Evaluation of Effectiveness of Chemotherapy in Cholera

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Abstract

Chloramphenicol has recently been criticised as antibacterial drug for cholera because of probable inactivation in the body and appearance of resistant strains of Vibrio cholerae. In the present study, chloramphenicol was compared with dihydroxymethyl furalazine in regard to amount of diarrhea, reduction of vibrios in stool and the drug concentration in stool and blood.

1. With oral administration of chloramphenicol, neither reduction of vibrios nor elevation of drug level in stool were seen.

2. Two cases with intravenous administration of chloramphenicol revealed high concentration of the drug and marked reduce of vibrios in stool.

3. In all cases with oral administration of furalazine, effective concentration of the drug in stool was regularly found and at the same time, remarkable decrease of the number of vibrios was recognized. Moreover, it was observed that vibrios disappeared in stool in almost all cases, as the level of the drug showed further elevation.

4. An untoward reaction of furalazine, vomiting, was seen in one case.

Furalazine can be recommended as a substitutional drug for treatment of cholera.

Contents

Introduction

The choice of drugs for the treatment of a infectious disease has been mainly based on the sensitivity test of the etiologic organism. However, it should be noticed that the effectiveness of chemotherapy is considerably influenced by the pathophysiology of the disease, and that it is closely related to the distribution and the metabolism of the drug in the body.

Cholera presents such an individual particular symptomatology [18] [23] among bacterial infections that the distribution of medicine given in the body is markedly different from those of normal persons or other diseases.[13]

The metabolism in vivo of the antibiotic, such as chloramphenicol, depends greatly upon the form of the drug and the route of administration.

On the other hand, strains of El Tor vibrios resistant to chloramphenicol and tetracycline (which are most commonly used for the treatment of chelera in the hospital) were detected recently in the epidemic in the Philippines. [16] [17] It was proven that the patients who excreted the resistant strains failed to be treated clinically by these drugs.

From these points of view, therefore, the evaluation of the antibiotic treatment of cholera should be re-investigated.

Chloramphenicol and tetracycline have popularly [1] [3] [4] [5] [8] [14] [15] [19] [22] been used for the treatment of cholera. From the above mentioned point of view, however, antibiotic treatment of cholera should be re-investigated. At the same time, some drugs which have a high and stable antibacterial activity against V. cholerae should be searched and a substitutional chemotherapy should be established.

Dihydroxymethyl furalazine, one of the derivatives of nitrofuran, has been examined as one of the drugs which could answer the purpose. [16] In the present study, a comparative investigation between furalazine and chloramphenicol in regard to the mode of action and effectivity was carried out in order to clarify the mechanism of therapy in cholera.

Materials and Methods

Since 1961, cholera El Tor has been endemic in the Philippines, and an outbreak has occurred every year in the rainy season from June to October in the city and suburbs of Manila.

The study has been carried out in Manila as a part of the Joint Cholera Study between the Pilippines-Japan and WHO.

Patients : Twenty-five adult patients with typical cholera symptoms, admitted to San Lazaro Hospital, Manila during September through December in 1970 were investigated; all patients were bacteriologically confirmed and treated with lactated Ringer's solution as long as diarrhea continued.

Collection of stool : The rectal rubber tube, "The Health" No.16 Izumo Rubber Manufacturing Co. Ltd., Tokyo, was inserted into the rectum continuously during the examination of the patient, who was

laid down on the cholera cot. The other end of the catheter was connected to a sterilized bottle which was calibrated. The bottle was changed every 30 minutes and the volume of the stool was measured and recorded. The stool was continuously collected for 6 to 14 hours depending on the condition of the patient. A small portion of collected stool was used for counting vibrios and another portion was stocked in a freezer for the determination of drug concentration.

Collection of blood specimen : A few ml of blood was taken from the patient on admission and every 3 hours for the determination of drug concentration in serum. And the plasma specific gravity was also measured by copper sulfate method using the same sample.

Quantitative examination of vibrios in stool : TCBS agar was used for quantitation of vibrios. Serial ten-fold dilution of stool was made with normal saline solution. On TCBS agar, 0.1ml of each diluent was streaked by Conradi's glass stick. After overnight culture, the number of colonies was counted.

Drugs : Chloramphenicol powder in capsule (250mg/cap.) was used for oral administration, and chloramphenicol succinate for intravenous injection. Both preparations were provided by Parke Davis Co.

Dihydroxymethyl furalazine was used for oral administration in form of granules. It was provided by Toyama Chemical Co. in Japan.

Dihydroxymethyl furalazine is a derivative of nitrofuran, and its chemical formula is as follows.

This drug shows a wide spectrum of antibacterial activity against various pathogenic organisms, Gram-positive and -negative. Particularly, Gram-negative rods as Shigella, Salmonella etc. are extremely sensitive to the drug.
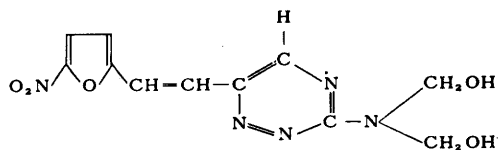
3-Di (hydroxymethyl) amino-6-
(5 nitro-2-furylethenyl)-1,2,4-triazine

Administration of drugs : Drugs were administered as shown in Table 1. One dose of each drug was given to the patient before collecting of stool. No other medication was given except intravenous fluid treatment during the period of examination.

Determination of the drugs in stool and serum : It was carried out by the bioassay method.

a) Chloramphenicol

Composition of medium used for the bioassay was as follows.

    i. Difco Nutrient Agar

        Bacto-Beef Extract   3g

        Bacto-Peptone   5g

        Bacto-Agar   15g

        23g of the mixture is diluted in 1000ml of distilled water and autoclaved for 15 minutes at 121°C

    ii. 0.1% methylene blue solution

    iii. 1% $NaNO_3$ solution

    iv. Indicator organism (Escherichia coli, strain NIHJ)

E. coli, strain NIHJ, was cultured overnight in the heart infusion broth. One or two ml of the culture was added to 100ml of Difco Nutrient Agar which was kept at 43-45°C in a water bath. Then, 3.8ml of 0.1% methylene blue solution and 1 ml

Table 1. Cases and Drugs.

