

THERAPEUTIC EFFECT OF MINOR ANTITUBERCULOSIS DRUGS ON ADVANCED PULMONARY TUBERCULOSIS

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This paper reported the clinical results of treatment with minor drugs, Kanamycin, Ethionamide and Cycloserine to 341 patients with severe pulmonary tuberculosis, whose organisms were known to be resistant to all major drugs.

The patients had already been treated with antituberculous chemotherapeutics more than a year, and were discharging big amount of bacilli in sputum, had more than two cavities with sclerotic wall or multilocular cavity with sclerotic wall or large cavity with sclerotic wall on radiogram and extent of lesions were moderately or far advanced.

Seventeen patients were treated with three minor drugs for the first time, and 11 out of 17 converted to negative on at least 3 months consecutive culture, 9 out of 17 on at least 6 months, 5 out of 15 on 9 months and 4 out of 15 on twelve months consecutive culture.

Among cases showing negative bacilli on at least 3 months consecutive culture, first negative result was observed as late as the fifth month after start of chemotherapy, therefore when negative conversion was not observed until 5 months after start of chemotherapy, the regimen should be changed to other regimen. In order to prevent bacteriological relapse, the minor drug regimen succeeded to obtain negative conversion must be continued for at least 9 months and more preferable 12 months after first negative result.

Among patients under this study with resistance to major drugs and with chronic advanced lesions, radiographical changes were slight and the closure of cavity was observed only in 16 of 402 cavities with sclerotic wall after six months chemotherapy of minor drugs for the first time.

INTRODUCTION

The overall therapeutic effect of minor drugs has been controversial¹⁾²⁾³⁾⁴⁾ because of the variety of drugs available, the differences in the combination adopted, as well as the different background factor of each clinical subject. Moreover, the interpretation of negative conversion, the problems of resistance, as well as the toxic effect of drugs have complicated the evaluation of therapeutic efficacy of minor drugs.

An attempt was made to study the therapeutic effect of minor antituberculosis drugs (Kanamycin, Ethionamide and Cycloserine) on advanced pulmonary

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tuberculosis with bacilli resistant to three major drugs, *i.e.*, Streptomycin, PAS and Isoniazide.

MATERIALS AND METHODS

The subjects studied were 341 cases of previously treated pulmonary tuberculosis patients with bacilli completely resistant to 10 μ of streptomycin, 0.1 μ of isoniazide and 1.0 μ of PAS, and then had been treated for more than 4 months with one or more of the minor drugs (Kanamycin, Ethionamide and Cycloserine).

The background factors of the 341 patients were: Out of 341 cases, 267 were males and 134 females; 170 were under 39 years of age and 171 over 40 years. The duration of previous chemotherapy was over 3 years in 239 cases, between 2 and 3 years in 51 cases, between one and 2 years in the remaining 51 cases. Monthly tests of sputum performed for four months prior to start of chemotherapy with minor drugs, were persistently positive for the bacilli in 269 cases, in 30 cases the bacilli were positive in three of four tests, in 21 cases in two and in 7 cases bacilli in only one. In 254 cases the bacilli were positive in smear and the culture yielded more than 200 colonies, in 38 cases bacilli were positive in smear and produced less than 200 colonies of culture and in the remaining 49 cases the bacilli were negative in smear but the culture yielded more than 200 colonies. Three hundred and thirty cases were far advanced (Fa), 11 moderately advanced (Ma) and none minimal (Mm) as classified by NTA classification. The type of lesions were far advanced mixed type in 172 cases, fibrocaceous type in 143 and caseoinfiltrative type in 26. Two hundred and forty-three cases had multilocular cavities with sclerotic wall and the other 98 cases large or multiple cavities with sclerotic walls. One hundred and fifty-two cavities were ring-form cavities with sclerotic wall, 106 were cavities in the sclerotic lesions and 311 were multilocular cavities with sclerotic wall.

The effects of the treatments were judged mainly on the basis of negative conversion of bacilli and improvement of chest X-ray findings. The negative conversion of the bacilli in this study means consecutively negative culture during three successive months. The effects of the treatments were separately evaluated in the first treatment and retreatment with minor drug, and treatment with three drugs combination, two drugs combination and with single minor drug.

Kanamycin was injected intramuscularly twice a week in a dose of 2 g per day. Ethionamide was administered orally every day in a daily dose of 0.5 g, and Cycloserine in a daily dose of 0.5 g.

