Effects of Acute Hypoxia on Antipyrine and Isoniazid Pharmacokinetics in Rats with Low and High Resistance to Oxygen Deficiency

V. I. Sharapov, M. A. Kolpakov, and O. R. Grek

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As shown in a number of studies, individuals may be classified as either slow or rapid "oxidizers" and/or "acetylators" according to the rates at which certain drugs are eliminated from their bodies [5, 8]. On the other hand, it has been known for a long time that a population of animals may be classified into groups according to their resistance to hyperbaric hypoxia [1]. Interindividual differences both in drug elimination rates and in resistance to hypoxia are determined by the totality of genotypic and phenotypic factors [1,7,8]. Given that the microsomal oxidation and acetylation of drugs are oxygen-dependent and that the overall strategy of survival of cells, tissues, and organisms in the presence of hypoxia is directed at restricting metabolic requirements [6], the relationship between drug metabolism and resistance to hypoxia is a subject of considerable current interest.

In this study we compared the pharmacokinetics of antipyrine and isoniazid in groups of rats with low and high resistance to hypoxia and then examined how pharmacokinetic parameters of these drugs might be altered in such rats by their exposure to acute hypobaric hypoxia.

MATERIALS AND METHODS

For the study, male Wistar rats weighing around 200 g with either high or low resistance to oxygen deficiency, as determined in preliminary tests by a method described elsewhere [1], were selected. Acute hypoxia was simulated in a pressure chamber by exposing rats to an "altitude" of 8000 m for 2 h for a study of isoniazid pharmacokinetics and to an "altitude" of 9000 m for 20 min for a

TABLE 1. Effects of Acute Hypoxia on Pharmacokinetic Parameters of Antipyrine in Low-Resistance (LR) and High-Resistance (HR) Groups of Rats. The Values are Means±SEM ($n=6-10$)

Group	$T_{1/2}$, h	V_d, mg/kg	Cl, ml/min×kg	k_{el}, l/h
LR control rats	113.9±4.9	419.0±24.7	2.6±0.1	0.37±0.02
HR control rats	131.9±3.2*	495.9±17.7*	2.6±0.1*	0.32±0.01*
LR hypoxic rats	95.8±4.4**	412.6±32.6	3.0±0.2	0.44±0.02**
HR hypoxic rats	159.3±6.1*,**	463.6±33.7	2.0±0.1*,**	0.26±0.01*,**

Note: * significant difference from the LR or HR test group ($p<0.05$); ** significant difference from the corresponding (LR or HR) control group ($p<0.05$).

Medical Institute, Novosibirsk; and Institute of Clinical and Experimental Lymphology, Siberian Division of the Russian Academy of Medical Sciences, Novosibirsk. (Presented by Yu.I. Borodin, Member of the Russian Academy of Medical Sciences)

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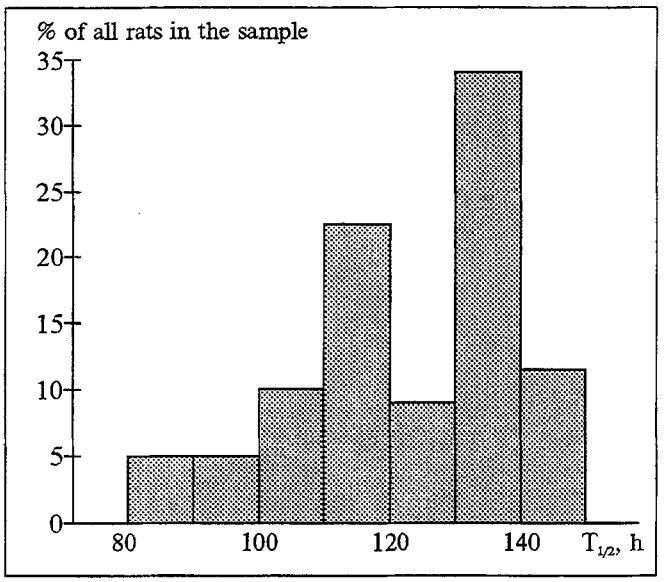

Fig. 1. Histogram showing the distribution of Wistar rats in the sample according to the elimination half-time ($T_{1/2}$) of antipyrine (normal distribution was rejected by Kolmogoroff's test).

study of antipyrine pharmacokinetics. Isoniazid and antipyrine were injected intraperitoneally in a dose of 100 mg/kg and 18 mg/kg, respectively. Drug-treated rats nonexposed to hypoxia served as controls. Antipyrine concentrations were measured by means of HPLC on a Millichrome-1A chromatograph [3] in blood samples taken at minutes 30, 60, 90, and 120 postinjection. Isoniazid concentrations were determined in blood plasma samples at 2.5, 3, 3.5, and 4 h postinjection using a modification [2] of the procedure described by Wollenberg [9]. Pharmacokinetic parameters - elimination half-time ($T_{1/2}$), elimination rate constant (K_{el}), distribution volume (V_d), and total clearance (Cl) - were calculated by conventional methods [4]. The results were treated statistically by Student's t test and Kolmogoroff's test. The differences between the test and control rats were considered significant at $p<0.05$.

