintaining a relative long clinical remission.

Materials and methods

Patients

The study group consisted of 13 patients, 3 females and 10 males, aged 48 ± 10 years (mean ± SD), with CH in active phase; the patients were enrolled consecutively. CH was diagnosed according to the International Headache Society (IHS) criteria (8). The study was carried out at an outpatient clinic basis. Patients were not suffering from uncontrolled hypertension, diabetes, peptic ulcer or diabetes mellitus. After obtaining informed consent from all patients, a complete clinical history was taken before the actual bout. Patients were instructed to record attacks using a dedicated headache diary, starting from day one of a new cluster period, and then to contact investigators and appear at the out-patient clinic on day eight. After the seven day run-in period, the steroid was invariably administered on day eight. At the end of the day of drug administration, the patients were dismissed and instructed to continue to fill in the headache diary and to contact medical personnel in case of recurrence, or in any case after 3–5 weeks, to report on the state of their headache.

The frequency of the pain attacks, the cluster period duration, as well as other individual, clinical features of the patients studied are reported in detail in Table 1. At the time of testing, patients were having regular headache attacks, and none of them had taken any prophylactic medication since the beginning of the period. For ethical reasons, patients were allowed to use sumatriptan 6 mg s.c. as acute treatment whenever required, both in the run-in period and for breakthrough attacks during the study. In case of headache recurrence after MPD, the patients would be given prophylactic treatment within two days of recurrence of attacks.

Procedures

A scheme of the study design is shown in Fig. 1. Before MPD administration, routine blood tests and ECG were taken. The treatment was always carried

### Table 1 Clinical features (of CH patients) before and after methylprednisolone (MPD) infusion. Values are expressed as mean ± SD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before MPD</th>
<th>After MPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster period duration in all patients (days) (n = 13)†</td>
<td>35 ± 12</td>
<td>27 ± 19</td>
</tr>
<tr>
<td>Cluster period duration in patients with recurrence after MPD (days) (n = 10) † §</td>
<td>36 ± 12</td>
<td>35 ± 13</td>
</tr>
<tr>
<td>Attack frequency/24 h in all patients (n = 13)</td>
<td>1.38 ± 0.42</td>
<td>0.83 ± 0.78*</td>
</tr>
<tr>
<td>(range)</td>
<td>(1–3)</td>
<td>(0–4)</td>
</tr>
<tr>
<td>Attack frequency/24 h in patients with recurrence after MPD (n = 10) § (range)</td>
<td>1.46 ± 0.46</td>
<td>1.08 ± 0.72</td>
</tr>
<tr>
<td>(1–3)</td>
<td>(0–4)</td>
<td></td>
</tr>
<tr>
<td>Interval between MPD administration and first subsequent attack (n = 10) (days and range)</td>
<td>–</td>
<td>3.8 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>(2–7)</td>
<td></td>
</tr>
</tbody>
</table>

*P = 0.05 vs. prior to MPD (Student’s t-test); † present vs. latest cluster period; § same group of patients.
out on the 8th day of the active phase. MPD 30 mg/kg body weight in 500 ml saline, was administered as a 3-h infusion, starting at 9.00 a.m.

In order to assess the MPD response, the following parameters were evaluated (1): the mean daily attack frequency over 7 consecutive days prior to MPD and during the 7 days following treatment (2); the mean interval and range between MPD and the occurrence of the first, subsequent attack.

The mean daily attack frequency during the observation period in patients with headache recurrence after MPD is shown in Fig. 2.

**Statistical analysis**

Normal distribution of clinical data was found with the Kolmogorov-Smirnov test. For the comparison of attack parameters before and after MPD treatment, statistical analysis was carried out, using paired t-test, the only exception being when comparing pain free days, in which case the Wilcoxon test was used. Differences were considered significant if $P < 0.05$. Data are expressed as mean ± SD.

**Results**

No major side-effects were noted after MPD administration. In all cases, attacks were discontinued after MPD and did not reappear for two or more days. The mean duration of the previous cluster period in each of our patients was found to be $36 ± 12$ days (based on their diary cards), while the mean duration of the actual period, with MPD, was $27 ± 19$ days. As shown in Table 1, there was a significant difference between the mean frequency of daily attacks during the 7 days preceding MPD administration and the 7-day period following treatment ($n = 13$; $1.38 ± 0.42$ and $0.83 ± 0.78$, respectively; $P = 0.05$ Student’s t-test). However, there was no significant difference when considering only patients with recurrence of attacks after MPD ($n = 10$; $1.46 ± 0.46$ and $1.08 ± 0.72$, respectively; $P = 0.23$ Student’s t-test). The total number of attacks was 126 ($n = 102$ if patients with no recurrence were excluded) before and 76 after MPD. CH attacks did not occur during the infusion, with the exception of one patient who experienced typical signs and symptoms 1.5 h after the beginning of the infusion. The mean number of pain-free days before MPD was $0.2 ± 0.4$, while after MPD it was $3.9 ± 2.2$ ($P < 0.005$, Wilcoxon test).

