

# The Investigation of Chloramphenicol in Treatment of *Cholera*

## Part I

**Masaaki IWANAGA, Setsuko SOGAME and Kazumine KOBARI**

*Department of Clinical Medicine, Institute for Tropical Medicine, Nagasaki University*

(Director : Prof. K. Kobari)

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### Abstract

In the recent the investigation of the pathophysiology and pathogenesis on cholera has made remarkable progress. However, the mechanism of diarrhea has not been completely clarified. It has been well known that antibiotics is considerably effective for treatment of cholera patient. Some problems, however, for instance, regarding the mechanism of effectiveness or a reasonable route of treatment still remain unsolved. In the present study, CP given orally and intravenously on cholera patients was hourly determined by bioassay as an approach to clarify the mechanism of antibiotics and also comprehension of pathophysiology of cholera.

Twenty-seven cholera cases, confirmed bacteriologically, admitted at the San Lazaro Hospital in Manila during the period from August through November 1968 were investigated for this study. Fourteen cases were intravenously treated with CP, and thirteen cases

orally. CP was determined in blood and stool consecutively. In the majority of cases treated by mouth, CP did not appear in stool and also was not proven in blood in half of cases; in others the blood level of CP was lower or elevated later than normal. On the contrary, in most cases treated with intravenous CP, higher concentration of CP in stool than in blood was proven; some of them showed twice higher concentration in stool than in blood. The number of vibrios in stool was inversely related to the concentration of CP in stool; namely, the majority of cases treated orally showed no reduce of vibrios, while marked decrease of the number was found in most cases with intravenous CP.

As, in the study, CP determination was done only by bioassay not by chemical assay, the problem whether CP may be inactivated remains unsolved. The comparative study of different preparation of CP has not been accomplished. These questions will be investigated in our further studies.

It has been suggested that the peculiar distribution of CP may be correlated to particular pathophysiological condition of cholera. In the therapeutic point of view, it has been noticed that intravenous treatment indicated more accurate effectiveness for discontinuing excretion of vibrios in stool than oral treatment, as far as the cases with severe diarrhea are concerned.

### Introduction

For a long time El Tor cholera, as an endemic disease, has confined to the Celebes. However, since 1961 it has lost its localized character and has spread to various places in South East Asia, so that the classical cholera had been gradually expelled. At present, the disease ranges over the broad area of South-East Asia, except for East Pakistan and some parts of India. The sudden epidemic of El Tor cholera stimulated investigators to study the pathophysiology of cholera, and this has resulted in epochal progress in the fluid treatment of cholera. As far as the mechanism of "rice water" diarrhea is concerned, the denudation theory by Virchow<sup>1)</sup> in 1879 had been accepted for about 80 years without any criticism. Recently, as El Tor cholera has been pathophysiologically investigated, hypotheses such as the sodium pump inhibition theory by Phillips<sup>2)3)</sup> in 1963, the hypersecretion theory by Greenough<sup>4)</sup> in 1965, etc., have been re-

ported. However, so far, the pathophysiological mechanism has not been completely understood.

As far as fluid treatment is concerned, various kinds of fluid have been tried for the therapy of cholera. The first study of fluid therapy for cholera based on biochemical analysis of blood and stool of the patient was conducted by Latta<sup>5)</sup> in 1831. When El Tor cholera was prevalent in the Philippines in 1961, the formula of fluid treatment by Phillips et al succeeded in considerably reducing the mortality rate of cholera patients. It was an epoch-making step in the fluid treatment of cholera.

At present, lactated Ringer's solution has taken the place of the combined use of normal saline and bicarbonate solution of Phillips, in order to rationalize the treatment for younger children.

Antibiotic treatment had also been considered as necessary for cholera. However,

the mechanism of effectiveness of antibiotics has not yet been clarified. Besides, the final decision, as to which antibiotic is the most effective or what kind of medication is preferable, has not been completed.

In the present study, the clinical observation, the quantitation of vibrios in stool

and the determination of chloramphenicol in blood and stool were carried out on cholera patients treated orally and intravenously with chloramphenicol (CP). The purpose of this study is to clarify the mechanism of antibiotic treatment in particular pathophysiological condition of cholera.

### Materials and Methods

1. Patients : Twenty-seven adult patients with typical cholera symptoms, admitted to San Lazaro Hospital, Manila, during August to November in 1968 were investigated : all patients were treated with lactated Ringer's solution, as long as diarrhea continued, 250 mg of CP was given orally every 6 hours for 3 days, and it amounted to 3 g in total. The antibiotic therapy started soon after the investigation.

2. Administration of CP for the examination : i) Oral administration ; two capsules (500 mg) of CP were administered in one dose for 13 patients. The preparation was chloromycetin capsule (250mg/cap) by Parke Davis Co.

ii) Intravenous administration ; 500 mg for 6 and 1,000 mg for 8 patients were administered in one dose. Chloromycetin succinate by Sankyo Co. was used.

3. Collection of the specimens: Blood specimens were taken once before administration and hourly 5 times after administration, but in some cases 2 or 3 times every 2 hours.

Stool specimen were taken once before administration and hourly 5 times after administration, and they were taken by using rubber tube directly inserted into the rectum.

The collection of the specimens started usually just after admission. However, in severely dehydrated cases in which it was difficult to extract blood and to take rectal

content by the rectal tubing, it was not feasible to collect specimens until improvement of dehydration by fluid treatment (Fig. 12).

In 4 cases, the rubber tube was fixed at the anus and the whole rectal content was collected every hour.

