Echocardiographic evaluation of verapamil in Friedreich’s ataxia

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SUMMARY Nine patients with hypertrophic cardiomyopathy associated with Friedreich’s ataxia were treated with the calcium antagonist verapamil, which is known to reduce myocardial hypertrophy and improve diastolic function in patients with idiopathic hypertrophic cardiomyopathy. Daily oral doses of 7 mg/kg were given for a mean (SD) of 24 (8) months. M mode echocardiography performed at the start of the study and at the end of follow up showed no significant difference between the treated group and an untreated control group of nine patients. Verapamil produced no changes in left ventricular wall thickness, mass index, left ventricular internal diameter, fractional shortening, peak normalised lengthening rate, peak rate of septal and posterior wall thinning, and time from minimum ventricular cavity dimension to mitral valve opening.

Myocardial calcium overload has been suggested as a cause of cardiac disease in Friedreich’s ataxia; however, verapamil had no beneficial effect on these patients with established myocardial hypertrophy.

Left ventricular hypertrophy (usually concentric and non-obstructive) has been found in 38% to 67% of patients with Friedreich’s ataxia.1–3 In a series of 18 cases our own group found echocardiographic evidence of concentric left ventricular hypertrophy in 39% of cases and asymmetric (non-obstructive) hypertrophy in 33%.4 St John Sutton et al found reduced diastolic function in most of their patients with Friedreich’s ataxia.5

Calcium antagonists have been effective in other forms of hypertrophic cardiomyopathy. Kaltenbach et al gave oral verapamil (480 mg daily) for more than a year to patients with obstructive hypertrophic cardiomyopathy.6 They found that QRS voltage, heart volume (determined radiologically), and left ventricular mass (determined haemodynamically) were reduced. Hirzel et al confirmed these findings7; as did Spicer et al in children.8 Verapamil has also been reported to improve left ventricle relaxation and filling in adults and children with hypertrophic cardiomyopathy.8–10

Other evidence encourages the use of calcium antagonists for cardiomyopathy. Sanchez-Casis et al described granular calcium and iron deposits in degenerate myocardial fibres in a patient with Friedreich’s ataxia.11 Lamarche et al, however, did not confirm this finding in an electron microscope study of three cases.12 It has been suggested but not confirmed that the cardiomyopathy associated with Friedreich’s ataxia may be the result of defective calcium transport through cell membranes with subsequent accumulation in the fibres.13–14 These reports prompted us to study the long term effect of verapamil on cardiomyopathy in patients with Friedreich’s ataxia.

Patients and methods

Thirteen patients with Friedreich’s ataxia diagnosed by Geoffroy’s criteria15 entered the trial. In all of them left ventricular hypertrophy of various grades of severity was seen on M mode echocardiography, and none of them had any contraindications to long term calcium antagonist treatment. They all gave their informed consent. Two patients dropped out within two months because of hypotension, another abandoned treatment, and a fourth did not report for follow up examinations after 7 months. The nine remaining patients (group 1) (5 male and 4 female),
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Table 1  Echocardiographic variables used to assess effect of verapamil treatment on heart muscle

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Interventricular septum thickness</td>
<td>IVSTh</td>
</tr>
<tr>
<td>(2) Left ventricular posterior wall thickness</td>
<td>LVVPWTh</td>
</tr>
<tr>
<td>(3) IVSTh/LVVPWTh ratio</td>
<td></td>
</tr>
<tr>
<td>(4) Left ventricular end diastolic diameter</td>
<td>LVEDD</td>
</tr>
<tr>
<td>(5) Left ventricular end systolic diameter</td>
<td>LVESD</td>
</tr>
<tr>
<td>(6) Left ventricular mass index</td>
<td>LV mass index</td>
</tr>
<tr>
<td>(7) Left ventricular fractional shortening</td>
<td>FS%</td>
</tr>
<tr>
<td>(8) Left atrium/aorta ratio</td>
<td>LA/AO</td>
</tr>
<tr>
<td>(9) Time from minimum left ventricular cavity dimension to the onset of mitral valve opening</td>
<td>LVEDD-MVO</td>
</tr>
<tr>
<td>(10) Peak normalised lengthening rate</td>
<td>dL/dt</td>
</tr>
<tr>
<td>(11) Peak rate of septal thinning</td>
<td>dW/dt</td>
</tr>
<tr>
<td>(12) Peak rate of posterior wall thinning</td>
<td></td>
</tr>
</tbody>
</table>

