

## LAENNEC Clinical Data

### A Double-Blind Study to Assess The Efficacy of LAENNEC on The Treatment of Chronic Hepatic Disease

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In 1933, Dr.V.P.Filatov reported using subcutaneous embedding method to apply refrigerated human placenta successfully treats cicatrical contracture and gastric ulcer. Our country(Japanese) Prof. Hieda also had tried to use human placenta on treatment of hepatic diseases, and it showed effective. Human placenta was dissolved by adding water to make commodity preparation namely LAENNEC. Regarding the studies on its theory and effect had been summarized by Prof. Hieda in “An approach to the treatment of liver cirrhosis and spontaneous gangren” (1968, published in Medical Review). After this, though there were some related clinical experience reports, from present knowledge of evaluation effect, these are not sufficient.

In order to confirm the efficacy of this preparation on chronic hepatic diseases, Double-blind, Cross-over test was this time. Effective results were reported bellow.

### **Object and Method**

#### **1. Object**

Subjects with chronic hepatic diseases were selected, i.e. GOT, GPT values revealed abnormal constantly. Acute hepatic dysfunction exists well trend in self-cure, easy to cure and natural relief, so acute hepatic dysfunction was excluded. Therefore all cases selected mainly liver cirrhosis and chronic hepatitis.[Table 2 (3)].

Involved medical institutions were 1<sup>st</sup> department of Internal Medicine, Nippon Medical School, Department of Internal Medicine, School of medicine, Keio University, Department of Internal Medicine,(Digestive Organs), Department of Internal Medicine,(Digestive Organs), Department of Internal Medicine, (Digestive Organs) Dai-San Hospital, The Jikei University, School of Medicine, Department of Internal Medicine, Tokyo Medical College, 1<sup>st</sup> Department of Internal Medicine, Faculty of

Internal Medicine, 1st Department of Internal Medicine, School of Medicine, Gunma University, Department of Internal Medicine, Mishuku Hospital, Tokyo, 3<sup>rd</sup> Department of Internal Medicine, Kyoto Prefectural University of Medicine, 2<sup>nd</sup> Department of Internal Medicine, School of Medicine, Kagoshima University, Department of Internal Medicine, Senso-Ji Hospital, Department of Internal Medicine, The Medical Institute of Sakai Foundation, Kyoundo Hospital, Department of Internal Medicine, Fukuoka Saisei-kai General Hospital, Department of Internal Medicine, Matsuyama Red Cross Hospital and Department of Internal Medicine, Sakai Municipal Hospital etc., a total of fifteen institutions.

The above medical institutions collected test reports of 144 cases. Excluded those cases which did not criteria (described later), there were 124 cases for final analysis (Table 1)

## 2. Administration method

Prior to administration observed for at least 1 week, then subject was given either LAENNEC(A) or Placebo(P), and exchanged two weeks later, this procedure would be repeated, total 8 weeks. (Cross-over), i.e.A-P-A-P group(as group I) and P-A-P-A group(as groupII).

Method : LAENNEC one ampoule 2ml intramuscular injection once daily. Placebo was mainly saline, its appearance, the container, mucosity, foamingness and pH value were all the same as LAENNEC.

About distribution double-blind test was counted with randomization table in each institution. The other randomization tables were kept by Mr.Ueda in safety box till study finished.

In addition, consideration of prior to this trial, it is possible that other hepatic medications had been used, so it is stipulated that those who did not use hormone or under this condition of having used other medications, the same medications and doses remained unchanged could be included.

## 3. Withdrawal criteria

Though having made stipulation to above objective and medications to be noted, some cases occurred problems during study in each institution. Thus, Mr. Ueda, Okayama, Namihisa and Horiguchi composed a committee and made the definition of withdrawal cases before the randomization tables were opened.

