Efficacy of the Hawthorn (Crataegus) Preparation LI 132 in 78 patients with chronic congestive heart failure defined as NYHA functional class II

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Summary

Seventy-eight male and female patients between the ages of 45 and 73, who were affected by chronic heart failure defined as NYHA functional class II, were treated either with Crataegus extract or with a placebo preparation. The extract LI 132 was administered to the patients in the form of 3 dragées a day (verum preparation) corresponding to a daily dose of 600 mg. Treatment was continued over a period of 8 weeks, with a wash-out phase of one week. The confirmatory parameter used to assess the efficacy of the preparation was the patients' working capacity which was measured using an ergometer bicycle. Before the start of the study, an increase in the patients' working capacity of at least half an exercise step on the ergometer bicycle (12.5 watt) was determined to be clinically relevant. Apart from the compatibility of the preparation, a score system was used to assess the severity level of the typical symptoms. From day 0 to day 56 of the trial, the median values obtained for the working capacity of the patients treated with the verum preparation were found to have increased by 28 watt, while the increase in the working capacity of the placebo patients was as little as 5 watt. The difference was statistically significant (p < 0.001). Apart from that, a significant reduction of the systolic blood pressure, of the heart rate and of the pressure-rate product was observed for the patients treated with the verum preparation, compared to the patients treated with the placebo preparation. Also, the clinical symptoms (score system) were found to have improved significantly. There were no severe side effects observed.

Key words: Crataegus extract, clinical trial, placebo controlled, chronic heart failure, ergometry, working capacity.

The extract of the dried drug (hawthorn leaves and blossoms) is indicated for the treatment of chronic heart failure defined as NYHA functional class II (Bundesanzeiger, 1984). This recommendation particularly applies to chronic heart failure in cases of coronary heart disease, since the use of the drug is reported not only to improve the pumping capacity of the heart, but also to reduce the patients' susceptibility to cardiac angina (Weiβ, 1991). In contrast to the cardiac glycosides and the digitaloids which mainly act on the cardiac muscle, hawthorn was found to act not only myocardially, but also peripherally on the vascular muscles, since it reduces the peripheral vascular resistance. This enables a more economical cardiac work, and causes the cardiac muscle to be strengthened (Pöpping, Fischer, Kammermeier, 1994).

So far, the efficacy of Crataegus preparations in the treatment of chronic heart failure has been investigated in a number of controlled clinical studies. However, the majority of these studies have been conducted on the basis of very simple methods, the objectivity and clinical relevance of which is not uncontested, since they were based on parameters such as the patients' general feeling of health or on the pressure-rate product (Iwamoto et al., 1981; Pozenel 1986; Pöpping et al., 1994). It was only in a few studies that cardiologically approved methods were used to test the patients' working capacity using an ergometer bicycle. The
studies conducted by Hanak and Brückel (1983) and Bodigheimer and Chase (1994), which were in compliance with the aforementioned criteria, and were based on a daily dose of 180 mg or 300 mg of Crataegus extract, yielded only a tendency towards an improvement of the working capacity, but did not yield any statistically significant differences in the verum and placebo groups.

For this reason, the dose used in this study was 600 mg of extract a day over a period of 8 weeks. Apart from the efficacy of the drug, the compatibility of this relatively high dose was investigated.

Patients, preparations and methods used: The study was designed as a multicentric placebo-controlled double-blind trial, in which at least 10 test centres with 10 patients each were involved. Each of the patients was assigned a consecutive random number upon his admission to the study. The randomization was performed in blocks of ten. The list of random numbers was not kept at the test institutes, but in a different place. The randomization code was disclosed to the individual test centres after completion of the study only. The physicians involved in the trial were handed sealed envelopes holding the data of patients, and were allowed to open such envelopes in the case of emergency only. At the end of the study, the envelopes had to be returned in a sealed condition.

The test preparation used consisted in dragées which contained 200 mg of Crataegus extract LI 132. The verum dragées were of the same appearance as the placebo dragées. The test samples had been labelled according to the testing recommendation for medical drugs. The daily dose used was 3 x 1 dragée, and the period of treatment was 8 weeks plus a wash-out phase of one week. The patients' compliance was checked by way of pill counting after 4 and after 8 weeks of treatment.

Admitted to the study were male and female patients between the ages of 45 and 73 with stable chronic heart failure defined as NYHA functional class II. The patients' initial maximum cardiac capacity measured by way of bicycle ergometry was required to range below 100 watt as a prerequisite. Not admitted to the study were patients affected by chronic heart failure defined as NYHA functional class III and IV, by cardiac angina at rest, cardiac infarction in the preceding 3 months, atrial fibrillation, ventricular extrasystoles of stage IV according to Lown, second- and third-degree atroventricular block, more than 20% overweight, obstructive respiratory tract diseases, and bodily defects which did not allow for the patient to be tested on the ergometer bicycle.

