CHANGES IN CONCENTRATION OF ISONIAZID-H^3 IN BLOOD SERUM AND TISSUES DEPENDING ON ITS DOSE AND MODE OF ADMINISTRATION

I. M. Bondarev, Ya. I. Azhipa, and L. P. Cherednichenko

UDC 615.281.221.1.033.073:539.16

A definite relationship has been found between the dose of isoniazid and its concentration in media and tissues of the body, as well as a connection between the isoniazid concentration in the serum and tissues. The concentration of isoniazid in pathological foci can thus be determined at various times after administration of the compound.

In the chemotherapy of tuberculosis, the search continues for the most effective methods of treatment: is it best to give daily doses of chemotherapeutic substances all at once [1, 8, 12], to give them by continuous intravenous drip [9, 10], to inject isoniazid intravenously from a syringe [5], to use an interrupted method of treatment [3, 11], or to use high doses of isoniazid at the upper limit of tolerance [2, 7]? These matters testify to the efforts being made by investigators to discover the most rational method of use of chemotherapeutic substances to obtain a speedy and lasting cure of patients with tuberculosis.

The therapeutic effect is largely dependent on the level of the bacteriostatic concentration of antibacterial compounds in the affected tissues of the body. It is generally accepted that isoniazid, which possesses high penetrating power, readily penetrates into small foci of tuberculous inflammation [4, 13]. However, it is found in the contents and walls of cavities in a much lower concentration than in the blood serum, in lung foci, and in unaffected lung tissue [6, 7]. Attempts have been made to increase the concentration of isoniazid in the contents and walls of cavities by increasing the dose of the compound slightly. Manthei et al. [13], in experiments on infected guinea pigs, showed that with doubling the dose of isoniazid (2.8-5.6 mg/kg), its concentration in infected tissues is increased only by 1.2 times. According to Temmere [4], the use of large doses of isoniazid (5-10 mg/kg) does not produce a proportional increase in its concentration in the blood and tissues.

The object of the present investigation was to study changes in the concentration of isoniazid in the blood serum and tissues depending on the dose of the compound and the method of its administration and also to determine the excretion of isoniazid-H^3 following daily oral and intravenous administration of the compound for 7 days. In addition, it was hoped to establish a mathematical relationship between the isoniazid concentration in the blood serum and tissues, including tissues affected by tuberculosis. No such experimental data could be found in the literature.

EXPERIMENTAL METHOD

Experiments were carried out on 59 healthy female rats and 12 infected with tuberculosis, weighing 150-200 g, and on 10 healthy guinea pigs and 12 guinea pigs infected with Mycobacterium tuberculosis,

Laboratory of Experimental Pathology and Therapy, Moscow Scientific-Research Institute of Tuberculosis, Ministry of Health of the RSFSR. Group Studying the Trophic Function of the Nervous System, Institute of Higher Nervous Activity and Neurophysiology, Academy of Sciences of the USSR. (Presented by Academician of the Academy of Medical Sciences of the USSR S. R. Mardashev.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 70, No. 10, pp. 31-34, October, 1970. Original article submitted March 27, 1970.

TABLE 1. Concentration of Isoniazid-H^3 in Animals after Administration for 7 Days in Daily Doses of 0.45 mCi/kg (0.3 mg/kg), M ± m

Mode of administration	Concentration of isoniazid-H^3 in % of total dose administered (numerator) and in μg/g tissues (denominator)					
	rats			guinea pigs		
	lung	liver	blood serum	lung	liver	blood serum
Orally	0,070± 0,001 / 0,004± 0,001	0,082± 0,002 / 0,005± 0,002	0,028± 0,003 / 0,002± 0,001	0,044± 0,003 / 0,003± 0,001	0,050± 0,003 / 0,003± 0,002	0,018± 0,001 / 0,001± 0,002
Intravenously	0,095± 0,002 / 0,008± 0,002	0,132± 0,003 / 0,011± 0,003	0,016± 0,002 / 0,001± 0,001	0,033± 0,002 / 0,003± 0,002	0,061± 0,002 / 0,005± 0,001	0,013± 0,002 / 0,004± 0,002

