CONTROLLED CLINICAL TRIAL WITH MINOCYCLINE IN TWO DOSAGE SCHEDULE IN RESPIRATORY INFECTIOUS DISEASES

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Summary

In this paper the serum concentration of minocycline was compared when minocycline was administered to three healthy male adults on two different dosage schedules by the cross over method; 200 mg initially followed by two daily doses of 100 mg each, or followed by a single daily dose of 100 mg for 6 days.

Accumulative raise of the drug was not found in either experiments and the greater difference between the results of the two experiments was observed in the minimum serum concentration than in the maximum one.

Double blind controlled trials by two dosage schedules (100 mg or 200 mg daily) were carried out in the patients with pulmonary infections at seven institutes. It was apparently noted that the administration of minocycline showed superior therapeutic effects when it was given at the two daily doses of 100 mg each, than at the single daily dose of 100 mg. As for the appearance of side effects such as gastrointestinal disturbance and floating sensation there was no difference between the two groups.

Introduction

It is noted that minocycline (MINO, 7-dimethyl amino-6-deoxy-demethyl-tetracycline) is one of the long acting tetracycline (TC) derivatives and is distinguished from other TC derivatives by its potent bacteriocidal activity against TC resistant staphylococci.

The blood concentration at 24 hours after the oral administration is still one thirds of that at 3 hours after the administration and is over the minimum inhibitory concentration against gram positive cocci. Therefore it was considered that this drug may have accumulative action by consecutive administration and maintain good therapeutic effect even with a single dose of 100 mg daily.

The purpose of this study was to clarify those points.

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Materials and Methods

1. Determination of serum concentration

The serum concentration was bioassayed by TORII's diffusion method using β-hemolytic streptococcus (Cook strain). Three healthy male adults were given MINO at the initial dose of 200 mg followed by 100 mg twice daily for 6 days. (The first experiment)

One week after the first experiment, the same persons were given MINO at the initial dose of 200 mg followed by 100 mg once a day for 6 days. (The second experiment)

The venous blood was taken at 3, 12, 15, 24, 27, 36, 39, 48, 51, 60, 63, 144, 147, 156, 159 and 180 hour in the first experiment and 180 hour in the first experiment and at 168 hour instead of 180 hour at the second experiment. All the collected serum was stored in the deep freezer at −20°C and the drug concentration was determined at one time for the all serum.

The volunteers took the same kinds of meals at the same time during these experiments.

2. Controlled clinical trial

The patients with respiratory infections including bronchitis, pneumonia, bronchopulmonary suppuration were selected for this study. These patients were divided into two groups ; a patient in one group (A-group) was given one capsule of MINO 100 mg in the morning and one capsule of placebo which was quite similar to that of MINO in its form and size at night. A patient in the other group (B-group) was given two capsules of MINO

Score	0	1	2	3
X-ray finding				
Size of cavity	none	1.5 cm	1.5～3.9 cm	4 cm～
Extend of basic lesion	none	minimum	moderately advanced	far advanced
Temperature	～37°C	37.1～37.9°C	38～39.9°C	40°C～
Cough	none	scanty	abundant	
Sputum	～4.9 cc	5～19 cc	20 cc～	
Rales	none	scanty	abundant	
Count of WBC	～7,900	8,000～11,900	12,000～	
Blood sedimentation rate (1 hour)	～10	11～49	50～99	100～

100 mg daily, one in the morning and one at night. Both groups were given 200 mg of MINO at the initial dose.

Therapeutic effects were examined on the following points and the score of 0～3 was given according to the result of the examination. In this examination the most severe case was to be given 20 scores in total.

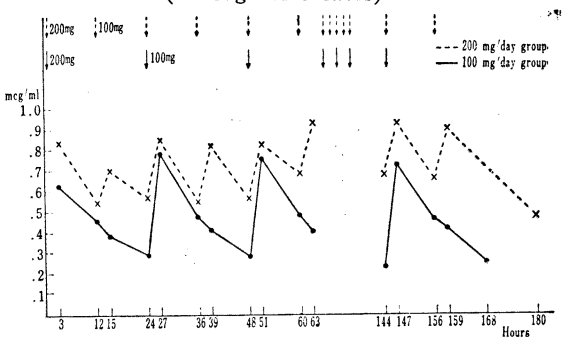
The therapeutic effect to individual symptom was observed after the 7 and 14 days of treatment by the change of the scores. Total scores at the 7th and 14th day of treatment were divided by those at the beginning of the treatment. The effectiveness of MINO was defined as considerable, moderate, slight or ineffective when the divided values were below 0.3, 0.31～0.5, 0.51～0.7 and over 0.71 respectively.

