THE BREAKDOWN OF PHTHIVAZID IN THE GASTROINTESTINAL TRACT

L. I. Grebennik, G. A. Smirnov,

and R. V. Gnevkovskaya

Department of Chemotherapy (Head – Prof. G. N. Pershin)
of the S. Ordzhonikidze All-Union Scientific-Research Chemopharmaceutical
Institute and the Institute of Tuberculosis (Director – Corresponding Member
AMS, USSR, Prof. N. A. Shmelev) AMS, USSR, Moscow
(Presented by Active Member, AMS, USSR, V. V. Zakusov)
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Phthivazid, in an acid medium, resembles isonicotinic acid hydrazide (HINA); it reacts with para-dimethylaminobenzaldehyde and picryl chloride and gives a number of other reactions characteristic of HINA. This is evidence that phthivazid breaks down in an acid medium into its constituent parts, HINA and vanillin. If phthivazid is split in the stomach, under the influence of hydrochloric acid, into its constituent parts, then no essential difference must exist between HINA and phthivazid in its metabolism and influence on the organism.

The literature indicates an essential difference in the metabolism of HINA and phthivazid in the human and animal organism. In a comparative study of HINA and phthivazid in rabbits, G. N. Pershin, S. A. Vichkanova, and S. S. Liberman [3] found that the bacteriostatic activity of the cerebrospinal fluid of those animals, which were receiving HINA per os, was significantly higher than in animals to which they gave phthivazid. One of the authors of this report [2], found that animals, which were getting phthivazid internally, excreted the phthivazid, combined with glucuronic acid, in the urine in appreciable quantities. All these findings affirm that phthivazid is absorbed in definite quantities from the gastrointestinal tract in the form of the intact molecule and behaves thereafter as an independent substance distinct from HINA.

In this article, we are reporting new experimental data which permit the assumption that, in the gastrointestinal tract of animals and man, phthivazid not only is not subjected to an intensive breakdown into its constituent parts (HINA and vanillin) but is even synthesized from these substances, if they are introduced into the stomach separately or in a mixture.

TABLE 1. The Concentration of Phthivazid and HINA in Rat Blood After Intragastric Administration of Phthivazid, HINA and HINA + Vanillin

Experiment No.	Preparation	Dose converted to phthivazid in (mg/kg)	Number of Animals	Content of HINA and phthivazid in the blood, converted to phthivazid (in α/ml) after				
				1 hour	2 hours	4 hours	8 hours	24 hours
1	Phthivazid	200	12	36	42	43	24	–
2	HINA + vanillin	200	12	37	47	47	22	–
3	HINA	200	12	80	82	66	25	–
4	Phthivazid	100	15	21	20	19	15	0–
5	HINA + vanillin	100	15	26	32	17	11	0–
6	HINA	100	15	65	60	41	15	0–

TABLE 2. Absorption, Excretion and Concentration, in the Blood of Tuberculosis Patients, of Phthivazid and HINA After Internal Reception of Phthivazid, HINA, and HINA + Vanillin

Expt. No.	Patient	Preparation	Dose	Concentration in the blood after 3 hours, calculated as phthivazid (in γ/ml)	Excreted in the urine (in % of administered dose)		Excreted in the feces (in % of administered dose)
					in free form	altogether	
1	P-va	phthivazid	1.16	4.8	10	45	11.7
		HINA	0.5	} 6.4	12	45	4
		plus vanillin.	0.66				
		HINA	0.5	8.4	10	75	2
2	O-ya	phthivazid	1.16	3.3	19.7	34	2
		HINA	0.5	} 4.3	27	49.6	3
		plus vanillin.	0.66				
		HINA	0.5	10.4	41	69	0
3	T-ko	phthivazid	1.16	2.4	7	36	20
		HINA	0.5	} 7.4	12	44.7	7.3
		plus vanillin.	0.66				
		HINA	0.5	9.4	10.5	50	3.6
4	G-va	phthivazid	1.16	2.4	8.3	28.5	22
		HINA	0.5	} 10	6.7	36.6	12.7
		plus vanillin.	0.66				
		HINA	0.5	9.5	10.5	73.5	0
5	L-i	phthivazid	1.16	1.8	7.8	24.8	10
		HINA	0.5	} 9	20	59.5	1.6
		plus vanillin.	0.66				
		HINA	0.5	9	10	57	2.0
6	G-v	phthivazid	1.16	1.3	6.8	29	11
		HINA	0.5	} 4.8	11.5	45.4	2.6
		plus vanillin.	0.66				
		HINA	0.5	6.4	22	87	7

