Résumé

ON THE STUDY OF PYRAZINAMIDE (I)

Determination of the Pyrazinamide Content of Blood after Oral Administration

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The method for estimating the pyrazinamide content of blood has already been reported by ALLEN, *et al*[1]. The author improved the method by means of using other anion exchange resine in other conditions.

The outline of this procedure is as follows : For the detection of the pyrazinoic acid, at first, colorless extracts of defibrinated blood are passed through Amberleit 1 R 4 B columns, washed with water, the columns are eluted with N/2 hydrochloric acid. The eluate, after adjusted to pH 6 to 10, is evaporated to dryness and the residue is thrown in pH 4.8 citrate buffer solution or water. In the case of dissolving in buffer solution, MOHR's salt buffer solution is added to 0.5% MOHR's salt concentration and then optical density read at 480 mμ. In the case of aqueous solution, without using any buffer solution, Na-nitroprusside and sodium carbonate are added and optical density is read at 475 mμ. For the detection of pyrazinamide, the hydrolysing procedure is added as same as ALLEN's method.

1) ALLEN, *et al.*, Anal. Chem., 25, 895(1953).

STUDIES ON THE PYRAZINAMIDE (II)

Blood Level and Urinary Excretion Studies Following the Administration of Pyrazinamide

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The present paper reports a study of blood levels and urinary excretion after oral adminstration of pyrazinamide ($PzNH_2$) and the comparable study of blood levels of $PzNH_2$ when administered orally with isonicotinic acid hydrazide (INAH).

Assays were performed by new analytical method[1], which is improved on the ALLEN's method.

Following administration of $PzNH_2$ the authors find $PzNH_2$ and pyrazinoic acid (PzOH) in blood and urine. Levels of $PzNH_2$ are higher always in blood but lower in urine than those of PzOH. For example, a single dose of 40 mg $PzNH_2$ per kg of body weight administered orally to normal human subjects, gained maximum blood levels of $PzNH_2$ of 30~35 mcg/ml at 1 to 5 hours and that of PzOH of 10~17 mcg/ml at 2 to 3 hours after administration. In the same experiment resulted in the recovery of 7 to 15% of the dose as $PzNH_2$ in the urine and 44 to 46% of the dose as PzOH over a period of 24 hours. From these figures, the absorption of $PzNH_2$ appears to be comparatively rapid but its extraction to be somewhat slow. In the transition of blood levels after administration, difference was not recognized between administration of $PzNH_2$ simply and combinated with INAH.

1) MARUYAMA, M. Chemotherapy (Japan) 4 (5) : 241~243 (1956).

A QUANTITATIVE ANALYSIS OF THE RESISTANCE OF *MYCOBACTERIUM TUBERCULOSIS* VAR. *HOMINIS* TO ANTITUBERCULAR DRUGS

(Report II)

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In order to compare genetic characteristics of streptomycin resistance and isoniazid resistance of *Mycobacterium tuberculosis* var. *hominis* with each other, the composition of population of colonies obtained by selection of one step in 20 mcg and 100 mcg of streptomycin per ml and in 1 mcg and 10 mcg of isoniazid per ml of Ogawa egg medium was analysed with respect to the degree of resistance to the drugs selected.

In descendents of mutants resistant to 20 mcg of streptomycin per ml of medium selected by one step of selection, mutants resistant to 20 mcg of streptomycin per ml were found only in percentages of 10 to 50 per cent. On the other hand, in descendents of mutants resistant to 100 mcg of streptomycin per ml of medium selected by one step of selection, mutants resistant to 100 mcg of streptomycin per ml were found in percentage of approximately 90 per cent.

In descendents of mutants resistant to 1 mcg of isoniazid per ml as well as of those resistant to 10 mcg of isoniazid per ml, mutants resistant to 1 mcg of isoniazid per ml were found in percentages of 60 to 80 per cent and those resistant to 10 mcg isoniazid per ml in percentages of 30 to 40 per

cent. These percentages were similar to the percentages of resistant mutants found in population of the isoniazid-resistant strain obtained by multiple steps of selection by 10 mcg of isoniazid.

Comparing these results with those of the composition of population of the streptomycin-resistant strain and of the isoniazid-resistant strain of the organism obtained by multiple steps of selection, which has been previously reported by us(*), it has been concluded as follows.

(1) The existence of several genes determining streptomycin resistance have been suggested, and it has been suggested that these genes differ from one another not only in potency but also in stability, and that at least two kinds of genes exist, one of which is unstable and determines low degree of resistance, and another of which is stable and determines high degree of resistance.

(2) Genes determining isoniazid resistance have been suggested to differ from one another in potency but to be of the same property that is relatively unstable.

(*) The composition of population of the streptomycin-resistant strain of *Mycobacterium tuberculosis* var. *hominis* is homogeneous, which has been selected by several steps of selection by 100 mcg of streptomycin. On the other hand, the composition of population is heterogeneous even in the isoniazid-resistant strain obtained by several steps of selection by 10 mcg of isoniazid.

(TSUKAMURA, M., & MIURA, K. : A comparison between characteristics of the composition of population in the streptomycin-resistant strain, in the isoniazid-resistant strain and in the PAS-resistant strain of *Mycobacterium tuberculosis* var. *hominis*. Annual report of the Japanese Association for Tuberculosis. in press.)

STUDIES ON ANTITUMOR AGENTS. I

Influence on Normal Embryo Tissues

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How three antitumor agents of nitrogen mustards, 8-azaguanine and sarkomycin influence on the proliferation of normal embryo tissues was studied. It is said that nitrogen mustards and sarkomycin, except 8-azaguanine, exhibit the inhibitory activity against the normal tissues with clinical dosage. In this experiment 8-azaguanine was also ineffective even at high concentrations. Nitrogen mustards and sarkomycin are not active especially upon the cancer, but have more or less disturbance to the body.

INFLUENCE OF EXERCISE ON THE RETENTION OF ANTIBIOTICS IN THE BODY. II

Chlortetracycline

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The absorption and urinary excretion of chlortetracycline after an oral single dose of 500 mg were measured in six healthy subjects. The test was given to each subject twice in rest and once after 30 minutes' exercise with a bicycle ergometer. The results are as follows :

1) The peak of serum concentration appears 4 hours after oral administration, and it is not affected by exercise.

2) In the twice repeated test in rest for serum concentration and urinary excretion, the results are similar in two subjects and different in the others. The results are quite different individually.

3) After exercise the serum concentration and urinary excretion are higher than those in rest in two subjects, and lower in one. In the other three subjects exercise does not affect their blood levels.

4) The results obtained seem to be independent on age, weight and amount of exercise of each subject.

5) It may be concluded that the influence of exercise on the absorption and urinary excretion of orally administered chlortetracycline is individually different.