Results

1. Serum concentration by consecutive administration

The average serum concentration of MINO in three healthy adults who were administered two different doses by cross over test were shown in Fig. 1 and Table 1.

Fig. 1. Serum concentration of minomycin (Average of 3 cases)



The averages of minimum serum concentration of MINO at 24, 48, 144 and 168 hours after the administration in the second experiment were 0.24, 0.24, 0.23 and 0.25 mcg/ml, respectively and those of maximum at 27, 51 and 147 hours were 0.78, 0.76 and 0.72 mcg/ml. The averages of minimum concentration of MINO at the 1st experiment at 24, 36, 48, 60, 144, 156 and 170 hours after the administration

Table 1. Blood concentration

Cace	Method	hours after 3	12	15	24	27	36	39	48	51	60	63	144	147	156	159	168	180
A	Once a day	0.52	0.42	0.34	0.29	0.64	0.39	0.30	0.25	0.60	0.38	0.34	0.25	0.56	0.36	0.36	0.18	
	Twice a day	0.64	0.38	0.38	0.54	0.78	0.34	0.72	0.46	0.58	0.54	0.78	0.68	0.90	0.66	0.94		0.50
B	Once a day	0.88	0.64	0.52	0.42	0.94	0.60	0.56	0.38	1.0	0.66	0.56	0.25	0.9	0.56	0.48	0.32	
	Twice a day	0.88	0.66	0.80	0.66	0.90	0.66	0.94	0.68	1.0	0.80	1.1	0.68	0.94	0.66	0.94		0.54
C	Once a day	0.5	0.34	0.29	0.15	0.78	0.46	0.38	0.19	0.68	0.40	0.3	0.2	0.72	0.46	0.38	0.25	
	Twice a day	1.0	0.6	0.74	0.56	0.88	0.66	0.80	0.56	0.94	0.68	1.0	0.68	0.94	0.66	0.80		0.36
Average	Once a day	0.63	0.47	0.38	0.24	0.78	0.48	0.41	0.24	0.76	0.48	0.40	0.23	0.72	0.46	0.40	0.25	
	Twice a day	0.84	0.54	0.64	0.57	0.85	0.55	0.82	0.57	0.84	0.67	0.96	0.68	0.92	0.66	0.89		0.47

were 0.54, 0.55, 0.57, 0.67, 0.68, 0.66 and 0.47 mcg/ml respectively, and of maximum at 15, 27, 39, 51, 63, 147 and 159 hours were 0.64, 0.85, 0.82, 0.84, 0.96, 0.92 and 0.89 mcg/ml respectively.

Therefore the values of minimum serum concentration were significantly different between the two experiments. In the first experiment serum concentration was about two times as high as that of the second experiment. But the values of maximum concentration in two experiments did not show much difference.

The accumulative raise of the serum concentration was not observed in either experiment within seven days.

2. Controlled clinical trial

Seventy patients were treated during the period of December 1970 to March 1971, but 10 were excluded; 5 for failing of follow up, 2 for side effects, 1 with pulmonary mycosis, 1 with lung cancer and 1 with pulmonary tuberculosis. (Table 2)

Table 2. Excluded cases

	A group	B group
Impossible to follow up	2	3
Side effect (Vomiting)		1
Side effect (Floating feeling)	1	
Pulmonary mycosis	1	
Lung cancer	1	
Pulmonary tuberculosis	1	
Total	6	4

Table 3. Variety of respiratory diseases

	A group	B group
Pneumonia or pulmonary suppuration	10	10
Bronchiectasis	3	4
Bronchitis	16	11
Mixed infection with tuberculosis	1	4
Pharingitis	0	1
Total	30	30

Table 4. Background factor

		A group	B group
Sex	Male	14	15
	Female	16	15
Age	−20	1	1
	21−30	3	6
	31−40	3	10
	41−50	4	2
	51−	19	11
Score at the beginning of treatment	15		1
	12−14	3	4
	11− 9	8	5
	8− 6	11	15
	5− 3	7	5
	2	2	

