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The Effect of "Tebafen" on Pulmonary Tuberculosis

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"Tebafen" is a drug which consists of four parts of Isoniazid and one part of nicotinaldehyde thiosemicarbazone (NAT) which is a Tibione (TBI) analogue synthesized by Hagenbach and Gysin. NAT has been studied by various investigators since it was reported by Levaditi,[1] Grunberg[2] and others that this substance was more effective than TBI *in vivo*.

More than one drug is commonly used in combination for treatment of pulmonary tuberculosis, but the combined therapy of TBI with other drugs is not widely performed in Japan. According to the writers' experiences with TBI, it is considerably antituberculous, but in comparison with streptomycin, p-aminosalicylic acid or isonicotinic acid hydrazide (INH), TBI has disadvantages that it causes loss of appetite more frequently and is less effective on weight gain.

The combined therapies with the above described drugs, however, are not always satisfactory in the treatment of pulmonary tuberculosis. In the writers' opinion, many kinds of drugs which do not produce cross-resistance of tubercle bacilli may be necessary to treat every case of pulmonary tuberculosis by chemotherapy alone. Consequently, the present writers intend to utilize TBI as much as possible and expect TBI analogues to be reformed.

Under this situation, Tebafen was offered to the writers, and preliminary experiments and clinical investigations were performed as follows:

Antituberculous activity *in vitro*:

1. *Bacteriostatic activity of NAT*:

The minimum inhibiting concentration of NAT for tubercle bacilli (H37 Rv) in Kirchner's medium containing 10 per cent serum is almost equal to that of TBI, as may be seen in table 1. This result is about coincidental with the report by Levaditi[1] that the minimum inhibitory concentration in Dubos medium was 60γ per ml.

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Table 1: Minimum Inhibitory Concentration for Tubercle Bacilli

Drug	Concentration in γ per ml.
INH	0.063
TBI	50.0
NAT	50.0

2. *Combined effect with INH*:

The combined effects of NAT or TBI with INH are illustrated in table 2. INH is more effective when it is used with either NAT or TBI than when it is used alone. It appears that the combined use of NAT with INH is more effective than that of TBI with INH.

Table 2: *In Vitro* Effects of Combined Use of INH with NAT or TBI

Drug	Minimum inhibitory concentration in γ per ml.
INH alone	0.063
INH+NAT (4:1)	0.016
INH+TBI (4:1)	0.031
INH+NAT (2:1)	0.016
INH+TBI (2:1)	0.031

3. *Bacteriostatic activity in the blood*:

The experiment was made by inoculating tubercle bacilli (H37 Rv) in Kirchner's media containing 90 per cent serum which was obtained from human who had been administered a certain drug, and the length of time that the bacteriostatic activity in the blood is maintained after administration of the drug was observed (Shioda's Method[3]).

As may be seen in table 3, the bacteriostatic activity was observed from 3 hours to 7 hours after administration when NAT alone was used.

Table 3: Transitions of Bacteriostatic Activity of Serum in Kirchner's Medium after Administration of Drug

Case number	240 mg. of INH	60 mg. of NAT	240 mg. of INH +60 mg. of NAT	240 mg. of INH +60 mg. of TBI
1	up to 7 hrs.	3 to 5 hrs.	up to 9 hrs.	up to 9 hrs.
2	up to 7 hrs.	3 to 5 hrs.	up to 9 hrs.	up to 7 hrs.
3	up to 5 hrs.	3 to 5 hrs.	up to 4 hrs.	up to 7 hrs.
4	up to 7 hrs.	3 to 5 hrs.	up to 7 hrs.	up to 7 hrs.
5	up to 7 hrs.	3 to 5 hrs.	up to 9 hrs.	up to 7 hrs.

The combined use of NAT with INH, namely the use of Tabafen, resulted in a longer antituberclous effect than use of INH alone.

TBI showed similar but less effect.

4. *Therapeutic effect for pulmonary tuberculosis*:

From the results of the above mentioned basal experiments, the combined use of

NAT and INH, namely the use of Tebafen, was considered significant, and clinical investigations in tuberculous patients were carried out.

Each tablet of Tabafen contains 40 mg. of INH and 10 mg. of NAT. In this laboratory, 2 tablets of Tabafen were administered 3 times daily, that is, 240 mg. of INH and 60 mg. of NAT were given daily in combination.

The result of the use of INH alone for a period of 5 months reported by the present writers[4] was employed as control in the present study.

The classification of the clinical findings was based upon the standard of The Committee of the Therapy of Tuberculosis of the Welfare Ministry. Complete detailed analysis is not within the scope of the present report. A summary of the results, however, indicates that:

The effects of therapy on high fever were obscure because of lack of patients who had high fever at the onset of therapy.

