

—Original Article—

THERAPEUTIC EFFECT OF CHLOROPHYLL-A IN THE TREATMENT OF PATIENTS WITH CHRONIC PANCREATITIS

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Summary

The favorable clinical effects of water-soluble form of chlorophyll-a in the treatment of patients with chronic relapsing pancreatitis are described.

1) 34 cases were treated with chlorophyll-a infusion and fairly favorable effect was obtained in 23 cases and some favorable effect, in 9 cases.

2) The most disgusting symptom of pancreatitis, the abdominal pain disappeared in a week or so with infusion of 5-20 mg of chlorophyll-a per day for 1-2 weeks, in all the effective cases.

3) Patients have become well controlled by intermittent administration of chlorophyll-a, even when they had recurrences.

4) 5 cases which had difficulty in the treatment by trasyolol, were also successfully treated with chlorophyll-a.

5) In all the cases treated with chlorophyll-a, no unfavorable side-effect, such as of allergic, or photosensitive, or hepatotoxic nature, was hitherto observed.

Key Words: *pancreatitis, chlorophyll-a, protease inhibitor.*

Introduction

The purpose of this paper is to describe the favorable clinical effect of water soluble form of chlorophyll-a in the treatment of pancreatitis, especially of chronic pancreatitis.

When treatment of pancreatitis is intended to start on an actual case, swift recall should usually be made on sound physiologic principles based on what is known and accepted today about the disease—etiology, pathology classification, manifestations, treatment, prog-

nosis etc. of the disease. This view seems especially important in case of pancreatitis because of its complexed clinical features.

Among informations on the basic pathochemical mechanisms of the pancreatitis, liberation of active trypsin in the pancreatic tissue would be considered the earliest and the most important in the early phase of the disease. The liberation of active trypsin, without doubt, might lead to causes of severe pain and other manifestations, and to the successive pathological process of pancreatitis¹⁾.

On the other hand, from clinical aspects, the most important thing is to see and define the severity of the disease at the beginning. In severe case of acute pancreatitis, circulatory

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collapse derived from neurogenic shock or fluid-electrolyte imbalance is encountered and not seldom becomes primary cause of death. Accordingly, frequent emphasis is placed on adequate parenteral replacement of the loss of electrolyte and fluid in these cases²).

For less severe or milder cases, it seems important that the liberation of active trypsin in the tissue should be suppressed in the first order. Because, it is widely accepted that the liberation of active trypsin in the tissue is in a key position in the chemical pathology of pancreatitis¹). For this purpose, the use of trasylol (trypsin-kallikrein-inhibitor) is often attempted today widely in the world. Though this remedy is widely considered enough effective in the most of the cases^{3,4}), immunization by its repeated administration has been reported to lead to anaphylactic shock in not smallest number of cases.

In 1968, we found a fact that some derivatives of chlorophyll-a have inhibitory effect on trypsin digestion and at the same time, we had an experience of a case who was successfully

treated with infusion of water-soluble form of chlorophyll-a^{5,6}). Since that time, clinical trials of this medicine have been repeated on patients with chronic pancreatitis by us and others. In this paper, the results of treatment with chlorophyll-a on 34 cases of the patients are reported and some discussion is made on the comparative effect of this medicine to trasylol.

Objects and Methods

The object of this study was totally 34 patients with chronic pancreatitis, among which, 11 were the cases who had been hospitalized to the ward of the first department of medicine at University Hospital, Medical School, University of Tokyo, during the certain period of the time between January 1968 and 1969 (Table 1), and 19 were the cases who were treated at the related outpatient clinic in Tokyo during the time between July 1969 and 1973 (Table 2), and 4 were also hospitalized patients observed during the same period as those of outpatient clinic (Table 3).

The water-soluble form of chlorophyll-a pre-

Table 1. Hospitalized patients

No.	Initial	Age	Sex	dose mg/day	Date of onset of effect	effectiveness	complication	comments
1	AH	36	M	20 mg	2nd	fairly enough		received TKI 6 months ago
2	MY	27	M	10 mg	1st	fairly enough	diabetes mellitus	Several severe attacks at 18 years ago
3	MH	45	M	10 mg	1st	fairly enough	cholelithiasis	
4	MI	46	M	10 mg	1st	fairly enough		received cholecystectomy
5	HM	51	M	10 mg	3rd	fairly enough	diabetes mellitus & lung tuberculosis	
6	OK	80	M	10 mg	5th	fairly enough		
7	NM	32	F	10 mg	1st-2nd	fairly enough		
8	TS	38	F	10 mg	1st	fairly enough		Fig. 1
9	TH	32	M	15 mg	5th	enough		diagnosed as acute pancreatitis twice, 1 and 2 years ago
10	KK	40	F	10 mg	7th	enough		
11	CE	64	M	20 mg		no	gastric ulcer	surgical operations for portal hypertension & biliary peritonitis

TKI: Trasylol.

