INACTIVATION OF ANTIBACTERIAL PREPARATIONS AND DRUG RESISTANCE OF PATHOGENIC AGENTS

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The blood concentration and therapeutic effectiveness of isoniazid was investigated following a single administration of the total daily dose of the drug to patients with pulmonary tuberculosis. It was found that in those patients in whom marked inactivation of isoniazid takes place a high blood level of the compound is maintained for a shorter time under these conditions than in weak inactivators. Correspondingly, in patients strongly inactivating isoniazid, delayed involution of the tuberculous infection was found. In patients who are weak inactivators, good results were obtained even if the pathogenic agent was to some extent resistant to isoniazid.

Important factors limiting the effectiveness of chemotherapy are inactivation of therapeutic substances and resistance of the pathogenic agent to them. The object of the present investigation was to study whether these factors can be overcome by modifying the conditions of treatment, notably by giving the total daily dose of the substance at once instead of, as is customarily done, dividing it into two or three fractional doses.

The model used was isoniazid, the most active of the chemotherapeutic preparations against tuberculosis. It is inactivated to a varied degree by different patients, and Mycobacterium tuberculosis develops resistance to it more frequently than to other preparations.

EXPERIMENTAL METHOD

The concentration of active isoniazid in the blood serum was investigated by vertical diffusion [9]. Inactivation of the drug was determined by the excretion of active isoniazid in the urine [1]. Sensitivity of the pathogenic agent to the drug was investigated by an indirect method using Shkol'nikova's semisynthetic medium [6]. The ratio between the blood concentration of active isoniazid and the sensitivity of the agent to the drug was determined by the tuberculostatic test [4,5]. Every month for five months of treatment of patients in the clinic survey roentgenograms and tomograms were taken of the lungs, and the sputum or bronchial washings were investigated by bacterioscopic and seeding methods.

EXPERIMENTAL RESULTS

In accordance with existing criteria [7], 45 patients were classified as weak inactivators of isoniazid and 19 as strong; the highest concentration of the drug determined in whole serum by Schmiedel's vertical diffusion method was 3 μg/ml [9].

As Table 1 shows, a high blood level of isoniazid was maintained for a shorter time in the strong inactivators than in the weak.

Investigations have shown [2,8] that daily contact between drug-sensitive tubercle bacilli and 2 μg/ml isoniazid for 2 h in vitro causes inhibition of their growth. Isoniazid persisted in the blood stream in concentrations exceeding 2 μg/ml in most of the weak inactivators investigated for a period of 9 h. A high concentration of isoniazid was maintained in most of the strong inactivators for a much shorter time: the isoniazid concentration 6 h after administration was below 2 μg/ml in 14 of the 18 cases.

However, the experiments cited [2,8] were carried out in vitro, and the isoniazid concentrations determined in this investigation were characteristic of the patients' blood. The effectiveness of chemotherapy can be used as an indirect index of adequacy of the isoniazid concentration at the actual lesions in the lung tissue.

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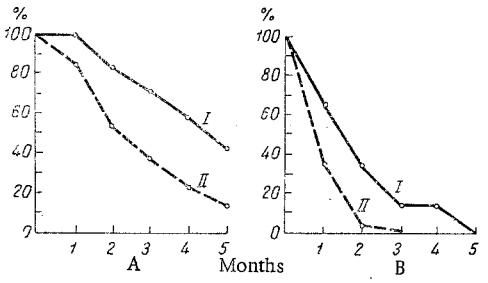

Fig. 1. Relationship between effectiveness of treatment and degree of isoniazid inactivation. A) times of closure of cavities (ordinate – percentage of patients with cavities); B) times of sterilization (ordinate – percentage of patients excreting tubercle bacilli); I) strong inactivators; II) weak inactivators.

