Pharmacokinetics of Antipyrine in Rats with Different Resistance to Hypoxia in Cold Stress

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 126, No. 11, pp. 513-515, November, 1998
Original article submitted December 22, 1998

It is shown that the parameters of antipyrine pharmacokinetics during cold exposure depend on individual resistance to hypoxia. High-resistant rats are characterized by less intense metabolism and more rapid normalization of pharmacokinetic parameters than low-resistant rats characterized by shortened elimination half-time corresponding to a more rapid metabolism of xenobiotics under conditions of cold stress.

Key Words: *pharmacokinetics; antipyrine; individual resistance to hypoxia; cold stress*

Antipyrine (AP) is primarily metabolized by cytochrome P-450-dependent liver monooxygenases, as evidenced by strong correlation between monooxygenase activity in liver bioptates and the rate of antipyrine elimination [5]. It was shown that changes in the intensity of oxidative metabolism of xenobiotics inversely depend on rat resistance to hypoxia [2,4].

In the present study we investigate the pharmacokinetics and metabolism of AP in rats with different resistance to hypoxia under conditions of cold stress.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats. The animals were divided into high- (HR) and low-resistant (LR) to hypoxia groups as described previously [1]. Experimental rats were placed into a low-temperature (2°C) ventilated chamber for 5 days, control animals were maintained at 21°C. Samples were obtained on days 3 and 5 of cold stress and on day 3 of recovery. AP was injected intraperitoneally in a dose of 18 mg/kg, blood was sampled 1.5, 2, 2.5, and 3 h postinjection.

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Plasma concentration of AP was measured by reverse-phase high performance liquid chromatography at 244 nm [3] in a Milichrom 1A chromatograph with a UV-detector. The following pharmacokinetic parameters were calculated: elimination rate constant, elimination half-life, apparent initial concentration, specific distribution volume, and total clearance of AP. Activity of cytochrome P-450 was assessed by measuring urine concentration of AP metabolites (norantipyrine, 4-hydroxyantipyrine, and 3-hydroxymethylantipyrine). Chromatograms were processed using calibration curves constructed with known concentrations of AP and its metabolites. The data were processed statistically using the Student *t* test.

RESULTS

Experiments showed that AP clearance in LR rats was higher then in HR rats by 33% (Table 1). In HR rats, acute cold stress successively decreased AP clearance so that elimination half-life increased by 26 and 66% on days 3 and 5, respectively. On day 3 of the recovery period, the AP elimination rate in these animals did not differ from the control.

In contrast to HR rats, in LR animals cold stress induced two-phase changes in the rate of AP elimination from the circulation: on day 3 of cold exposure elimination half-life decreased by 27%, while on

0007-4888/98/0011-1098$20.00

TABLE 1. Pharmacokinetics of AP in Rats with Different Resistance to Hypoxia under Conditions of Cold Stress ($M\pm m$, n=4-8)

Parameter	Group	Control	Cooling		Poststress period, day 3
			day 3	day 5	
Elimination half-time AP, h	HR	2.361±0.123	2.981±0.184*	3.926±0.309*	2.115±0.243
	LR	1.774±0.118+	1.293±0.129*+	2.649±0.412*	3.175±0.102*+
Total clearance AP, ml/h/kg	HR	860.4±67.2	702.8±59.7	854.1±146.3	721.1±96.9
	LR	489.6±60.3+	725.8±47.9*	743.3±168.2	458.5±40.6
Specific distribution volume AP, ml/kg	HR	2422.2±454.3	2072.3±168.1	3813.2±102.6*	2894.3±335.6
	LR	914.7±180.7+	859.4±100.1	948.3±123.3+	1089.4±198.7
Apparent initial concentration AP, μg/ml	HR	18.33±0.68	16.80±0.94	21.43±3.14	19.98±1.15
	LR	10.63±1.66+	22.43±1.15*+	24.91±2.41*	16.44±2.31*
Elimination rate constant, h^{-1}	HR	0.395±0.056	0.266±0.057*	0.185±0.04	0.33±0.04
	LR	0.75±0.04+	0.960±0.054*+	0.058±0.02*+	1.08±0.05*+

Note. Here and in Table 2: $p<0.05$: *compared with the corresponding control, +compared with HR rats.

day 5 of cold stress and in the poststress period this parameter increased by 50 and 79%, respectively.

Thus, comparative study revealed marked differences in the pharmacokinetics of AP in intact animals with different resistance to hypoxia. LR rats are characterized by more intense metabolism and higher rate of AP elimination. This is evidenced by a higher rate of production and urinary excretion of AP metabolites. The total urinary content of AP metabolites in LR rats surpassed that of HR animals by 44%(Table 2). In HR rats, metabolic clearance decreased in response to acute cold exposure. This was manifested in prolonged elimination half-time, increased specific distribution volume and apparent initial concentration, and decreased elimination rate constant with a minimum on day 5 of cold exposure. After termination of cold stress all pharmacokinetic parameters in HR rats returned to the initial level.

This response to cold stress is probably aimed at essential restriction of oxygen utilization in metabolic clearance of xenobiotics. This assumption is confirmed by a progressive decrease in AP metabolite production in HR rats by 37 and 63% on days 3 and 5 of cold exposure, respectively (Table 2). By contrast, LR rats were characterized by a shortened elimination half-time together with reduced specific distribution volume and enhanced clearance of AP on day 3 of cold exposure, which suggests that high activity of monooxygenase systems is preserved under these conditions. Intense metabolic processes under conditions of acute cold exposure may contribute to impaired adaptive capacity of the oxygen-dependent metabolic systems responsible for the temperature homeostasis.

TABLE 2. Total Content of AP Metabolites in Urine (μg/ml) from HR and LR Rats under Conditions of Cold Stress ($M\pm m$)

Days	Metabolite content	
	HR	LR
Control	532.1±98.1 (n=8)	764.0±27.2 (n=8)+
Cooling day 3	335.2±84.2 (n=8)	866.1±28.4 (n=6)*+
Cooling day 5	196.5±17.1 (n=7)*	235.7±19.4 (n=4)*
Recovery day 3	521.9±59.8 (n=6)	280.6±72.5 (n=4)*+

Note. *+$p<0.01$ compared with HR rats.

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