Case No.	Age	Sex	Medication	Time of Observation
1	19	F	FL 250mg oral	12 hrs.
5	61	F	FL 250mg oral	7
6	27	F	FL 250mg oral	7
7	66	M	FL 250mg oral	9
8	42	M	FL 250mg oral	8
9	65	M	FL 250mg oral	10
15	31	F	FL 250mg oral	10.5
16	41	M	FL 250mg oral	12
18	31	M	FL 250mg oral	6
19	33	F	FL 250mg oral	14
24	24	M	FL 250mg oral	12
26	45	F	FL 100mg oral	10
10	55	M	CP 250mg oral	9
11	27	M	CP 250mg oral	9
12	45	M	CP 250mg oral	10
13	21	F	CP 250mg oral	14
14	55	F	CP 250mg oral	10
17	34	F	CP 250mg oral	12.5
20	39	M	CP 500mg oral	12.5
22	24	F	CP 500mg oral	11
23	35	M	CP 500mg oral	12.5
25	26	F	CP 500mg oral	12.5
2	16	M	CP 1000mg iv	7.5
4	22	M	CP 1000mg iv	7
21	25	M	CP 1000mg iv	3.5

CP : Chloramphenicol   FL : Furalazine

of 1% sodium nitrate solution were added. After mixing them well, 1.5 or 2.0ml of the melted agar which was prepared by the above method was distributed in small test tubes. The mixture in the test tubes was kept at room temperature until the agar became solid and successively stocked in a refrigerator until used.

For the determination of chloramphenicol level in stool and blood, the standard curves were made by using the standard chloramphenicol which was specially prepared. As the solvents of the standard drug, the plain rice watery stool was used

for the examination of stool and normal human serum was prepared for the examination of blood.

The stool or serum specimens stocked in the freezer were melted and homogenized by shaking, and 0.3 or 0.4ml of each sample was poured on the medium in the test tube. After the test tubes were placed in a refrigerator at 4°C for 3 to 4 hours, they were incubated overnight at 37°C. The length of the blue inhibitory zone appearing in each tube was measured by using a slide scale. The concentration of the active drug in samples was determined by comparison with the standard curve, which was made simultaneously.

b) Dihydroxymethyl furalazine
   i. Difco Nutrient Agar, same as used in determination of chloramphenicol
   ii. 1% methylene blue solution
   iii. Bacterial suspension : Bacillus subtilis PCI 219 was cultured on the ordinary nutrient agar slant at 37°C for 48 hours, and successively placed in a refrigerator for 5 to 7 days to form the spores. The organism was suspended in the normal saline solution with a proportion of one loopful organism per one ml of saline solution. Then, the bacterial suspension was stocked in a refrigerator until used.

In 100ml of Difco Nutrient Agar kept at 60°C, 0.15ml of 1% methylene blue solution and 0.3ml of bacterial suspension were added. After mixing well by shaking, the medium was distributed in test tubes with the same method as for the chloramphenicol bioassay.

The standard curve was drawn by the

same procedure as was used for chloramphenicol determination.

The stool or serum for examination was melted and homogenized by shaking. 0.3 or 0.4ml of each sample was placed on the medium in the test tubes. Then, they were placed in a refrigerator for two hours and successively incubated overnight at 37°C. Reading of the result was taken after incubation.

Results

1) Volume of stool

During the period of the study, the volume of stool excreted during each 30 minute period is shown in Table 2. The samples were

Table 2. The volume of stool collected in every 30 minute period and its frequency

Volume	Frequency	%	
0 - 50 ml	48	9.7	
50 - 100	69	14.0	
100 - 200	99	20.1	
200 - 300	104	21.1	91.2
300 - 400	71	14.5	
400 - 500	58	11.8	
500 - 600	16	3.2	
600 - 700	16	3.2	
700 - 800	5	1.0	
800 - 900	2	0.4	8.8
900 - 1000	3	0.6	
1000 -	2	0.4	
Total	493	100 %	

taken 493 times altogether. The volume between 0 and 500ml was seen is 449 samplings out of 493 (91.2%). In 42 samplings the volume showed more than 500 ml. The largest amount, more than 1000ml, was found twice.

Generally the volume of stool excreted in 30 minutes was almost constant in each case, except one or two hours after the beginning of rehydration. In 9 cases which showed high plasma specific gravity, the amount of stool for first 1 or 2 hours was especially small.

2) Relation between volume of stool and number of vibrios

On admission the number of vibrios in stool was the same (10^7-10^9/ml) in every patient who had not been given antibacterial drugs. The fact was not related to the amount of stool on admission.

In 5 cases (1, 5, 7, 9, 16), the number of viable vibrics in stool started to decrease in 2 to 3 hours after administration of the drug, especially furalazine, although diarrhea still continued in the same amount as before.

Even in 3 cases (7, 9, 16) whose stool contained no vibrios for several hours, it was observed that the volume of stool every 30 minutes showed no considerable change.

It was noticed that there was no relation between the volume of stool and the number of vibrios in stool during the early stage of cholera.

3) Influence of drugs on volume of stool

a) Furalazine

In twelve cases given furalazine orally, no marked change in the stool volume was found during the period of collection. As shown in fig. 1 (case No. 7), the stool volume during each 30 minutes amounted to 200 to 400ml, mostly approximately 400ml, for 9 hours after the oral administration of 250mg furalazine. However, no tendency to reduce in stool amount was noted during the period of observation.
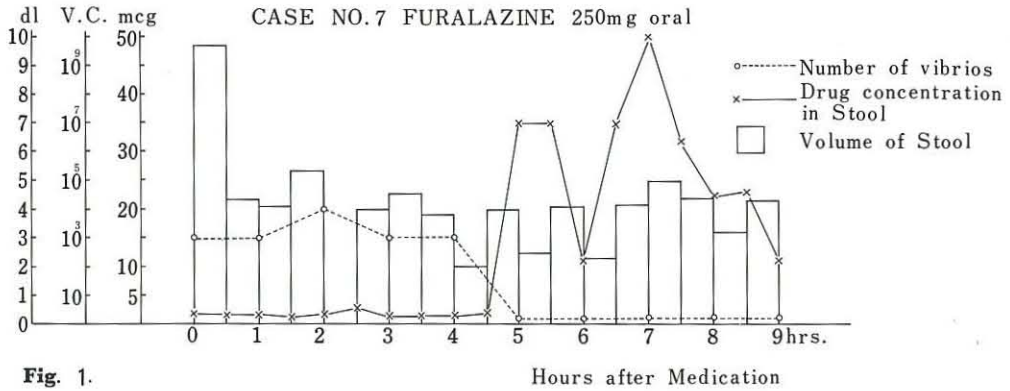
Fig. 1.

