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# Pharmacological Study in Meige's Syndrome with Predominant Blepharospasm

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**Summary:** Objective quantification of the symptoms of Meige's syndrome is difficult and has not been performed in the majority of pharmacological studies of Meige's syndrome published so far. The aim of the present study was to reexamine the therapeutic potential of biperiden, clonazepam, haloperidol, and lisuride using an objective method of quantification of the symptoms. Eleven patients received daily i.v. injections of biperiden, 5.0 mg; clonazepam, 1.0 mg; haloperidol, 2.5 mg; lisuride, 0.05 mg; and placebo in randomized order. The symptoms of the patients [idiopathic blepharospasm (IB), in 11 patients, oromandibular dystonia (OMD) in four patients] were quantified by a blind observer counting the frequencies and recording the cumulative duration of sustained spasms of IB and OMD over periods of 4 min before, and 15, 30, 60, 90, and 120 min after the i.v. challenges. Baseline quantification of IB and OMD was performed at identical intervals on randomized days of the trial. Significant improvement of the IB scores was found in response to biperiden and clonazepam and a trend toward improvement in response to lisuride (Wilcoxon test). Evaluation of the individual IB scores of each patient following the various drug challenges failed to predict the therapeutic potential of these drugs for subsequent oral treatment. Key Words: Meige's syndrome—Idiopathic blepharospasm—Symptoms, quantification—Pharmacology.

The pathogenesis of Meige's syndrome—idiopathic blepharospasm (IB) and oromandibular dystonia (OMD)—is unknown. No common neuropathological substrate has so far been identified (1,2). It has been shown that brainstem lesions (3,4) and hydrocephalus (5) may sometimes underlie Meige's syndrome. Despite a large number of studies testing the effects of substances with known influence on the dopaminergic (1,2,4,6–19,22,23), cholinergic (2–4,6–12,18–22), and

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GABA-ergic system (1–3,4,11,18,21–23), the pharmacology underlying this condition is unclear. One of the problems in drug trials of Meige's syndrome lies in the tendency of the symptoms to show spontaneous fluctuations. Another problem is the difficulty of quantifying IB and OMD.

In the present study a number of drugs previously shown to be effective in Meige's syndrome were reexamined using an objective method of quantification of the symptoms in a double-blind placebo-controlled single-dose challenge design. Furthermore, we examined the value of the single-dose challenges in predicting the therapeutic potential of subsequent chronic oral treatment with these substances.

## PATIENTS AND METHODS

Eleven Meige patients gave their informed consent to participate in the study (for characteristics and data, see Table 1). None of the patients had been treated with neuroleptic agents before the onset of Meige's syndrome. In six patients tremor was present, which was classified as essential tremor. In one female patient essential myoclonus was diagnosed. The myoclonus was also verified in one grandson (the son of one son) and was reported to exist in four grandsons (the sons of two other sons). Family history of tremor was positive in one patient.

TABLE 1. *Patient characteristics and data*

| |
|---|
| Five men, six women |
| Age 50–78 years, mean 62.0 ± 8.7 years |
| Disease duration 1–27 years, mean 5.7 ± 7.2 years |
| Previous treatment of Meige's syndrome: five patients |
| Family history of dystonia: negative in all patients |
| Two patients: blepharospasm only |
| Nine patients: blepharospasm plus oromandibular dystonia (with the blepharospasm predominating) |
| Concomitant symptoms: |
| Essential tremor |
| Without family history of tremor: five patients[a] |
| With family history of tremor: one patient[b] |
| Spasmodic torticollis: two patients |
| Essential myoclonus with positive family history: one patient |
| Severity of Meige's syndrome: according to Tolosa and Lai (7) |
| Grade 2: one patient |
| Grade 3: four patients |
| Grade 4: two patients |
| Grade 5: two patients |
| Grade 6: one patient |
| Grade 8: one patient |
| CT scan |
| Normal in six patients |
| Diffuse cortical atrophy in two patients |
| Arteriosclerotic encephalopathy in one patient |

[a] Mean age 60.6 ± 6.7 years.
[b] Age 56 years.

