METHOD FOR TREATMENT OF CONGESTIVE HEART FAILURE WITH COENZYME Qn

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8 Claims

ABSTRACT OF THE DISCLOSURE

Congestive heart failure is successfully treated with the aid of ubiquinone 5n (coenzyme Qn), n=7 to 10, inclusive.

This invention relates to a method for treatment of congestive heart failure which comprises administering ubiquinone of the formula

\[
\text{H}_2\text{C}_2\text{O} \quad \text{CH}_3 \quad \text{CH}_3
\]

\[
\text{H}_2\text{O} \quad \text{[CH}_2\text{CH}_2\text{C} \quad \text{CH}_2\text{H}_2\text{II}
\]

wherein n is an integer from 7 to 10, inclusive, to a sufferer from the disease. Hereinafter in this specification ubiquinone is also referred to as "ubiquinone 5n" wherein n has the same meaning as in the above formula. Ubiquinone 5n is also designatable as coenzyme Qn.

Congestive heart failure is one of the most important and common disorders of heart functions, and is caused by poor contraction of the heart due to various etiologies.

Among the various etiologies, there are primarily a mechanical one which includes outflow load and inflow load and, secondarily, heart muscle damage itself.

Congestive heart failure has reference to such conditions that poor contraction is caused due to these etiologies, entailing insufficient blood output to each organ and tissue of the body, including congestion occurring posteriorly of the heart. Therefore, cardiac enlargement, dyspnea and edema are clinically observed as major symptoms of congestive heart failure.

Heretofore, digitalis has mainly been used in the treatment of congestive heart failure. In the treatment of congestive heart failure employing digitalis, however, intoxication due to, for example, administration of excessive amount of digitalis, has often occurred.

It is necessary to maintain a concentration of electrolyte, especially potassium, at a desired level, and it is often necessary to supply potassium due to inappropriate concentration of the electrolyte. Recently, it has been proposed to employ pure glycoside in place of powder of leaves of digitalis for attaining a constant activity, but the use of the pure glycoside tends to cause an increase in instances of intoxication. This fact is supported by an increase in the ratio of effective dose to toxic dose in the cases of aged patients, serious heart diseases, heart muscle damage, cor pulmonale, renal disease, dysthyreosis and liver function disturbance.

In addition to digitalis, xanthine derivatives have been employed for treating congestive heart failure, which are effective in the dilatation of the coronary artery and to increase cardiac output, and also as diuretic; and these derivatives have mainly been used together with digitalis in the treatment of lung congestion. But thorough going caution must be paid in the treatment of congestive heart failure with such xanthine derivatives, since they increase the oxygen consumption of the heart muscle as side effect, whereby symptoms of congestive heart failure are often exacerbated.

When congestive heart failure cannot be satisfactorily cured or improved by administration of digitalis alone or when digitalis intoxication is apt to be caused, diuretics have often been used as an auxiliary agent of digitalis, in addition to the above-mentioned xanthine derivatives, though they do not act directly on the heart muscle. Typical examples thereof are mentioned below:

Thiazides.—These are inhibitors of carbonic anhydrase and exhibit diuretic action due to their accelerative effect of excretion of sodium and chloride, but they often cause gastrointestinal disorder or eruption. Moreover, as they cause hypo-potassemia due to their action of excretion of potassium, digitalis intoxication is frequently to be expected.

Organic mercury preparations.—They inhibit succinic dehydrogenase and restrain reabsorption of sodium and chloride to give a diuretic effect, but they are contraindicated for those patients who have renal disturbance.

When excessive diuretic action is effected by administration of the organic mercury preparations, patients are sensitive to digitalis intoxication, and conversely when diuretic action is not effected, patients are sensitive to mercurial accumulation.

Acetazolamides.—These are inhibitors of carbonic anhydrase and show diuretic effect by inhibiting reabsorption of sodium, but there are observed such side effects as lassitude, drowsiness and paresthesia.

Anti-alderosterone.—These have been used as diuretics since alderosterone are considered to be a causing factor of edema, but they are inferior in diuretic effect to the above-mentioned medicines.

Adrenal cortical hormones.—They have been used as a last alternative only in a case when the above-mentioned medicines are not effective, because of their rather strong side effects.

As mentioned above, diuretics have widely been used in the treatment of congestive heart failure, but such use is bound up with the fatal defect that it is very difficult to make a proper administration, mainly due to their strong side effects.

The foregoing illustrates generally the hitherto-known methods for treatment of congestive heart failure. The hitherto-known methods, however, are not completely effective for such treatment.