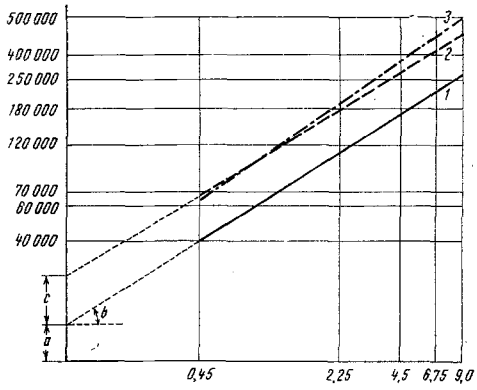

Fig. 1. Change in concentration of isoniazid-H^3 in blood serum and tissues of rats following oral administration of different doses of the compound. 1) Blood serum; 2) lung; 3) liver. Abscissa, dose of isoniazid-H^3 administered (in mCi/kg); ordinate, concentration of isoniazid-H^3 (pulses/min/g). Logarithmic scale.

weighing 250-300 g. The animals were infected by injection of a 3-week culture of M. tuberculosis, strain Bov-8, into the lungs, in the rats in a dose of 10 mg in 0.2 ml of a mixture of petroleum jelly and lanoline, and guinea pigs in a dose of 5 mg, in 0.1 ml physiological saline.

Isoniazid-H^3 was given by mouth to 25 rats in doses of 0.3, 1.5, 3, 4.5, and 6 mg/kg, with activities of 0.45, 2.25, 4.5, 6.75, and 9 mCi/kg body weight. The animals were killed by decapitation 1 h after administration of the compound, the time when the concentration of isoniazid-H^3 in the blood serum and tissues of rats reaches its maximum [6]. Isoniazid-H^3 was injected intravenously into 24 rats in a dose of 0.3 mg/kg, with activity of 0.45 mCi/kg body weight, and these animals were sacrificed after 5, 15, 30, and 45 min and 1, 2, and 6 h. Isoniazid-H^3 was given by mouth daily for 7 days to five rats and five guinea pigs and injected intravenously daily for 7 days (five rats and five guinea pigs) in a dose of 0.3 mg/kg with activity of 0.45 mCi/kg body weight. These animals were sacrificed 24 h after administration of the compound. Isoniazid-H^3 was given by mouth to 12 rats and 12 guinea pigs in doses of 5, 10, 20, and 150 mg/kg with activity of 0.45 mCi/kg body weight, and these animals were sacrificed after 1, 2, and 6 h. The blood serum, lungs, liver, cavities, and foci were investigated. Samples were prepared by the method of Meade and Stiglitz [14]. The specimens were counted in a Belin "Carbotrimeter" – a liquid scintillation counter working at 1600 V and −8°C. The results of measurements of radioactivity were expressed in pulses/min, as percentages of the total activity administered, and in μg/g tissues.

RESULTS

Analysis of the data showed that with an increase in the dose of isoniazid by 5, 10, 15, and 20 times, its concentration in the blood serum, lungs, and liver does not increase in a linear fashion but proportionally to the logarithm of the dose of the compound (Fig. 1). In other words, the relationship between the dose of isoniazid-H^3 and its concentration in the liquid media and tissues of the body is such that its concentration at any time after administration of the compound can be determined. The relationship can be expressed by the formula

$$y = a + bx, \tag{1}$$

where y is the concentration of isoniazid-H^3 in the test object; x the dose of isoniazid-H^3; a is a constant for a given straight line, reflecting the initial point for counting; and b is a constant reflecting the angle of slope of the straight line. Since the values of a and b are always known and are constant for each straight line, knowing the dose of isoniazid administered, this formula can be used to calculate its concentration in any test object.

