# THE EFFECT OF SULFATHIAZOLE IN DELAYING THE EMERGENCE OF ISONIAZID RESISTANCE IN TUBERCULOUS PATIENTS

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In 1953 it has been reported by KIMINO, ABO and KATSUNUMA[1] that a marked clinical improvement of pulmonary tuberculosis has been produced by the combined use of isoniazid plus sulfathiazole. Concomitantly with this report, KIMINO[2] reported the *in vitro* effect of sulfathiazole in delaying the emergence of isoniazid resistance in *Mycobacterium avium*, and then TSUKAMURA, SUZUKI and KIMINO[3] reported that the effect was produced not only by sulfathiazole but also another sulfonamide drugs(sulfisoxazole, sulfamerazine, sulfadimezine, *etc.*), and studied the mechanism of sulfonamides in delaying the *in vitro* emergence of isoniazid resistance in *M. avium*. It has been also found by TSUKAMURA[4] that, among sulfonamides, sulfathiazole and sulfisoxazole inhibit most effectively the growth of *Mycobacterium tuberculosis* and *Mycobacterium avium* on an egg medium as well as on a synthetic medium.

Independently of our studies, NAITO[5,6] and SAITO and his associates[7] have reported that the combined use of isoniazid plus sulfisoxazole, which is less toxic to human bodies than sulfathiazole, has given a very marked therapeutic effect on patients with pulmonary tuberculosis, and their results have been supported by USHIBA and his associates[8]. The effect of sulfisoxazole in delaying the *in vivo* emergence of isoniazid resistance is not yet certainly demonstrated. Therefore, it is the purpose of the present paper to demonstrate the effect of sulfathiazole in delaying the emergence of isoniazid resistance in tubercle bacilli of patients.

## Materials and Methods

Eighty-one patients with far-advanced pulmonary tuberculosis and discharging continuously positive sputa from chronic cavities were observed for the study. These patients had previously not received the administration of isoniazid and were treated in 1953 to 1955 in the Obuso National Sanatorium by the following three methods. The first group consisted of 11 patients and received the combined chemotherapy of isoniazid plus sulfathiazole, isoniazid 0.2g daily plus sulfathiazole 2.0g with sodium bicarbonate 2.0g daily. The adminstration was performed during 3~7 months. The second group consisted of 63 patients and received the adminstration of isoniazid alone, isoniazid 0.2 to 0.3g daily. The adminstration was performed during 3 months. The third group consisted of 7 patients and received the adminstration of sulfathiazole alone, sulfathiazole 2.0g with sodium bicarbonate 2.0g daily. The administration was performed during 1~3 months.

The examination of the emergence of isoniazid resistance in tubercle bacilli was performed after the adminstration of 3 months by the direct method using OGAWA's egg medium slants. The emergence of isoniazid resistance was defined as the growth of tubercle bacilli on medium containing 1 mcg of isoniazid representing approximately above 20% of that on medium containing no drug.

## Results and Discussion

A marked improvement in clinical figures was observed on the first group (isoniazid plus sulfathiazole in combination) as well as on the second group (isoniazid alone), and the therapeutic effect appeared to be better in the first group than in the second group (See reference (1)). However, no improvement was observed on the third group (sulfathiazole alone). The side effect of sulfathiazole was not seen excepting that such an increase of appetite as observed frequently on the second group was not seen on the first group. Any abnormality in blood figures and liver functions also was not seen in patients adminstrated by sulfathiazole.

A significant difference between two groups (the first and the second groups) was observed in the emergence of isoniazid resistance. Among the first group, only 1 case of patient has showed the emergence of isoniazid resistance, while 35 cases of patients have showed it after the same period (3 months) of treatment among the second group. According to the $X^2$-test, this difference is not significant at the level of 5% but at the level of 6% (*). Therefore, the results indicate at the 94%

(*) The test was made excluding 3 cases of the first group who showed sputum conversion.

| Group | INH-sensitive | INH-resistant | Total |
|---|---|---|---|
| I (Isoniazid plus sulfathiazole daily) | 7 | 1 | 8 |
| II (Isoniazid alone) | 28 | 35 | 63 |

$X^2=3.50$ $P=0.06$

confidence rate that the emergence of isoniazid resistance in tubercle bacilli of patients has been delayed more effectively by the combined use of isoniazid plus sulfathiazole than by the use of isoniazid alone.

In view of the above *in vivo* results and of the *in vitro* results previously reported by us[3,4], it appears that sulfonamides are more or less effective for delaying the *in vivo* emergence of isoniazid resistance and, among sulfonamides, sulfathiazole and sulfisoxazole may be most hopeful for the purpose of delaying the *in vivo* emergence of isoniazid resistance. However, considering that sulfisoxazole is less toxic to human bodies than sulfathiazole, sulfisoxazole may be more suitable for clinical use.

## Conclusion

The emergence of isoniazid resistance of tubercle bacilli in tuberculous patients has been considerably effectively delayed by the combined use of isoniazid plus sulfathiazole. The combined chemotherapy with isoniazid plus sulfathiazole has been performed in eleven patients without any significant side effect during 3~7 months.

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