Previous therapy was discontinued 2 weeks before the onset of the study. Each patient received single daily intravenous injections of each of biperiden, 5.0 mg; haloperidol, 2.5 mg; clonazepam, 1.0 mg; lisuride, 0.05 mg; placebo (saline 0.9%), 2 ml, in a randomized order on consecutive days. On one randomized day of the trial a baseline measurement of the symptoms was performed without injection of a drug or placebo. Due to their long half-lives, haloperidol and clonazepam injections were followed by a drug-free period of at least 48 h. The patients received their injections on each trial day at a constant time between 8 and 10 a.m. The symptoms of Meige's syndrome were quantified before ($t_0$) and 15 ($t_{15}$), 30 ($t_{30}$), 60 ($t_{60}$), 90 ($t_{90}$), and 120 ($t_{120}$) min after the challenges. On the baseline days the measurements were performed at identical intervals. At each measurement point ($t_0$ through $t_{120}$), a blind observer counted the frequency of IB and recorded the cumulative duration of sustained periocular spasms over an observation period of 4 min. In four patients OMD was measured in the same way following the IB measurement. In the remaining five patients with OMD the expression of OMD was so mild that a measurement of this symptom was not performed. The cumulative duration of sustained IB/OMD in seconds was added to the frequency of IB/OMD to arrive at an IB and an OMD score.

For statistical evaluation of IB, the mean ranks of the $t_0$ − IB scores were compared with those of the consecutive scores (Wilcoxon matched pairs signed-rank test). To avoid multiple comparisons between $t_0$ and the other scores, the means of the $t_{15} + t_{30}$ − IB scores (phase 1) as well as of the $t_{60} + t_{90} + t_{120}$ − IB scores (phase 2) were calculated and their mean ranks compared with those of the $t_0$ − IB scores. Since OMD was measured in only four patients it was not statistically evaluated.

In addition to statistical evaluation of the group response of IB we also evaluated each individual patient's IB and OMD scores following the various challenges. The IB and OMD scores were classified as improved in response to a substance when the sum of the mean of the $t_{15}$ through $t_{120}$ scores plus the single standard deviation of the $t_{15}$ through $t_{120}$ scores was less than the $t_0$ score of that day and also less than the mean of all six $t_0$ scores of the patient minus the single standard deviation of the six $t_0$ measurements. The IB and OMD scores were classified as deteriorated in response to a substance when the mean of the $t_{15}$ through $t_{120}$ scores minus the single standard deviation of the $t_{15}$ through $t_{120}$ scores was larger than the $t_0$ score of that day and also larger than the sum of the mean of all six $t_0$ scores of the patient plus the single standard deviation of the six $t_0$ scores.

After the acute challenges, each patient received that substance for oral therapy to which he or she had shown the best response in the i.v. trial. The doses of oral therapy were slowly built up until either improvement was observed or intolerable side effects occurred. During chronic oral treatment, the patients and their spouses were interviewed by means of a semistandardized questionnaire assessing subjective improvement and improvement in activities of daily living. Furthermore, patients were asked if they wanted to continue the treatment.

## RESULTS

Analysis of the IB scores obtained on the placebo and the baseline days and of all $t_0$ – IB scores revealed marked fluctuations of the severity of IB in the individual patients (Table 2). In general the IB scores fluctuated less during one day than from day to day. The amplitudes of the fluctuations (expressed by the single standard deviations from the mean scores) did not correlate with the severity of the symptoms (expressed by the mean scores). The intravenous application of an effective substance such as biperiden and placebo (see below), however, led to an attenuation of the fluctuations (decrease of the standard deviation of the IB scores) in parallel with an improvement of the mean IB score. In response to biperiden IB scores improved significantly in phase one (two-tailed $p = 0.001$) and phase two (two-tailed $p = 0.002$, Wilcoxon matched pairs signed-rank test) (Table 3).

In nine patients clonazepam produced significant improvement in phase 1 and a trend toward improvement in phase 2 (two-tailed $p = 0.014$ and 0.06, respectively). Two patients were excluded from statistical analysis because of improvement of IB score due to marked sedation following clonazepam.

A severe orthostatic collapse occurred in one patient in response to lisuride. Therefore, we did not administer lisuride to two patients who had cardiomyopathy. In the remaining nine patients a trend toward improvement of IB score was observed (two-tailed $p = 0.09$).