Hours after Medication

Case No. 7 The color of stool became yellowish in five hours after medication. The stool was almost constant in amount.

Fig. 8.

Hours after Medication
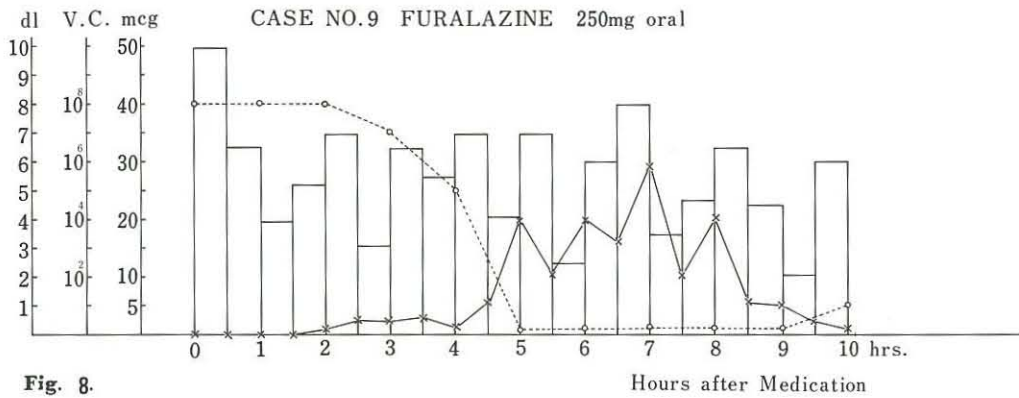

Case No. 9 The rice watery stool changed yellowish in five hours after medication.

b) Chloramphenicol

Chloramphenicol was given orally 250mg in 6 cases and 500mg in 4 cases. Three cases with intravenous administration of 1000mg chloramphenicol were compared with the cases having oral treatment.

No case showed remarkable difference in the volume of stool during every 30-minute period for 9 hours more or less after the medication.
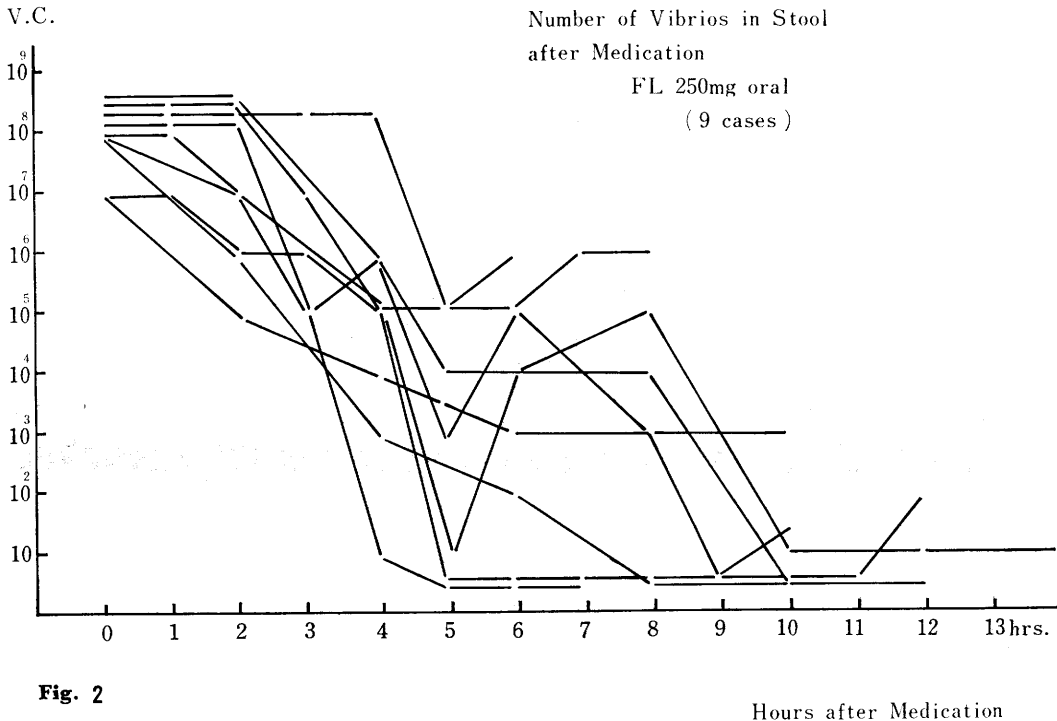

Fig. 2

Number of Vibrios in Stool
after Medication
FL 250mg oral
(9 cases)

Hours after Medication

As indicated in fig. 3 (case No. 17), the volume of stool during every 30-minute period ranged from 100 to 700ml. Difference of amount seemed not to be related to the time after the medication.

