EXPERIMENTAL DATA ON THE EFFECT OF PHTHIVAZID AND TUBAZID ON THE BODY

R. M. Izabolinskaya, L. S. Kogosova

From the Pathophysiological Laboratory (Head – Active Member AMN SSSR N. N. Gorev) and the Biochemical Laboratory (Head – Senior Scientific Assistant R. M. Izabolinskaya) of the F. G. Yanovskii Ukrainian Research Institute of Tuberculosis (Director – Docent A. S. Mamolat), Kiev

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In addition to their bacteriostatic action on Mycobacterium tuberculosis, phythivazid* and tubazid** also have a definite pharmacodynamic effect on the body as a whole. In the foreign literature, for instance, there are reports that tubazid and certain other derivatives of isonicotinic acid have an influence on the autonomic nervous system, exerting a sympatheticomimetic action [12, 17].

There are many conflicting experimental and clinical findings in connection with the effect of isonicotinic acid preparations on carbohydrate metabolism, but the majority of these suggest that under the influence of various nicotinic acid preparations the blood sugar level rises and diabetic hyperglycemia is increased [13, 16 and others]. Certain workers have attempted to explain the hyperglycemic effect of these preparations by increased mobilization of glycogen from the liver and muscles, but no direct evidence in favor of this is produced [20]. The deleterious effect of isonicotinic acid on the liver has been shown experimentally [16, 15, 21 and others] and confirmed by clinical observations [14].

Our previous studies of the action of phthivazid on the neuro-humoral changes in the blood showed that the use of this drug was accompanied by normalization of the disturbances of the mediator system observed in patients with tuberculosis. So far as the effect of phthivazid on carbohydrate metabolism is concerned, experimental findings and clinical observations indicate that it has a weak insulin-like action [7, 10]. The positive action of phthivazid on liver function has been demonstrated both experimentally and clinically [2, 6, 7 and others].

We undertook the task of comparing the effects of phthivazid and tubazid on certain interconnected metabolism processes in the body, the reactions of which are to a large extent determined by the functional state of the autonomic division of the central nervous system.

Our previous investigations showed that in healthy rabbits and in rabbits inoculated with tuberculosis, receiving phthivazid by mouth for 4-5 weeks, the liver glycogen content was considerably higher than in healthy and tuberculous animals not receiving phthivazid. Besides an accumulation of glycogen in the liver, a fall in the lipid content was observed in the healthy animals (in animals receiving phthivazid – 11.4g% of lipids, in healthy controls – 17 g%).

In rabbits taking phthivazid by mouth we observed a lower degree of accumulation of fat in the liver during

* Isonicotinoyl- (3-methoxy-4-oxybenzal) hydrazone.– Translator.

** Isoniazid. – Translator.

Mean Values of the Lipid Content in the Liver and the Glycogen Content in the Liver and Muscles of Control Rabbits and of Rabbits Receiving Phthivazid and Tubazid

Number of animals	Control rabbits		Rabbits received phthivazid			Rabbits received tubazid			
	liver glycogen	liver lipids	Number of experiments	liver glycogen	liver lipids	Number of experiments	liver glycogen	muscle glycogen (in g%)	liver lipids
15	2,5 (2,0—4,0)	17,0 (12,7—21,0)	15	4,2 (3,3—4,8)	15,0 (11,0—17,5)	15	1,8 (0,8—3,0)	0,6 (0,4—0,8)	19,8 (15,0—24,0)

Note. The limits of variation are given in brackets.

fatty infiltration due to carbon tetrachloride. These results are in agreement with those of N. P. Skakun and I. P. Turko [7], who obtained good therapeutic results from the use of phthivazid in dogs with experimental hepatitis due to carbon tetrachloride. The favorable effects of phthivazid on certain liver functions, shown experimentally, provide a basis for the use of phthivazid in the treatment of a number of diseases of the liver [11].

EXPERIMENTAL METHOD

In the present communication we described the results of investigations carried out on 3 groups of rabbits (15 animals in each group), weighing about 2 kg, and kept under identical conditions of diet and general care. One group received phthivazid in a dose of 100 mg/ kg body weight by mouth for 5-6 weeks, the second group received tubazid (10 mg/ kg body weight) for the same length of time and the third group acted as control animals.

Investigations were carried out before the drug was given, 2 weeks after it had been started, and then at the end of its administration, i.e., after 5-6 weeks. Some animals were examined once more, 4-5 days after the end of administration of the drug. At the same time the chemical factors of nervous excitation in the blood were estimated. These estimations were not only made at at the time mentioned above but also 4 hours after the first administration of the nervous excitation preparation, since we know from the investigations of V. A. Buskina, L. I. Grebennik and E. É. Fialko [1, 3, 9] that the maximum concentration of phthivazid in the blood is noted 2-4 hours after its administration.

The animals were killed by air embolism 5-6 weeks after receiving phthivazid and tubazid, and estimations were made of the lipid content (by Leites' method) and the glycogen content (by Pflüger's method) of the liver. Because of reports in the literature of the possible mobilization of glycogen from the muscles under the influence of isoniazid, we also investigated the muscle glycogen in the rabbits receiving tubazid.