Table 2. Out-patients

No.	Initial	Age	Sex	dose mg/day	Date of onset of effect	effectiveness	complication	comments
1	GA	35	M	15 mg DI	2nd	fairly enough		Fig. 2
2	NF	36	M	10 mg DI	2nd	fairly enough		received TKI 1 year ago
3	AH	39	M	20 mg DI	3rd	fairly enough		gallstone attack during pancreatic episode
4	FM	39	M	15 mg DI	1st	fairly enough		
5	YK	51	M	10 mg IM	1st	fairly enough	gastric ulcer	
6	HE	20	F	10 mg DI	1st	fairly enough		
7	MK	22	F	10 mg DI	2nd	fairly enough		
8	NA	25	F	10 mg DI	1st	fairly enough		
9	SK	25	F	10 mg DI	3rd	fairly enough		
10	MN	25	F	10 mg DI	3rd	fairly enough		
11	TC	31	F	15 mg DI	1st	fairly enough		
12	FT	28	M	5 mg IM	a few hours	enough	gastric ulcer	IM of chlorophyll-a only when he had severe pain
13	KS	36	M	10 mg IM	a few hours	enough	duodenal ulcer	IM of chlorophyll-a only when he had severe pain
14	HK	40	M	10 mg DI	5th	enough	gastric ulcer	
15	SH	45	M	15 mg DI	3rd	enough	gastric ulcer	
16	HK	21	F	10 mg DI	1st	enough		experienced circulatory shock after TKI
17	KN	24	F	15 mg DI	5th	enough		
18	NF	54	F	10 mg DI	2nd	enough	chronic hepatitis	
19	DK	48	F	10 mg DI		no		

DI: direct infusion. IM: intramuscular injection.

paration used in this study was supplied by Nampo Pharmaceutical Company, Tokyo, and this was developed by its Research Laboratory. Each Ampule contains 5 mg of chlorophyll-a in 5% 1ml glucose solution. Injected dose of

chlorophyll-a in a day was 5-20 mg and administered by intravenous infusion being mixed with 200-500 ml of saline or 5% glucose solutions, singly or divided in two time a day. Total amount of administered chlorophyll-a

Table 3. Hospitalized patients

No.	Initial	Age	Sex	Dose mg/day	Date of onset of effect	effectiveness	complication	comments
1	HT	40	M	15 mg DI	2nd	fairly enough		see the text
2	YR	45	M	10 mg DI	3rd	fairly enough	duodenal ulcer	see the text
3	EM	47	M	10 mg DI	2nd	fairly enough		see the text
4	UM	37	F	15 mg DI	5th	fairly enough	protein-losing gastroenteropathy	see the text

was different from patient to patient, ranging 30-1,960 mg. Total treating period with chlorophyll-a also varied, ranging 3 days to about 3 years. For the treatment of out-patients group, a definite administration program was set as is seen in later pages. Other administration methods, if any, are indicated in the related tables.

Trasylol (trypsin-kallikrein-inhibitor) was used in 5 cases, in one of which chlorophyll-a was used in combination with trasylol. 2 among the above cases, were given trasylol by us and other 3 cases were administered at other institutions in previous time, the details of which were not clear. The dose of trasylol we administered to the patients was 25,000-100,000 units each time, mixed with some 500 ml of 5% glucose and total amount administered was up to 75,000-750,000 units during the time of 3-30 days.

Determination of amylase in serum and urine was performed by the method of Smith-Roe (Table 2, 3), though in some cases, it was measured by Wohlgemuth method (Table 1)⁷⁾.

Diagnosis was made according to the criteria being based on the appropriate evidences available in clinical symptoms and signs, laboratory tests, surgical tests and histopathological informations. The type of chronic pancreatitis was basically identified according to the concepts appeared in the classification

adopted at Marseilles Symposium⁸⁾. As authors believe that too strict categorization of the pancreatic cases, so that the concept may have fear to exclude cases from pancreatitis, would not be advantageous especially for exploration of therapeutic measures, our diagnostic concept must have been broadened in relation to other clinics.