4) Influence of drugs on number of vibrios

in stool

a) Furalazine

It was observed in all cases that the number of vibrios in stool began to decrease mainly after 3 to 4 hours after the oral administration of 250mg of furalazine. How-
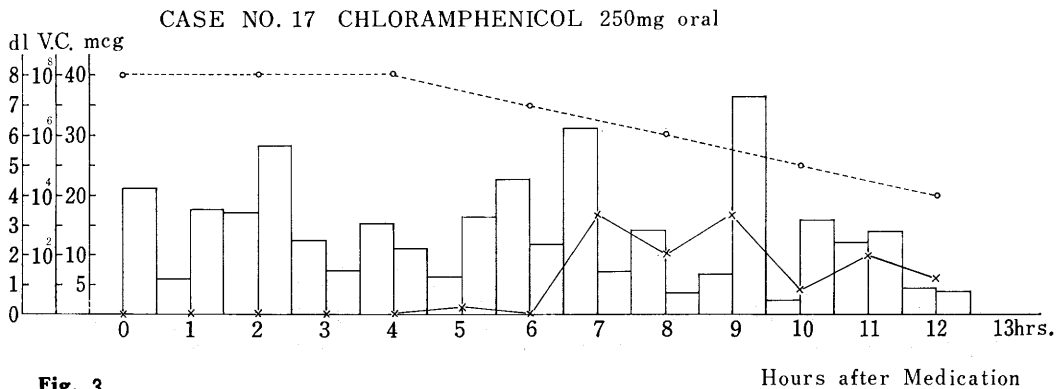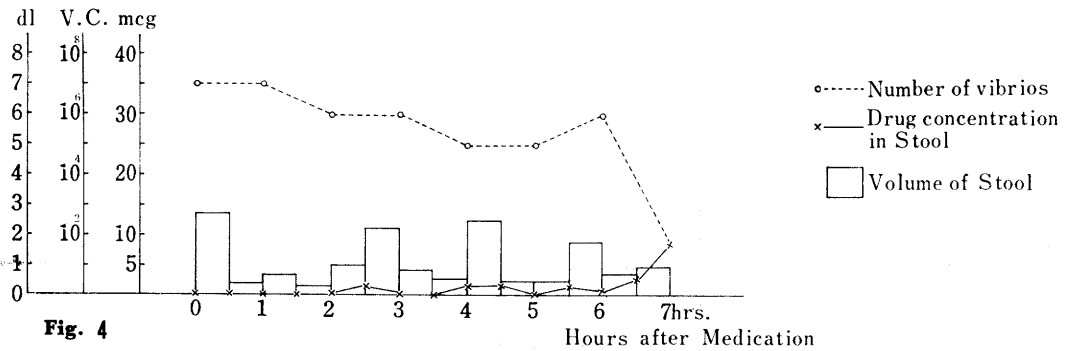

CASE NO. 17 CHLORAMPHENICOL 250mg oral

Fig. 3

Hours after Medication

ever, in case No. 6 (fig. 4) whose stool was   not copious, the number of vibrios was not
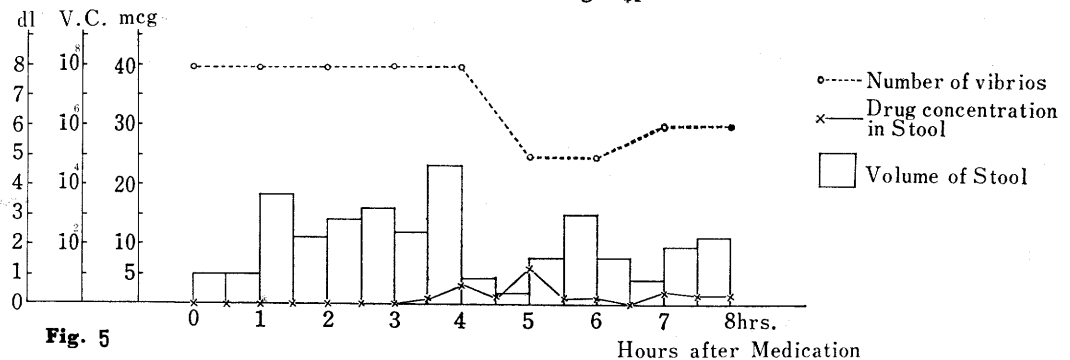
CASE NO. 6 FURALAZINE 250mg oral

Fig. 4

Hours after Medication

reduced until 7 hours after the start of treatment. The reduce in the number of vibrios was not remarkable in case No. 8

(fig. 5) which showed vomiting soon after the medication.

CASE NO. 8 FURALAZINE 250mg oral

Fig. 5

Hours after Medication

The time from the beginning of decrease   of vibrios until the elimination of vibrios in

CASE NO. 1 FURALAZINE 250mg oral

Fig. 6

Hours after Medication
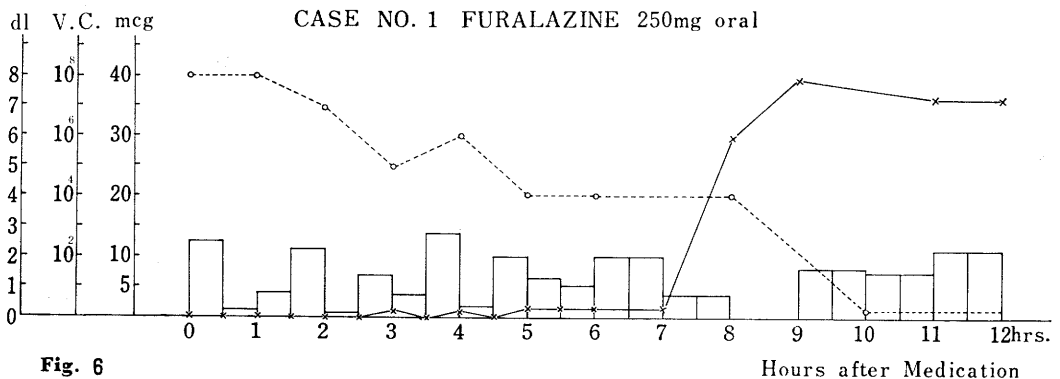
stool was 2 to 8 hours. For instance, in cases No. 1 (fig. 6) and 5 (fig. 7), the reduce of vibrios was found in 3 hours after the medication in both cases, and vibrios disappeared from the stool in the fifth hour in case No. 5 and the tenth hour in case No. 1.