4. Determination of CP : Collected stool was heated at 60°C for 60 minutes in water bath. Blood was centrifuged to separate the serum. Concentration of CP in stool and serum was measured by bioassay method using *E. coli*, strain NIHJ, as an indicator organism. Pile (vertical) diffusion method was applied in the test tube. And the result was judged after 20 to 24 hours incubation at 37°C. Standard concentration curve was drawn by using known amount of CP in normal saline solution. The formula of the medium for the bioassay is as follows.

Nutrient agar (Difco)	100ml
Methylenblue (0.1%)	3.8ml
Sodium nitrite (1.0%)	2.0ml
<i>E. coli</i> (NIHJ) broth culture for 20 hours	0.5ml

5. Bacteriological examination : On the collected stool, the following examination were conducted.

Quantitation of the vibrios in stool

The motility of the vibrio in stool

Biochemical behavior and sero type of the isolated vibrio

Drug sensitivity

The number of vibrios was counted on TCBS agar by using 10 fold dilution method. The motility of the vibrio was observed under the dark field microscope. Stool culture was

carried out every day by enrichment method. The patient was discharged as bacteriologically negative for vibrio for 2 consecutive days.

**The distribution of CP in blood and stool**

1. Oral administration cases

i) General trend: A general trend in the cases of oral administration was represented by case No. 1 and No. 2 as shown in Fig. 1 and Fig. 2. It was noticed that CP was determined neither in blood nor in stool. In the majority of cases, some inhibiting substance against the indicator organism, although it was of low concentration, was recognized in stool. However, the concentration of CP in stool had not risen until 5 hours after administration. CP was not found in blood in 6 cases; in 3 cases it was detected in small quantities at 2 hours, in 1 case at 3 hours and in 2 cases at 5 hours.

Vibrio count in stool was usually around  $10^7$  on admission, and no change was seen in the number of vibrios even after medication with CP, in that CP could not be detected in stool. Besides, the motility of vibrio also seemed to be unaffected by one dose of CP.

ii) Other different results in a few cases: CP was determined in some degree in stool. Blood also showed a significant level of CP about 2 hours after the administration. Then, the viable count of vibrios in stool was found to decrease, as shown in Fig. 3.

2. Intravenous administration cases

i) General trend: A general trend in the cases of intravenous administration was represented by case No. 9 as shown in Fig. 4. In stool, there was something which inhibited the growth of the indicator organism as mentioned above. In the majority of cases, the CP concentration in blood showed higher

than 5 mcg/ml at 1 hour after administration. And in a few cases, within 3 to 4 hours after administration, the CP concentration in stool was twice as high as that in blood.

ii) Other different results in a few cases: No peculiar difference was recognized in CP concentration in blood, as compared to the general trend. In stool, however, the concentration was much lower than in blood and viable count of vibrios in stool was not changed, as shown in Fig. 5. Such results were seen in 2 cases out of 14.

Oral Administration 500mg : Case No. 1

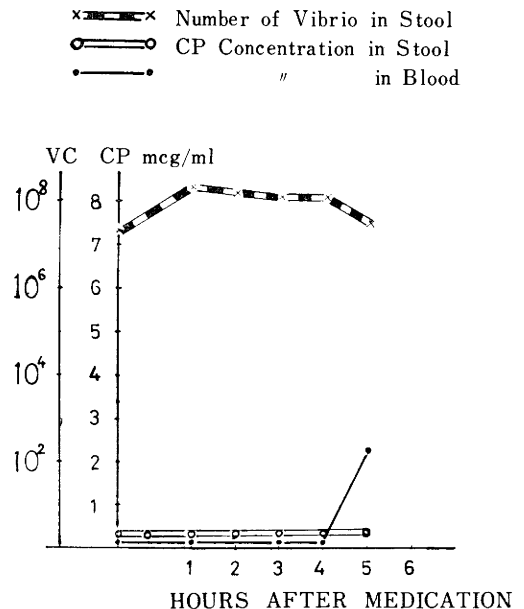


Fig. 1

Oral Administration 500mg : Case No.2

x---x Number of Vibrio in Stool  
 o---o CP Concentration in Stool  
 .---. " in Blood

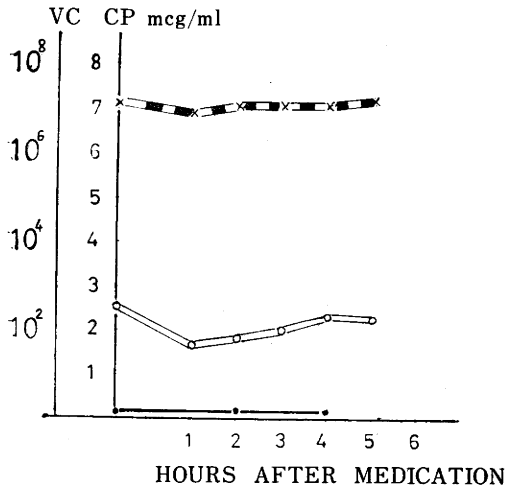


Fig. 2

Intravenous Administration 500mg : Case No.9

x---x Number of Vibrio in Stool  
 o---o CP Concentration in Stool  
 .---. " in Blood

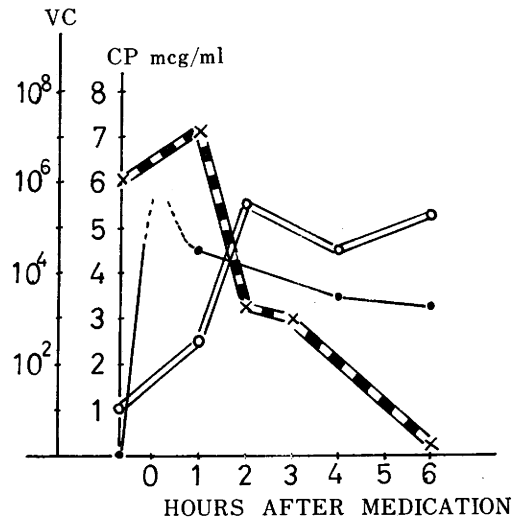


Fig. 4

Intravenous Administration 1000mg

: Case No.5

Oral Administration 500mg : Case No.3

x---x Number of Vibrio in Stool  
 o---o CP Concentration in Stool  
 .---. " in Blood

x---x Number of Vibrio in Stool  
 o---o CP Concentration in Stool  
 .---. " in Blood

