Clinical and Manometric Effects of Nifedipine in Patients with Esophageal Achalasia

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The effect of a new calcium antagonist, nifedipine, which has a spasmyloytic activity on smooth muscle cells, was studied on the esophageal function of 20 patients with achalasia of mild and moderate degree. The study was carried out by using constantly perfused catheters and recording the pressure variations at the lower esophageal sphincter, before and after sublingual administration of 10-20 mg of nifedipine. The drug significantly decreased the lower esophageal sphincter pressure for more than 1 h. A clinical trial was also carried out by assessing the improvement of symptoms in achalasia patients taking sublingually a dose of 10-20 mg of nifedipine before each meal. After 6-18 mo of nifedipine therapy these patients underwent a placebo treatment, whereas an additional group of 9 achalasia patients was treated first with placebo followed by nifedipine. The nifedipine treatment gave excellent or good results in a large majority of patients of both groups. The moderate results were only 5 and the poor responses only 3. The clinical improvement induced by nifedipine was statistically significant when compared, not only with the pretreatment clinical state, but also with the results of the placebo treatment. No tachyphylaxis and few side effects were seen either during the manometric recordings or the longest periods of therapy. This study suggests that nifedipine may be advantageously used in the medical treatment of achalasia of mild or moderate degree.

The drugs that block the transmembrane calcium influx, named calcium antagonists (verapamil, D-600, nifedipine, etc.), commonly used for relieving the spasm of the arterial musculature (1-3), have been found to have a relaxant effect on smooth muscle cells of the gut wall (4-7). Among these substances, nifedipine shows the best antispastic activity on blood vessels, especially if their hypertone is myogenic in origin or calcium dependent (3), as the interdeglutitive tony of the lower esophageal sphincter (LES) (8-13). The results of "in vitro" and "in vivo" studies (7, 12-15) suggested that these drugs might be beneficial in the treatment of pathological states associated with LES hypertension such as achalasia. Thus we evaluated, in a series of achalasia patients, the effect of nifedipine on the LES pressure after acute administration and the efficacy of long-term treatment in reducing clinical symptomatology.

Materials and Methods

Manometric Studies

The study was carried out on a total of 20 patients, 6 males and 14 females, mean age of 42 yr (range 20-64 yr), with manometric, radiologic, and endoscopic evidence of achalasia in one of the first two stages, according to the classification of Adams et al. (16). As is known, these two stages do not include the cases of decompensated achalasia, in which the LES no longer allows the passage of the food from the huge esophagus into the stomach and so requiring an urgent surgical or dilatory treatment to alleviate the continuous regurgitation. Informed consent was obtained from all patients. The mean diameter of the esophagus, measured radiologically, was 4.39 cm (range 2.9-8 cm) and the average duration of the disease was 6.7 yr (range 2-15 yr). Six of these patients had been submitted to pneumatic dilatations with Mosher probe, at least 6 mo previously and in 4 of these cases the results were unsatisfactory.

The intraesophageal pressures were transmitted to Statham P23 Db transducers by using an assembly (ED 4.5 mm) of three constantly perfused polyvinyl catheters (ID 1.2 mm) with radially oriented side-hole recording orifices (D 1.2 mm) 5 cm apart. Each catheter was perfused with saline solution (NaCl 0.9%) by using 50 ml greased glass
After an overnight fasting, the probe was passed orally through a mouth-opener into the stomach. The LES pressure was recorded with a slow gastroesophageal pull-through of the probe, by testing each of the three radially oriented recording orifices. The probe was then fixed, at the level of the recording orifice which showed the highest LES pressure, by using a plaster stuck to the mouth-opener. The LES pressure was measured in mmHg and expressed as the average between end-expiratory and end-inspiratory levels, using the mean resting intragastric pressure as the zero reference. A belt pneumograph was used to record respiration.

After a basal recording period of 15 min, nifedipine was administered, sublingually, in order to avoid possible stasis of the capsule in the gullet, and the LES pressure variations were then recorded for a further 60 min. The dose of nifedipine was 10 mg in 10 patients (group A) and 20 mg in the other 10 patients (group B). The two groups A and B were well matched with regard to age (43.5 and 40.5 yr, respectively), the disease duration (5.6 and 6.6 yr, respectively), and the diameter of the esophagus (4.64 and 4.14 cm, respectively). In order to be sure of the accuracy of the measurement of the LES pressure, a brief push and pull-through of the same recording orifice was carried out every 10 min. In each case the LES pressure values were taken every minute from the beginning to the end of the examination. The average of the basal period was calculated as a whole, whereas after nifedipine administration the LES pressures were averaged for 5-min periods.