The mediators of the blood were tested on biological objects: cholinergic drugs on the denervated dorsal muscle of the leech (after preliminary treatment with proserine) and on the isolated frog's heart. Blood for testing was taken from the auricular vein of the rabbit and stabilized with synanthrol. In order to prevent decomposition of the unstable acetycholine, the blood was collected in a syringe which contained a small quantity of proserine as a cholinesterase inhibitor.

EXPERIMENTAL RESULTS

The study of the neuro-humoral changes in the blood of healthy rabbits, before receiving phthivazid, showed that the blood of these animals did not cause contraction of the denervated dorsal muscle of the leech and had no negative ino-chronotropic effect on the isolated frog's heart. The first examination of the rabbits 4 hours after the start of phthivazid administration showed, however, that the blood of the majority of the experimental animals contained a biologically active substance, evidently parasympathetic

in origin, for it caused contraction of the isolated dorsal muscle of the leech. Examination of these same rabbits throughout the experiment (after 2 weeks, and then at the end of phthivazid feeding) revealed that the parasympatheticomimetic effect of the blood was the more apparent the longer the period of action of the drug on the animal.

Investigations on the sugar concentration in the peripheral blood of these animals showed that its level varied between normal limits (from 70 to 100 mg%) in the individual animals throughout the period of administration of the drug; this agrees fully with investigations on patients receiving phthivazid.

The prolonged administration of tubazid led to different changes in the experimental animals. Tubazid brought about sympatheticomimetic changes in the mediator system, which were clearly seen 2 weeks after the start of its administration and reached very high figures at the end of the experiment (the positive inotropic action of the blood at the end of administration of the drug varied from 120 to 200% the blood of the control animals had an insignificantly positive inotropic effect of from 10 to 42%).

In all the animals receiving tubazid the blood sugar rose, and in some of them it reached 125-135 mg%, as compared with an initial level of 70-90 mg%. The mean increase in the blood sugar for the whole group of rabbits over its initial concentration before receiving tubazid was 35 mg%. The increase in the blood sugar level was proportional to the duration of administration of the drug: for example, estimations of the blood sugar 5 days after administration had ended showed that the hyperglycemic effect of tubazid was unstable and lasted only while the drug was given.

The effect of phthivazid and tubazid on the lipid and glycogen content of the liver also differed (see table)*

It will be seen from the table that the glycogen content of the liver in rabbits receiving phthivazid was much higher than that in rabbits receiving tubazid, and higher still than that in the control animals, according to both the mean value and the limits of variation.

The small decrease in the glycogen content of the muscles in rabbits receiving tubazid may possibly be due to mobilization of glycogen from the muscles and to intensification of the processes of glycogenolysis in both muscles and liver, which lead to a hyperglycemic effect

In order to exclude the direct action of phthivazid and tubazid on the blood, we made a series of observations: the drugs were added to 5 ml of whole blood from a rabbit (in a test-tube) in a concentration equivalent to that in the blood of the experimental animals during administration of phthivazid or tubazid (phthivazid — 4-7 γ/ml, tubazid — 6-8 γ/ml). This blood was investigated in the usual manner on biological test objects. It was found that the blood so tested did not cause contraction of the proserinized dorsal muscle of the leech and had no effect on the isolated frog's heart, no matter whether phthivazid or tubazid were added to it.

The parasympatheticomimetic effect of phthivazid and the sympatheticomimetic effect of tubazid thus did not depend on the direct action of these drugs on the blood; these effects must evidently be due to the complex changes developing in the animal as a result of the administration of these drugs.

It may be concluded from the results obtained that phthivazid and tubazid act differently on certain physiological functions of the body. Phthivazid, for instance, when giving by mouth, leads to the development of parasympatheticomimetic changes in the mediator systems of healthy animals, does not alter the sugar content of the blood when its initial level is normal and possesses a glycogen-forming action, while at the same time restricting the accumulation of fat in the liver.

In these conditions, tubazid causes a well marked sympatheticomimetic effect and also raises the blood sugar, creating in individual rabbits a hyperglycemic effect which increases with the duration of administration of the drug, but is unstable and disappears on stopping the drug. Prolonged administration of tubazid lowers the glycogen content of the muscles and liver and leads to accumulation of a large amount of fat in the liver. This action of tubazid on the glycogen and fat contents of the liver may possibly partially explain the deleterious effect of the drug on liver function, which is observed clinically.

*The experimental results were treated statistically and the mean square deviation and the mean error determined, the cube of which did not exceed the mean value found. The arithmetric means obtained were thus significant.

The difference in the action of these two drugs on certain functions of the body suggests that phthivazid is superior to tubazid in its more sparing physiological action. In the choice of antibacterial drugs, clinicians must be guided by the differences in the action of these on the various functions of the body.

SUMMARY

The author studied the effect of phthivazid and tubazid on some physiological functions of rabbits.

It was found that phthivazid, administered per os to healthy animals for a long period of time, promotes parasympathomimetic shifts in the mediator system, has no effect on the blood sugar leve, and possesses a glycogen-forming effect, thus evidently limiting the accumulation of fat in the liver.

Under the same conditions tubazid evokes a pronounced sympathomimetic effect, increases the blood sugar level, reduces the glycogen content in the muscles and liver, and promotes fat accumulation in the liver.

The difference in the action of these two preparations on the body suggests that phthivazid has an advantage over tubazid due to its more sparing physiological effect.

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