CASE NO. 5 FURALAZINE 250mg oral

Fig. 7

b) Chloramphenicol

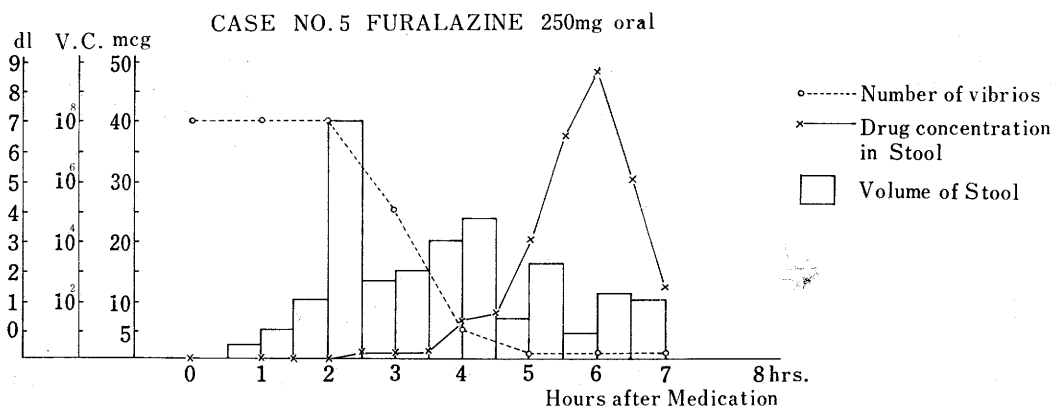It was noticed in cases treated with chloramphenicol that the decrease of vibrios in stool was not remarkable, although the number of organisms decreased gradually in some cases. The results were not widely different between the groups receiving 250mg and 500mg of oral administration (fig. 9, 10).
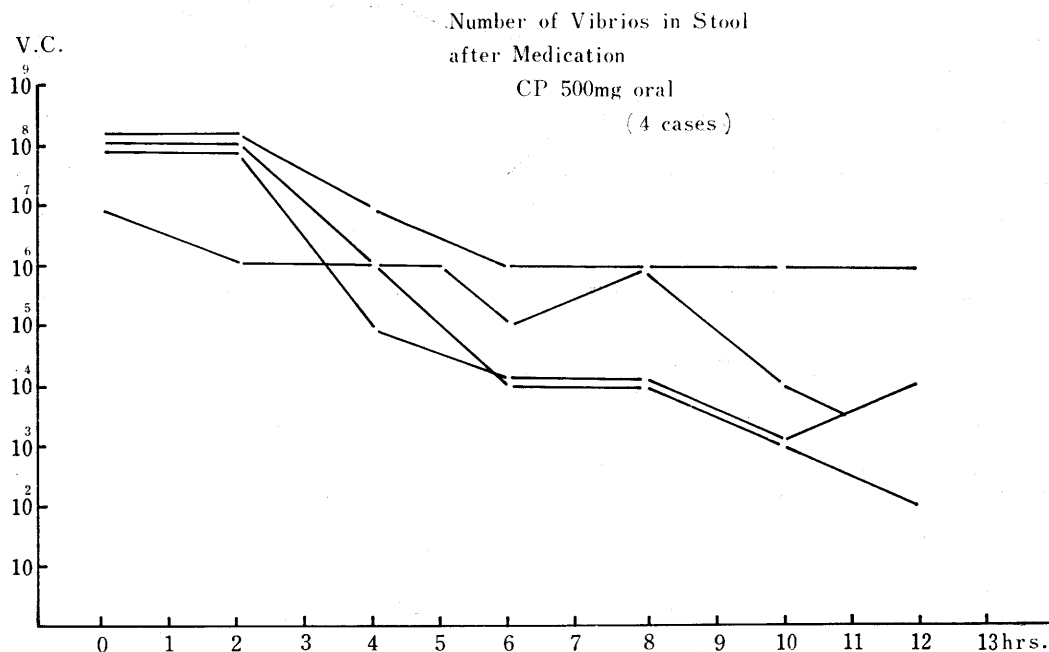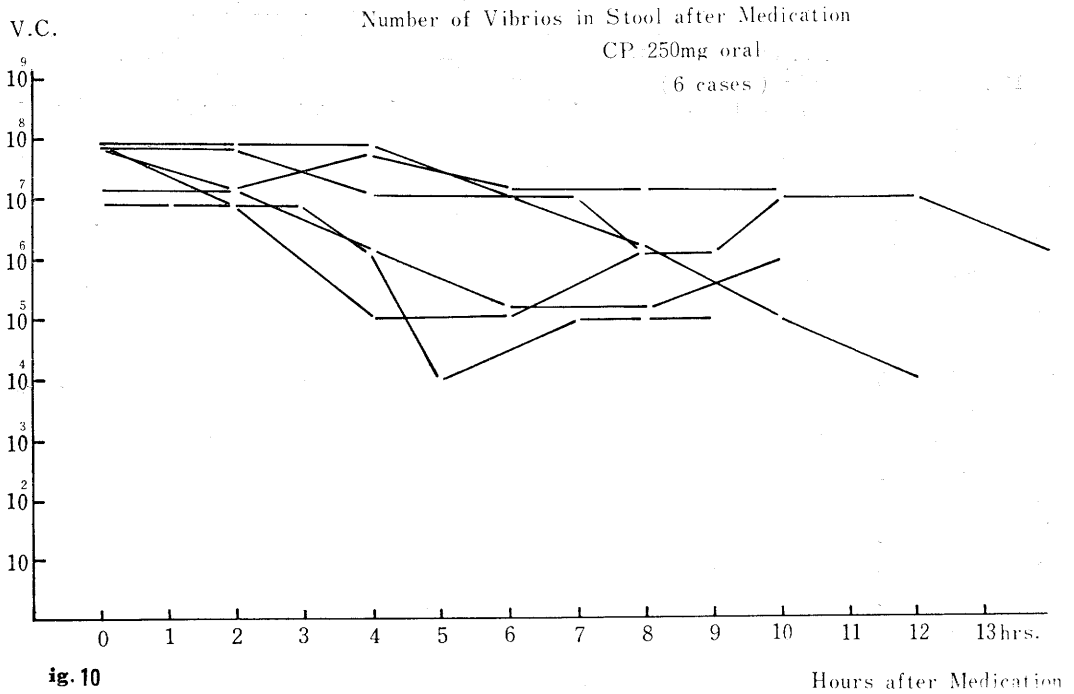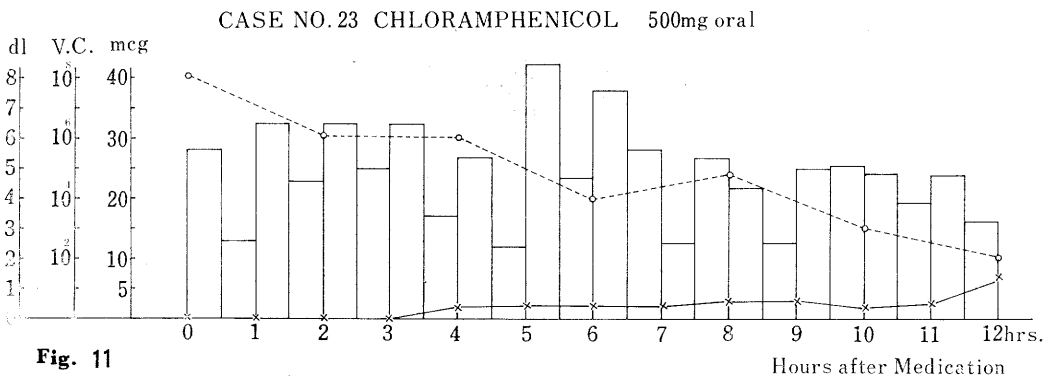
Number of Vibrios in Stool after Medication