Then, the following statistical calculations were made: (a) The Student's t-test for paired data was used, within group A or B, to evaluate the significance of the differences between the values of the basal period and those of each 5-min period, after nifedipine administration; and (b) the maximum decrease, irrespective of time, was calculated for each patient and the mean for each group was obtained, using the Student's t-test for unpaired data, in order to compare the differences between the two groups.

Clinical Studies

The clinical trial was carried out on two groups of patients:

1. One was treated with nifedipine followed by placebo (NP group).
2. The other was treated with placebo followed by nifedipine (PN group).

Regrettably, we were not able to double-blind this study because sublingual nifedipine has a characteristic taste. A single blind design, however, was used and the disadvantage met with this kind of design was overcome by using two groups of patients and crossed administrations.

The first group of patients (NP) included all patients submitted to the manometric test with nifedipine.

The nifedipine therapy was planned on a long-term basis of at least 6 mo. This medication was taken sublingually in a dose of 10-20 mg, 15-30 min before each meal. If after a 1-wk trial, the patient still experienced dysphagia, another 10-30 mg were given before eating, up to a maximum dose of 60 mg/day. Clinical interviews were carried out after 1 wk, at 3 monthly intervals and at other times if symptoms warranted it. If clinical improvement was neither achieved nor continued, other forms of therapy were then considered.

To obtain accurate information concerning the evolution of the disease between clinical controls, the patients were asked to keep a standardized diary of their symptoms. (Each patient received a book of cyclostyled sheets. Each sheet was relative to a period of 1 wk and showed a vertical list of symptoms related to the disease on the left side, expressed in simple terms. The rest of the sheet was subdivided into seven vertical spaces, one for each day of the week. The patients were asked to complete daily, the appearance or absence of each symptom and if present, its intensity and duration.) In addition to this, the patients were at liberty to telephone the doctor at any time they felt the necessity. The clinical control at three monthly intervals was planned to comment on the diary content with the patients, to weigh them and, if necessary, to program x-rays or manometric controls.

The clinical grading of these patients was based on the incidence and degree of dysphagia, retrosternal pain, regurgitation, and weight loss, after the criteria proposed by Vantrappen and Hellemans (18). In this way, the patients were subdivided into four classes: class I, excellent results, in the case of complete disappearance of symptoms; class II, good results, when dysphagia or pain of short duration was experienced during the meal, less than once a week; class III, moderate or fair results, which did not last longer than a few minutes, did not prevent the patient from finishing his meal and was not associated with regurgitation and weight loss; class IV, poor results, in the case of persistent regular dysphagia accompanied by regurgitation or daily retrosternal pain.

After a period of 6-18 mo, the therapy with nifedipine was interrupted, simultaneously, by a period of treatment with placebo.

The second clinical group (PN) made up of 9 achalasia patients with similar clinical, radiologic, and manometric profiles as those treated with nifedipine, was placed on sublingual placebo therapy, using the same criteria for study as nifedipine. The patients of this group were 3 males and 6 females, mean age of 40.6 yr (range 24-53 yr), and showed a mean diameter of the esophagus, measured radiologically, of 4.88 cm (range 3.1-6.8 cm), whereas the duration of the disease was in mean 4.9 yr (range 1.5-6.1 yr). However, two of these patients underwent dilatatory treatment with Mosher probe, 4 and 6 mo, respectively, before the placebo treatment, but with little improvement.
After a placebo treatment period of 4-6 mo the patients of this group began the nifedipine treatment after the same criteria as described for the other group. This therapy is still in progress and to date has reached the duration of 4-6 mo. The clinical data were collected and graded in the same way as described for the other group.

The statistical study was carried out by using the Wilcoxon rank-file test, both in the first group (NP) and in the second group (PN), in order to evaluate the significance of differences:

1. Between the clinical data measured in basal conditions and those obtained during nifedipine treatment.
2. Between the data measured in basal conditions and those during placebo administration.
3. Between the data obtained during nifedipine treatment and those during placebo administration.

Results

Manometric Studies

The administration of nifedipine, both at the dose of 10 mg (group A) and 20 mg (group B), caused the following changes: (a) a statistically significant decrease of the LES pressure (Figure 1) with the maximal inhibitory effect being achieved after an average of 19.5 min (range 10-40 min) in group A and of 26 min (range 10-40 min) in group B. The degree and the duration of the inhibitory effect was higher in group B than in group A, because the decrease of LES pressure in group A was statistically significant starting from the 10-min period to the 35-min period, whereas in group B the statistical significance was reached at the 5-min period to the end of the observation period. (b) The maximum decrease in LES pressure, irrespective of time, obtained in group B (−32.2 mmHg ± 3.55 SEM) was significantly (p < 0.001) greater than that of group A (−18.4 mmHg ± 2.04 SEM).