Haloperidol and placebo did not produce a significant change in the IB scores. A significant deterioration of IB score was noted, however, in both phases 1 and 2 on the baseline days (two-tailed $p = 0.003$ and 0.001, respectively).

Side effects of the intravenous challenges are summarized in Table 4. No correlation was found between age and the occurrence of side effects. The effects of the intravenously administered substances on IB and OMD of each patient were as follows: In one patient, IB score improved significantly in response to biperiden (patient 10), and in another one to lisuride (patient 11). One patient showed

TABLE 2. *Blepharospasm scores of the patients in the study*

| Patient no. | A | B | C | D |
|---|---|---|---|---|
| 1 | 69.0 ± 47.0 | 42.4 ± 57.2 | 22.4 ± 14.9 | 121.2 ± 70.8 |
| 2 | 72.4 ± 27.8 | 112.0 ± 37.8 | 112.2 ± 13.6 | 128.8 ± 26.6 |
| 3 | 102.8 ± 33.8 | 114.6 ± 79.2 | 120.4 ± 37.0 | 7.2 ± 4.9 |
| 4 | 90.0 ± 14.8 | 38.4 ± 36.2 | 72.8 ± 12.3 | 50.8 ± 9.2 |
| 5 | 68.0 ± 17.0 | 153.0 ± 45.8 | 118.0 ± 18.2 | 125.8 ± 16.2 |
| 6 | 170.0 ± 18.6 | 140.8 ± 64.8 | 112.4 ± 14.4 | 162.8 ± 16.1 |
| 7 | 57.0 ± 20.8 | 71.2 ± 17.0 | 42.0 ± 14.8 | 48.8 ± 6.3 |
| 8 | 177.0 ± 88.2 | 183.0 ± 102.6 | 222.8 ± 22.5 | 138.4 ± 71.2 |
| 9 | 143.4 ± 23.8 | 122.0 ± 36.4 | 19.4 ± 9.6 | 125.2 ± 17.0 |
| 10 | 114.6 ± 23.6 | 80.2 ± 25.4 | 21.2 ± 3.7 | 77.2 ± 9.0 |
| 11 | 264.0 ± 27.8 | 225.6 ± 50.4 | 181.2 ± 8.3 | 259.2 ± 6.8 |

Mean scores plus single standard deviations of the $t_0$ through $t_{120}$ measurements of the baseline days (A), the $t_0$ measurements of all six trial days (B), the $t_{15}$ through $t_{120}$ measurements of the biperiden (C), and the placebo days (D).

**TABLE 3.** *Results of the acute drug challenges, the placebo injections, and the baseline measurements of blepharospasm*

| | Mean IB scores $t_0$ | Mean IB scores $\frac{t_{15} + t_{30}}{2}$ (Phase 1) | Two-tailed p | Mean IB scores $\frac{t_{60} + t_{90} + t_{120}}{3}$ (Phase 2) | Two-tailed p |
|---|---|---|---|---|---|
| Baseline days (N = 11) | 85.6 | 125.6 | 0.003 | 130.0 | 0.001 |
| Placebo days (N = 11) | 104.8 | 112.6 | NS | 115.6 | NS |
| Biperiden (N = 11) (5.0 mg i.v.) | 123.0 | 90.4 | 0.001 | 100.6 | 0.002 |
| Clonazepam (N = 9) (1.0 mg i.v.) | 138.4 | 110.0 | 0.014 | 121.8 | NS (p = 0.06) |
| Haloperidol (N = 11) (2.5 mg i.v.) | 123.0 | 124.0 | NS | 150.2 | NS (p = 0.17) |
| Lisuride (N = 9) (0.05 mg i.v.) | 136.6 | 133.0 | NS | 110.2 | NS (p = 0.09) |

Comparison of the $t_0$ – IB scores with the IB scores of phase 1 and 2 by means of the Wilcoxon matched pairs signed-ranks test.

IB, idiopathic blepharospasm; NS, not significant.

deterioration of IB score in response to haloperidol (patient 6). One patient had an improvement of IB score in response to biperiden and clonazepam (patient 9), and one patient to clonazepam and placebo (patient 3). In one patient deterioration of the IB score was noted on the baseline day (patient 4). In one patient OMD score improved following haloperidol (patient 1). However, the patient experienced marked sedation in response to this substance.