Especially, among the hitherto-known medicines for
the treatment of congestive heart failure, only digitalis and xanthine derivatives act directly on the muscle of the heart. Moreover, in view of the undesirable side effects of digitalis and xanthine derivatives as mentioned above, it has been a desideratum in the art to provide effective and low toxic medicine for the treatment of congestive heart failure.

The desideratum has now been realized by the method of the present invention which comprises administering ubiquinone 5n of the formula

\[
\begin{align*}
 & \text{CH}_2O - \text{CH} - \text{C} - \text{C} \ldots - \text{C} - \text{CH}_2 \ldots \text{CH} - \text{OH} \\
 & \text{wherein } n \text{ is an integer of } 7 \text{ to } 10 \text{ inclusive, to a sufferer from the congestive heart failure.}
\end{align*}
\]

The principal object of this invention is to provide a method for the treatment of congestive heart failure, and this object is realized by administering ubiquinone to a sufferer from the disease.

Ubiquinone is also sometimes designated coenzyme Q and is one of the coenzymes which is present in animal and plant organs, and in microorganisms such as yeast, especially in the mitochondria of the cells and comprises such multiple homologues as ubiquinone 5, ubiquinone 10, ubiquinone 15, ubiquinone 35, ubiquinone 40, ubiquinone 45, ubiquinone 50, etc., according to the number of units in the isoprene chain. Therefore, ubiquinone 5n can be isolated from the above-mentioned sources. Ubiquinone 5n can also be prepared advantageously by utilizing the process described in Japanese Patent Publication Nos. 1,877/1955 and 10,169/1957.

In the present invention, ubiquinone 35, ubiquinone 40, ubiquinone 45 and ubiquinone 50 are used singly or in combination. Among them, ubiquinone 35 is practically used.

The acute toxicity of ubiquinone 35 is LD₅₀₋₀₋₀₋₀₋₀ of 4000 milligrams per kilogram when administered intraperitoneally to mice. Toxic manifestations are not observed with daily intraperitoneal injection of 10, 20 and 50 milligrams per kilogram, respectively, in rats for 30 days and no changes are observed histologically in the pituitary, thyroid, thymus, heart, lungs, liver, adrenals, spleen, kidneys or testes.

The dose of ubiquinone in the method of this invention varies depending upon the severity of the congestive heart failure and the administration method. However, the daily dose for an adult is generally about 0.6 to 40 milligrams per kilogram of body weight in oral administration, and about 30 to about 2000 milligrams per day in oral administration calculated on the body weight of the adult as 50 kilograms. The daily intravenous administration dose for an adult of ubiquinone is about 0.1 to about 20 milligrams per kilogram of body weight. When ubiquinone is administered in combination with any other drugs, the above-mentioned doses may be suitably changed.

In the present invention, it is preferable to administer ubiquinone by injection, especially intravenous injection, for realizing the object of the present invention.

According to the method of this invention, ubiquinone can be administered as it is or in a composition consisting of ubiquinone and a pharmaceutically acceptable liquid or solid carrier which is not incompatible with ubiquinone. The composition can take the form of tablets, powder, granule, capsules, injection or suspension. The solid carrier, which may be admixed with ubiquinone, can be, for example, cornstarch, lactose, talc, stearic acid, magnesium stearate, gums, or the like. The liquid carrier for injection or suspension can be, for example, water, vegetable oils, detergents, surface active agents, etc.

The following illustrative examples of preparations containing ubiquinone as an active ingredient are given:

1. A capsule containing 5.0 milligrams of ubiquinone 35 and 77.0 milligrams of granular lactose.
2. A capsule containing 20.0 milligrams of ubiquinone 35 and 230.0 milligrams of granular lactose.
3. A capsule containing 10.0 milligrams of ubiquinone 45 and 140.0 milligrams of granular lactose.
4. A capsule containing 20.0 milligrams of ubiquinone 35 and 230.0 milligrams of granular lactose.
5. An injection composition containing 10 milligrams of ubiquinone 35, 100 milligrams of surface active agent (ethylene oxide adduct of hydrogenated castor oil), 10 milligrams of benzyl alcohol, 9 milligrams of sodium chloride, and distilled water in an amount to make the whole amount 1 milliliter.
6. An injection composition containing 10 milligrams of ubiquinone 45, 100 milligrams of surface active agent (ethylene oxide adduct of hydrogenated castor oil), 10 milligrams of benzyl alcohol, 9 milligrams of sodium chloride, and distilled water in an amount to make the whole amount 1 milliliter.
7. Vial injection composition containing 50 milligrams of ubiquinone 50, 500 milligrams of polyethylene oxide sorbitan monoleate, 50 milligrams of benzyl alcohol, 45 milligrams of sodium chloride and distilled water in an amount to make the whole amount 5 milliliters.
8. Vial injection compositions containing 100 milligrams of ubiquinone 35, 1,000 milligrams of surface active agent (ethylene oxide adduct of hydrogenated castor oil), 100 milligrams of benzyl alcohol, 90 milligrams of sodium chloride, and distilled water in an amount to make the whole amount 10 milliliters.
9. A capsule containing 100 milligrams of ubiquinone 45 and vegetable oil.
10. A capsule containing 100 milligrams of ubiquinone 40 and 250 milligrams of granular lactose.