RESULTS

1) *Negative conversion of tubercle bacilli*

a) In Fig. 1 were plotted the rates of negative conversion according to months following administration of minor drugs. By single minor drug treatment a maximum negative conversion rate of 12% is observed in the third month, with no further rise thereafter. In cases of combination treatment with two minor drugs the negative conversion rate became fairly high, rising to about 45% in the fifth or sixth month, and remained so thereafter. Contrary to the above, in cases of combination treatment with three minor drugs the negative conversion rate in the first month was 25% and gradually rose to 75% in the sixth month. In these advanced cases, therefore, therapeutic efficacy can be rather expected only by combination treatment of minor drugs.

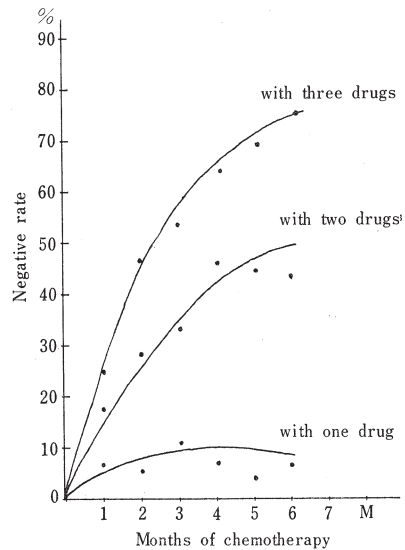


FIG. 1. Bacilli negative rate by month following administration of minor drugs.

b) Table 1 shows the rates of negative conversion of the bacilli in case of first treatment or retreatment. No negative conversion occurred by retreatment with minor drugs regardless of the number of drugs used. The treatment with a single minor drug for the first time resulted in negative conversion rate of 3.7%, a combination treatment with two drugs 36.5%, and with three drugs 64.7%. With treatment of two drugs of which one was used for the first time and the other for the second, the negative conversion rate (15.7%) was higher than in case of treatment with one minor drug only for the first time, while in cases of combination treatment with two drugs for the first time and one drug for the second time, the negative conversion rate (50.0%) was also slightly higher than in case of combination treatment with two drugs for the first time. Thus, higher therapeutic effects can be expected when a minor drug that has already been used is administered in combination with others which have never been used.

c) The rates of consecutive negativity of bacilli during 3, 6, 9 and 12 months are shown in Table 2. In the group of combination treatment with three drugs for the first time the rates of consecutive negativity of bacilli were 64.7% during 3 months, 52.9% during 6 months, 33.3% during 9 months and 26.6% during 12 months. In the case of combination treatment with two

TABLE 1. Negative Conversion Rate for the First Time and for Retreatment

a)

Treatment with minor drugs	For the first time		
	No. of cases	No. of conv. cases	Conversion rate
With one drug	191	7	3.7%
With two drugs	63	23	36.5%
With three drugs	17	11	64.7%

b)

For Retreatment			
Combination method	No. of cases	No. of conv. cases	Conversion rate
(Single)	15	0	0%
Both drugs retreat	13	0	0%
One drug for the first and one drug retreat	19	3	15.7%
Three drugs, all retreat	5	0	0%
One drug for the first and two drugs retreat	6	0	0%
Two drugs for the first and one drug retreat	12	6	50.0%

TABLE 2. Period of Consecutive Negative Culture Following Treatment with Minor Drugs for the First Time

Period of consecutive negative culture	With three drugs	With two drugs	With one drug
3 months	11/17 64.7%	23/63 36.5%	7/191 3.7%
6 months	9/17 52.9%	12/61 19.5%	4/191 2.1%
9 months	5/15 33.3%	11/60 18.5%	2/190 1.0%
12 months	4/15 26.6%	9/57 15.8%	2/190 1.0%

drugs for the first time the rates were 36.5%, 19.5%, 18.5% and 15.8%, respectively and 3.7%, 2.1%, 1.0% and 1.0%, respectively in the cases of single treatment for the first time. Thus, in the case of advanced pulmonary tuberculosis with bacilli resistant to all major drugs, the rate of negative conversion during 12 months was almost 26.6% even with combination treatment of the three minor drugs for the first time.

d) Fifty cases having negative conversion for more than three months

were studied with reference to the time interval between the start of chemotherapy with minor drugs and the first negative culture (Table 3). Forty-two cases (84.0%) showed negative conversion within 3 months after the start of therapy and all 50 cases became converted within 5 months. From these data, it would seem that for the case where no negative conversion occurred within 5 months, the regimen adopted is not effective.

TABLE 3. Time Interval between Start of Chemotherapy and First Negative Culture

Month after start of minor drug chemotherapy	1	2	3	4	5	6	7
No. of cases	22	11	9	5	3	0	0
	—84.0%—						

2) Relapse of tubercle bacilli

a) Figure 2 shows the relation between period of consecutive negativity and relapse of bacilli at the following month. The longer the period of negative state, the lower the rate of bacilli relapse.