Judgement of curative effect of chlorophyll-a studied was made by the grade of improvement in the clinical symptoms and signs and laboratory tests, emphasizing especially on the improvement of abdominal physical signs and relief of the pain.

As for the concomitant complications, the cases were omitted from the study in which clinical symptoms and signs were considered directly related to and those seem to have been secondary to the complication present. Therefore, the complication listed in the tables should be deemed to be the ones of less significance.

Results and Case Presentation

34 patients, 20 male and 14 female, were studied. The type of chronic pancreatitis in all 11 hospitalized cases listed in Table 1 was considered of progressive nature at the time of their admission. The hospitalized patients listed in Table 3 were the cases which have some difficulty in control of the complaints

under the treatment program, which was set for out-patients. The nature of their diseases themselves were of less severe grade. 19 cases, 9 male and 10 female, were treated out-patiently under the definite treatment program (Table 2). The program was as follows: daily dose set for each patient as listed in Table 2, was administered daily during the first week and in the second week, the same dose was given for 3 days in every other day, and in the third week, the patients were called just to receive clinical observation and for laboratory tests in three days of the week.

The grade of curative effect of chlorophyll-a treatment was defined as fairly enough effective, enough effective and not effective. Its judgement was based on the improvements in abdominal physical signs, serum and urine amylase levels and other clinical tests, such as X-ray examination tests, and finally, the categorization into 3 grades was made according to the length of time, within which abdominal pain had subsided; namely, when the recurrent pain disappeared within 5 days from the start of chlorophyll-a treatment, it was categorized as fairly enough effective, and when it was accomplished after 6 days, it was as enough effective, and when the pain was not cured, it was as not effective even in the case in which improvement in other signs and tests was observed. During the chlorophyll-a treatment, the patients were not administered any other medicine, such as anticholinergics.

Ages of the patients were distributed in the range between 27 and 64, except one case of 80 years old male.

24 hour urine amylase levels of hospitalized patients were in the range of 8,300-15,800 Smith-Roe unit in 24 hours urine at highest (2, 3, 4, 5, 6, 8 in Table 1). The case 1-1 showed 198,000 Smith-Roe unit in 24 hour urine and the case 1-7 showed 1,024 Wohlgemuth unit in the urine respectively, at the time of their

admission.

In the cases of out-patient group, the amylase levels were in the range of 140-1,030 unit in sera and 280-7,010 Smith-Roe unit in 24 hour urine. As for the cases listed in Table 3, amylase levels were already normal at the time of their admission, though their urine amylase levels were recorded in the range of 350-900 Smith-Roe unit before.

All these high levels of amylase returned to normal range after the treatment program was accomplished. In some cases, increase of amylase level was again observed when the patient had recurrent attacks afterward, but it returned to normal after repeated chlorophyll-a treatment.

Concomitantly with the improvement of amylase level, symptoms and signs such as abdominal pain, fullness, loss of appetite, weakness, fever etc. disappeared in almost all the cases, some of the clinical course of which are illustrated in the section of case presentation downward.

We identified categorization of the results as follows: In hospitalized cases in Table 1, there were 8 fairly enough effective ones and 2 enough effective ones among 11 cases. In the outpatients group which consists of 19 cases, there were 11 fairly enough effective, 7 enough effective and 1 not effective cases. All the cases in Table 3 were revealed as fairly enough effective. Finally, among 34 cases in this study, the chlorophyll-a treatment was observed fairly enough effective in 23 cases, enough effective in 9 cases and not effective in 2 cases.

Phenomena common to almost all the cases observed after administration of chlorophyll-a in this study were summarized as follows: The most prominent effect was found in rapid relief of abdominal pain and next, in the decrease of serum and urine amylase levels. The relief of abdominal pain was usually occurred in 20-30 minutes after chlorophyll-a infusion. But the

most of the patients experienced the recurrence of slight upper abdominal pain 4-5 hour after the infusion had been finished, and this pain again had subsided in 10-20 minutes without any treatment. The decrease of amylase levels also occurred in rather short time after the infusion had been finished. However, there was observed a very peculiar fact that there was slight increase of urine maylase levels in many of the cases in few hours after the first trial of chlorophyll-a infusion or in the second day of chlorophyll-a treatment program, and these increments were observed transient and after 3 days, amylase levels decreased steadily to normal value within a week.