Variables were aged from 10 to 34 years (mean age (SD) 21.9 (7.5)), with body surfaces between 1.05 and 1.8 m² (mean (SD) area 1.43 (0.27)). Another nine patients with the same condition (group 2) served as controls. There were 6 male and 3 female patients aged from 10 to 36 years old (mean (SD) age 20.3 (8.1)), with body surfaces between 0.9 and 1.8 m² (mean (SD) area 1.45 (0.24)). Patients had cardiological examinations every three months for 13 to 37 months in group 1 (mean (SD) 24 (8.4) months) and 10 to 49 months in group 2 (mean 24 (SD) 13 months). Age, body surface area, and length of follow up were similar in the two groups. Echocardiographic findings of groups 1 and 2 were compared with those of 25 normal subjects (group 3) of similar mean (SD) age (20.6 (9.7) years) and body surface area (1.44 (0.15) m²). Patients took verapamil (7 mg/kg daily) as two or three separate oral doses. Venous blood samples were taken from seven of the nine patients within four to six hours of a dose of verapamil and were assayed for unchanged drug and metabolites (norverapamil D₁61 to D₁80). Blood concentrations (mean (SD) 128 (118) ng/ml) were within therapeutic range (41 to 327 ng/ml).

Table 2  Statistical comparison (Kramer test) of echocardiographic variables in patients with Friedreich’s ataxia treated with verapamil (group 1), untreated patients (group 2), and healthy subjects (group 3)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 vs Group 3</th>
<th>p</th>
<th>Group 2 vs Group 3</th>
<th>p</th>
<th>Group 1 vs Group 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSTh (mm)</td>
<td>11.1 (1.4)</td>
<td>6.5 (1.0)</td>
<td>&lt;0.01</td>
<td></td>
<td>10.2 (1.3)</td>
<td>6.5 (1.0)</td>
</tr>
<tr>
<td>LVVPWTh (mm)</td>
<td>10.9 (1.6)</td>
<td>6.1 (1.2)</td>
<td>&lt;0.01</td>
<td></td>
<td>10.0 (0.8)</td>
<td>6.1 (1.2)</td>
</tr>
<tr>
<td>IVS/LVVPW</td>
<td>1.0 (0.2)</td>
<td>1.1 (0.2)</td>
<td>NS</td>
<td></td>
<td>0.9 (0.1)</td>
<td>1.1 (0.2)</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>38.4 (5.3)</td>
<td>44.8 (4.2)</td>
<td>&lt;0.01</td>
<td></td>
<td>41.5 (4.6)</td>
<td>44.8 (4.2)</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>25.2 (5.7)</td>
<td>26.9 (3.4)</td>
<td>NS</td>
<td></td>
<td>26.5 (4.5)</td>
<td>26.9 (3.4)</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>111.9 (26)</td>
<td>62.5 (16)</td>
<td>&lt;0.01</td>
<td></td>
<td>112.8 (18)</td>
<td>62.5 (16)</td>
</tr>
<tr>
<td>FS%</td>
<td>34.1 (8.3)</td>
<td>39.7 (4.8)</td>
<td>&lt;0.05</td>
<td></td>
<td>36.2 (7.6)</td>
<td>39.7 (4.8)</td>
</tr>
<tr>
<td>LA/AO</td>
<td>1.1 (0.1)</td>
<td>1.1 (0.1)</td>
<td>NS</td>
<td></td>
<td>1.1 (0.0)</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.4 (0.3)</td>
<td>1.4 (0.1)</td>
<td>NS</td>
<td></td>
<td>1.4 (0.3)</td>
<td>1.4 (0.1)</td>
</tr>
</tbody>
</table>

See Table 1 for abbreviations.
rate and peak rate of septal and posterior wall thinning were used to assess diastolic function. Time from minimum left ventricular cavity dimension to onset of mitral valve opening was used as an index of left ventricular relaxation. We did not measure the isovolumic relaxation time (that is the interval between the second heart sound and mitral valve opening) because in some cases an accompanying phonocardiogram was not available; also, this interval has been reported to be an unreliable indicator of ventricular relaxation in patients with hypertrophic cardiomyopathy.

We used the Kramer test and covariance analysis for statistical analysis; the former is suitable for comparison of means from groups of unequal sizes and the latter for adjusting values obtained at the end of follow up so that the influence of differences between the initial means for the two groups is eliminated.

Results

Tables 2 and 3 show the echocardiographic data from patients with Friedreich's ataxia treated with verapamil (group 1), data from similar patients not receiving treatment (group 2), and data from normal subjects (group 3).