And the relapse rates were about 6% when negative state exceeded 3 months, and 0% when the negative state exceeded 10 months.

b) The relapse rate during the following 3 months was 23.9% and during the 6 months was 47.5% when the negative state period was 3 months, 12.5% and 19.4% respectively after the negative state of 6 months and 5.3% and 6.6% after 9 months and no relapse was seen when the negative state period was 12 months (Table 4).

c) The bacteriological relapse rate of the patients treated with a combination of three drugs was lower than that with a combination of two of them or with a single drug, but when the period of negative state exceeded three months, the numbers of the drugs used did not seem to influence the bacteriological relapse rate.

d) In cases in which negative conversion had once occurred by the administration of minor drugs, an investigation was made on duration of treatment necessary to prevent bacteriological relapse. Table 5 shows the relation between period of negative state and relapse rate during the 4 months

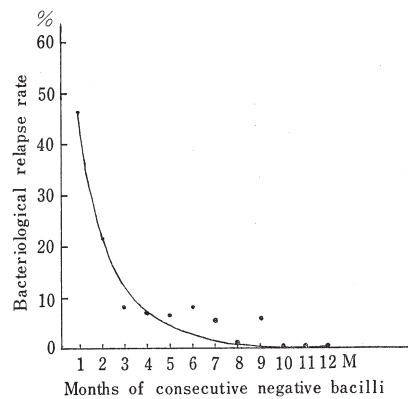


FIG. 2. The relation between period of consecutive negative bacilli and relapse of bacilli.

TABLE 4. Duration of Consecutive Negative Culture and Bacteriological Relapse

Duration of consecutive negative culture	Bacteriological relapse rate			
	During 3 months		During 6 months	
3 months	11/46	23.9%	19/40	47.5%
6 months	3/24	12.5%	4/21	19.4%
9 months	1/19	5.3%	1/15	6.6%
12 months	0/14	0%	0/5	0%

TABLE 5. Duration of Consecutive Negative Culture and the Change of Regimen

Duration of consecutive negative culture before the change of regimen	3-5 months	6-8 months	9-11 months	12 months or longer
Bacteriological relapse rate during 4 months after the change of regimen	5/8 62.5%	2/5 40.0%	0/3 0%	0/1 0%

following the new regimen of treatment; *i.e.*, minor drug administration was interrupted or the number of drugs was reduced. In 7 of 13 cases where the number of minor drugs was reduced or its administration was interrupted within 8 months after the negative conversion, bacilli relapse occurred. However, in the remaining 4 cases in which the number of minor drugs were reduced or its administration was interrupted, later than 8 months after the negative conversion, no bacilli relapse was observed.

3) Changes in X-ray findings

In these advanced pulmonary tuberculosis patients with bacilli resistant to drugs, the improvements of X-ray finding were extremely slight following treatment with minor drugs.

a) The changes of cavities after treatment with minor drugs for 6 months are shown in Table 6. The rate of improvement was 15.2% in ring form cavity with sclerotic walls (35.7% with combination of three drugs, 21.8% with combination of two drugs and 8.7% with a single drug), 7.6% in cavity in the sclerotic lesion (15.4% with combination of three drugs, 14.3% with combination of two drugs and 0.3% with a single drug), and 2.2% in multilocular cavity with sclerotic walls (8.5% with combination of three drugs and 3.4% with combination of two drugs and 0.5% with a single drug).

The closure of cavity was seen in 5.3% of ring form cavity with sclerotic wall, in 0.9% of cavity in sclerotic lesion and in 0% of multilocular cavity with sclerotic wall. Cyst-like change of the cavity was seen in 4.0% of ring form cavity with sclerotic wall, in 0.9% of cavity in sclerotic lesion and in

TABLE 6. Radiographical Changes in Cavities with Sclerotic Wall treated with Minor Drugs for six Months

Type of cavities	No. of cavities	Improvement			Unchanged	Enlarged
		Diminutive	Cyst-like	Closed		
a	152	5.9%	4.0%	5.3%	73.6%	11.2%
		15.2%				
b	106	5.8%	0.9%	0.9%	88.6%	3.8%
		7.6%				
c	311	0.9%	1.3%	0%	92.0%	5.8%
		2.2%				

- a: Ring-form cavity with sclerotic wall
 b: Cavity in the sclerotic lesion
 c: Multilocular cavity with sclerotic wall

TABLE 7. Radiographical Changes in Multilocular Cavities with Sclerotic Wall of Patients Treated for 1 year with Minor Drugs for the First Time