(11) An intramuscular injection composition containing 50 milligrams of ubiquinone 35 in vegetable oil, in an amount to make the whole amount 1 milliliter.

Clinical evaluation for treatment of cardiovascular diseases

(1) Material and method.—There were chosen 15 inpatients in the test who were suffering from congestive heart failure due to various kinds of cardiovascular diseases, including 6 cases of arteriosclerotic heart disease, 4 cases of hypertension, 6 cases of hypertensive heart disease, 4 cases of arteriosclerotic heart disease and one case of chronic cor-pulmonale.

Ubiquinone 35 was intravenously administered (50 milligrams daily) to the in-patients as an aqueous solution prepared by dissolving 100 milligrams of ubiquinone 35 in 10 milliliters of water, for 1 to 5 weeks depending upon the severity of the individual congestive heart failure.

In most cases, ubiquinone 35 was administered together with digitalis preparations; in some cases, ubiquinone 35 in place of digitalis administration was exclusively used in in-patients, and in cases where congestive heart failure was observed with digitalism, only ubiquinone 35 was administered.

(2) Result.—Results are shown in Table 1 and the summary thereof is shown in Table 2 where the effectiveness of ubiquinone 35 on congestive heart failure is evaluated with consideration of alleviation of dyspnea, reduction of hepatoma and edema. There are observed both increase of daily amount of urine and improvement of electrocardiographic findings in patients with congestive heart failure due mainly to arteriosclerotic heart disease, especially coronary arteriosclerosis.
### TABLE 1—CASE REPORTS TREATED WITH COENZYME Q