RESULTS

As shown in Tables 1 and 2, the pharmacokinetics of both drugs in high-resistance (HR) rats differed from that in their low-resistance (LR) counterparts. In the LH controls, the elimination rate of antipyrine was 1.2 times higher and the V_d was 18% greater than in the HR controls; these two groups did not differ in Cl values. HR rats responded to acute hypoxia by a significant slowing of antipyrine metabolism and LR rats by its significant acceleration. The rats of these two test groups did not differ significantly in V_d values. The Cl of antipyrine was significantly lower in the HR group as a result of its depressed biotransformation.

LR and HR rats also differed substantially in the pharmacokinetic parameters of isoniazid. In the HR control group, the rate of its acetylation was 2.1 times higher while V_d and Cl were considerably lower (4.1-fold and 2.0-fold, respectively) than in the LR control group. In response to acute hypoxia, the metabolism of isoniazid was strongly inhibited in the HR group. Thus, its $T_{1/2}$ was almost 2 times longer and its K_{el} much lower than in the HR controls, whereas its V_d was 4.8 times greater; as a consequence, the Cl of this drug in the HR group was about 2.5 times higher. In the LR rats, the pharmacokinetics of isoniazid did not change significantly in response to hypoxia.

Comparison of metabolic transformations undergone by the drugs in the hypoxia-nonexposed (control) rat population showed that the distribution of its members in terms of $T_{1/2}$ values of both antipyrine and isoniazid was bimodal, with peaks occurring in the regions 110-120 min and 130-140 min for antipyrine and 0.45-0.6 h and 1.05-1.2 h for isoniazid (Figs. 1 and 2). It was then found that rapid acetylators and slow oxidizers were all HR rats, whereas slow acetylators and rapid oxidizers were all LR animals. A genetically determined reverse relationship between the oxidation and acetylation rates of drugs has also been observed in humans [5, 8]. Our finding that these rates were interdependent in groups of rats differing in resistance (low or high) to hypoxia indicates that the oxidation and acetylation processes

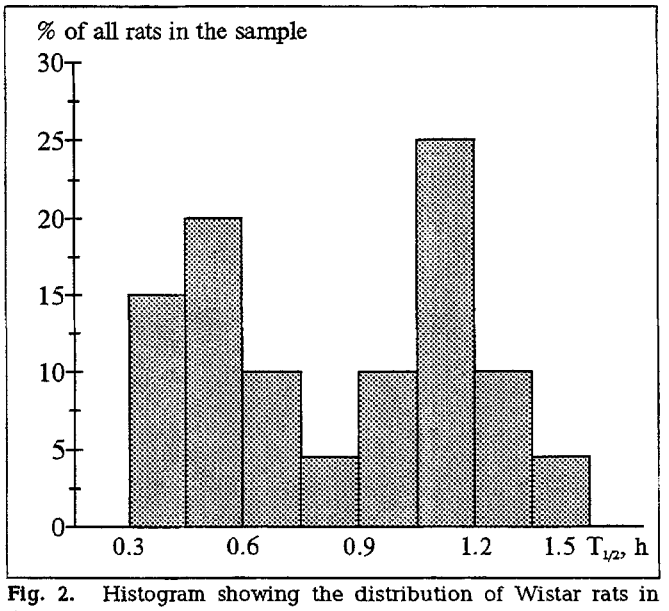

Fig. 2. Histogram showing the distribution of Wistar rats in the sample according to the elimination half-time ($T_{1/2}$) of isoniazid (normal distribution was rejected by Kolmogoroff's test).

TABLE 2. Effects of Acute Hypoxia on Pharmacokinetic Parameters of Isoniazid in Low−Resistance (LR) and High−Resistance (HR) Groups of Rats. The Values are Means±SEM ($n = 6 - 10$)

Group	$T_{1/2}$, h	V_d, mg/kg	Cl, ml/min×kg	k_{el}, 1/h
LR control rats	1.16±0.04	793.7±87.6	472.9±43.8	0.61±0.02
HR control rats	0.54±0.04*	191.2±48.8*	238.3±56.4*	1.30±0.08*
LR hypoxic rats	1.22±0.10	977.8±135.3	551.5±53.4	0.58±0.05
HR hypoxic rats	1.06±0.02**	909.6±107.9**	592.5±64.3**	0.66±0.01**

Note: * significant difference from the LR or HR test group ($p<0.05$); ** significant difference from the corresponding (LR or HR) control group ($p<0.05$).

are linked to the individual sensitivity of the organism to oxygen deficiency. In the HR rats, acute hypoxia caused inhibition of the enzymes involved in phases 1 and 2 of the transformation of xenobiotics. This appears to be the most rational response of oxygen-dependent systems to hypoxia because it limits oxygen expenditure for plastic processes occurring in the cells.

In summary, this study demonstrated that the oxidation and acetylation of drugs in a population of rats were interdependent and that these two processes were also dependent on the individual resistance of the rats to acute hypoxia and in particular on how their drug-metabolizing systems responded to it.

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