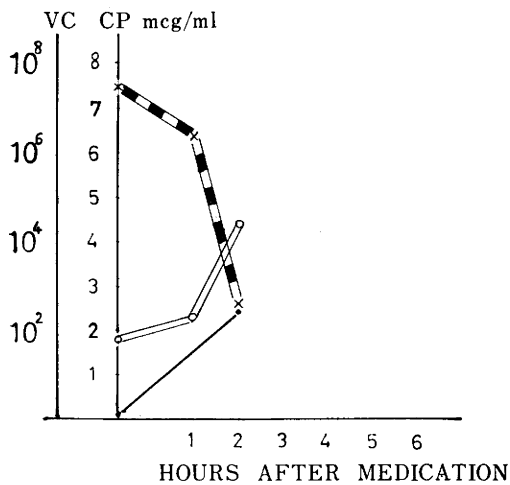


Fig. 3

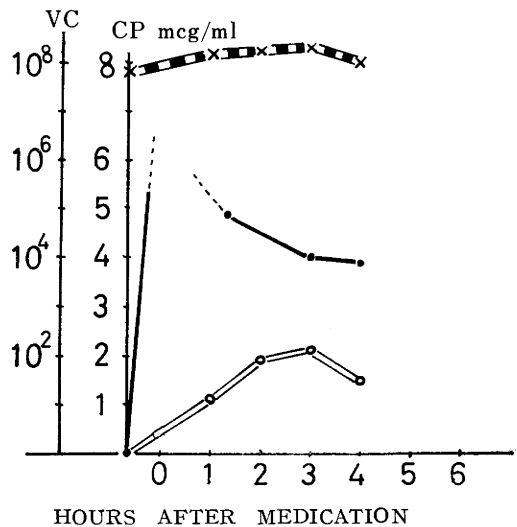


Fig. 5

### 3. Summary of CP distribution

i) Oral administration: CP concentration in stools are summarized in Fig. 6. The stool before administration contain some substance which inhibits the growth of the indicator organism corresponding to about 2 mcg/ml of CP. It is not clear whether the inhibition is due to drugs taken before admission or some substances which are contained in cholera stool. Therefore, the concentration below 3 mcg/ml was considered to be insignificant, as far as the concentration in stool was concerned. CP concentrations in bloods are summarized in Fig. 7. A dotted line shows hourly concentration of CP in a healthy adult after oral administration of the same dose. CP concentration showed 3 mcg/ml at 1 hour, and reached the peak of 4 mcg/ml at 2 hours after administration. Then the concentration gradually went down to 2 mcg/ml in 6 hours. In comparison with this concentration, that of cholera patients showed quite different figures in hourly concentration of CP in blood. In only 3 cases, the concentration was about half as low as that in the normal at 2 hours after administration. However, 5 hours after administration, the concentration in 5 cases became closer to the normal value. The determination was not performed from 6 hours after administration. Therefore, it cannot be said if CP may appear in blood later than 6 hours after administration.

In 3 cases out of 13, CP was detected in stool about 2 hours after oral administration. However, it is difficult to confirm that orally taken CP has passed through the intestine and has been excreted from the anus in 2 hours, because, in these 3 cases, CP was also detected in blood within 2 hours after administration. Therefore, it is not clear whether the CP in the stool was coming

through the intestinal tract or through the body fluid.

ii) Intravenous administration: CP concentrations in stool are summarized in Fig. 8 (500 mg) and Fig. 9 (1,000 mg). The concentration less than 3 mcg/ml may also be unreliable because of the reason previously mentioned. Being different from the cases of oral administration, CP concentration in stool reached more than 3 mcg/ml, and the number of vibrio in stool decreased significantly. In 2 cases in which CP concentration in stool was not raised to 3 mcg/ml, the amount of watery diarrhea was much less than that in the other cases.

CP concentrations in blood are summarized in Fig. 10 (500 mg) and Fig. 11 (1,000 mg). The concentration reached the peak at about one hour after administration in almost all cases. After the peak, it gradually went down, and these curves may be close to those of the normal.

iii) Comparison between oral and intravenous administration: The CP concentration in blood after oral administration was quite different from that of the normal, while the process after intravenous administration seemed to be almost normal.

As far as the concentration in stool is concerned, only few cases with oral administration of CP showed a level higher than 3 mcg/ml. However, the majority cases of intravenous administration showed the concentration to be higher than 3 mcg/ml. Thus, a higher concentration of CP was seen in both blood and stool of intravenous administration cases than in oral cases.

