A Preliminary Study on the Therapeutic Effects of a Calcium Antagonist (Diltiazem) on Primary Congestive Cardiomyopathy

A Clinical Survey of 15 Cases

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SUMMARY

The clinical effects of diltiazem in 15 patients with congestive cardiomyopathy were observed. Symptoms were controlled in 66% and cardiac enlargement improved in 73.3%. There was a decrease in cardiac silhouette on X-ray in 18.82±3.2% (p<0.01), with an increase of EF(%), CO, CI and a decrease of TPR on two-dimensional (2-D) echocardiogram (p<0.01). Prior to treatment, the cardiac status of 8 cases was grade III and 7 cases grade IV; after treatment 1 case was grade I, 8 grade II, 5 grade III and 1 grade IV. This improvement might be due to the blockade of calcium channels and the fact that diltiazem has the least negative inotropic effect among the calcium antagonists. The dosage, route of administration, and prevention of side effects are discussed.

Additional Indexing Words:
Calcium antagonist Diltiazem Primary congestive cardiomyopathy

PRIMARY congestive cardiomyopathy is the most common type of primary cardiomyopathy. Since the etiology of the disease remains unknown and the myocardial lesion is diffuse in extent, therapy is usually unsatisfactory. Based on experimental evidence of the vasodilatory effect of diltiazem and its improvement of myocardial function, clinical observations following the administration of this drug were made in 15 patients with primary congestive cardiomyopathy admitted to our hospital from April, 1984 to January, 1986. This study was designed to investigate the therapeutic effects, side effects and possible mechanism of action and thus to evaluate a new approach to the therapy of primary congestive cardiomyopathy.
SUBJECTS AND METHODS

Fifteen patients were studied. Primary congestive cardiomyopathy was diagnosed according to the Goodwin and Oakley criteria. Ten were men and 5 women; their ages ranged from 17–67 (average 41.1±4.3). The clinical course ranged from 6 months to 12 years (average 27.5±7.1 months).

Before diltiazem therapy all patients were treated with digoxin or diuretics for several weeks. Diltiazem was given when these conventional approaches failed to result in clinical improvement; the initial dosage was 30 mg /8h which was then gradually increased up to 60 mg; one patient received 90 mg. Thirteen patients were followed over a period of 3–6 months, and the other 2 were observed for not less than 1 month. Based on the therapeutic scheme the patients were divided into 2 groups; Group I received diltiazem only, and Group II was treated with diltiazem combined with nitoral.

Clinical observation included symptoms, signs, cardiac X-ray in three positions, 2-D echocardiogram, ECG, routine blood and urine examinations, hepatic and renal function and serum electrolytes. Swan-Ganz catheterization were carried out in three. Hemodynamic data from each case was recorded 3 times/day for 3 days. The cardiac function was assessed according to the criteria of functional classification suggested by the New York Heart Association.

RESULTS

1. Improvement of symptoms and signs: Symptoms and signs were compared before and after therapy in the same individual. After therapy, symptoms and signs were controlled or improved as shown in Tables I and II.

2. Improvement of cardiac function: Before treatment, cardiac function was evaluated to be Grade III in 8 and Grade IV in 7 patients. After treatment in 14 of the 15 patients, there was improvement in cardiac function; only 5 patients were estimated to be in Grade III and 1 in Grade IV.

3. Effects on ECG and hemodynamics: After diltiazem therapy, follow-up ECG showed 64% of cases of multiple, multifocal and parasystolic premature arrhythmias were controlled, but without any significant changes in cardiac block or QRS patterns. 66.7% of the cases showed less deviation of ST segment and lowering or inversion of T wave.

The results of Swan-Ganz floating catheterization carried out in 3 patients are shown in Table IV.

4. Effects on the size of cardiac silhouette: There were marked decreases in the area of the cardiac silhouette on X-ray after therapy in both absolute
### Table I. Improvement of Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Controlled (%)</th>
<th>Improved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitation</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>93.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Nocturnal paroxysmal dyspnea</td>
<td>93.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Chest distress</td>
<td>66.7</td>
<td>33.3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>100.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Syncope</td>
<td>100.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Table II. Improvement of Signs