Table 5. Clinical course at the 2nd week

		Temperature	Cough	Sputum
Normal at the beginning of treatment	A group	7	0	5
	B group	6	1	7
Returned to normal	A group	9 (64.3)	8 (38.1)	9 (60)
	B group	10 (71.5)	13 (65.0)	9 (64.3)
Improved	A group	1 (7.1)	6 (28.6)	1 (6.7)
	B group	0	5 (25.0)	4 (28.6)
Unchanged	A group	3 (21.4)	7 (33.3)	5 (23.3)
	B group	2 (14.2)	2 (10.0)	1 (7.1)
Worsened	A group	1 (7.2)	0	0
	B group	2 (14.2)	0	0
Unexamined	A group	9	9	10
	B group	10	9	9

A group 100 mg once daily
B group 100 mg twice daily

( )=%

Of the sixty patients who were the subjects of the trial, thirty patients were given MINO once daily (A-group) and thirty twice daily (B-group).

The conditions of the patients were similar in two groups as to the kind of infection, sex, age, body weight, isolated bacilli from the sputum, TC sensitivity and the total score of the test given at the beginning of the treatment which were 7.43 for A-group and 7.83 for B-group. Therefore it was considered that the backgrounds of both groups were similar enough to enable the comparative studies on the therapeutic effects.

1) Evaluation of clinical findings

a) Temperature

The numbers of patients who became well in the first or the second week were shown in Table 5.

Table 6. Summarized evaluation by attending physician

	A group	B group
Considerable improvement	4 (13.3)	6 (20.0)
Moderate improvement	12 (40.0)	13 (43.4)
Slight improvement	7 (23.4)	11 (36.6)
Inffective	7 (23.4)	0

( ) = %

No significant difference was observed between the two groups.

b) Cough

The numbers of patients who got over the cough were larger in B-group than in A-group. The test by chi-square distribution showed that significant differences were observed between the two groups in the second week. (P-2.5%) (Table 5)

c) Sputum, rales

The number of the improved cases in B-group was higher than that in A-group. However no significant difference was found.

d) X-ray findings

X-ray findings were evaluated by the standard of GAKKEN (The Research Committee for Chemotherapy of Tuberculosis). The number of cases which showed moderate or marked improvement was larger in B-group than in A-group. However, no significant difference was found.

e) Other clinical findings

The clinical evaluation on WBC and BSR revealed no significant difference between the two groups.

2) Summarized evaluation of clinical findings

The summarized evaluation of the results was as in Table 6. There were no ineffective cases in B-group, while there were 7 cases in A-group. The difference between the two groups was significant. (P-2.5%)

Table 7. Summarized evaluation by score

Clinical course	Observation	A group	B group
Considerable improvement −0.3	1 w	8 (27.6)	10 (33.3)
	2 w	5 (23.8)	13 (65)
Moderate improvement 0.31−0.5	1 w	8 (27.6)	10 (33.3)
	2 w	6 (28.6)	2 (10)
Slight improvement 0.57−0.7	1 w	3 (10.3)	7 (23.4)
	2 w	5 (23.8)	2 (10)
Ineffective 0.71−	1 w	10 (34.5)	3 (10.0)
	2 w	5 (23.8)	3 (15)
Unexamined	1 w	1	0
	2 w	9	10

( ) = %

Table 8. Side effects

	A-group	B-group
Gastrointestinal disturbance	6 (2)	2 (1)
Sore tongue	1	0
Floating sensation	3 (1)	3
None	23	26
TotaL	33	31

No. of braxket means dropped out cases.

The evaluation by chi-square using the score showed that the number of ineffective cases in A-group at the first week was higher than that in B-group with significance. (P-2.5%) The number of considerably improved cases in B-group at the second week was higher than that of A-group with

significance. (P-1.0%) (Table 7)

3) Side effects

The numbers of cases of side effects were shown in Table 8; 10 cases in A-group and 5 cases in B-group complained gastrointestinal disturbance. Three cases in A-group and one in B-group discontinued taking the drug due to the side effects.