The time course of serum and urine amylase levels of the case 2-1 is given as a typical example in order to show the way by which amylase levels may decrease after chlorophyll-a treatment. Serum amylase levels on the first day were 1,030 unit before the chlorophyll-a infusion and 450 unit just after the infusion; on the 3rd day, 400 unit before and 162 unit after; on the 6th day, 95 unit before the infusion. The above value represents unit per 100 ml of blood. Urine amylase output per hour during the same treating schedule, were; on the first day, 3,673 unit before chlorophyll-a infusion and 5,580 unit after the infusion; on the 2nd day, 7,010 unit before and 5,690 unit after; on the 3rd day, 1,210 unit before and 486 unit after; on the 4th day, 271 unit before and 29 unit after the chlorophyll-a infusion (Fig. 2).

This case had another recurrent attack 7 months after the above experiment, on which occasion, change of the amylase values followed very similar course mentioned above, and at this time, amylase levels returned to normal in 6 treating days.

Case Presentation

Hospital Patients (Table 1)

Case 1-1. 36 year male

He was hospitalized as an emergent patient because of the severe attack of abdominal pain with a clear sign of paralytic ileus. As he had been diagnosed as acute pancreatitis and the treatment with trasyolol had led him to a complete remission several years ago, at the time of the second admission, he was diagnosed as recurrence of acute pancreatitis. The dose of trasyolol used at the previous time was 50,000 unit each time for several days. On the second admission, he had started to receive chlorophyll-a infusion at the dose of 20 mg per day since his 2nd hospital day. The serum amylase level was 560 Smith-Roe unit and urine amylase level was 198,000 unit at the time of admission. In the second treating day, most of the symptoms including abdominal pain had subsided and all of his complaints and increased levels of amylase had also disappeared in a week. One year later, when he had another recurrent attack, he was treated again with chlorophyll-a and had got a complete remission.

Case 1-7. 32 year female (illustrated in Fig. 1)

This was the case that we had made the first trial of chlorophyll-a to pancreatitis and its results were already published before^{5,6}. Her first attack of pancreatitis had occurred at 28 years of age and since that time, she had become almost unable to conduct her normal social life, because of the presence of various persistent symptoms including abdominal pain. At her 31 years of age, she was treated for the first time with trasyolol and it gave her some favorable effects except persistent dull pain. On the recurrence at her 32 years of age, she was transferred to the University Hospital, University of Tokyo. At the time of admission, she complained of severe abdominal pain and movable tumorous mass with consistency increment was palpable on her upper abdominal region. The highest urine amylase level of 4,096 Wohlgemuth unit was recorded. She was

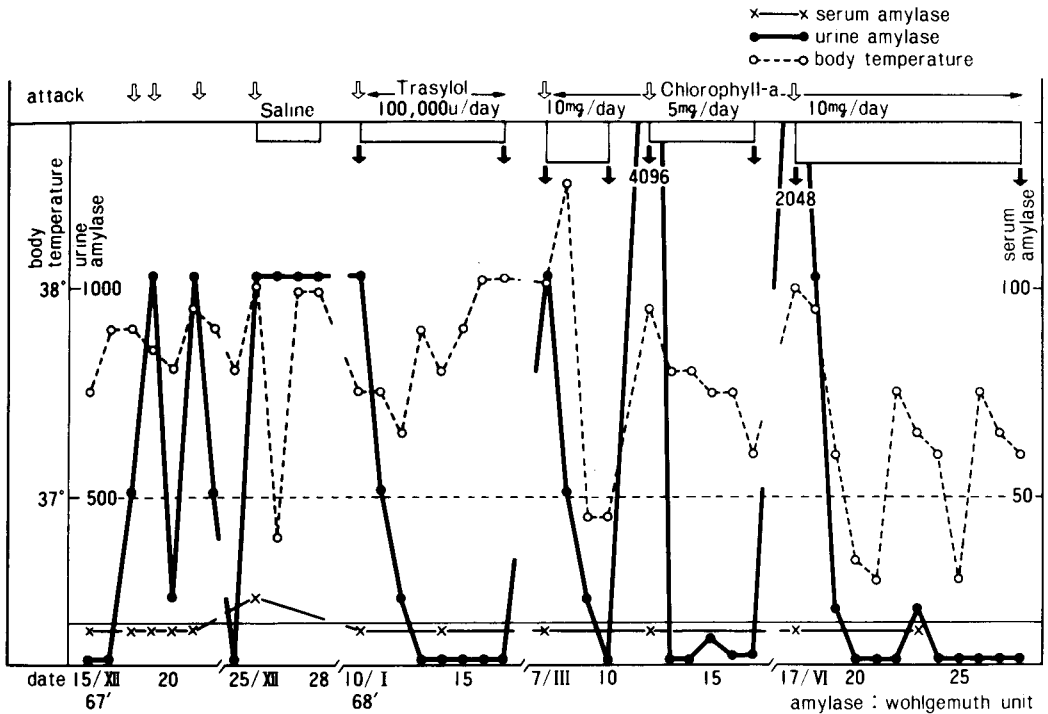


Fig. 1. Clinical course of chronic relapsing pancreatitis (case 1-7).