It was noted that there was a difference in the amount of stools during the 5 hour period of examination, between the cases which showed higher concentration of CP in stool and others. Concerning the three cases

CP CONCENTRATION IN STOOL  
ORAL 500mg

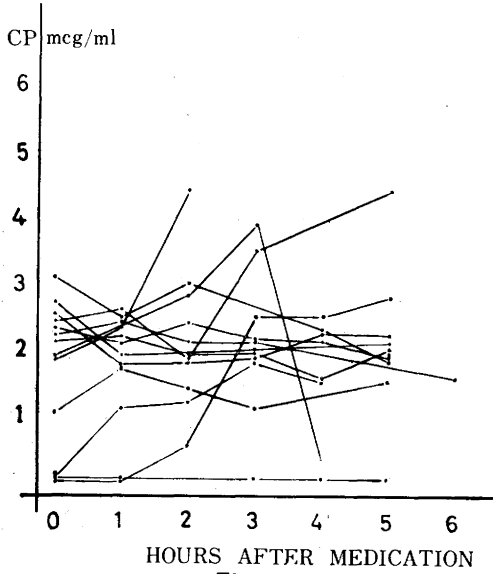


Fig. 6

CP. CONCENTRATION IN BLOOD  
Oral Administration 500mg

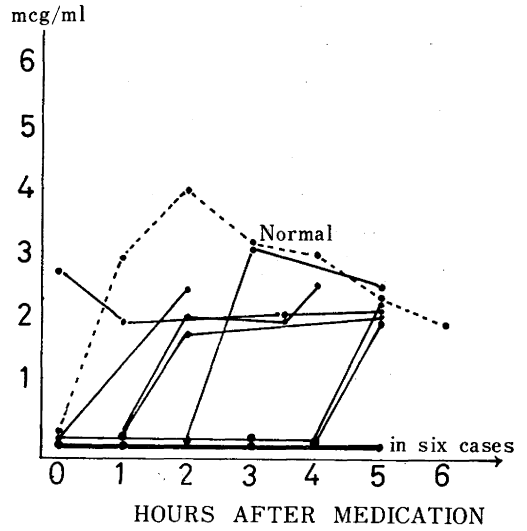


Fig. 7

CP CONCENTRATION IN STOOL  
Intravenous Administration 100mg  
CP

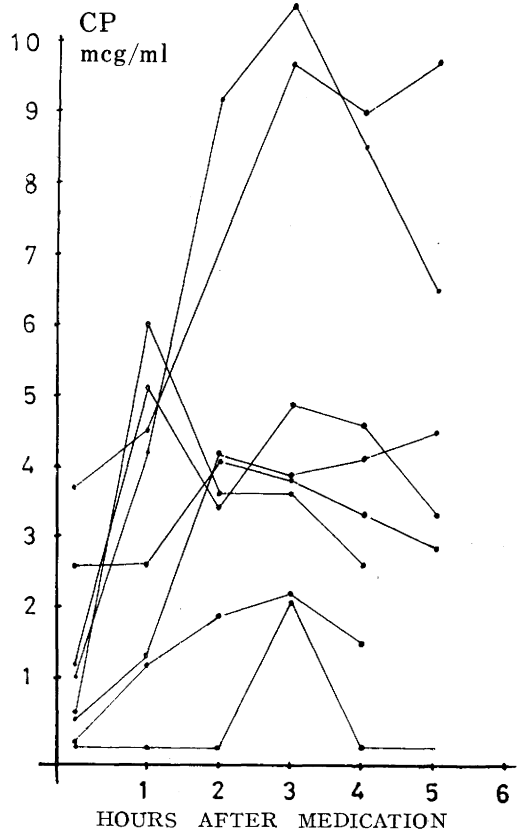


Fig. 9

CP CONCENTRATION IN STOOL  
Intravenous Administration 500mg

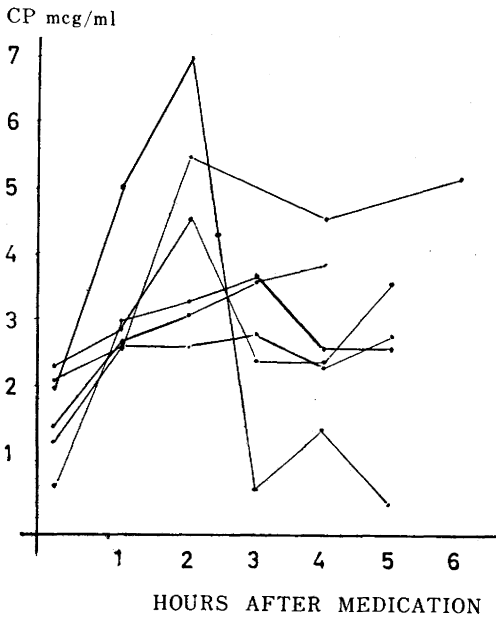


Fig. 8

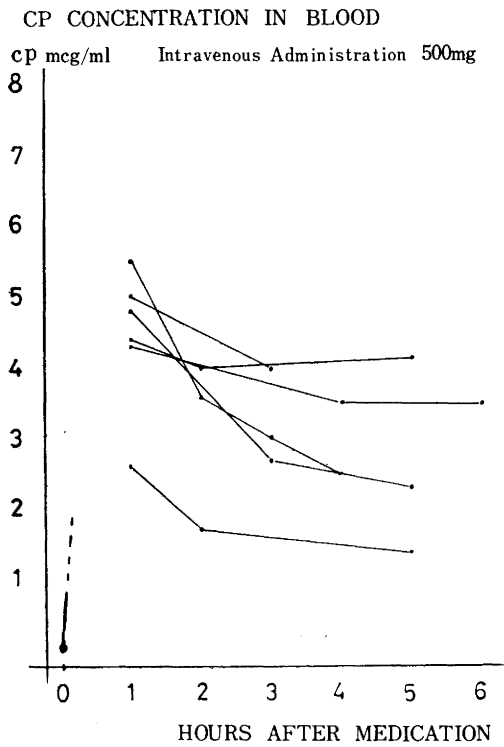


Fig. 10

of oral administration with low CP concentrations in stool, the amount of stool was 1,500 ml in average, while in the other 10 cases, it was 2,800 ml on average. On the other hand, cases of intravenous administration gave the opposite result; namely the amount of stool in 2 cases of which CP