Discussion

Minocycline is one of the analogues of tetracycline, however, it is distinguished from other TC analogues by having some bacteiocidal action against cocci and higher potency against TC-resistant staphylococci.[1,2,3] Our laboratory studies also revealed that the MIC of MINO against staphylococci isolated from the patients was below 0.2 mcg/ml while MIC of TC was 0.39 mcg/ml, and many TC resistant staphylococci were inhibited by the concentration of 0.78 to 0.56 mcg/ml.[4]

It is reported by STEINBIGEL, *et al.* that the MINO was the most active of the seven TC analogues (MINO, DOCT, MC, CTC, DMCT, OTC and TC) against all the tested coccal organisms except enterococcus and most of the important gram negative bacilli except the strains of proteus.[5] They also reported about the serum concentration that at the smaller amounts, MINO yielded higher level of antibacterial action in the serum than DMCT, MC, DOCT, and this level was sustained longer than those of DMCT or MC.[6]

It is reported by many investigators that the serum concentration of MINO reached to the peak of 4.4~0.7 mcg/ml at 3 hours and sustained the level of 1.56~0.41 mcg/ml for 24 hours.[2,3,4,7,8,9,10] Therefore, it is considered that the MINO might be accumulative by the consecutive administration. But, the studies on the consecutive administration for 48 or 72 hours already carried out revealed that there was no accumulative tendency in MINO.[2,3]

CAPBEL also reported that the accumulative raise was not found in his experiment where the drug was given at the single initial dose of 200 mg followed by 100 mg once a day for one week.[11]

However, the reports on the accumulation of the drug at the two divided doses of MINO 200 mg daily for one week were not found.

Three healthy men were administered 200 mg of MINO initially, followed by 100 mg twice a day for 6 days. (the first experiment) One week after that, the same persons were administered the MINO 200 mg initially followed by the 100 mg once a day for 6 days. (the second experiment)

The accumulative raise of the drug was not found in either experiment. The average concentration of maximum levels in the first experiment and that of maximum levels in the second experiment were 0.85 mcg/ml and 0.78 mcg/ml respectively. The average concentration of seven minimum levels in the first experiment and that of three minimum levels in the second experiment were 0.59 mcg/ml and 0.24 mcg/ml respectively. Therefore it could be said that there were greater difference in the minimum concentration than in the maximum between the two groups.

Above mentioned data showed that the serum concentration of the drug following the administration of single dose of 100 mg a day never dropped below the therapeutic effective levels within 24 hours. So, controlled double blind trial with MINO by two dosage schedules (100 mg and 200 mg) was conducted in the cases of respiratory infections.

The methods of the clinical evaluation for the infectious diseases have many problems. The Japan Society of Chemotherapy have discussed these problems.[12] In this study the same method as was used by FUKAYA was adopted as we found that his modified evaluation method showed reasonable results in the evaluation of the therapeutic effect for pulmonary suppuration.[13,14]

All patients were treated at the seven institutes related to Keio Hospital during the period of December 1970 to March 1971. The number of the analized cases except dropped out cases was thirty for the single dose of 100 mg (A-group) and thirty for the two doses of 100 mg (B-group). There were no significant differences between conditions of the two groups as to the kinds of diseases, sex, age, the severity of disease by the score, the kinds of bacilli and TC sensitivity of isolated bacilli at the beginning of the treatment.

The number of cases who got over the cough in the second week was significantly larger in the B-group than in the A-group. The ineffective cases were observed more often in A-group than in B-group by the evaluation of each attending physician. The considerably improved cases were significantly larger in B-group than in A-group. Therefore it can be said that the therapeutic effect of two doses of 100 mg a day was superior to that of single dose of 100 mg a day.

STEINBERG, *et al.* reported that administration of MINO by 300 mg produced moderate to sever gastro-

intestinal symptoms when it was given in single oral dose after an overnight fast. Present investigation showed that the cases of gastrointestinal disturbance were 10 in A-group and 5 in B-group, but significant difference was not found between the two groups.

It is apparent from this result that the therapeutic effect of the two doses of 100 mg a day is superior to that of the single dose. Therefore MINO should be administered in the two doses of 100 mg a day for respiratory infections. And it was considered that the difference of therapeutic effect between the two groups might be caused not by the difference of maximum serum concentration but by that of the minimum serum concentration.

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