Patients with Friedreich's ataxia (groups 1 and 2) had significantly (p<0.01) thicker interventricular septal and posterior left ventricular walls. They also had significantly (p<0.01) higher left ventricular mass indices and significantly (p<0.01) slower peak rates of posterior wall thinning. Peak rates of septal thinning were significantly (p<0.05) slower in patients with Friedreich's ataxia than in normal subjects. The end diastolic diameter of the left ventricle was significantly smaller in patients of group 1 than in group 3, but there was no significant difference between groups 2 and 3. The left ventricular fractional shortening was significantly less in patients in group 1 (but not in patients in group 2) than in group 3 (p<0.05).

There were no differences between groups for time from minimum left ventricular cavity dimension to onset of mitral valve opening or for peak lengthening rates. Tables 4 and 5 summarise the initial and final echocardiographic findings obtained in patients of groups 1 and 2. Palpitation in one patient and recurrent headache in another abated while they were on verapamil. None of the patients developed evidence of heart failure during long term verapamil treatment.

Discussion

Our results are at variance with those reported by other workers who used similar doses of verapamil to treat patients with hypertrophic cardiomyopathy. We found that long term treatment with verapamil of patients with cardiomyopathy as-
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Table 5  Statistical comparison (covariance analysis*) of echocardiographic variables of left ventricular diastolic function and relaxation at the beginning and at the end of follow up in patients treated with verapamil (group 1) and those who were not (group 2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before verapamil</th>
<th>After verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>LVESD-MVO (ms)</td>
<td>57 (26)</td>
<td>28 (39)</td>
</tr>
<tr>
<td>Lng rate (s^-1)</td>
<td>3.7 (0.6)</td>
<td>4.0 (0.9)</td>
</tr>
<tr>
<td>dS/dt (cm/s)</td>
<td>4.3 (1.4)</td>
<td>4.5 (1.6)</td>
</tr>
<tr>
<td>dW/dt (cm/s)</td>
<td>6.7 (1.9)</td>
<td>7.2 (3.2)</td>
</tr>
</tbody>
</table>

*None of the variables was significantly different. See Table 1 for abbreviations.

associated with Friedreich's ataxia produced no detectable difference by echocardiography between treated and untreated patients after mean follow up of two years. Our findings do, however, accord with those of Rosing et al who did not see any significant reduction of septal or posterior wall thickness in the left ventricle of 31 patients treated by long term administration of verapamil and followed up for at least one year.23 The reduction of left ventricular thickness reported by Kaltenbach et al, by Kuhn et al, and by Spicer was <2 mm and was sometimes only of borderline significance.5 8 22

Our results do not support the hypothesis that intramyocardial calcium accumulation is an important factor in the pathogenesis of cardiac disease in Friedreich's ataxia. Although the hypothesis rests on apparently good experimental evidence, the fact remains that verapamil did not reduce established myocardial hypertrophy. The role of calcium accumulation in the pathogenesis of myocardial hypertrophy in patients with Friedreich's ataxia can probably only be established by a study in which verapamil is given early in the course of disease, when neurological and cardiac signs and symptoms are just beginning to appear—that is, before myocardial cells are replaced by fibrotic tissue.9 24

Our data on basal diastolic function accord broadly with those reported by St John Sutton et al in a study of seven patients with Friedreich's ataxia.5 All patients with hypertrophic cardiomyopathy (groups 1 and 2) had a highly significant reduction of the posterior wall thinning peak rate and a significant reduction in septal thinning rate compared with normal subjects. The peak rate of left ventricular lenthening, on the other hand, was not significantly reduced (in St John Sutton's series this variable was slightly less than normal values in two of seven cases). Unlike St John Sutton et al we did not find that the time from minimum left ventricular cavity size to onset of mitral valve opening was significantly increased.

We found that oral verapamil had no beneficial effects in group 1, not even on the diastolic indices of left ventricular function. This finding is seldom referred to in published reports, and only then in patients with hypertrophic cardiomyopathy other than Friedreich's, and also chiefly in connection with studies of the short term effects of the drug. Even in this limited area, the results of various studies are not in complete accord.9 25 26

In conclusion, long term oral treatment with verapamil at high doses was readily tolerated by all our patients. In particular, there was no deterioration of left ventricular systolic function or evidence of heart failure. Verapamil, a calcium antagonist, did not reduce left ventricular wall thickness, possibly because interstitial fibrosis in these patients with Friedreich's ataxia was already advanced. Left ventricular diastolic function was not significantly improved by long term verapamil treatment.

In our opinion routine verapamil treatment is not justified in symptom free patients who have Friedreich's ataxia complicated by hypertrophic cardiomyopathy. Alone or in association with other drugs, however, verapamil might be useful in the treatment of supraventricular tachyarrhythmia in selected cases.

We thank Mrs Loredana Parinello for the statistical analysis, and Dr R Padrini for the blood verapamil assays.

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