(a) Exclusion of diagnosed acute hepatitis

(b) Prior to enroll into the trial, those cases with icterus index above 25 units. Serum

bilirubin above 4mg/dl, GOT and GTP above 300 units being considered as probably aggravated cause to hepatic dysfunction were excluded

- (c) For the cases associated with complication, committee analyzed each case, and made the decision of whether the case will be defined as withdrawal case before randomization tables were opened. For example, those with hepatocarcinoma or complications of urinary bladder cancer were excluded.
  - (d) Exclusion of all cases using improper medications (Such as Chlorpromazine, etc, which can cause hepatic dysfunction significantly.)
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#### 4. Evaluation method

For evaluation measurements, subjective symptoms were unreliable, so liver function test values (GOT, GPT, serum total protein, albumin,  $\gamma$ -globulin, TTT, ZTT and total cholesterol) were taken as parameters. About handling of each test value and logarithmic transformation in normal distribution were dealt with logarithmic transformation method.

For evaluation of the efficacy, values in pre-administration and post administration 2 weeks, 2 weeks and 4 weeks, 4 weeks and 6 weeks, 6 weeks and 8 weeks were respectively analyzed by statistic method by Mr. Onoda.

### **Results**

Before the trial, gender, disparity in age, different category in diseases and concurrent medications in two groups were determined. The evaluation results were described on Table 2. Each group did not show significant difference, i.e. distribution of two groups was without deviation.

Summary of efficacy, showed as Table 3, only showed values of significant changes.

Among liver function tests, GOT and GPT were changed most significantly. i.e., according to LAENNNEC administration, in the same group GOT values in pre-administration and post administration 2 weeks, 2 weeks and 4 weeks, GPT values in pre-administration and post administration 2 weeks, 2 weeks and 4 weeks, 6 weeks and 8 weeks were determined. In the result, the change trend showed obvious reduction(Fig.1, 2).

The obviously changed GOT values were recorded on table 4, those of GPT were recorded on table 4, those of GPT were recorded on Table 5.

About statistic method, GOT results in pre-administration and post administration 2

weeks, and the comparison result on A administration and P administration were recorded on Table 6. With above the same statistic method, liver function test values in different period were sorted out respectively.

Because the data was too much only above results were shown.

Besides, though Al-P and TTT value between pre-administration and post administration 2 weeks shown obvious reduction, while administration of Placebo Al-P also shown reduction. It is difficult to determine the effect of the medication. While administration of Placebo 2 weeks and 4 weeks, albumin showed obviously increased. It maybe because the effect of Placebo showed faster or that of LAENNEC shown more slowly between pre-administration and post administration 2 weeks, it is also difficult to make decision. Same as above, while administration of Placebo between pre-administration and post administration 2 weeks A/G shown obvious reduction (aggravation), and in 6 weeks, 8 weeks  $\gamma$ -globulin shown obviously increased (aggravation), for this it is also difficult to make decision.

About side effects, during trial one case was suspected to occur side effect. There were no specific abnormal events while administration of Placebo, but when changed to injection of LAENNEC once later. Occurrence of local redness, subsequently local itching was reported. Second day injection was in deltoid of the other side, the same redness, slight swelling and itching as first day occurred again. So it is recognized that these were the side effects of this preparation and the treatment was stopped. After stopping using the preparation, the case was observed for a certain period and found no specific abnormal, liver function test did not show aggravation.

In addition, complaint of injection site pain while injection in three cases, but it also happened in Placebo injection. It is considered that muscles occurred nonspecific reaction to injection.

### **Discussion**

About effect evaluation to treatment of hepatic diseases, there are still many problems. There is no standard method available yet. At present, though we are familiar with many kinds of evaluation method for effect of medications, just as what Mr. Gao Chiao said that the reliability is low.

Recently, double-blind test is adopted as the most effective method to exclude selective error in cases and evaluation error in effect. It is also used in hepatic medication field. Such as acute hepatitis and natural cure diseases, it is impossible that treatment and placebo were carried out in same case.