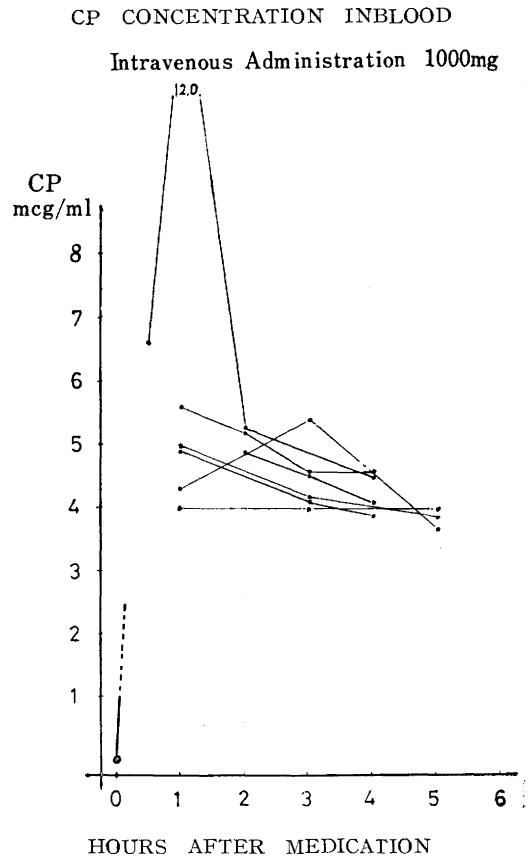


Fig. 11

concentration was lower than 3 mcg/ml was 1,050 ml on average; and the other 12 cases which showed higher concentration in stool, evacuated 3,300 ml of stool on average.

**Clinical details**

1. Case reports

Case No. 1 39-year-old male

Chief Complaint : Watery diarrhea

Present illness : The patient was admitted on October 7, at 10 : 30 hours because of frequent watery diarrhea from 10 hours before admission. A few hours before admission, hoarseness and leg cramp developed.

Status on admission : His consciousness was clear. He seemed to have a typical "cholera face". Cold perspiration was seen

on the face and neck; however, the skin of the extremities was dry, and the turgor was prominently diminished. The hand showed "Washerwoman's Hand", namely, the skin was wrinkled, as well as the feet, as if they had been in water for a long time. Pulse rate was 80/min with regular rhythm and weakened. Blood pressure was 118 at maximum and 60 at minimum. Nothing peculiar was observed in heart and lungs. Abdomen was sunken a little. He did not complain



of abdominal pain, and the bowel sound was not audible. He complained of twinges in the calves, especially on pressure; and occasionally cramp of the calves developed.

The loss of the body-fluid was estimated as 1945 ml through calculation by Phillip's formula for 54.9 Kg of body weight and 1.034 of plasma specific gravity.

The process after admission : Infusion therapy with lactated Ringer's solution started soon after admission. There was no defecation of watery stool within 2 hours (Fig. 12). Cramp and pain in calves rapidly subsided but the hoarseness and "Washerwoman's Hand" were slow to recover. Blood pressure was 120 at maximum and 70 at minimum at 2 hours, and 140 over 70 at 5 hours after administration. Body temperature was 37.2°C at 2 hours and 37.5°C at 5 hours after admission.

In the morning of second hospital day, no clinical sign was seen except watery diarrhea, which was light yellow in color. Body temperature was 37.0°C; pulse rate was 60/min; blood pressure was 132 at maximum and 68 at minimum. Body weight was 53.7 Kg. Around noon the appearance of stool became muddy, and in the evening the diarrhea ceased.

He was discharged on October 12, sixth hospital day, as clinically improved and negative for vibrio El Tor for 2 consecutive days.

During his hospitalization, diarrhea continued for 28 hours, amounting to 5,500 ml in total and the infusion fluid reached to 9,000 ml.

Case No. 2 27-year-old male

Chief Complaint : Watery diarrhea

Present illness : The patient was admitted at 7:20 hours on October 23 because of watery diarrhea since around 20:00 hours on October 22. Before admission he has

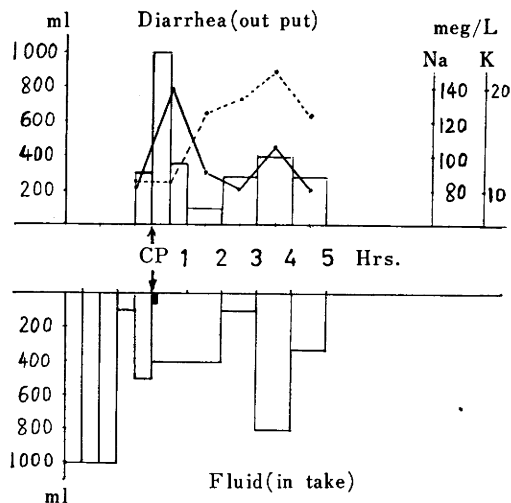


Fig. 12

The amount of diarrhea and fluid infusion for 7 hours after admission. (case No.1)

The concentration of sodium and potassium in hourly stool was measured.

..... K, ——— Na.

vomitted once at midnight and soon twinges and cramps of calves had developed.

Status on admission : The patient was somnolent but he could answer questions. He had a typical cholera face with cyanosis in the lips. "Washerwoman's Hand" was moderate in degree. Turgor of the skin was strikingly diminished but not clammy. Respiration was deep and frequent. Pulse rate was 120/min, and occasionally showed irregular rhythm. Blood pressure was 80 at maximum. Heart sound was low. The abdomen was a little sunken without any pain, and the abdominal sound was not audible. He complained of twinges in the calves. The loss of body fluid was estimated as 2,400 ml for 50 Kg of the body weight and 1.037 of the plasma specific gravity.