CP 500mg oral

(4 cases)

Fig. 9

Hours after Medication

V.C.   Number of Vibrios in Stool after Medication

                               CP. 250mg oral

                                    (6 cases)

ig. 10   Hours after Medication

However, in the control cases with intra-venous treatment, the number of vibrios decreased markedly after the injection of chloramphenicol as shown in fig.12 (case No.4).

CASE NO. 23 CHLORAMPHENICOL   500mg oral

Fig. 11   Hours after Medication

5) Concentration of drugs in stool and serum

  a) Furalazine

The effective concentration of furalazine was considered to be approximately 0.1mcg/ml of the stool, considering the sensitivity of isolated vibrios to furalazine and the reduce of vibrios in stool. The stool with effetive concentrationof drug began to be evacuated 3 to 5 hours after medication, mostly in 4 hours.

The maximum concentration in the stool ranged from 4.0 to 50mcg/ml of stool, and it was reached within 5 to 9 hours, except for one case, which took 14 hours as seen in Table 3.

Table 3.   Concentration of Drugs and Number of Vibrios in Stool

Case No.	Medication	No. of vibrios before medication	When the reduce of vibrios was found for the first time			When the maximum concentration of the drugs was found		
			Hrs. after medication	No. of vibrios	Drug concentration	Hrs. after medication	No. of vibrios	Drug concentration
10	CP 250mg	10^6/ml	5	10^4/ml	5mcg/ml**	8	10^5/ml	30mcg/ml**
11	CP 250mg	10^8	4	10^5	0.15	2	10^7	0.6
12	CP 250mg	10^8	6	10^7	$0.1 >$	5	10^7	0.6
13	CP 250mg	10^8	4	17^7	$0.1 >$	12	10^7	1.0
14	CP 250mg	10^7	4	10^6	6.6	4	10^6	6.6
17	CP 250mg	10^8	6	10^7	$0.1 >$	7	10^6	17.5
20	CP 500mg	10^8	4	10^7	10	4	10^7	10
22	CP 500mg	10^8	4	10^6	2.5	6	10^5	4
23	CP 500mg	10^7	4	10^6	0.2	12	10^2	6.6
25	CP 500mg	10^8	4	10^5	1.0	8	10^4	1.2
2	CP 1000mg***	10^7	3	10^5	2.2	7	10^4	12
4	CP 1000mg***	10^8	1	10^3	65	1	10^3	65
21	CP 1000mg***	10^8	2	10^7	23	3	10^4	100
1	FL 250mg	10^8	3	10^5	$0.06 >$	9	$10 >$	40
5	FL 250mg	10^8	3	10^5	$0.06 >$	6	$10 >$	48
6	FL 250mg	10^7	4	10^5	$0.06 >$	7	10	8
7	FL 250mg	10^3*	5	10^1	14	7	$10 >$	50
8	FL 250mg	10^8	5	10^5	6.2	5	10^5	6.2
9	FL 250mg	10^8	4	10^5	1.0	7	$10 >$	29
15	FL 250mg	10^7	4	10^4	$0.06 >$	8	10^3	4
16	FL 250mg	10^8	4	10^3	0.09	9	$10 >$	16
18	FL 250mg	10^2*	4	$10^1 >$	3.7	5	$10 >$	5.5
19	FL 250mg	10^8	4	10^5	0.4	14	$10 >$	14.5
24	FL 250mg	10^8	4	10^5	0.08	9	$10 >$	35

*   medication was given before admission
**   microgram per milliliter
***   intravenous administration

There was no relation between the concentration of drug and volume of stool in each 30 minutes. On the contrary, the number of vibrios was closely correlated to the concentration of the drug in the stool. The reduce of vibrios was usually recognized when the concentration of the drug reached an effective level.

It was seen, in other words that the sooner the drug concentration became effective, the more rapidly the number of vibrios decreased.

The elimination of vibrios in the stool was not achieved in case No. 8 (fig. 5) which failed to receive a sufficient dose of the drug because of vomiting and of which the concentration was not high enough .

In the majority of cases, a high concentration continued for about 4 hours. In three cases, the number of vibrios increased again as the drug level came down.

Yellowish-colored watery stool was observed within 4 to 5 hours after the administration of furalazine, which indicated a higher concentration of the drug, higher than 3mcg/ml of stool.

According to the bioassay determination, the drug was not detected in the blood of any patient except one, in whom the drug was slightly proven, as shown in Table 4.