However it is possible (Cross-over method) in chronic hepatic diseases. Applying of this method is the most ideal to eliminate all cases deviation and resolve problems of concurrent medications. If the trial was repeated again respectively, and the results were confirmed again, it is considered that this method was more integrated than other evaluation methods for effect of medication. Besides, if evaluation effect is objective measurement similar to liver function test, it is unnecessary to carry out double-blind test. For decision to withdrawal cases, in order to avoid withdrawing cases, which may cause favorable results to the trial, the decision of withdrawal cases was made before opening the randomization table. This method plays very important role in eliminating error.

As shown below table 2, cases distribution, gender, age, different category in diseases and concurrent hepatic medications prior to administration were tested. The difference test was carried out between group I and III. The result shown no significant difference, whereas similar to value in initial random distribution.

There are various liver test values, including sensitive and insensitive method, from icterus index evaluation to detoxication method etc. based on designed plan of administration of LAENNEC 2 weeks, then changed one time to administration of Placebo needed 4 weeks, repeat again needed 8 weeks i.e. 2 months. Considering this preparation in injection, mainly used inpatients. However hospitalization in internal department are limited in 2 months namely 8 weeks. If subjects were discharged in half way, the trial will be difficult to be carried out. We were worried about trial continuation. In addition, as everyone knows effect of injection is faster than that of oral, it is considered that 2 weeks is enough to observe effect in this preparation. But if only 2 weeks, provided the test is insensitive, it is possible that before effect of medication is confirmed the trial will may have proceeded to Placebo period. This is main reason why taking GOT, GPT as parameters to evaluate effect.

To the sensitive extent, BSP is also similar to GOT, GPT, under majority liver cirrhosis (half in our trial), BSP value is mostly affected by existing of ascites. The value shows ascities extent, not hepatic diseases release. For this reason, BSP was not adopted as evaluation measurement.

About constant effect of medication, namely after administration of LAENNEC for 2 weeks, changed to Placebo, it is impossible that not considering whether the effect affected to Placebo period, that is to say whether Carry-over Effect existed. The best way to prevent this occurrence of possibility is prolonging administration period. Because of abovementioned clinical reason, the administration period was still 2 weeks.

The results were as expected, while test of the results, showing phenomenon of effect of medication involved to Placebo period. With the lapse of time, all test values during changing administration occurred unavoidable difficult cases. But for determining whether it occurred with the lapse of time, it was compared with related pre-symptoms groups. In the result, about occurrence of cases in difficult examination, except Cholesterol Ester type shown significant difference between 4~6 weeks group, other groups, comparing with related pre-symptoms groups, shown no significant difference under all conditions.

Above, the study used unprecedented strict method. In GOT changes, one group was between pre-administration and post administration 2 weeks ( $p < 0.01$ ), one group was changed to LAENNEC 2 weeks later and 4 weeks later ( $p < 0.05$ ). Among significant differences, groups after using LAENNEC showed lower. GPT change was also the same, between pre-administration and post administration 2 weeks ( $p < 0.025$ ), post 2 weeks and post 4 weeks ( $p < 0.05$ ), post 6 weeks and post 8 weeks ( $p < 0.025$ ), shown significantly low.

This preparation contains various Amino acids, possesses effects of anti-fatty liver, improvement of hepatocyte function, reviving tissue respiration and enhancement of regeneration function in hepatic parenchyma. And it can improve GOT, GPT value. If application over 2 weeks, this action will improve ZTT and albumin etc. About these comments have been reported.

Conclusion from above results: based on evaluation of GOT, GPT values, LAENNEC is an effective medication on treatment of chronic hepatitis and liver cirrhosis.

### **Comment**

For study efficacy of LAENNEC on treatment of chronic hepatitis and liver cirrhosis, double-blind, Cross-over method was adopted. Using liver function tests, especially GOT, GPT tests to evaluate efficacy. The results obtained appreciation of [through GOT, GPT evaluations to prove that application of LAENNEC obtained obvious effect].