Apart from these pregnant or nursing women, and patients known to be addicted to alcohol, drugs or medical drugs were not admitted to the study. For the time of the study, the patients were not allowed to take cardially active preparations and cardiac glycosides, ACE-inhibitors, sympathomimetics, antiarrhythmics, vasodilators, beta blockers, calcium antagonists and long-acting nitrates. The patients were allowed to take diuretics if the diuretics had been administered to the patients in consistent quantities over a period of at least 4 weeks before the start of the study, and if the same doses were maintained during the study.

Basically, the patients were free to stop treatment and to drop out of the study, and all patients affected by severe side effects or by severe intermittent diseases which would not provide for the study to be continued or for its results to be evaluated, would have been advised by the attending physicians to stop treatment. Reasons had to be given for each drop out.

Before the start of the study, the maximum working capacity of the patients measured by way of bicycle ergometry was fixed as a confirmatory target parameter, i.e. the maximum wattage achieved by the patient over a period of 3 minutes on the ergometer bicycle, with the wattage stepped up in increments of 2.5 watt. If the patient's tolerance time was shorter in respect of the last increment, such exercise level was entered into the calculations with 8.33 watt/min.

As secondary target criteria the clinical symptoms, the patients' subjective feelings of health and the compatibility of the test medication, as well as the blood pressure, heart rate and pressure/rate product at rest and under load were used. The subjective symptoms were evaluated using a score system which included a number of 8 typical troubles ("general decrease in vitality", "exhaustion", "fatigability", "effort dyspnoea", "night dyspnoea" among others).

Each item was assessed semi-quantitatively using the severity levels 0 to 3 ("none", "slight", "median", "severe"). This drug study was conducted according to the principles of the Helsinki declaration. The positive vote of an independent ethics committee was obtained before the start of the study.

Statistical evaluation: All of the parameters were analyzed by way of elementary statistics, including the median values, standard deviations and minimum and maximum values obtained for them, and a frequency distribution curve was established for the categorization variables. For the purpose of statistical determination of the differences obtained in respect of the target parameters, the non-parametric procedures used in the Wilcoxon test (comparison of check times in the medication groups) and in the Mann-Whitney U-test (comparison of the medication groups) were used. As far as the categorization variables are concerned, the Chi square statistic was used.

Results: 78 patient records were returned by the attending physicians. The sociodemographic data of the patients are given in table 1. As far as the evaluation of results in respect of the drug's efficacy is concerned, 2 patients (1 verum, 1 placebo) had to be excluded from the study, since in the case of these two patients the wash-out phase had not
Efficacy of the Hawthorn (Crataegus) Preparation LI 132

been adhered to despite the premedication which had been provided for. In addition, another 2 patients of the verum group had to be excluded from the study for reasons of insufficient compliance (returned more than 20 dragees on the 56th day of the study). In the case of another 4 patients (3 placebo, 1 verum), the 25 watt increments had not been adhered to in any of the ergometer bicycle checks, and hence the results obtained for these patients could not be included in the evaluation of the ergometry test.

Table 1. Summary of the sociodemographic data of the total of 78 patients.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Crataegus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of patients:</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>male</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>female</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.4 (± 6.5)</td>
<td>60.3 (± 7.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.0 (± 9.1)</td>
<td>168.2 (± 7.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.5 (± 10.9)</td>
<td>70.6 (± 8.8)</td>
</tr>
</tbody>
</table>

The statistical test conducted before the start of the study yielded comparable data for the different patient groups as far as the sociodemographic data, the time of treatment and the total of main and secondary target criteria of this study are concerned.

There were no differences observed between the patient groups in respect of associated diseases and pre- and concomitant medication, which could have been relevant to the outcome of the study.

The median value obtained for the working capacity of the patients by way of bicycle ergometry was 79 watt for the verum group on the day 0, and on the 28th day of treatment was 99 watt, and on the 56th day was 107 watt. The values obtained for the placebo group were 71 watt, 74 watt and 76 watt. The differences between the two groups, which were obtained using the U-test were of high statistical significance (p < 0.001, Fig. 1) on the 28th and 56th day of treatment.

Fig. 2 additionally shows the number of patients in the verum and placebo group, who achieved an exercise level of up to 150 watt on the 56th day of treatment. It may be seen from this figure that nearly all patients from both groups achieved an exercise level up to 75 watt, while a considerable proportion of the patients in the verum group achieved higher levels of 100 or 125 watt.

The Figures 3 and 4 show the behaviour of the blood pressure and of the heart rate under maximum load. Under verum, the systolic blood pressure was found to have dropped significantly from 171 to 164 mmHg, and the heart rate to be reduced from 115 to 110 beats per minute from the 0 to the 56th day of treatment. There were no significant changes observed for the diastolic blood pressure under verum, and for the blood pressure and heart rate under placebo.