Table 4. Concentration of Drugs in Blood. (Bioassay)

Case No.	Medication		Hours after Administration				
			0	3	6	9	12
10	CP	250mg oral	0	0	0	4.0*	
11	CP	250mg oral	0	0.7	1.3	?	
12	CP	250mg oral	0	0	0	0	
13	CP	250mg oral	0	0			
14	CP	250mg oral	0	0	0	0.4	
17	CP	250mg oral	0	0.4	0.4	6.0	0.4
20	CP	500mg oral	0	6.0	5.2	1.1	
22	CP	500mg oral	0	6.0	3.0	2.0	7.0
23	CP	500mg oral	0	0	0	0.4	?
25	CP	500mg oral	0	1.5	1.7	3.0	
1	FL	250mg oral	0	0			
5	FL	250mg oral	0	0			
6	FL	250mg oral	0	0			
7	FL	250mg oral	0	0	0		
8	FL	250mg oral	0	0	0		
9	FL	250mg oral	0	0	0	0	
15	FL	250mg oral	0	0	0	0	
16	FL	250mg oral	0	0	0	0	
18	FL	250mg oral	0	0			
19	FL	250mg oral	0	(+)*	(+)*	(+)*	(+)*
24	FL	250mg oral	0	0	0	0	0

(+)* : slightly detected
CP   : Chloramphenicol FL : Furalazine
   * : mcg/ml

b) Chloramphenicol

The concentration of chloramphenicol in stool was extremely low in the majority of cases given 250mg or 500mg of chloramphenicol orally. Only 2 cases indicated 30mcg/ml in the eighth hour (case No. 10) and 17.5mcg/ml (case No. 17) after the seventh hour as indicated in Table 3.

It was, however, noticed that the number of vibrios in stool did not decrease even in cases which revealed a higher concentration of chloramphenicol.

In two cases out of three receiving intravenous administration of 1000mg chloramphenicol, rapid and marked decrease of vibrios in stool was seen, as well as higher concentration of the drug in stool. In case No. 2 (fig. 12), the concentration

Fig. 12
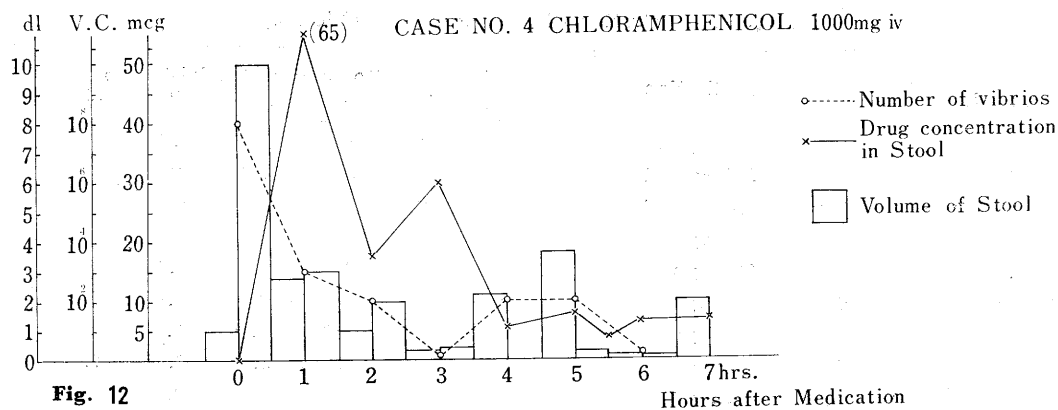
of the drug in stool was low within 6 hours fter medication and at the same time the

viable count showed no remarkable reduce until eighth hour.

Fig. 13
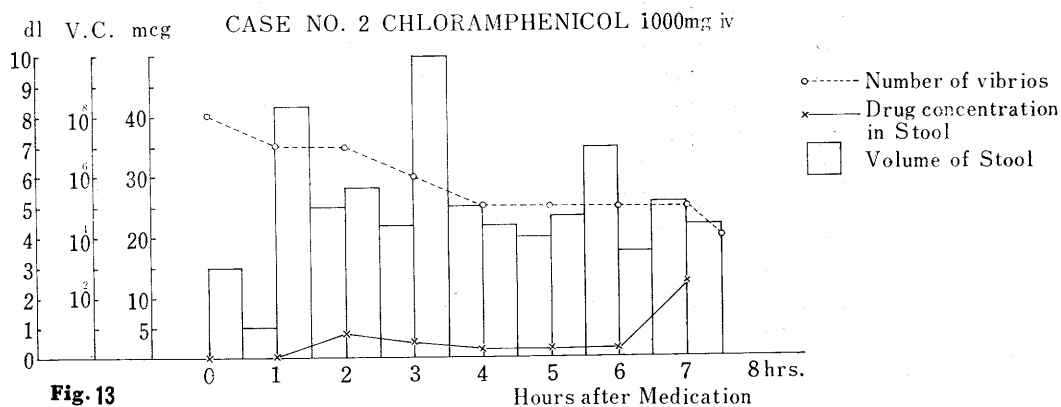
The blood concentration of the drug is shown in Table 4. A difference between the oral group of 250mg chloramphenicol and that of 500mg was seen; three cases in the

latter group indicated high concentration within 3 hours, although little or nothing of the drug was found in the former.

Table 5.   Drug Sensitivity Test of El Tor Vibrios isolated
at San Lazaro Hospital, Manila in 1970 (Utsunomiya)

MIC mcg/ml Drugs	0.195	0.39	0.78	1.56	3.12	6.25	12.5	25	50	100	Total
CP			267	400	6			11			684
TC			670	4					10		684
SM							292	375		17	684
FL	663	19		1	1						684

CP : Chloramphenicol   TC : Tetracycline
SM : Streptomycin   FL : Furalazine
The test was carried out by using dilution method

Discussion

It has been well known in the recent past that antibiotics are effective for reducing the duration of diarrhea and excretion of vibrios in stool, and chloramphenicol and tetracycline are popularly used for the treatment of cholera cases. [1] [3] [4] [5] [8] [14] [15]

However, some undesirable results of chloramphenicol treatment for cholera have been noted by Iwanaga et al. [13] And also it has been reported that several cases failed to be responded to chloramphenicol because of resistant strains to the drug. [16]

At the same time, the mechanism of the effects of antibacterial treatment of cholera has not been fully clarified.