Chemotherapy	No. of cavities	Improvement			Unchanged	Enlarged
		Diminutive	Cyst-like	Closed		
With three minor drug combination	13	7.7%	15.4%	0%	69.2%	7.7%
		23.1%				
With two minor drug combination	43	4.6%	7.0%	0%	86.1%	2.3%
		11.6%				
With one minor drug	114	1.7%	0.9%	0%	93.9%	3.5%
		2.6%				

1.3% of multilocular cavity with sclerotic wall.

b) By combination treatment with three drugs for one year, improvement was obtained in 3 of 13 (23.1%) multilocular cavity with sclerotic wall and 2 (15.4%) showed cystlike change. In no instance, however, the closure of cavity was obtained by combination treatment for one year (Table 7). These data suggest that there is only a possibility of open healing of multilocular cavity with sclerotic wall. In ring form cavity with sclerotic walls, the closure of the cavity was seen in 2 of 8 (25.0%) and cyst-like change was not seen. In cavity in the sclerotic lesion, the closure of the cavity was seen in 1 of 7 (14.3%) and no cyst-like change was seen after combination treatment with drugs for one year.

c) The effects of treatment with minor drugs on the total chest X-ray findings are shown in Table 8, and are mostly disappointing.

d) As shown in Table 9, the improvement of X-ray findings was more frequent in those showing negative conversion of bacilli, and conversely negative conversion was more frequent in those showing improvement of X-ray findings.

TABLE 8. X-ray Findings and Combination Treatment
(Minor drug for the first time, 6 months)

Chemotherapy	No. of cases	Improved	Unchanged	Worsened
With three minor drug combination	17	11.8%	70.5%	17.7%
With two minor drug combination	63	9.5%	79.5%	11.0%
With one minor drug	191	3.1%	75.0%	21.9%

TABLE 9. X-ray Findings and Negative Conversion Bacilli in Sputa
a)

	No. of cases	Improved	Unchanged	Worsened
Converted to negative	50	16.0%	80.0%	4.0%
Not converted to negative	291	3.1%	76.0%	20.9%

b)

Course of total X-ray findings	No. of cases	Converted to negative	Not converted to negative
Improved	15	46.5%	53.5%
Unchanged	264	15.4%	84.6%
Worsened	62	3.4%	96.6%

4) Drug resistance and negative conversion of bacilli

In Table 10 is shown the relationship between drug sensitivity of the bacilli before administration of minor drugs and negative conversion resulting from treatment with these drugs. Though negative conversion was not seen at all in case of treatment with "resistant" drug only, the negative conversion rate rose with increase in number of "sensitive" drugs administered.

TABLE 10. Negative Conversion in Bacilli (More than Three Consecutive Months) and Sensitivity of Bacilli to Minor Drugs Tefore Treatment

Treatment	Susceptibility pattern	No. of cases	No. of converted cases	Conversion rate
With one minor drug	*S	46	2	4.4%
	*R	58	0	0%
With two minor drug combination	SS	15	1	6.6%
	SR	20	2	10.0%
	RR	16	0	0%
With three minor drug combination	SSS	6	2	33.3%
	SSR	8	2	25.0%
	SRR	7	1	14.2%
	RRR	11	0	0%

*S: Sensitive

*R: Resistant { Kanamycin, 100 γ resistant
Ethionamide, 25 γ resistant
Cycloserine, 20 γ resistant

SUMMARY

1) Minor antituberculosis drugs were administered to pulmonary tuberculosis patients (341 Cases), who were known to be resistant to them and who had been treated with major drugs (Streptomycin, PAS and Isoniazide) for over one year. In all these cases bacilli were positive both on smear and culture, and all these case had advanced lesions with multilocular and/or large cavity with sclerotic wall. The efficacy of treatment was studied by negative conversion and relapse of bacilli, and the changes of X-ray findings. The minor drugs examined were Kanamycin, Ethionamide and Cycloserine.

2) The rate of negative conversion of the bacilli was 64.7%, in the cases of combination treatment with Kanamycin, Ethionamide and Cycloserine, 36.5% with two drugs combination of these three and 3.7% with single drug. In therapy with minor drugs the regimen of treatment should be changed when negative conversion does not occur within five months after commencement of therapy. From the aspect of bacteriological relapse the interruption of therapy or reduction in number of combination drugs should be conducted when the negative state has continued for 8 months.

3) In treatment with minor drugs of such advanced cases an improvement in X-ray finding can be seen slightly. No closure of cavity is found in cases of multilocular sclerotic cavities, but cyst like changes are recognized in some cases, indicating the possibility of open healing to occur.

4) At the present stage it can be said that the combined use of minor drugs is clearly more effective than the use of a single drug, also that their prolonged administration is more effective.

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