The mean interval between MPD administration and the occurrence of the first subsequent attack was
3.8 ± 2.2 days (range: 2–7 days) (Fig. 2). These results concern 10 cases, since 3 of the 13 patients (23%) did not experience any attack recurrence after MPD treatment. The clinical features (i.e. headache frequency, period duration, etc.) in two of the patients did not show peculiar aspects when compared to those of the patients with a recurrence after MPD. However, one patient without recurrence had a previous period duration of two weeks. Three patients with attack recurrence 7 days after MPD injection were followed up to 10 days to ascertain the temporal pattern. The recurrence of attacks after MPD is reported in Fig. 3.

Discussion

The beginning of the active period is likely to be the most suitable period for evaluating the efficacy of a given drug in CH. Indeed, the chances of a spontaneous recovery increase with the advancement of the bout, so that in the medium-late phase of the CH period the observations made on the effects of a given agent become unreliable. Accordingly, in our study we chose the very onset of a cluster period (from day 8 onwards) to test the effect of MPD in a selected group of patients with a well-established headache pattern. By using the experimental design described above, it would conceivably be possible to reach a clear-cut conclusion on any protective effect of parenteral MPD and on the temporal aspects.

In our study, 77% of CH patients (10 out of 13, in the active phase) showed a stereotyped response, i.e. cessation of attacks for 2 or more days following the treatment. The mean duration of the pain-free period was of the same order of magnitude as that observed by others in a previous study (7). However, the spectrum of the response was much wider when more patients were included. In addition, the patients with no recurrence did not show peculiar features of their headache.

Prednisone and 6-alpha-methylprednisolone, at variance with betamethasone and dexamethasone, have similar anti-inflammatory potency, Na⁺ retaining effects and duration of action (intermediate, i.e. 12–36 h of biological half-life), and act at equivalent doses (9). The different action may thus be partly explained by the peculiar regulation of gene expression exerted by these agents (10). There is no currently accepted standard for the administration of steroids in CH, although consensus recommendations and guidelines have been published (11).

According to current literature, and as far as effectiveness alone is concerned, prednisone can be considered as a first-line drug in episodic CH. This drug may be particularly helpful in those patients who, on the basis of previous experience, are expected to have a bout duration of no longer than 3–5 weeks at the time of initiation of the treatment. However, similar to what is commonly observable with indomethacin in chronic paroxysmal hemicrania (CPH) (12, 13), the disease process is only curbed, not extinguished, by steroids in CH.

To our knowledge, only one controlled trial (using prednisone) has so far been carried out (see Table 2 for the main previous studies). As in most other studies, the present one was carried out without a placebo control, but with each patient acting as his own control. In future studies comparisons with a control group could be carried out. Indeed, previous reviews on this subject suggest that there may be a placebo effect in CH (14, 15).

The aim of the present study was to elucidate whether a single, high-dose MPD treatment as monotherapy is able to maintain a stable clinical remission in episodic CH, preventing the patients from further pain episodes. In line with the findings obtained by Cianchetti et al. (7) in a single case, a relatively clear-cut response was obtained, which confirmed the short-term efficacy MPD, but also clearly demonstrate that there is a tendency to recurrence of attacks in the majority of patients.

Had MPD been effective in an absolute fashion, complete disappearance of attacks would have occurred: in fact, this was the case only in 23% of patients. The three patients with no further attacks may have experienced a spontaneous recovery: the previous active period in these patients had lasted 40, 55, and 14 days, respectively. In most of our patients, attack recurrence was reported after a short pain-free period (mean 3.8 days). On recurrence, the pattern of attack frequency was similar to that reported in the run-in period. The long-lasting benefit from a single bolus of MPD in interrupting the bout might be coincidental. In
clinical practice we are aware that in particular experimental circumstances (i.e. sleep recording in the hospital, clock-time rhythmicity of attacks, etc.) the regular pattern of attack may change or stop.

A recent report showed that 250 mg boluses of MPD on three consecutive days, followed by prednisone 90 mg/day orally, with gradual tapering in 4 weeks, induced a significant reduction of attack frequency in episodic CH for several weeks. However, these findings cannot be compared to our own results due to the different study design (type of drugs, doses, mode of administration). The drug was, moreover, introduced at different stages of the cluster period (mean 21.8 days after cluster onset) in the other study (3).

In agreement with previous studies, our data confirm that patients with episodic CH single, high-dose systemic steroid administration may invariably interrupt attack recurrence for a few days, but MPD is ineffective in maintaining complete clinical remission.

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References