Pharmacokinetics of Antipyrine and Isoniazid in Rats During Their Adaptation to Cold

A. R. Kolpakov, M. A. Kolpakov, and L. E. Panin

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The pharmacokinetics of the drugs antipyrine and isoniazid was studied in Wistar rats in the course of their adaptation to cold (+5°C) over 35 days. The significant increases recorded in the clearance of these drugs were mainly due to their accelerated elimination during the first week of cold and to their increased volume of distribution subsequently (on days 15-22). By the end of the 35-day observation period, the pharmacokinetic parameters of both drugs were close to the pre-exposure levels except that the clearance of isoniazid remained significantly elevated. For this animal model of adaptation to cold, no inhibition of the xenobiotic-metabolizing function of the liver was noted.

Key Words: *adaptation to cold; antipyrine and isoniazid pharmacokinetics*

Prolonged exposure of humans or animals to low temperatures elicits a set of responses involving many organs and systems. The adaptation to cold is often due to a reduction in the specific function of an organ or tissue. For instance, an increase in the energy cost of muscular contraction, leading to diminished performance efficiency, has been demonstrated for the myocardium and smooth musculature of cold-adapted animals [1,10].

An important part in cold adaptation is played by the liver [8]. In the few relevant (and contradictory) studies which have been reported and which used various methods and durations of exposure to low temperature, rises as well as falls were noted in the activity of the hepatic monooxygenase system mediating the first phase of the biotransformation undergone by xenobiotics [7,15]. However, the question of how adaptation to cold affects conjugation processes (the second phase of biotransformation) has not been addressed in the literature.

Institute of Biochemistry and Institute of Clinical and Experimental Lymphology, Siberian Division of the Russian Academy of Medical Sciences, Novosibirsk

In this study on rats we examined, at various times during their exposure to cold, the pharmacokinetics of antipyrine (AP), the metabolism of which in the liver is catalyzed by cytochrome P-450, and that of isoniazid (IN), whose metabolism there is associated with N-acetyltransferase.

MATERIALS AND METHODS

The study was conducted on two groups of male Wistar rats weighing about 200 g. They were each kept in a separate cage (cold chamber) at a temperature of +5°C under artificial illumination (using a 12 h light/12 h darkness schedule) for 35 days. The Hart model of adaptation to cold we used is widely accepted in the physiology of thermoregulation, although it has recently been claimed that this model is excessively rigorous [5]. In preliminary tests we had found that keeping rats in individual cages for 6 weeks at 26°C had no appreciable effect on the pharmacokinetics of either AP or IN.

To obtain baseline data, pharmacokinetic parameters were first measured on day 7 before the rats were exposed to cold. After they had been

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TABLE 1. Impact of Exposure to Cold on AP Pharmacokinetics in Rats ($M \pm m$, $n = 7$)

Parameter	Baseline values	Days of measurement				
		1	8	16	22	35
K_{el}, liters/h	0.35±0.03	0.41±0.04	0.48±0.02*	0.37±0.03	0.39±0.03	0.35±0.05
$T_{1/2}$, h	2.07±0.18	1.73±0.14	1.47±0.05*	1.93±0.18	1.79±0.15	2.12±0.29
V_d, ml/kg	987.3±88.6	941.8±95.0	1033.3±124.2	1376.1±156.5*	1196.3443.6*	893.9±85.4
Cl, ml/h×kg	331.7±17.5	374.8±19.6	485.7±54.1*	503.4±59.9*	469.1±25.0*	298.8±23.5

placed in individual cold chambers, measurements were repeated on days 1, 8, 15, 22, and 35 of exposure. These particular intervals were selected on the basis of the results of our previous study [4]. Rats of group 1 were injected intraperitoneally with AP (18 mg/kg), and the plasma concentrations of this drug were then determined by high-performance liquid chromatography [6] on the indicated days. Group 2 rats were injected by the same route with IN (100 mg/kg) and its plasma concentrations were determined spectrophotometrically [3] on the same days.

The following four pharmacokinetic parameters were calculated by commonly used formulas [9]: elimination half-time ($T_{1/2}$), elimination rate constant (K_{el}), volume of distribution (V_d), and total clearance (Cl). The results were processed statistically using the nonparametric Kolmogoroff-Smirnoff test.

RESULTS

The adaptation to cold substantially altered the pharmacokinetic parameters of AP (Table 1). By day 8 of adaptation, its K_{el} had increased by 37.1% while its $T_{1/2}$ had decreased by 29%. On days 15 and 22, the V_d of AP exceeded the baseline level by 39.4% and 21.2%, respectively. Its Cl was significantly increased on days 8, 15, and 22. Accelerated AP elimination has been reported to occur at times when the total level of cytochrome P-450 and the activities of its individual isoenzymes are elevated [13].