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis(s)</th>
<th>Daily dosage (mg)</th>
<th>Method of administration</th>
<th>Duration (days)</th>
<th>Combined use of digitals</th>
<th>Symptoms and signs before treatment</th>
<th>Effectiveness after treatment</th>
<th>Side effects</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>M</td>
<td>Mitral stenosis with aortic insufficiency</td>
<td>50</td>
<td>Intravenous injection</td>
<td>20</td>
<td>+ Dyspnea, moist, liver 1 lb. felt, daily amount of urine 600 cc.</td>
<td>Dyspnea disappeared.</td>
<td>None</td>
<td>Good.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>M</td>
<td>Hypertensive heart disease</td>
<td>50</td>
<td>Intravenous injection</td>
<td>15</td>
<td>+ Weakness, exertional shortening of breath, liver 2 lb. felt.</td>
<td>Weakness, shortness of breath disappeared, liver decreased to 1 lb.</td>
<td>Do.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>M</td>
<td>Mitral stenosis</td>
<td>50</td>
<td>do</td>
<td>8</td>
<td>- Fit of dyspnea everyday, digitalis intoxication.</td>
<td>Fit of dyspnea disappeared.</td>
<td>Do.</td>
<td>Excellent.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>F</td>
<td>Mitral insufficiency</td>
<td>50</td>
<td>do</td>
<td>10</td>
<td>- Dyspnea, moist, liver 2 lb. felt, pretibial edema, oliguria, RCO: STV 859 depressed</td>
<td>Dyspnea, moist, liver 2 lb. felt, edema disappeared, urine amount increased, ECO: ST depression disappeared.</td>
<td>Do.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>M</td>
<td>Arteriosclerotic heart disease</td>
<td>50</td>
<td>do</td>
<td>7</td>
<td>+ Fit of dyspnea</td>
<td>Fit of dyspnea unchanged, digitalis, thiaside not effective.</td>
<td>Do.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>do</td>
<td>50</td>
<td>do</td>
<td>20</td>
<td>- Weakness, cough, liver swelling.</td>
<td>Weakness disappeared, cough decreased, urine amount increased, cold feeling of legs disappeared.</td>
<td>Do.</td>
<td>Excellent.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>M</td>
<td>Chronic myocardial infarction</td>
<td>50</td>
<td>do</td>
<td>12</td>
<td>+ Cough, sputum, moist, daily amount of urine 600 cc.</td>
<td>Cough, sputum, daily amount of urine 1,000 cc.</td>
<td>Do.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>F</td>
<td>Hypertensive heart disease</td>
<td>50</td>
<td>do</td>
<td>35</td>
<td>+ Dyspnea, cough, ECO: T wave inverted.</td>
<td>Dyspnea decreased, cough disappeared, ECO: T wave disappeared.</td>
<td>Do.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>F</td>
<td>Mitral insufficiency</td>
<td>50</td>
<td>do</td>
<td>21</td>
<td>- Dyspnea, liver 5 lb. felt.</td>
<td>Dyspnea decreased, bradycardia, liver 3 lb. felt, urine amount increased.</td>
<td>Do.</td>
<td>Excellent.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>F</td>
<td>Mitral insufficiency</td>
<td>50</td>
<td>do</td>
<td>21</td>
<td>- Dyspnea, heart rate 90, moist, liver 2 lb. felt.</td>
<td>Dyspnea disappeared, heart rate 70, moist, liver 0.5 lb. felt.</td>
<td>Do.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>31</td>
<td>M</td>
<td>Mitral stenosis</td>
<td>50</td>
<td>do</td>
<td>7</td>
<td>- Exsanguination shortening of breath, edema.</td>
<td>Exsanguination, breath, edema disappeared.</td>
<td>Do.</td>
<td>Good.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>51</td>
<td>M</td>
<td>Chronic cor-pulmonale due to pulmonary hypertension</td>
<td>50</td>
<td>do</td>
<td>8</td>
<td>+ Dyspnea, edema</td>
<td>Dyspnea, edema disappeared.</td>
<td>Do.</td>
<td>Excellent.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>77</td>
<td>F</td>
<td>Hypertensive heart disease</td>
<td>50</td>
<td>do</td>
<td>10</td>
<td>+ Dyspnea</td>
<td>Dyspnea disappeared.</td>
<td>Do.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>54</td>
<td>M</td>
<td>Arteriosclerotic heart disease</td>
<td>50</td>
<td>do</td>
<td>10</td>
<td>- Dyspnea, moist, liver 2 lb. felt, daily amount of urine 400 cc.</td>
<td>Dyspnea, moist, liver 2 lb. felt, daily amount of urine 600 cc.</td>
<td>Do.</td>
<td>Excellent.</td>
<td></td>
</tr>
</tbody>
</table>

Criteria of judgments.—Excellent: Cases whose symptoms and signs of congestive heart failure disappeared or improved remarkably when Coenzyme Q is administered additionally during digitalis treatment, or when administered singly after interruption of the digitalis treatment. Good: Cases whose symptoms and signs are decreased. Not effective: Cases whose symptoms and signs are unchanged or worsened.

### TABLE 2—SUMMARY OF THE EFFECTIVENESS OF COENZYME Q ON CONGESTIVE HEART FAILURE

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Excellent</th>
<th>Good</th>
<th>Unchanged</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvular disease</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Arteriosclerotic heart disease</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Chronic cor-pulmonale due to pulmonary hypertension</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

Having thus disclosed the present invention, what we claim is:

1. A method for the treatment of congestive heart failure which comprises administering an effective amount of ubiquinone 5n of the formula

\[
\text{CH}_2=\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2
\]

wherein \( n \) is an integer from 7 to 10 inclusive, to a sufferer from congestive heart failure.

2. A method according to claim 1 wherein \( n = 7 \).

3. A method according to claim 1 wherein \( n = 8 \).
4. A method according to claim 1 wherein \( n \) is 9.

5. A method according to claim 1 wherein \( n \) is 10.

6. A method according to claim 1 which comprises administering orally to an adult human a daily dose of from 0.6 to 40 milligrams, per kilogram of body weight, of ubiniquinone of said formula.

7. A method according to claim 1 which comprises parenterally administering to an adult human a daily dose of from about 0.1 to about 20 milligrams, per kilogram of body weight, of ubiniquinone of said formula.

8. A method according to claim 7 wherein the parenteral administration is by intravenous injection.

References Cited

UNITED STATES PATENTS

3,113,073 12/1963 Grim 167—58

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ALBERT T. MEYERS, Primary Examiner.
H. M. ELLIS, Assistant Examiner.