In addition, to compare the manometric effects with the clinical results, a semiquantitative evaluation of these manometric data was carried out on the basis of both the LES pressure minimal value (MnP) measured after nifedipine and the duration (D) of the inhibitory effect. Each value of MnP and D was compared with the mean value of MnP (mMnP) and D (mD), obtained, after nifedipine, in the corresponding manometric group. Thus the manometric results were classified as the following: excellent: MnP < mMnP and D > mD; good: MnP < mMnP and D < mD; moderate: MnP > mMnP and D > mD; and poor: MnP > mMnP and D < mD.

Neither was nifedipine observed to improve the impaired LES response to swallows, nor was it observed modify the motor activity of the esophageal body.

Figure 1. Mean values ± standard errors (m ± SEM) of LES pressures measured in mmHg during the basal period and during the 5-min periods subsequent to nifedipine sublingual administration in the two groups at different doses: A. (10 mg) and B. (20 mg).
Table 1. A Summary of Clinical Data Relative to the Twenty Achalasia Patients Treated with Nifedipine Followed by Placebo

<table>
<thead>
<tr>
<th>No.</th>
<th>Patients</th>
<th>Manometric result</th>
<th>Daily dose (mg)</th>
<th>Clinical class Before therapy</th>
<th>Clinical class During therapy</th>
<th>Follow-up (mo)</th>
<th>Clinical class During nifedipine</th>
<th>Clinical class During placebo</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>1</td>
<td>P.G.</td>
<td>Excellent</td>
<td>30</td>
<td>IV</td>
<td>I</td>
<td>12</td>
<td>I</td>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>P.P.</td>
<td>Excellent</td>
<td>30</td>
<td>IV</td>
<td>I</td>
<td>6</td>
<td>I</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>S.A.M.</td>
<td>Excellent</td>
<td>30</td>
<td>III</td>
<td>I</td>
<td>6</td>
<td>I</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>R.S.</td>
<td>Excellent</td>
<td>30</td>
<td>III</td>
<td>I</td>
<td>9</td>
<td>I</td>
<td>II</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>P.P.</td>
<td>Moderate</td>
<td>30</td>
<td>IV</td>
<td>III</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>G.W.</td>
<td>Poor</td>
<td>00</td>
<td>IV</td>
<td>IV</td>
<td>Op.</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>7</td>
<td>B.G.</td>
<td>Good</td>
<td>40</td>
<td>IV</td>
<td>II</td>
<td>9</td>
<td>II</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>M.B.</td>
<td>Moderate</td>
<td>30</td>
<td>IV</td>
<td>III</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>F.F.</td>
<td>Excellent</td>
<td>30</td>
<td>IV</td>
<td>I</td>
<td>12</td>
<td>I</td>
<td>III</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>R.G.</td>
<td>Good</td>
<td>40</td>
<td>IV</td>
<td>II</td>
<td>12</td>
<td>II</td>
<td>II</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>N.E.</td>
<td>Good</td>
<td>40</td>
<td>IV</td>
<td>II</td>
<td>9</td>
<td>II</td>
<td>IV</td>
<td>3</td>
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<tr>
<td>12</td>
<td>R.L.</td>
<td>Excellent</td>
<td>30</td>
<td>III</td>
<td>I</td>
<td>12</td>
<td>I</td>
<td>II</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>F.C.</td>
<td>Moderate</td>
<td>30</td>
<td>IV</td>
<td>III</td>
<td>6</td>
<td>—</td>
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</tr>
<tr>
<td>14</td>
<td>B.M.</td>
<td>Good</td>
<td>30</td>
<td>IV</td>
<td>I</td>
<td>9</td>
<td>II</td>
<td>IV</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>F.A.</td>
<td>Excellent</td>
<td>30</td>
<td>IV</td>
<td>I</td>
<td>18</td>
<td>I</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>G.G.</td>
<td>Good</td>
<td>40</td>
<td>IV</td>
<td>II</td>
<td>6</td>
<td>II</td>
<td>III</td>
<td>6</td>
</tr>
<tr>
<td>17</td>
<td>B.G.</td>
<td>Moderate</td>
<td>30</td>
<td>IV</td>
<td>III</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>S.A.</td>
<td>Moderate</td>
<td>40</td>
<td>IV</td>
<td>IV</td>
<td>Op.</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>19</td>
<td>M.L.</td>
<td>Good</td>
<td>40</td>
<td>IV</td>
<td>II</td>
<td>6</td>
<td>II</td>
<td>IV</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>S.G.</td>
<td>Excellent</td>
<td>30</td>
<td>III</td>
<td>I</td>
<td>6</td>
<td>I</td>
<td>III</td>
<td>3</td>
</tr>
</tbody>
</table>

The classification into four clinical classes and the grading of the manometric responses in excellent, good, moderate, or poor are explained in the text. Op. = patient submitted to Heller's operation after the failure of the 1-wk trial with nifedipine. These patients were excluded from all clinical evaluations, whereas patients Nos. 5, 8, 13, and 17 were excluded only from the placebo treatment as they underwent esophageal dilatations after 6 mo.