In the remaining patients neither improvement nor deterioration of IB and OMD scores was observed after intravenously administered substances.

The outcome of the oral treatment of the patients subsequent to the intravenous challenges is summarized in Table 5. Because IB was the predominant symptom in all patients with OMD, oral therapy aimed also in these patients at an improvement of IB scores.

## DISCUSSION

In the acute trial a significant improvement of IB scores was observed in response to biperiden (Table 3). Sedation occurred in three patients only in a mild form; in one of these three patients IB score improved in response to intravenous biperiden. It is, therefore, likely that the improvement in IB score was not due to sedation but to the anticholinergic effect of biperiden. In accordance with previous studies our findings suggest a cholinergic preponderance in Meige's syndrome (2–4,7–12,18–22).

**TABLE 4.** *Side effects of the intravenous drug challenges*

| Drug (patients) | | No. of patients | Total no. of patients with side effects |
|---|---|---|---|
| Biperiden (11) | Lightheadedness | 2 | |
| | Dryness of the mouth | 4 | |
| | Nausea | 2 | |
| | Mild sedation | 3 | |
| | Cognitive impairment | 1 | 9 |
| Clonazepam (11) | Marked sedation | 2 | |
| | Moderate sedation | 3 | |
| | Lightheadedness | 3 | 8 |
| Haloperidol (11) | Moderate sedation | 3 | |
| | Lightheadedness | 2 | |
| | Deterioration of idiopathic blepharospasm | 1 | |
| | Acute generalized dystonia | 1 | 5 |
| Lisuride (9) | Mild sedation | 2 | |
| | Orthostatic collapse | 1 | |
| | Orthostatic hypotension | 2 | |
| | Nausea | 1 | |
| | Hyperhydrosis | 2 | 6 |

In the acute trial a significant improvement of IB scores was also observed in response to clonazepam (Table 3), which is in accordance with the findings of other authors (3,4,21,22). The IB scores of two patients showing marked sedation in response to clonazepam were not included in the statistical evaluation, since the improvement of IB scores in these patients was probably due to sedation and not to a specific GABAergic effect. In three additional patients moderate sedation occurred following clonazepam. Two of these patients showed a moderate attenuation of IB. Therefore, it is uncertain whether the significant improvement of IB scores in the evaluated nine patients was mainly due to the GABAergic effect of clonazepam or due to the sedative properties of the substance.

A clear trend toward improvement of IB was noted in response to lisuride (Table 3). The drug has been found to be effective in Meige's syndrome in several previous studies (12,13,15–17). Evaluation of the individual IB scores revealed a remarkable improvement of IB without sedation in one patient following intravenous lisuride. Two patients experienced mild sedation without improvement of the symptoms. It is, therefore, likely that the relief of IB was due to the specific dopaminergic and/or serotoninergic properties of lisuride and not due to an unspecific sedative effect of the drug.

The intravenous application of haloperidol did not improve IB (Table 3). There was even a trend toward deterioration observed. Analysis of the individual IB and OMD scores revealed an increase of IB in one patient and an attenuation of OMD in another patient reporting moderate sedation. One patient developed an acute generalized dystonia in response to intravenous haloperidol.

In several previous studies haloperidol was found to be effective in the treatment of Meige's syndrome (7–12). However, there are also reports on patients with Meige's syndrome not responding to treatment with haloperidol