No marked variation between the effects of Tebafen and those of INH on slight fever was noted. (table 4)

Table 4: Effects of Therapy on Slight Fever

months of treatments	drug	subsided		unchanged		elevated
		No. of patients	%	No. of patients	%	No. of patients
1	Tebafen	3	23.1	10	76.9	0
	INH	47	26.7	126	73.2	3
2	Tebafen	2	16.6	10	83.4	0
	INH	50	33.6	99	66.3	0
3	Tebafen	3	27.2	8	72.8	0
	INH	34	30.9	76	69.1	2

The effect of drugs on appetite were indistinct, as the appetites were essentially unaffected in the majority of the patients. (table 5)

Table 5: Effects of Therapy on Appetite

months of treatments	drug	markedly improved		improved		unchanged		lost	essentially normal
		No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	No. of patients
1	Tebafen	0		1		0		1	19
	INH	37	12.2	133	43.9	133	43.9	8	33
2	Tebafen	0		0		0		2	19
	INH	42	14.6	112	39.1	133	46.3	3	32
3	Tebafen	0		0		0		4	15
	INH	32	15.0	86	40.2	96	44.8	2	26

INH alone was more effective for weight gain than Tabafen. (table 6)

Table 6: Effects of Therapy on Body Weight

months of treatments	drug	markedly gained		gained		unchanged		de-creased	essentially normal
		No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	No. of patients
1	Tebafen	0		0		8	100.0	1	12
	INH	4	1.3	40	13.4	254	85.3	9	24
2	Tebafen	0		2	25.0	6	75.0	1	12
	INH	20	7.0	59	20.6	208	72.5	8	23
3	Tebafen	0		2	28.9	5	71.1	1	12
	INH	21	10.4	55	27.1	127	62.5	7	21

Tebafen was more effective than INH in retarding the erythrocytes sedimentation rates. (table 7)

Table 7: Effects of Therapy on Erythrocytes Sedimentation Rate

months of treatments	drug	returned to normal rate		retarded		unchanged		acceler-ated	essentially normal
		No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	No. of patients
1	Tebafen	1	10.0	2	20.0	7	70.0	1	8
	INH	29	12.2	36	15.1	173	72.7	40	72
2	Tebafen	2	20.0	4	40.0	4	40.0	1	8
	INH	33	15.0	46	21.0	140	64.0	39	79
3	Tebafen	4	44.4	3	33.3	2	22.3	2	7
	INH	19	11.7	35	21.5	109	66.8	33	65

It appears that INH was slightly more effective than Tebafen on coughs. (table 8)

Table 8: Effects of Therapy on Cough

months of treatments	drug	completely relieved		diminished		unchanged		wor-sened	essentially no cough
		No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	No. of patients
1	Tebafen	0		1	8.2	13	91.8	0	7
	INH	15	6.5	84	36.5	131	57.0	3	110
2	Tebafen	4	28.6	2	14.3	8	57.1	0	7
	INH	22	10.5	100	47.5	88	42.0	0	112
3	Tebafen	4	33.3	2	16.7	6	50.0	0	7
	INH	29	19.3	71	47.3	50	33.4	1	92

Tebafen was markedly more effective than INH on the presence of acid-fast bacilli in sputum. (table 9)

Table 9: Effects of Therapy on Presence of Tubercle Bacilli in Sputum

months of treatments	drug	became negative		reduced		unchanged		increased	essentially negative
		No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	No. of patients
1	Tebafen	3	25.0	0		9	75.0	0	9
	INH	27	11.9	58	25.6	142	62.5	5	208
2	Tebafen	5	45.5	0		6	54.5	1	9
	INH	40	19.4	57	27.6	109	53.0	5	100
3	Tebafen	5	62.5	1	12.5	2	25.0	1	9
	INH	41	25.8	50	31.4	68	42.8	9	81

Tebafen was more effective than INH to reduce the amount of sputum. (table 10)

Table 10: Effects of Therapy on Amount of Sputum

months of treatments	drug	disappeared		decreased		unchanged		increased	essentially no expectoration
		No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	No. of patients
1	Tebafen	1	5.2	4	21.1	14	73.7	2	0
	INH	11	3.6	113	36.6	185	59.8	11	30
2	Tebafen	2	10.4	7	37.0	10	52.6	2	0
	INH	14	4.8	130	44.2	156	51.0	18	29
3	Tebafen	3	17.6	8	47.1	6	35.3	1	1
	INH	13	5.3	99	40.4	133	54.3	22	27

No remarkable variation between the effects of Tebafen and INH alone on roentgenographic appearances of the chest was noted. (table 11)

Table 11: Effects of Therapy on Roentgenographic Appearance Three Months after Start of Treatment

drug	total No. of cases	improved		unchanged		worsened		roentgenogram was not taken at this time
		No. of cases	%	No. of cases	%	No, of cases	%	
Tebafen	21	12	57.1	8	38.1	1	4.8	0
INH	128	62	60.7	34	33.3	6		26

5. *Side Effect*:

No subjective symptoms considered to be caused by drug reactions were noted.

No marked changes were noted in bromsulphalein test for liver function (table 12),

qualitative test of urobilinogen in the urine (table 13) and blood counts (table 14).

Table 12: Effects of Therapy on Bromsulphalein Test

months of treatment	markedly improved	slightly improved	unchanged	worsened	essentially normal
1		1			6
2		1			6
3		2	1	2	7

Table 13: Effects of Therapy on Qualitative Test of Urobilinogen in Urine

months of treatment	markedly improved	slightly improved	unchanged	worsened	essentially normal
1	1				4
2	1		1	2	4
3	1		1	3	8

Table 14: Effects of Therapy on Blood Counts

		increased	unchanged	decreased
erythrocytes		1	4	4
hemoglobin		1	6	2
leukocytes		2	4	3
differential counts	neutrophils	2	1	5
	eosinophils	2	4	2
	monocytes	2	4	2
	lymphocytes	5	1	2

Conclusion:

Although no statement relating to the development of drug-resistant strains of tubercle bacilli can be made at this time, it appears that Tebafen is somewhat more effective than INH in the basal and clinical investigations described above.

References

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