In this situation, it was considered that the antibacterial therapy of cholera should be re-investigated precisely.

For the purpose of the study, the volume of stool which was collected in each 30-minute period, the number of vibrios in these samples and the concentration of the drug in stool and blood were investigated during the first few hours after admission.

The volume of stool collected within one or two hours after admission was different individually; in some cases with severe dehydration only a small amount of stool was excreted and in other cases, the volume of the first collected sample was extraordinarily large, probably because of retention of fluid in the rectal ampulla.

The volume of stool collected in each 30-minute period became almost constant from about 2 hours after the treatment, although a slight fluctuation of the volume was seen in some cases.

It was noteworthy that the volume of stool was not influenced by any antibacterial treatment.

It was confirmed that there was no relation of the amount of stool with the type, dosage and route of administration of the drug. In addition, the concentration of the drug was not correlated to the volume of stool.

On the other hand, the number of vibrios was usually 10^7-10^9/ml of stool on admission. It was supposed that the multiplication of vibrios in the intestine was inhibited at the threshold of 10^9/ml. [8] [10] [24]

It was noted that there was no proportion between the stool amount and the number of vibrios. [24]

Diarrhea continued for a few hours even when vibrios disappeared from the stool. This fact should be important in view of the pathogenesis of diarrhea. [2]

It implies that no growth or presence of vibrios in the intestine is needed for continuation of diarrhea. It is presumed that diarrhea may continue for at least 10 hours by means of a single stimulation of the intestinal mucosa as the trigger theory. [2]

It has been shown that the amount of stool can not be a criterion for the comparison of effectiveness between chloramphenicol and furalazine. Thus, a change of the number of vibrios can be only one indicator to decide the effect of the drug.

Changes of number of vibrios in caess with oral administration of 250mg and 500mg chloramphenicol are summarized in fig. 9 and 10. No marked reduce of vibrios was found in any case; particularly in group receiving 250mg chloramphenicol, some cases showed almost no change of the number of vibrios for about 10 hours after the medica-

tion. Even in cases of 500mg chloramphenicol, the decrease of vibrios was gradual and not satisfactory. There were no cases in which vibrios disappeared from the stool. The fact should be due to the low concentration of drug in the stool, except in two cases.

On the other hand, concentration of chloramphenicol in the blood was rather high in cases of oral 500mg administration, although the drug appeared in little concentration in the blood of cases receiving 250mg chloramphenicol.

Anyway, a paradoxical finding of the drug concentration of stool can not be comprehended by the blood concentration in both groups.

It is presumed that a large part of the drug may be inactivated in the intestine.

Two cases with intravenous administration of 1000mg of chloramphenicol out of 3 cases showed a striking difference from those with oral administration in regard to the reduce of vibrios and the drug concentration in the stool.

The same finding was mentioned by Iwanaga et al, [13] and was confirmed by the previous experience of the author in 1969.

It is not clear whether the difference between the oral and intravenous administration should be due to preparation of chloramphenicol, succinate and ordinary powder, or the route of administration.

From the public health point of view, it should be a priority to eliminate vibrios from the stool of the patient as soon as possible. For this purpose, intravenous administration is more satisfactory than oral within the first few hours after admission. [24]

It has been observed at San Lazaro Hospital that chloramphenicol was less effective than before for treatment of cholera patients; particulary the duration of positive culture for Vibrio cholerae has been prolonged in some cases in spite of strains sensitive to chloramphenicol.

Moreover, several resistant strains to chloramphenicol have been found since 1969. [16]

Such a situation in treatment of cholera has demanded some substitutional drugs for the antibacterial treatment of cholera. According to the sensitivity test shown in Table 5, dihydroxymethyl furalazine was selected because of its highest sensitivity.

As far as the concentration of furalazine is concerned, the drug reached an effective concentration in stool within 2 to 4 hours, while it was not proven in blood in almost all cases; it was presumed that the major part of the drug can be excreted in stool without absorption. [12] [25]

It is worth noticing that the number of vibrio indicated the tendency of rapid decrease in the majority of cases taking furalazine orally. Furthermore, it should be emphasized that vibrios disappeared completely in stool in almost all cases.

The reduce and elimination of vibrios in the stool was comprehensible by means of drug concentration in stool. In other words, the drug was excreted in satisfactory concentration to kill the vibrios.

Furalazine was used in form of yellowish granules. It was noticed that yellowish watery stool was found within about five hours after administration in some cases.

This phenomenon can be helpful to estimate the time that the drug takes to pass through the intestine. It can give an useful guide in deciding the intervals of drug administration.

In conclusion, furalazine was much more effective than chloramphenicol concerning

the reduce or elimination of vibrios in stool.

Besides, since the effect of 250mg furalazine was superior to 500mg chloramphenicol, it is more than twice as effective as chloramphenicol for treatment of cholera.

One other kind of the nitrofuran derivatives was reported as chemotherapeutica by Chaudhuri et al [6] [7] and Pierce et al. [20] However, the sensitivity of this drug is inferior to that of furalazine.

This drug was compared preliminarily with other antimicrobial agents for its effect in reducing the duration of diarrhea and excretion of vibrio in stool. [15]

Only one disadvantage of the drug (furalazine) is nausea and vomiting caused by stimulation of stomach. However, the vomiting was not frequently seen.

Summary

Twenty five adult patients with typical cholera symptoms, admitted to San Lazaro Hospital, Manila, were investigated. Chloramphenicol was compared with dihydroxymethyl furalazine in regard to amount of diarrhea, reducing the vibrios in stool and concentration in stool and blood after taking it.

1. With oral administration of chloramphenicol, neither reduction of vibrios nor elevation of drug level in stool were seen.

2. Two cases with intravenous administration of chloramphenicol revealed high concentration of the drug and marked reduction of vibrios in stool.

3. In all cases with oral administration of furalazine, effective concentration of the drug in stool was regularly found and at the same time, a remarkable decrease of the number of vibrios was recognized. Moreover, it was observed that the vibrios disappeared from the stool in almost all cases, as the level of the drug showed further elevation.

4. An untoward reaction of furalazine, vomiting, was seen in one case.

Acknowledgement

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