**TABLE 5.** *Chronic oral treatment—substances, dosages, duration and outcome of treatment, side effects*

| Drug | Patient no. | Daily dosage (mg) | Improvement of IB score | Duration of improvement | Side effects not tolerated | Oral treatment continued | Response to the i.v. challenge with this drug |
|---|---|---|---|---|---|---|---|
| Biperiden | 3 | 6.0 | Yes | 6 weeks | Constipation | No | No |
| | 4 | 5.0 | No | | | No | No |
| | 5 | 3.0 | Yes | 6 weeks[b] | | No | No |
| | 6 | 4.0 | Yes | >10 months | | Yes | No |
| | 7 | 5.0 | Yes | 4 weeks[b] | | No | No |
| | 8 | 7.0 | No | | | No | No |
| | 9[a] | 8.0 | No | | | No | Yes |
| | 10 | 8.0 | No | | | No | Yes |
| Clonazepam | 1 | 1.5 | No | | | No | No |
| | 2 | 5.0 | Yes | 16 months | | No | No |
| | 3 | 4.0 | Yes | 6 weeks | Sedation | No | Yes |
| | 4 | 1.5 | No | | | No | No |
| Lisuride | 2 | 1.6 | Yes | 4 weeks[b] | | No | No |
| | 11 | 2.4 | Yes | >16 months | | Yes | Yes |
| Haloperidol | 1 | 4.5 | No | | | No | No |
| | 3 | 3.0 | No | | Akathisia | No | No |
| | 4 | 3.0 | No | | | No | No |

IB, idiopathic blepharospasm.

[a] Patient 9 also responded to clonazepam in the acute trial. He refused to take clonazepam in the chronic treatment phase because previous oral therapy with biperiden had failed.

[b] After the indicated duration, loss of efficacy of treatment.

(1,9,10,12,19,22,23) or showing a deterioration of symptoms under treatment with this substance (9,10,12).

Our results suggest that the substance is presumably not effective in Meige's syndrome. Haloperidol may even cause a deterioration in IB scores and cause marked untoward CNS side effects (4,12).

The results of the acute challenges and the chronic treatment indicate that biperiden, clonazepam, and, in single cases, lisuride are effective in Meige's syndrome (Tables 3 and 5) suggesting no uniform pharmacologic profile in this disorder (12). It can be assumed that the pharmacologic basis of Meige's syndrome varies from patient to patient. It is possible that the observed imbalance of some neurotransmitter systems (acetylcholinergic preponderance and dopaminergic, serotoninergic, and GABAergic hypofunction) does not signify the pathogenetic basis of the disorder but rather a modulation of these systems in response to a so far unknown pathophysiological mechanism.

In the chronic treatment phase only two of the four patients showing improvement in response to intravenous drug challenges had a therapeutic benefit with the identical substances (patients 3 and 11). On the other hand two patients not responding to any of the intravenous drug challenges (patients 2 and 6) showed sustained improvement of IB score in the chronic treatment phase. Thus, it is evident that the acute challenges in the present study have failed to predict in the majority of our cases the therapeutic potential of subsequent chronic oral treatment with identical agents.

Several factors may contribute to this failure.

1. Idiopathic blepharospasm tends to fluctuate considerably (see Table 2). Therefore, it is difficult to distinguish drug effects from spontaneous fluctuations in small groups of patients. In individual patients the differentiation of drug effects from fluctuations is nearly impossible unless the fluctuations of the symptoms are very small. Measurements of IB and OMD at short intervals (e.g., intervals of 15 min throughout the observation period) would probably improve the significance of acute drug challenges. The marked spontaneous fluctuations of the symptoms in the majority of our patients have probably also contributed to the extraordinarily low $t_0$ – IB scores on the baseline days (see Table 2). Thus the "significant deterioration" of IB scores in phase 1 and 2 of the baseline days is presumably an artifact resulting from marked spontaneous fluctuations of the symptoms.

2. In two patients responding to the intravenous application of biperiden, dose-limiting side effects occurred when they were treated with this drug in the oral treatment phase at daily dosages of 7 and 8 mg, respectively. One may assume that higher dosages of biperiden would have possibly been of therapeutic benefit in these patients.

3. Our results have shown that several neurotransmitter systems are presumably involved in Meige's syndrome. A bolus may show an effect that is not reproducible when the identical substance is given orally.

No relation was found between age and age at onset of the disease and the results of the acute drug challenges and the oral therapies. There was no signifi-

cant difference between patients with essential tremor and those without essential tremor. Side effects did not correlate with age of patients.

Our method for assessment of the efficacy of the drugs applied requires some modifications (shorter intervals of IB and OMD measurement after intravenous application of the substances, repeated application of identical drugs and placebo, and several baseline assessments). The principles of this method, however, might be useful for testing if a substance is of clinical pharmacological interest in the treatment of Meige's syndrome.

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