TABLE 1. Concentration of Active Isoniazid in Blood of Patients after Taking 0.6 g Isoniazid

Time after administration of isoniazid (in h)	Nature of inactivation of isoniazid	Number of patients	Concentration of isoniazid (in μg/ml)				
			over 3	2–3	0,8–1,9	under 0,8	0
			number of patients				
3	Weak	24	24	—	—	—	—
	Strong	12	9	3	—	—	—
6	Weak	26	25	1	—	—	—
	Strong	18	3	1	6	3	5
9	Weak	26	22	1	3	—	—
	Strong	18	—	—	1	3	14
12	Weak	11	7	—	—	4	—
	Strong	15	—	—	1	—	14
18	Weak	11	1	1	6	1	2
	Strong	15	—	—	—	—	15
24	Weak	12	—	—	2	1	9
	Strong	16	—	—	—	—	16

Two homogeneous groups of patients (67 in each) differing only in the degree of inactivation of isoniazid were chosen. They were patients with recently discovered destructive pulmonary tuberculosis, excreting tubercle bacilli sensitive to all preparations of the 1st and 2nd series. Combined treatment with isoniazid, streptomycin, and PAS in a single daily dose (0.6, 1, and 9 g, respectively) was given in the hospital. The results are given in Fig. 1. They reveal a definite relationship between the effectiveness of treatment and the degree of isoniazid inactivation: sterilization and, in particular, closure of the cavities took place much later in strong inactivators.

Previous investigations [3] showed that the result of treatment of strong inactivators with fractional doses of therapeutic agents can be improved by increasing the total daily dose through an increase in the dose given on each occasion.

The results described above and the clinical recommendations apply to patients excreting tubercle bacilli sensitive to isoniazid.

The effects of administration of a single daily dose to patients excreting tubercle bacilli resistant to the drug were studied in 22 patients, 10 of whom were weak inactivators, excreting tubercle bacilli resistant before treatment to isoniazid in a concentration of 1 μg/ml. Good therapeutic results were obtained in these patients, mainly attributable to streptomycin and PAS. However, closure of cavities and disappearance of tubercle bacilli occurred at the times characteristic of weak inactivators excreting strains of tubercle bacilli sensitive to isoniazid before treatment. The bacteriostatic action of isoniazid was also confirmed by the results of the tuberculostatic test, which was positive in all ten patients: tubercle bacilli from the patient did not grow on plasma from that patient's blood taken after receiving the chemotherapeutic preparation [4, 5].

Assessment of the therapeutic effect in the remaining 12 patients showed that good results were obtained in patients excreting tubercle bacilli resistant to isoniazid in concentrations of 5 and even 10 μg/ml if these patients were weak inactivators and the tuberculostatic test was positive. Meanwhile, no effect was obtained for the same levels of resistance if the tuberculostatic test was negative, even in weak inactivators.

Tubercle bacilli resistant in vitro to 1, 5, and 10 μg/ml isoniazid thus behave as "clinically sensitive" to the compound if the total daily dose of isoniazid is given at once. Consequently, an individual approach must be adopted to selection of the isoniazid therapeutic program and of the optimal dose of the drug. Consideration must be paid to the character of inactivation of isoniazid by the patient and to the drug resistance of the tubercle bacilli or the tuberculostatic test.

LITERATURE CITED

1. L. I. Grebennik, Probl. Tuberk., No. 4, 69 (1961).
2. T. I. Kozulitsyna, Transactions of the Central Institute of Tuberculosis [in Russian], Vol. 13, Moscow (1964), p. 230.
3. N. M. Rudoi, Probl. Tuberk., No. 3, 78 (1962).
4. N. M. Rudoi, Lab. Delo, No. 7, 427 (1966).
5. N. M. Rudoi and A. S. Libenson, in: Authors' abstracts of papers read at a Scientific Session of the Central Institute of Tuberculosis [in Russian], Moscow (1966), p. 82.

6. Shkol'nikova, Cited in: Technical Notes on the Organization and Performance of Laboratory Investigations for the Detection of Mycobacterium tuberculosis, the Study of Isolated Strains, and Determination of Concentrations of Isoniazid in the Blood [in Russian], Moscow (1966), p. 19.
7. N. A. Shmelev, T. I. Kozulitsyna, and G. A. Smirnov, Probl. Tuberk., No. 6, 32 (1961).
8. A. Armstrong, Am. Rev. Resp. Dis., 81, 498 (1960).
9. A. Schmiedel, Beitr. Klin. Tuberk., 119, 206 (1958).