again treated with trasylo1 for 25 days, the dose of which was 50,000 unit per day for the first 10 days and 25,000 unit per day for successive 15 days. During that time, increased level of urine amylase of 1,024 Wohlgemuth unit before treatment, had decreased rapidly to 8 unit in 5 treating days and the abdominal pain had become also fairly well controlled, but she had continued to suffer from the fever of about 38°C. One month later, she had had another attack, when trasylo1 administration was again started. But she continued to suffer from obstinate nausea, vomiting and high fever, though the abdominal pain and elevated urine amylase levels had disappeared in short time. Then, we started the chlorophyll-a infusion, which gave her dramatic effects on every symptoms and signs and she could get complete remission for the first time only by this treat-

ment. At present time, she enjoys her normal social life. From this case, informations on cross-over effects of trasylo1 and chlorophyll-a could have been obtained, on which some discussion will be made in later pages.

Out-clinic Patients (Table 2)

Case 2-1. 35 year male (illustrated in Fig. 2)

He had the first attack of pancreatitis at his 33 years of age and 6 months later thereof, he had another severe recurrence, when he had received an emergent surgical operation, being diagnosed as acute pancreatitis. The operation was the setting of drainage for the inflammatory fluid accumulated in the abdominal cavity. After the operation, he received trasylo1 infusion at the dose of 50,000-100,000 unit daily for 14 days, total amount of which he received was 1,225,000 unit. He had got a complete remission and was discharged. During 2

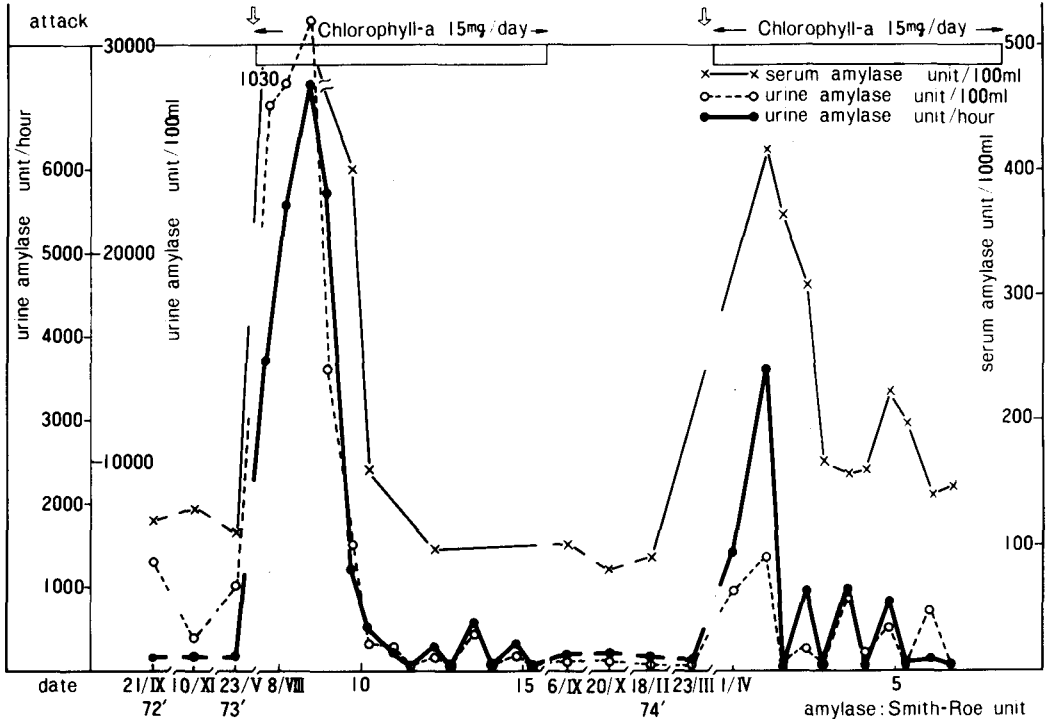


Fig. 2. Clinical course of chronic relapsing pancreatitis (case 2-1).

years since that time, he repeatedly had 3 recurrent attacks and every time, he was treated with trasylol infusion. At his 4th attack, he experienced a very severe circulatory shock just after the intravenous injection of trasylol, and he had recovered from the shock with intensive emergency cares. Up to that time, he had received trasylol of totally 1,350,000 unit.