The exposure to cold also strongly affected the pharmacokinetic parameters of IN (Table 2). After 8 days of exposure, its K_{el} was 12.7% above the baseline and its $T_{1/2}$ was 16.1% below it. On day 15, its V_d was increased by 48.5%, but tended to decrease later. Its Cl rose 15.9% above the baseline as early as on day 1 and remained elevated throughout the adaptation period, exceeding the pre-exposure level by 29.9% on day 8, 50.3% on day 15, and 21.4% on day 35.

Thus, in this study the use of AP and IN as test drugs that reflect predominantly the activity of systems metabolizing xenobiotics in the liver [11, 12] revealed accelerated elimination of both drugs (increases in K_{el} and Cl and decreases in $T_{1/2}$), indicating enhanced activity of the reactions proceeding in the first as well as in the second phases of biotransformation. By the end of the observation period, the metabolic rates of both AP and IN had returned to near-baseline values. After approximately 3 to 4 weeks of adaptation to cold, the distribution volumes of both drugs were increased, and their clearance was at its peak during that period. The increased distribution volumes of xenobiotics noted at certain times of adaptation to cold paralleled by their increased clearances may be due to enhanced blood flow through the liver [2]; indirect evidence supporting this view is provided by the reported increase in liver weight [14].

The accelerated elimination of both AP and IN observed in the present study suggests that the enzyme systems involved in the biotransformation of these xenobiotics were responding to cold in a similar fashion, and that the metabolic function of the liver was not inhibited in this animal model of adaptation to cold.

TABLE 2. Impact of Exposure to Cold on IN Pharmacokinetics in Rats ($M \pm m$, $n = 7$)

Parameter	Baseline values	Days of measurement			
		1	8	15	35
K_{el}, liters/h	0.71±0.11	0.77±0.09	0.80±0.08*	0.65±0.08	0.70±0.11
$T_{1/2}$, h	1.12±0.15	0.96±0.10	0.94±0.13*	1.15±0.13	1.12±0.17
V_d, ml/kg	628.3±105.3	636.5±110.0	624.4±49.3	932.9±97.6*	768.9±151.6
Cl, ml/h×kg	374.8±30.1	434.5±47.4*	486.9±39.0*	563.3±16.7*	455.1±43.7*

REFERENCES

1. Yu. S. Alyukhin, *Fiziol. Zh. SSSR*, **61**, № 5, 749-753 (1975).
2. K. M. Lakin and Yu. F. Krylov, *Biotransformation of Drugs* [in Russian], Moscow (1981).
3. A. V. Morozov, N. D. Shatalova, and S. I. Platov, *Probl. Tub.*, № 7, 51-53 (1991).
4. L. E. Panin, A. R. Kolpakov, N. G. Kolosova, and O.V. Dobronravova, in: *Problems of Thermoregulation and Temperature Adaptation* [in Russian], Novosibirsk (1992), pp. 51-53.
5. Yu. F. Pastukhov, *Ibid.*, pp. 158-172.
6. I. A. Rakhmanov, A. V. Semenyuk, I. M. Slyn'ko, *et al.*, *Khim.-Farm. Zh.*, № 3, 351-354 (1989).
7. A. V. Semenyuk, L. I. Kolesnikova, D. V. Sitnikova, *et al.*, *Byull. Eksp. Biol. Med.*, **95**, № 1, 37-39 (1983).
8. V. P. Skulachev, *Energetics of Biological Membranes* [in Russian], Moscow (1989).
9. V. N. Solov'ev, A. A. Firsov, and V. A. Filov, *Pharmacokinetics* [in Russian], Moscow (1980).
10. M. A. Yakimenko, in: *Physiology of Thermoregulation* [in Russian], Leningrad (1984), pp. 223-237.
11. L. Barstow and R. E. Small, *Pharmacotherapy*, **10**, № 4, 280-288 (1990).
12. D. A. P. Evans, *Pharmac. Ther.*, **42**, 157-234 (1989).
13. O. A. Gromova, N.E. Polyakova, N.F. Kozlovskaya, *et al.*, *J. Basic Clin. Physiol.*, **3**, Suppl., 184 (1992).
14. I. T. Mak, E. Shrago, and C. E. Elson, *Biochim. Biophys. Acta*, № 722, 302-309 (1983).
15. K. Matsuyama, H. Sawahara, A. Noda, *et al.*, *Chem. Pharm. Bull.*, **34**, № 11, 4753-4759 (1986).