<table>
<thead>
<tr>
<th>Improvement of signs</th>
<th>Percentage of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac enlargement improved</td>
<td>73</td>
</tr>
<tr>
<td>Cardiac arrhythmias under control</td>
<td>64</td>
</tr>
<tr>
<td>Blurred S₁ intensified</td>
<td>81</td>
</tr>
<tr>
<td>Gallop rhythm disappeared</td>
<td>100</td>
</tr>
<tr>
<td>Systolic 4th sound disappeared</td>
<td>100</td>
</tr>
<tr>
<td>Systolic cardiac murmur at apex improved</td>
<td>46</td>
</tr>
<tr>
<td>Lungs clear, no rales</td>
<td>80</td>
</tr>
<tr>
<td>Hepatic enlargement improved</td>
<td>100</td>
</tr>
<tr>
<td>Edema in lower extremities disappeared</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table III. Improvement in Cardiac Function

<table>
<thead>
<tr>
<th>Period</th>
<th>Before therapy</th>
<th>After therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA</td>
<td>III (8)</td>
<td>I (0)</td>
</tr>
<tr>
<td>classification</td>
<td></td>
<td>II (8)</td>
</tr>
<tr>
<td>(Number of</td>
<td></td>
<td>III (0)</td>
</tr>
<tr>
<td>cases)</td>
<td></td>
<td>IV (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV (1)</td>
</tr>
</tbody>
</table>

### Table IV. The Results of Swan-Ganz Catheterization

<table>
<thead>
<tr>
<th>Hemodynamic indexes</th>
<th>Before therapy</th>
<th>After therapy</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{X} \pm SE \text{ (mmHg)} )</td>
<td>( \bar{X} \pm SE \text{ (mmHg)} )</td>
<td></td>
</tr>
<tr>
<td>PAP</td>
<td>36.33±1.45</td>
<td>23.00±3.22</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PCWP</td>
<td>23.00±1.73</td>
<td>19.33±1.86</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
and relative terms, the changes in Group I were more obvious ($p<0.01$). The results are shown in Table V.

5. Changes in indexes derived from echocardiograms (Table VI): After diltiazem therapy, the left atrial dimension (LAD), SV, CO and CI increased significantly ($p<0.05$ or $<0.01$). The elevation of EF and lowering of TPR were also significant ($p<0.01$). In Group I the decreases in LVEDD and LVEDV were significant ($p<0.05$), while the changes in Group II were not.

6. Changes in heart rate and blood pressure after therapy: After therapy the heart rates increased slightly, and the blood pressure decreased slightly but within normal ranges ($p>0.05$).
7. Case reports: Patient 1, a 16 year old female, suffered from palpitations, dyspnea, suffocation, frothy bloody sputum and pitting edema intermittently for 20 months, and was diagnosed as having primary congestive cardiomyopathy. She was unresponsive to conventional treatment, and was then treated with diltiazem. The X-ray (Fig. 1) on the left shows marked cardiac
enlargement and increased lung markings on P-A view before treatment. Her symptoms and signs were greatly improved on diltiazem therapy. After 6 months of therapy, the cardiac silhouette decreased by 24.6% and lung markings decreased as shown on the right side.

Patient 2, a 30 year old female, developed palpitations, dyspnea, orthopnea and edema of the lower extremities 6 months prior to admission and was diagnosed as having primary congestive cardiomyopathy. The X-ray (Fig. 2) showed marked generalized cardiac enlargement with pleural effusion on the left side, not responding to conventional therapy. After 6 months of therapy, the cardiac silhouette was returning to normal size.

**DISCUSSION**

I. Analysis of clinical effects of diltiazem in primary congestive cardiomyopathy

Before diltiazem therapy all patients were in grade III-IV congestive cardiomyopathy, the area of the cardiac silhouette in 86.7% cases was 150% of the predicted value, LVEDV was $250.3 \pm 22.4 \text{ cm}^3$ (normal $108.86 \pm 24.39$), and EF $32.8 \pm 2.9\%$ (normal $60.08 \pm 10.66\%$). Conventional therapy was not satisfactory, while after diltiazem therapy almost 100% of the patients had marked improvement. Symptoms were well controlled in 66% and cardiac enlargement improved in 73.3%. The cardiac function improved by one grade in 13 cases, and by three in one. About 64% of the patients with tachycardia or premature beats reverted to normal rhythm; 80% of blurred S1, all S4 and all diastolic gallop rhythms disappeared or improved.

The absolute area of cardiac silhouette on X-ray decreased to $34.61 \pm 6.03 \text{ cm}^2$, with a relative decrease in cardiac silhouette of $18.82 \pm 3.25\%$ ($p<0.01$) after therapy (Table V). Table VI shows an increase in EF (%), SV, CO, CI and a decrease in TPR on 2-D echocardiogram ($p<0.01$). A comparison between the 2 subgroups showed the changes in indexes in Group I to be more pronounced than those in Group II. In addition, LVEDV and LVEDD in Group I decreased significantly after therapy ($p<0.05$). However, the results in Group II were not significant, probably due to the fact that the disease in Group II was more severe. Our impression was that treatment with nitoral is not so effective in cases of severe congestive cardiomyopathy.