Clinical Studies

The results of the long-term administration of nifedipine in the first group (NP) showed a statistically significant (p < 0.01) clinical improvement (Table 1) with a mean daily dose of 34.5 mg. Excellent and good results (class I and II) were obtained in 14 of the 20 patients, moderate results (class III) in 4 and poor results (class IV) in 2. In these latter 2 cases, the therapy was stopped after a 1-wk trial, and the patient was referred to a surgeon for Heller's operation. In the 4 cases with moderate results after 6 mo of therapy with nifedipine, a series of pneumatic dilatations was started with subsequent benefit. The average observation period was 8.66 mo (range 6-18 mo), excluding the 2 patients who underwent Heller's operation. In those 14 patients who responded, the therapy continued to be effective even after the longest periods of observation.

A good correlation between the manometric effect of nifedipine and its clinical effect was also observed. However, in the majority of cases the improvement of symptoms was limited to a period of a few hours following the drug administration; the dysphagia reappeared if nifedipine was not taken.

Manometric studies were repeated in some patients after 6 and 12 mo of therapy and did not show a decrease of the LES tone in basal conditions, when compared with the values found before the beginning of the treatment. These patients, however, did show a manometric response to the sublingual administration of the drug, similar to that observed before the treatment.

Radiologic controls performed in some cases at 6 mo intervals demonstrated no significant enlargement of the esophageal diameter.

When nifedipine was replaced with placebo there was a statistically significant (p < 0.01) deterioration in symptoms (Table 1). In only 4 cases was it possible to complete the planned observation period, as the others withdrew from the placebo, because of the severity of symptoms.

The evaluation of the results obtained in the second group (PN) of 9 patients showed no statistically significant (p > 0.05) improvement after placebo administration for a mean period of 5 mo (Table 2). Only 2 cases showed a moderate improvement whereas the others had persistence or deterioration in their symptoms.

When placebo was replaced by nifedipine, a statistically significant (p < 0.01) improvement in symp-
tomatology was observed: excellent or good results (class I and II) in 7 of the 9 patients, a moderate result (class III) in 1, and a poor response in another (class IV). The latter was referred to the surgeon for Heller's operation after a week's trial. The average period of observation, excluding the latter case, was 4.5 mo and the daily dose used was 32.5 mg.

The side effects of this therapy were rare. Taken in order of occurrence, side effects in the first group (NP) included venous dilatation and swelling of the ankles, both of mild degree (3 cases), heat at the extremities (3 cases), headache (3 cases), and blood hypotension (1 case), appearing just after the drug intake. Side effects in the second group (PN) included headache with epigastric fullness (1 case), blood hypotension, and heat at the extremities (1 case). As these side effects were not severe, the therapy was continued in all cases, and the symptoms were decreased or disappeared spontaneously.

Comment

The results of the first part of this study indicate that the sublingual administration of nifedipine in achalasia patients significantly decreases the lower esophageal sphincter basal tone, measured manometrically. This effect is probably due to the block of calcium transmembrane influx which determines the LES tone, both in basal conditions (7,12,13) and after administration of some agonists like bethanecol, gastrin, phenylephrine, etc. (14). Even if the impaired mechanism of the post-deglutitive opening of the LES is not improved, nifedipine may provide a decrease in the resistance of the achalasic LES, without affecting the esophageal body contractions (19), unlike other spasmyloptics (20,21).

This effect has been demonstrated to be clinically important, as the patients with achalasia submitted to therapy with nifedipine, at a mean daily dose of 30-40 mg, showed a noticeable improvement in symptoms. Patients showing a poor manometric response to nifedipine also showed a poor clinical response to this drug (Table 1). We are aware that the observation period is relatively short and that the experimental design of the clinical trial is not the one currently used. But a better double-blind trial was not possible because of the characteristic flavor of nifedipine administered sublingually. The sublingual way was necessary to bypass the gullet block, just as the parenteral way was used for anticholinergics (22-24). However, the interruption of nifedipine administration by a period with placebo was followed by a significant deterioration in symptoms.

On the other hand, a group of achalasia patients treated with placebo, did not show significant variations in symptomatology, but when placebo was replaced by nifedipine, a significant clinical improvement took place.

On the basis of the results of the clinical trial we can conclude that sublingual nifedipine may be effective in reducing clinical symptomatology in achalasia patients.

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