METHOD AND RESULTS

We carried out our experiments on male rats weighing 200-250 g. Phthivazid in doses of 100 and 200 mg/kg, HINA and vanillin in equivalent quantities in the form of a solution or suspension in starch jelly, were introduced into the stomachs of the animals through a metal tube. Animals in the first group received phthivazid, in the second group, HINA, in the third group, HINA, together with an equivalent amount of vanillin. After 1, 2, 4, 8, and 24 hours we measured the concentration of HINA and phthivazid in the animals' blood, by the para-dimethylaminobenzaldehyde reaction [3].

The results of the experiments (Table 1) indicate that markedly less of the HINA which had been introduced into the stomach along with an equivalent quantity of vanillin, accumulates in the blood of rats, than after the introduction of HINA alone; the concentrations are the same as those obtained after the administration of phthivazid alone. This can be explained by the fact that the HINA in the stomach, in a fixed proportion to combine with vanillin, is converted to phthivazid and is then absorbed, not as HINA, but as phthivazid.

The experimental findings in animals in the investigation of the effect of vanillin on HINA metabolism are of clinical interest if these findings can be applied to man. In this connection, we studied the action of vanillin on HINA metabolism in tuberculosis patients. We discontinued all medication for 3 days for the patients under study; then we gave HINA once, in a 0.5 g dose, and collected the urine and feces for 2 days to measure the products of

the metabolism of HINA and phthivazid. Three hours after the intake of the preparation by the patients, we took blood from the veins to determine the blood concentration of HINA and phthivazid. Later, in the same manner, in the same patients, we tested a mixture of HINA with vanillin and phthivazid in doses equivalent to 0.5 g HINA.

The results obtained (Table 2) show that, in the human organism, as in the animal organism, the metabolism of HINA differs markedly from the metabolism of phthivazid in every index tested. HINA is absorbed in a larger quantity than phthivazid from the gastrointestinal tract and is excreted in the urine, and, in large concentrations accumulates in the blood.

When patients receive HINA together with vanillin internally, the metabolism of HINA assumes, in every index tested, a position midway between HINA and phthivazid. Thus, for example, three hours after the patients receive 0.5 g HINA or an equivalent quantity of phthivazid (1.16 g), the blood concentration of these substances, calculated on the basis of phthivazid, is 6.4 - 10.4 γ/ml for HINA and 1.3 - 4.8 γ/ml for phthivazid. After reception of HINA together with vanillin, the blood concentration of HINA is 4.3 - 10 γ/ml. Excreted in the urine is 68.6% (50-87%) of the administered dose of HINA and 33% (25-45%) of the phthivazid; after reception of HINA together with vanillin, 53.5% (37-59%) of the quantity administered is excreted.

Our finding, that the HINA, which is administered into the stomach together with vanillin, is absorbed and excreted from the organism in the same way as phthivazid, argues that these substances – HINA and vanillin – react actively with each other to form molecules of phthivazid and that, in the phthivazid molecule, the attachment between HINA and vanillin is quite strong.

SUMMARY

Introduced into the stomach of tuberculous patients together with vaniline hydraside of isonicotinic acid, HINA is absorbed, accumulated in the blood and excreted from the body in considerably smaller quantities than after its administration alone, approaching phthivazid by metabolism. This may be explained by the fact that in the body HINA forms hydrason (phthivazid) by combining with vanillin.

LITERATURE CITED

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