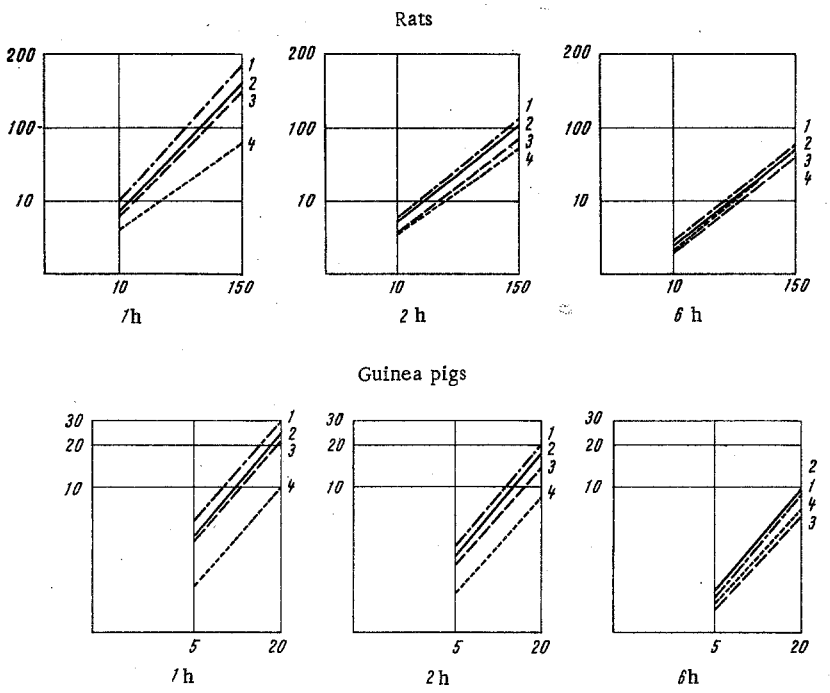

Fig. 2. Diagrams of isoniazid-H^3 concentrations in blood serum (2), intact lung (3), a tuberculous focus (1), and a cavity in the lung (4) after oral administration of the compound. Abscissa, dose of isoniazid-H^3 administered (in mg/kg); ordinate, concentration of isoniazid-H^3 (in μg/g). Logarithmic scale.

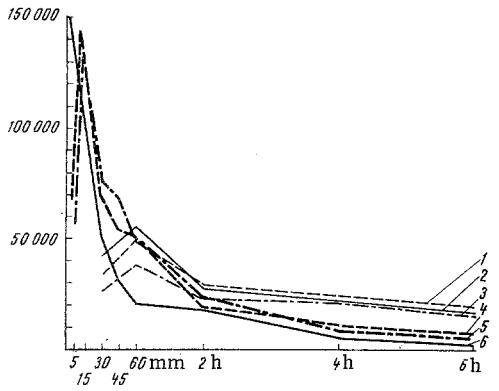

Fig. 3. Concentration of isoniazid-H^3 in blood serum and tissues of healthy rats after oral (thin lines) and intravenous (thick lines) administration of 0.45 mCi/kg isoniazid-H^3. 1,4) Liver; 2, 6) blood serum; 3, 5) lung. Abscissa, time after injection; ordinate, concentration of isoniazid-H^3 (pulses/min/g).

However, it is only in the blood serum of each patient that the physician can always obtain the isoniazid concentration, and in the tissues he can only determine it in postmortem material. It is important, therefore, that if the isoniazid concentration in the serum be known, it can be determined also in the tissues, especially those affected by tuberculosis, and this can easily be calculated from the following formula:

$$y = a + bx \pm c, \qquad (2)$$

where y, x, a, and b have the values indicated above (1); c is the distance through which the straight line reflecting the level of concentration of isoniazid in the test tissue is displaced upward or downward.