At his 5th severe attack, he was shipped to our clinic as an ambulant patient and he immediately started to receive chlorophyll-a infusion at the dose of 15 mg per day in 500 ml of 5% xylitol solution. The amylase levels before treatment were 950 Smith-Roe unit/100 ml in serum and 17,000 unit/100 ml in urine. In the second treating day, most of his complaints including abdominal pain had disappeared and he continued to receive chlorophyll-a for more 3 weeks out-patiently until he had got a com-

plete remission. Since that time, he could have been controlled well only by chlorophyll-a infusion, though he had had recurrent attacks of less severity 2 or 3 times a year. Nowadays, he can conduct almost normal social life, which had never been possible during past few years.

Case 2-3. 39 year male

He visited our clinic at his 3rd attack of the pancreatitis. In X-ray survey, he revealed to have pancreatolithiasis. We studied about his parathyroid hormone levels in the serum and found that it had been apparently elevated. The true etiology of his pancreatitis, thus, has been suspected due to primary hyperparathyroidism, of which the detail was reported in elsewhere. He received 20 mg of chlorophyll-a in a day divided into 2 times, for 1 week and more 3 days, and he had got a complete remission.

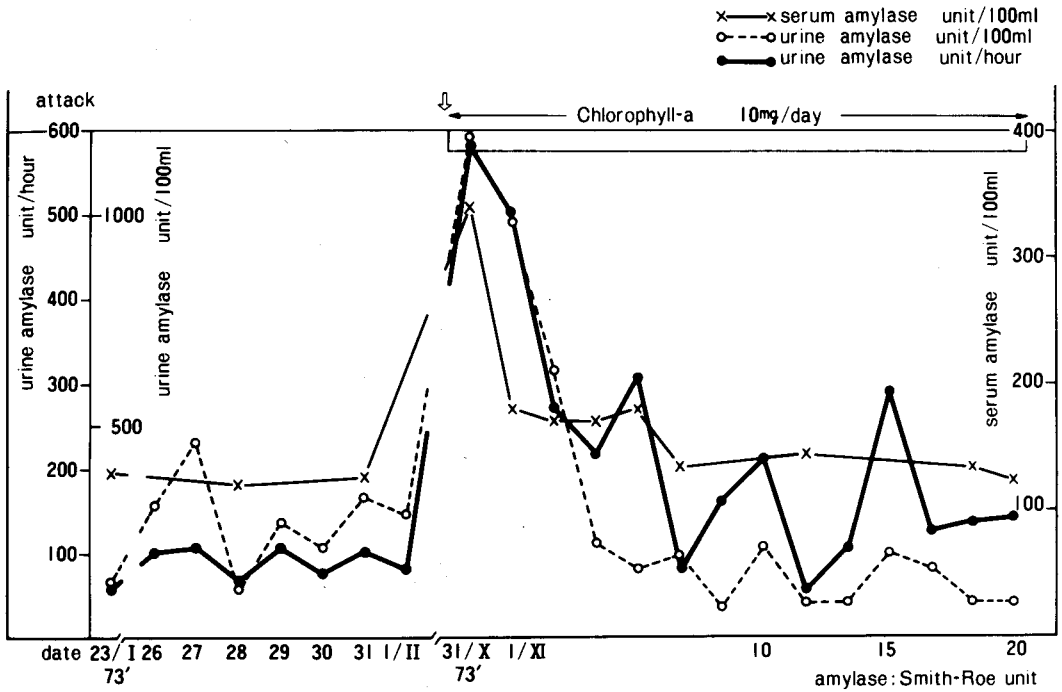


Fig. 3. Clinical course of chronic relapsing pancreatitis (case 2-5).

Case 2-5. 51 year male (illustrated in Fig. 3)

This was the case that was already reported, and the out-line of the clinical course is illustrated in Fig. 3⁶.

Case 2-2, 4, 6, 7, 8, 9, 10 and 11. 2 males and 6 females

The amylase at their recurrence were between 120 and 390 unit in sera and between 350 and 900 unit in urine. All these cases showed good response and all their complaints disappeared in 3 days after chlorophyll-a infusion. But on the days when they did not receive chlorophyll-a in the 2nd week, some of them had slight abdominal pain, which was lightened automatically in the 3rd week and they had become free of complaints.

