
 Résumé

THE EFFECT OF PYRAZINAMIDE FOR
THE APPEARANCE OF
STREPTOMYCIN AND ISONICOTINIC
ACID HYDRAZIDE-RESISTANT
MUTANTS IN *MYCOBACTERIUM*
TUBERCULOSIS VAR. *HOMINIS*,
STRAIN AOYAMA B. (Part 2)

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The effect of pyrazinamide was examined, for the appearance of streptomycin- and isonicotinic acid hydrazide-resistant mutants.

Mycobacterium tuberculosis var. *hominis*, strain Aoyama B was used in these studies. The medium used were 1% Ogawa's (Tatsuji) egg medium (KH_2PO_4 , 1.0 g, Sodium glutamate, 1.0 g, Distilled water, 100 ml, Eggs, 200 ml, Glycerine, 6.0 ml, 2% Malachite-green, 6.0 ml, pH, 7.0), 3% Ogawa's egg medium (KH_2PO_4 , 3.0 g, The others equal to the above; pH, 6.5), and 5% Ogawa's egg medium (KH_2PO_4 5.0 g, The others equal to the above; pH, 6.0).

Prior to sterilization, streptomycin, isonicotinic acid hydrazide or pyrazinamide were added to media to give an appropriate final concentration of drug. Each tube was poured with 10 ml of the medium and slanted by sterilization at 85 to 88°C for 50 minutes. The activity of streptomycin after sterilization was regarded as one half of that before sterilization, and activities of other agents were regarded as not influenced by sterilization.

(1) Pyrazinamide did not inhibit the growth of the population of *Mycobacterium tuberculosis* var. *hominis*, strain Aoyama B, even at 400 mcg per ml of drug concentration, but pyrazinamide inhibited the growth of individual cells.

(2) When Dubos albumin medium was used, it was suggested by the growth curve of *Mycobacterium tuberculosis*, that the lag phase should be delayed, and the generation time should be extended by pyrazinamide.

(3) We could not find out the difference in the effect of pyrazinamide in the medium of pH 6.0, or 7.0.

(4) It was not found, that the combined effect of pyrazinamide-isoniazid, was not found in the Ogawa's egg medium, of 3% and 5%, but it was found in the medium of 1%.

(5) The appearance rate of isoniazid- and streptomycin-resistant mutants were not influenced

by pyrazinamide in Ogawa egg medium (1%).

(6) In the one step selection, appearance rate of isoniazid-resistant mutants was found in the medium, contained isoniazid alone, and isoniazid-pyrazinamide at the same time. But it was found the decrease of the appearance rate of streptomycin-resistant mutants in the medium, contained streptomycin and pyrazinamide at the same time, as compared with in the medium, that the mutation mutated by streptomycin has been antagonised by pyrazinamide.

(7) For the clinical use, the combined use of streptomycin-pyrazinamide would be superior to that of isoniazid-pyrazinamide.

INFLUENCE OF EXERCISE ON THE
RETENTION OF ANTIBIOTICS
IN THE BODY. REPORT 3.
STREPTOMYCIN

Relationship between Amounts of Exercise
and Development of Adverse Effects

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Seven patients with pulmonary tuberculosis and six healthy subjects were administered with dihydrostreptomycin (DHSM).

Their absorption rate and urinary excretion rate of intramuscularly injected DHSM during rest were compared with that of post-exercise (in all subjects with 30 minutes' walking, and in four of six healthy subjects with 30 minutes' bicycle ergometer). Transitory untoward side effects of intramuscularly injected DHSM appeared were also individually compared.

The results obtained are as follows:

1) The absorption rate of intramuscularly injected DHSM during rest is individually different.

2) No definite tendency was observed in the influence of exercise on the absorption rate of intramuscularly injected DHSM.

3) In all cases the urinary excretion is parallel with the blood level.

4) There was no relationship between onset of adverse effects and absorption rate; nor between blood level and duration of blood level of intramuscularly injected DHSM.

5) The blood level of DHSM, on the appearance of adverse effects is individually different.

6) From the data obtained, it seems obvious that these transitory adverse effects are due to impurities contained in commercial DHSM.