Besides the formula given above (2), the isoniazid concentration in affected tissues of the body can also be determined graphically, if its concentration in the blood serum is known (Fig. 2). These graphs show that after 1 h the isoniazid concentration in the blood serum is higher than in the contents of a cavity but lower than in a focus of infection ($P < 0.001$), while after 2 h it is approaching its concentration in a focus of infection, although as before it remains higher than in the cavity and lower than in the focus ($P < 0.001$), and after 6 h it is close to its concentration in the focus and slightly higher than in the cavity ($P < 0.001$).

A similar relationship can also be induced clinically for determining the concentration of isoniazid in foci and cavities, knowing its concentration in the blood serum.

Experiments on 24 rats showed that when isoniazid-H^3 was injected intravenously, its concentration in the serum reached a maximum after 5 min and in the tissues after 15 min. This indicates rapid redistribution of isoniazid-H^3 and high permeability of cell membranes to this compound. The concentration of isoniazid-H^3 in the lung and liver at the peak period was close to its concentration in the blood serum. Elimination of isoniazid-H^3 from the blood serum took place somewhat more rapidly than from the body tissues, so that after 6 h the isoniazid-H^3 concentration in the lung and liver was higher than in the blood serum ($P < 0.001$; Fig. 3).

The isoniazid-H^3 concentration in the blood serum and body tissues at the peak period after intravenous injection was 2.5 times higher than the maximal level of its concentration after oral administration. Later, however, it fell more rapidly than after oral administration (Fig. 3).

During daily intravenous and oral administration of isoniazid-H^3 to guinea pigs and rats for 7 days, it was found that after 24 h isoniazid-H^3 could be detected in the blood serum and tissues only in negligible amounts (Table 1).

A definite mathematical relationship thus exists betwen the dose of isoniazid and its concentration in the media and tissues of the body within the investigated dose range (0.45-9 mCi/kg). A connection was also found between the isoniazid concentration in the blood serum and in the body tissues. On the basis of these experimental data, the clinical study of the relationship thus obtained can be recommended, so that the concentration of the compound canbe determined in areas affected by the disease, knowing its level in the blood serum.

LITERATURE CITED

1. L. M. Bondarev, in: Collected Scientific Transactions of Rostov-on-Don Medical Institute [in Russian], No. 14, Rostov-on-Don (1960), p. 567.
2. I. M. Bondarev, A. A. Klebanova, L. I. Zhigalina, et al., in: The Control of Tuberculosis [in Russian], Minsk (1968), p. 192
3. V. V. Navrotskii, A. I. Pertsovskii, and V. P. Belogurova, Probl. Tuberk., No. 11, 39 (1968).
4. V. A. Temmere, in: Problems in Tuberculosis [in Russian], No. 3, Riga (1958), p. 153.
5. Yu. G. Tregubov, in: Prophylaxis, Diagnosis, and Treatment of Cavernous Forms of Pulmonary Tuberculosis [in Russian], Chernigov (1969), p. 180.
6. L. P. Cherednichenko, in: Clinical Features, Diagnosis, and Treatment of Pulmonary and Extrapulmonary Tuberculosis [in Russian], Moscow (1967), p. 59.
7. L. P. Cherednichenko, Probl. Tuberk., No. 5, 80 (1969).
8. A. N. Chistovich, G. I. Vavilin, and E. I. Volodin, Proceedings of the First All-Russian Congress of Tuberculosis Specialists [in Russian], Moscow (1960), p. 29.
9. F. V. Shebanov and Yu. G. Grigor'ev, Probl. Tuberk., No. 9, 14 (1967).
10. R. Benda, R. Morelec, et al., Rev. Tuberc. (Paris), 17, 90 (1953).
11. H. Bloch, Am.Rev. Resp. Dis., 84, No. 6, 824 (1961)
12. L. Brander, Acta Tuberc. Scand., 43, 299 (1963).
13. R. Manthei, L. Roth, W, Barclay, et al., Arch. Internat. Pharmacodyn., 98, 183 (1954).
14. R. C. Meade and R. A. Stiglitz, Internat. J. Appl. Radiat., 13, 11 (1962).