II. The mechanism of diltiazem therapy in primary congestive cardiomyopathy

1. By blocking the calcium channels and decreasing peripheral resistance
Diltiazem is a 1,5-benzothiazepine derivative. Its chemical structure is quite different from that of verapamil and nifedipine. Breemen's experiments\(^1\) showed that diltiazem mainly blocks the activated calcium channels, in a dose dependent fashion. It has been suggested that unlike other calcium antagonists, diltiazem causes inhibition of stimulated calcium influx by interacting with the calcium pathways involved in excitation, rather than by competing with calcium ions for entry. Hidaka\(^2\) revealed that the drug might bind to the calcium dependent regulatory protein named calmodulin to control binding with Ca\(^++\) through calcium influx. In turn these, interfered with MLC-kinase activity, inhibited the binding of actin with myosin and relax vascular smooth muscle. In addition, Ca\(^++\) also was extruded from the cell through a calcium activated pump or passively via sodium-calcium exchange. In Walsh's experiment,\(^3\) it was shown that diltiazem had the least influence on cardiac myocontractility as compared with isoptin and nifedipine in awake dogs. For these reasons, diltiazem has an advantage in improving left ventricular function.

2. By abolishing the spasm of micro-arterio-capillaries and improving the myocardial lesions

Ashraf et al\(^4\) found that large amounts of transmembranous Ca\(^++\) influx led to over-contraction, dissolution of myofibrils and a series pathological changes characteristic of cardiomyopathy. Previous to this stage, if a calcium antagonist was injected intracutaneously into the hamster, the spasm of micro-arterio-capillaries could be abolished and the dissolution of myofibrils could be prevented. Some authors\(^5\) suggested that these improvements might be due to the reduction of the ATP fraction and levels of lactic acid and free fatty acid, increasing the activity of enzymes or preserving the function of chondrisomes.

3. Antiarrhythmic effects

By blocking the Ca\(^++\) pathway diltiazem prolonged the refractory period of the A-V nodal and A-V accessory pathways. Thus supraventricular premature beats and tachycardiac arrhythmias could be controlled. However, unless the ventricular ectopic rhythm was due to coronary spasm, the effect was not so satisfactory. In our group, most cases of tachycardia except atrial fibrillation were controlled. These effects might be related to hemodynamic and myocardial improvement. Nevertheless, the control of arrhythmias could further improve the cardiac function and increase cardiac output.

III. Clinical use of diltiazem

1. According to the results of high performance liquid chromatographic assay,\(^6\) the terminal half life of diltiazem after intravenous injection was 4.5±
1.3 hrs. With repeated oral administration there was some accumulation of
the drug. Zelis' experiments showed that a clinical effect might be achieved
with a serum concentration of 50 ng/ml. With an oral dose of 30 mg a se-
rum concentration of 28 ± 21 ng/ml could be reached, while concentrations
resulting from 60 mg and 90 mg doses were 31–246 and 44–274 ng/ml, re-
spectively. In our group we found that a dose of 60 mg/8 hrs resulted in good
therapeutic effects with only minimal side effects.

2. It has been reported that diltiazem side effects, such as headache,
peripheral edema, flushing, fatigue or digestive disturbances, are quite rare
(0–4%).7) In our series none of these were found. However, 2 cases showed
sinus bradycardia (in one of them a rate below 46/min), which recovered
after withdrawal of the drug; mild prolongation of the P-R interval occurred
in 1 case. There was 1 case of transient LBBB at baseline. After therapy
it became persistent but recovered after drug withdrawal. One case showed
widening of the QRS interval and treatment was thus interrupted. Some
authors7) have pointed out that the drug suppressed the A-H period and A-V
node conduction, while others showed that at a high concentration (5 ng/ml)
of diltiazem the Vmax of Purkinje fibers could be decreased by about 20%.
The drug must be used with caution if the patient already shows BBB. In
our group no marked disturbances of hepatic or renal function were found.

3. Generally, diltiazem is contraindicated in sick sinus syndrome, se-
vere A-V block, digitalis intoxication, hypotension and severe impairment of
hepatic and renal function.6)–8) Because a small negative inotropic effect
might occur, administration of the drug to patients with severe heart failure
must be handled with care.

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