Case 2-12, 13, 14, 15, 16, 17 and 18. 4 males and 3 females

Those 7 cases were the ones that could not finish the treatment program, but they had got

complete remission finally in the 3rd week. Their amylase levels were between 130 and 280 unit in sera and between 350 and 560 unit in urine before treatment. In most of the cases, the abdominal pain was cured in short time after the chlorophyll-a infusion and they stopped to come to the clinic until they again had felt abdominal pain 2-3 days later. They continued to receive chlorophyll-a more or less for 3 weeks.

Case 16 complained of persistent abdominal dull pain longer time. Therefore, we decided to combine trasylol with chlorophyll-a in the last 3 days of 2nd week of the program. Additional 3 weeks later, when we gave him another combination of trasylol with chlorophyll-a, he had fallen into sudden circulatory collapse. He had recovered from the shock by intensive emergency cares. At present, he has been well controlled only with chlorophyll-a treatment.

Additional Hospitalized Patients (Table 3)

All these cases were treated out-patiently with chlorophyll-a daily for 2 weeks and showed insufficient response in the disappearance of abdominal symptoms, though the abdominal pain and elevated urine amylase level ranging between 350 and 800 unit returned to normal within a week. They were continually suffering from nausea, vomiting and loss of appetite, and for the sake, they were hospitalized. After the 2nd day of their admission, all above symptoms had disappeared.

Among the cases listed in Table 3, the case 4 was a little unusual. His complication to pancreatitis was protein-losing enteropathy, and he showed low level of serum albumin and slight edema on especially lower extremities. His amylase levels at the admission time were 180 unit in serum and 350u in urine and finally, the elevated levels had decreased to normal after 2 weeks chlorophyll-a treatment. Together with chlorophyll-a treatment, he was given purified serum albumin simultaneously in the infusing solution.

Discussions

As many existing concepts about the causes and mechanisms of pancreatitis in man even now seem to be fragmentary, conflicting, theoretical and inferential, we easily realize that not a few doctors could not agree with theories, classifications, etiology, therapeutic measures, and even prospective views on histopathological change of pancreatitis presented in every kind of papers. Accordingly, in the actual clinical practice of pancreatitis, so many kind of therapeutic measures, such as application of serum albumin⁹⁾, corticosteroid¹⁰⁾, propiouracil¹¹⁾, trasyolol^{3,4)}, guanidic acid esters^{12,13)} etc., have been proposed and used. The last two are the substances that have anti-trypsin activity.

The activation of trypsin in the pancreatic

tissue is thought without doubt to play a key role in the development of pathochemical process of the disease¹⁾. Therefore, application of medicine that has inhibitory activity against trypsin, has been thought to be the most useful and pathognomonic one in the treatment of pancreatitis. One of the most typical ones of this kind is trasyolol.

The discovery of anti-trypsin activity of chlorophyll-a derivatives that happened in our laboratory in 1968^{3,4)}, has enhanced us to explore this type of medicine and to solve the problems that exist on the use of trasyolol, i.e. its decisive side-effect, anaphylactic shock which is not seldom encountered after its repeated administration. On the same occasion of discovery about the chlorophyll, we could have an opportunity to use water-soluble form of chlorophyll-a to a patient with chronic relapsing pancreatitis who had been hospitalized in the gastroenterological ward of our University Hospital. Most luckily, we could yield very successful result. The patient had been almost cured for the first time (Fig. 1). Nowadays, these facts have provoked more interests among physicians in the U.S.¹⁴⁾, Israel and other countries in the world, and some of their experimental results have been published^{15,16)}.

Clinical trial of chlorophyll-a has been increasingly performed also at other hospitals and clinics in Japan and their results have been more and more reported¹⁷⁻²²⁾.

In this paper, we report on the clinical results in the treatment of chronic relapsing pancreatitis on 34 cases treated with chlorophyll-a preparation. In 34 cases presented here, we identified its usefulness in totally 32 cases.

The diagnostic criteria and classification of pancreatitis are thought to be extremely important from the aspect of evaluation of effectiveness of newly explored medicine, as well as

from practical clinical aspect. Proper diagnosis and classification can best be made not only by the cardinal scales of clinical, laboratory, surgical and histopathologic evidences available during an episode of acute phase of pancreatitis, but also by certain residuals and sequelae which may be present after or between acute episodes. Moreover, it should be also born in mind that there must be the cases in which there is absence of any antecedent episode of pain and only there is pancreatic calcification observed.