Figure 5 shows the development of the pressure rate product as a standard of orientation in respect of the cardiac work. In correspondence with the aforementioned values obtained for the factors forming part of this product, significant differences between the two groups were observed as far as the reduction of cardiac work in the treatment with Crataegus was concerned.

The Figures 6 and 7 give typical examples of the development of the severity level of the cardiac troubles and symptoms. Figure 8 gives a summary of the development of the median score values of the total of heart-specific items. The differences between verum and placebo patients were of high statistical significance after 28 and 56 days of treatment. In addition to this, figure 9 gives the absolute frequency of symptoms in the verum and placebo groups prior to and after treatment.

Figure 10 gives the results in respect of the physicians' assessment of efficacy, which confirm the superiority of the
verum preparation. In both of the patient groups, the compatibility of the preparation was good. In the verum group, temporary nausea was reported by one patient, and single cardiac trouble by another patient on the 8th day of treatment. In the placebo group, dryness of the mouth and internal restlessness were reported by one patient each. In all of the cases, it was doubted by the attending physicians that the troubles reported were connected to the test medication.

Discussion: This study was conducted with substantially higher doses and over a longer period of time than were the Crataegus studies available so far. This is supposed to answer the question of the extent to which the efficacy of the preparation drug, as indicated by the results obtained by bicycle ergometry, is dependent on the dose and period of treatment.

A comparative evaluation of the results of this study is possible in respect of the studies conducted before by Bödigheimer and Chase (1994) in particular. The design of the study and the groups of patients admitted to were very similar in both of the studies, in which the same verum preparation was used. However, Bödigheimer and Chase provided for a daily dose of 300 mg of extract to be administered to the patients over a period of 4 weeks only. When using this dose, the median values obtained for the working capacity of the patients were found to have improved by 15 watt under verum, and by 9 watt under placebo in the course of treatment of 4 weeks, and hence the difference between verum and placebo was as little as 6 watt. In this study, the improvement measured over the same period of time after deduction of the placebo effect was 17 watt, with the differences between the two groups increasing by another 6 watt until the 56th day of treatment. It may be seen from such differences that the clinical efficacy of Crataegus extract is also dose- and time-related.

The dose-relatedness of the positive inotropic effect of
Fig. 4. Same as figure 3, except for median values obtained for the heart rate under maximum ergometric load. There was a significant reduction observed for the verum patients. (** = p < 0.01).

Fig. 5. Median values of the pressure/rate product. Just as in the figures 3 and 4, there were significant differences observed between the two groups in favour of the verum therapy. (* = p < 0.05, ** = p < 0.01).

The hawthorn extract used in this study was confirmed very recently in experiments on isolated cardiac muscle cells. The increase of the extract concentration in the test medium from 30 to 120 g/ml yielded an increase in the contraction amplitude by almost factor 4. Hence, the relative increase of effects observed in the clinical experiment after doubling the dose of 300 mg (used by Bödigheimer) to 600 mg which were used in this study, almost corresponds to the dose/effect relation which was proved in the pharmacological experiments.

According to the results of this study, the compatibility of the hawthorn extract is guaranteed for higher doses also. There was no connection established by the attending physicians between the test medication and the temporary cardiac trouble reported by one patient of the verum group, although it is true that there could be a causal relation in respect of the vasodilatative effect and the significant reduction of the systolic blood pressure in exercise. The fact speaking against such a relation, however, consists in the simultaneous decrease of the heart rate, which would have to increase through a typical peripheral vasodilator to cause such cardiac trouble.

Another question to be answered is whether the results of the study are clinically relevant. Does chronic heart failure defined as NYHA functional class II represent an indication for pharmacotherapy at all – no matter how compatible such therapy may be? It is not possible to answer this question in a global manner, i.e. to answer it irrespective of the individual case of treatment. It may be seen from figure 2 that no improvement in the patients' working capacity was observed at all in the treatment with the Crataegus preparation for exercise levels below 75 watt, whereas a distinct improvement was observed for exercise levels of 100 and 125 watt. After 56 days of treatment, 21 patients of the verum group, but only 4 patients of the placebo group had achieved an exercise level of 125 watt. From this we can
Fig. 6. Changes in the frequency and severity levels observed for the symptom “general decrease in vitality” under verum and placebo medication in the course of treatment over a period of 56 days.

Fig. 7. Same as figure 6, except for the symptom “effort dyspnoea”.

Fig. 8. Median values obtained for the total score of subjective troubles. Just as for the confirmatory parameters (figure 1), there was a significant increase in the differences between the two groups observed until the 56th day of treatment (*** = p < 0.001).
conclude that especially patients who are exposed to physical load corresponding to 100–125 watt will benefit from the treatment with Crataegus, if the drug is administered in adequate doses. This does not only apply to the construction worker, but also to the pensioner who has to climb several flights of stairs to reach his apartment.

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