The process after admission : In 5 hours after admission, 3,900 ml of fluid was given,

however, 2,900 ml of watery diarrhea was defecated. The amount of infusion fluid was not yet enough to supplement the body fluid. The recovery of the body condition was delayed.

On second hospital day, he complained of fatigue and had no appetite. Body temperature was 37.2°C, pulse rate was 60/min and blood pressure was 120 at maximum and 78 at minimum. Watery diarrhea, dark green in color, still continued.

On third hospital day, diarrhea ceased with the last one, muddy in character, around 2:00 hours. In the afternoon he had a good appetite without any complaints.

He was discharged on October 29, seventh hospital day, as clinically improved and bacteriologically negative for vibrio El Tor for two consecutive days. During his hospitalization the diarrhea continued for 42 hours: the total amount of diarrhea was 13,500 ml and infusion fluid amounted to 19,000 ml.

Case No. 3 38-year-old male

Chief complaint: Watery diarrhea and vomiting

Present illness: The patient was admitted at 10:20 hours on August 26 because of profuse watery diarrhea without abdominal pain since midnight and vomiting soon after the onset of diarrhea. Cramps in the calves had developed few hours before admission.

Status on admission: His consciousness was clear but he was a little excited and appeared anxious. Typical cholera face and prominent "Washerwoman's Hand" were observed, and his voice was husky. Skin was dry with diminished turgor. The extremities were cold, however, the body temperature was 37.0°C. Pulse was not palpable on radial artery. It was difficult to analyse the heart sounds because of the weak tone and predominant rales in breathing. He

suffered from bronchial asthma. Abdomen was a little sunken, and there was no pain. Abdominal sound was not audible. He vomited severely during the physical examination. He complained of twinges in the calves and slight cramps occurred in them occasionally. Body weight was 30.0 Kg and the specific gravity of plasma was 1.041. Then the loss of body fluid was estimated to be about 1,920 ml.

Process during hospitalization: The recovery of the general status was rapid. In 3 hours after admission 3,600 ml of fluid had already been infused and 2,000 ml of watery diarrhea was evacuated. He was mentally quiet and the countenance was quite normal. Hands and feet were getting warm, and skin turgor was improved. "Washerwoman's Hand" however, was still observed in moderate. Pulse rate was 92/min, blood pressure was 98 at maximum and 60 at minimum and heart sound was resonant. In the auscultation of the lungs, bubbles and whistling were audible all over the field. Twinges and cramps in the calves had already disappeared. The diarrhea ceased in the evening of the third hospital day.

He was discharged on September 2, eighth hospital day, as clinically improved and bacteriologically negative for vibrio El Tor for two consecutive days.

During his hospitalization, diarrhea continued for 57 hours: the total amount of diarrhea was 18,000 ml and the infusion fluid amounted to 24,000 ml.

Case No. 4 51-year-old female

Chief complaint: Watery diarrhea, vomiting

Present illness: The diarrhea started in the afternoon on September 23, it became watery and frequent in the midnight. At 3:50 hours on September 24, she was admitted to Philippine General Hospital; there

she was given antiemetics. However, she was suspected to be suffering from cholera and transferred to San Lazaro Hospital at 9:00 hours on that day.

Status on admission: Her consciousness was clear but she seemed to have a typical cholera face. Her voice was extremely husky; it was rather aphonic. Diminished turgor, cold perspiration and "Washerwoman's Hand" were prominent on the skin. Body temperature was 36.2°C. Pulsation was feeble on radial artery, and it was difficult to count the rate. Heart rate was 88/min without accentuation of second pulmonary tone. Respiration was deep and frequent.

Abdomen was flat without pain and abdominal sound was not audible. Body weight was 52.0 Kg, and specific gravity of plasma was 1.043. Then the loss of body fluid was estimated as 3,740 ml.

Process during admission: In 5 hours after admission, 5,000 ml of fluid had already been infused. Then slightly sunken eyeballs and "Washerwoman's Hand" were still observed. Her general condition, however, had clearly improved. Pulse rate was 84/min with normal tension. Abdominal sound was accentuatedly audible but she did not complain of abdominal pain.

On third hospital day, watery diarrhea, dark green in color, was still evacuated occasionally in the morning, but it ceased in the afternoon. In this case, CP concentration in stool was twice as high as that in blood.

She was discharged on September 30, eighth hospital day, as clinically improved and bacteriologically negative for vibrio El Tor for two consecutive days.

Case No. 5 26-year-old-male

Chief complaint: Watery diarrhea, cramp in the calves

Present illness: The patient was admitted

at 10:10 hours on September 25 because of severe watery diarrhea and following cramp in the calves since about 7:00 hours on that day.

Status on admission: His consciousness was clear but he had a typical cholera face with a painful expression. Diminished turgor and slight cold perspiration were seen on the skin. "Washerwoman's Hand" was moderate in degree. Body temperature was 36.0°C.

Pulsation was feeble and the rate was 100/min. Heart sound was faint. He complained of severe twinges in the calves, and severe cramp occurred in them during the physical examination.

Body weight was 56.0 Kg, and specific gravity of plasma was 1.040. Then the loss of body fluid was estimated as 3,360 ml.

Process during admission: In 5 hours after admission, 5,000 ml of fluid had already been infused and 1,500 ml of watery diarrhea was evacuated. General condition was prominently improved, however, "Washerwoman's Hand" was still slightly observed. Abdominal sound was well audible.