In this study, we basically used the classification that was adopted in the symposium on pancreatitis held at Marseille, France, in 1963⁸⁾. Namely, it was reported as follows: (I) acute pancreatitis, (II) recurrent acute pancreatitis, (III) recurrent chronic pancreatitis, and (IV) chronic pancreatitis. In this study, we emphasized on disappearance of the abdominal pain and the clinical findings which were directly associated with acute phase of pancreatitis, as standards for the effectiveness of chlorophyll-a treatment. Moreover, there must be some fear that our chronic pancreatitis should appropriately classified as recurrent acute pancreatitis in some cases in the light of the relation to Marseille Symposium. But we don't think there is any problem about the relation between the classification of pancreatitis and effectiveness of the tested medicine in this study. At the same time, the facts should be born in mind that histopathologic changes may vary in different area of the pancreas and that the changes might reside in the tissue and the acute attacks may continue to recur at some future date, even when the presumed causative factors are eliminated, in indefinite and unpredictable number of patients.

The true mechanism in which chlorophyll-a may exert its favorable effect on pancreatitis, remains unclear. We have published the observations that chlorophyllins, the chelated

metal of which is substituted by various metals, had shown inhibitory effects on some group of proteases in varying grade from protease to protease in vitro^{5,6)}. The proteases which had been suppressed in their activity are trypsin, chymotrypsin and kallikrein which are thought to be involved in the process of pancreatitis. Lately, Yamamoto et al. reported that chlorophyll-a inhibits activities of amylase²³⁾ and lipase²³⁾ in vitro. The evidences by us and others support the view that chlorophyll absorbed or intaken into the blood or tissue is to be metabolized into bile²⁵⁾, and that there should be numerous intermediate metabolites in the tissue and the bile. Therefore, our tentative hypothesis for the possible mechanism of action of chlorophyll-a injected, is that chlorophyll-a is brought to the liver and subjected to metabolism to be reformed in various intermetabolites, and again brought to the pancreatic tissue to react with released inflammatory proteases there in the form of various metabolites of chlorophyll-a including chlorophyllins.

From the clinical observations, chlorophyll-a seems to have during effect when it is injected. Relief of the abdominal pain was observed to occur in 20-30 minutes after the chlorophyll-a infusion had been finished, which was thought due to the direct action of infused chlorophyll-a. The delayed effect of injected chlorophyll-a was also observed clinically and experimentally, about which some discussion is made elsewhere in this paper and in the separate paper²⁶⁾. This during effect was thought due to later release of accumulated chlorophyll-a in some tissues, such as liver, or being combined with α_2 globulin fraction in the blood. As discussed in a separate paper²⁶⁾, injected chlorophyll-a exerted its clinical effects in cooperation with serum naturally occurring protease inhibitors, which would naturally be involved in pancreatitis.

As for other biochemical effect of chloro-

phyll-a, we observed that injected chlorophyll-a had stimulatory effect on apo-lipoprotein synthesis in vitro in rat liver and on excretion of free form of cholesterol into bile. Thus, mechanisms by which chlorophyll-a exerts its clinical effect, seem to be not simple as are discussed above.

Chlorophyllin exerts its inhibitory effect on proteases in vitro, but when it is injected intravenously, it will be readily excreted into urine.

As for the side effect of chlorophyll-a injection, if any such as the one of allergic, or of photosensitivity, or hepatotoxic which are sometimes observed in trasytol or other porphyrin-related substances, nothing commentable has been hitherto observed.

Trasytol is thought fairly enough effective in most less severe and milder cases of pancreatitis. But there must be always fear for anaphylactic reaction in the repeated use of trasytol. The combination of trasytol with chlorophyll-a in the treatment of pancreatitis in this study, seem not to have had any advantage as compared with single use of trasytol or chlorophyll-a. We experienced 2 cases of allergic reaction to trasytol among 34 cases studied.

Recently, Orda et al.¹⁶ at the department of surgery of Tel-Aviv University reported on the dramatic effect of chlorophyll-a administration on the experimental pancreatitis of Guinea pigs. He reported that he could increase the survival rate of fatal experimental pancreatitis in Guinea pigs by 40%, which was produced by 7.5% sodium taurocholate injection into the pancreatic parenchyma, by the simultaneous use of chlorophyll-a. Though all non-treated control Guinea pigs had died within 24 hours, 40% of the tested group had survived finally.

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