On second hospital day, no abnormal findings were observed. Even diarrhea had already ceased after the last one in the early morning.

He was discharged on October 2, eighth hospital day, as clinically improved and bacteriologically negative for vibrio El Tor for two consecutive days.

During his hospitalization, diarrhea continued for 24 hours; the total amount of diarrhea was 9,000 ml and infusion fluid amounted to 16,000 ml.

## 2. Summary of the clinical course

On admission patient was severely dehydrated and in collapse. Characteristic symptoms which are due to dehydration and collapse were usually observed in every case.

As fluid treatment started soon after admission, peculiar signs due to dehydration and collapse subsided within a few hours, and the general condition improved soon.

However, diarrhea continued until second or third day of hospitalization, even when other symptoms disappeared almost completely. The process of recovery of diarrhea was individually different; the amount of stool and period of continuation of diarrhea were not similar. The effectiveness of CP between oral and intravenous administration was not comparable: because only the first medication was performed by a different route in order to investigate the origin of diarrhea and the mechanism of the effectiveness of CP.

3. Bacteriological findings

i) Observation of stool under the dark-field microscope

Before CP administration, numerous vibrios were moving in a unique pattern like that of lightening. And even after CP administration, no change was seen on the movement of vibrios in the cases without increase of CP concentration in stool. However, in the cases in which CP concentration was high, the number of vibrios in a field (400 x) decreased, the motion turned dull and finally it ceased.

In the majority of cases with high concentration of CP in stool, long spiral forms which seemed to consist of several vibrios in chain were observed at the beginning of the appearance of CP in stool; some of them were moving irregularly or in a reptospiral movement as well. As the motion ceased, the number of organisms in the field became scarce.

ii) Sensitivity to drugs

The sensitivity of the isolated vibrios to several antibiotics is summarized in Fig. 13.

The vibrios were most sensitive to chloramphenicol and tetracycline; the MIC of these

DRUG SENSITIVITY (MIC)  
OF E1 Tor Vibrio 27 STRAINS

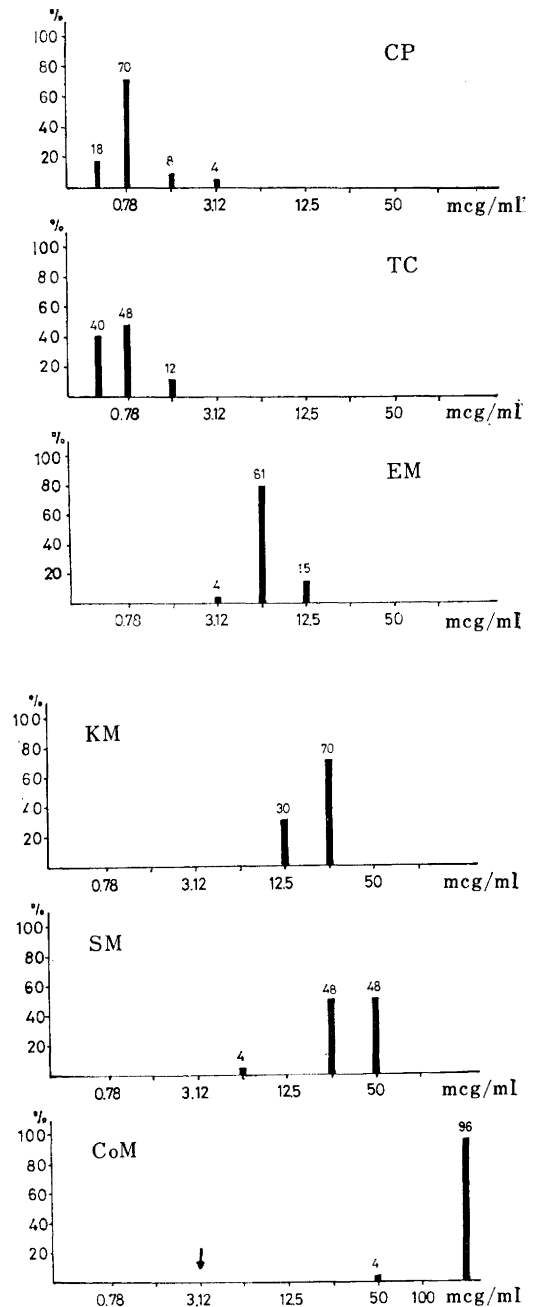


Fig. 13

CP, chloramphenicol. TC, tetracycline.  
EM, erythromycin. KM, kanamycin.  
SM, streptomycin. CoM, colistin.

The sensitivity of classic vibrio, strain NIH35, to colistin was 3.12mcg/ml in MIC. (arrow)

antibiotics were 0.78 mcg/ml or less in most of strains. The sensitivity to erythromycine was inferior to the above mentioned drugs, and that to kanamycine and streptomycine was much inferior. So it was noted that no trend of increasing resistance in the sensitivity patterns of vibrio to antibiotics has

been recognized in the present study, compared with the previous reports<sup>12)</sup>.

Colistin was used to differentiate El Tor type from the classic strain instead of Polymixin B; all strains were resistant to colistin in 100 mcg/ml of concentration.

### Discussion

CP which was orally administered did not appear in blood and was not excreted in stool, and CP which was given intravenously appeared considerably in stool in most cases.

They might be a clue for the clarification of the origin of diarrhea and the mechanism of antibiotic treatment for cholera patients. To solve an enigma on the whereabouts of orally given CP in the body, the following presumption might make the position clear:

- (1) CP may remain somewhere in the intestine during the period of examination, 5 to 6 hours.
- (2) CP may be appeared to be missing in stool due to unsuitable sampling procedure.
- (3) CP may be absorbed through the intestinal wall, but remain in some organ of the body without appearing in blood.
- (4) The main part of CP may be inactivated in the gastrointestinal tract.

The intestinal content of cholera patients was usually watery without color of bile or feces, and its PH was higher than normal, about 8.5. Item (1) and (2), mentioned above, suggest the declined solubility of CP due to such particular character of the intestinal content, or unusual rapid transit time through the intestinal tract.

From item (3), it can be considered that CP may be retained in certain organ or tissue without appearing in blood. Because CP

which is absorbed in the intestine passes through three kinds of tissues with capillary before appearing in subcutaneous vein; the three tissues are the liver, the lungs and the muscle and/or skin. In severe dehydration in cholera, the peripheral or microcirculation is seemed to be disturbed that CP may be easily adsorbed in the tissues and inactivated there, especially in the liver. Item(4) is a plausible idea, but the possibility that the major part of CP was inactivated in the gastrointestinal tract could not be confirmed because the determination of CP was depended on the bioassay only, and not on the chemical measurement. The comparison of concentration of CP in blood and stool by means of both biological and chemical determination will be reported in our further studies.

In cases with CP succinate given intravenously, CP was found in higher concentration in stool as well as in blood. It is presumed that the origin of unusual high level of CP concentration in stool should be correlated to the mechanism of outpouring body fluid into the intestinal lumen. The mechanism includes two categories, namely secretion and filtration.

If CP flows out into the lumen of the intestine from the body fluid, it can be presumed that the larger amount of CP may be accumulated in the intestine under the condi-

tion which is lacking of absorptive ability. A peculiar pathophysiological condition of cholera and the origin of diarrhea in cholera might be understood by means of seeking after CP in blood and stool.

Unfortunately, however, the comparison of two different preparation of CP, powder and succinate, was not able to be investigated with references to metabolism and distribution in the human body. This problem also will be clarified in our further investigation.

From the therapeutic point of view, it was seen from the study that the one oral dosis of CP could not suppress the multiplication of vibrios because of a low concentration of CP in stool. On the other hand, CP which

was intravenously administered was able to inhibit the growth of vibrios in the intestine by an extremely high concentration in stool. Therefore, as far as the antibiotic treatment for cholera is concerned, the first step of the treatment should be intravenous administration, or intravenous and oral administration combined.

It should be noticed that the one dosis of CP medication could deteriorate not only the motility of vibrios but also their morphology.

Therefore, the rapid diagnostic procedure by using dark-field microscope should be carefully applied. So far, highly resistant strains of vibrio to the ordinary antibiotics have not been found in the Philippines.

### Summary

Cholera patients admitted to the San Lazaro Hospital in Manila, Philippines, during the period August-November 1968 were investigated. CP was orally given in 13 cases and intravenously in 14 patients. The clinical observation, bacteriological examination of stool for cholera vibrios and determination of CP in stool and blood were conducted.

CP which was orally given did not appear in blood and was not excreted in stool, and

on the contrary, intravenously administered CP was found in stool at a higher concentration than that in blood. This fact indicated an interesting suggestion for the mechanism of the production of intestinal fluid in cholera and suggested how cholera should be treated with antibiotics.

In addition, the influence of antibiotics on the motility and morphology of vibrios in stool was noticed.

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## コレラの治療におけるクロラムフェニコールの研究

### 第 1 編

岩永正明・十亀節子・小張一峰

長崎大学熱帯医学研究所 臨床部 (主任小張一峰教授)

### 摘 要

コレラに関してその病態生理並びに発症機序に関する研究は近年著しく進歩したが、下痢の発症機序に関しては必ずしも全貌が明らかにされていない。また抗生物質がコレラの治療に著明な効果を示すことは一般に認められているがその作用機序に関しては不明の点が残されておりかつ薬剤の投与方法に関する疑問もある。

こうした問題点の解決の一つのアプローチとしてクロラムフェニコールをコレラ患者に経口的及び経静脈的に与えその血液並びに便中における時間的消長を検討することによって抗生物質の作用機転およびコレラの特異な病態生理を理解しようとした。

患者は1968年8月から11月まで、マニラのサン・ラザロ病院に入院し、細菌学的にエルトルコレラと診断された27名を選んだ。そのうち14名は静脈内に、13名は経口的にクロラムフェニコールを与え血中並びに便中のクロラムフェニコールの出現および消長を時間的に追究した。

その結果、経口的に与えた13例のうち大半の例においてはクロラムフェニコールは便中に出現することなく、血中濃度は半数は全く上昇せず他は正常よりも遅延しあるいは低濃度に証明されたにすぎなかった。静脈内に投与した14例については大多数において投与2時間後に血中よりも高濃度に便中への出現がみられ、中には血中濃度の2倍に達するものもあった。

便中のコレラ菌数は便中のクロラムフェニコール濃度に逆比例した消長がみられた。即ち経口投与例の大多数においては菌数の減少は殆どみられなかったが静注例ではその大多数においてコレラ菌数の著明な減少がみられた。

以上の観察例の中で、クロラムフェニコールの定量は生物学的方法にのみ頼ったためにその不活性化という点に問題を残している。また静注したものと経口的に与えたものではクロラムフェニコールの剤形が異なり、腸管内における溶解度その他について更に検討すべき余地がある。しかし全般的にみて経口的に投与されたクロラムフェニコールが血中に出現せず静注したものが高濃度に便中に出現したという事実はコレラの下痢あるいは腸内に大量に貯留する液体の成因についていろいろな意味の示唆を含んでいる。また抗生剤療法における排菌に対しては、急性期のコレラに関する限り静脈内投与が経口投与に比較してより適確な効果を示すことが実証された。