Pharmacokinetics of Amixin after Repeated Peroral Administration to Mice

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 140, No. 12, pp. 661-663, December, 2005
Original article submitted April 7, 2005

Pharmacokinetics of amixin was studied after repeated administration (5 days) to animals. Perorally administered amixin is characterized by high bioavailability and is present in the circulation in high concentrations for a long time. The main pharmacokinetic parameters were estimated by the method of linear regression because of slow elimination of amixin from organs and tissues. Our results indicate that repeated treatment with amixin holds much promise for the prevention and therapy of chronic diseases (particularly hepatitides).

Key Words: *amixin; repeated peroral administration; pharmacokinetics*

Pharmacotherapeutic activity of drugs depends on their effective concentration in the action biophase. Advances in modern pharmacotherapy are related not only to the development of highly effective drugs, but also to optimization of the route and regimen of treatment [2]. The reaction to therapy is determined by individual characteristics of the organism, which must be taken into account during selection of the therapeutic scheme [8].

Repeated administration of amixin is used in the treatment of viral hepatitides and herpes infection, combination therapy for infectious, allergic, and vital encephalitis, and prevention of influenza and acute respiratory viral infections. It determines the necessity of studying pharmacokinetic parameters of this drug after repeated administration [1,3,4,10].

Here we studied pharmacokinetic parameters of amixin after repeated administration to experimental animals.

MATERIALS AND METHODS

Experiments were performed on 66 outbred male mice weighing 22-30 g. The animals fed a standard laboratory diet, were kept under the natural light/dark cycle, and had free access to water. We used synthetic ^{3}H-amixin with a specific activity of 2.3 Ci/mol (InterKhim) [7].

The drug in a dose of 50 mg/kg was administered perorally for 5 days. The dose of amixin was selected taking into account its specific activity. The animals were anesthetized with nembutal and decapitated 0.25, 0.5, 1, 2, 4, 24, 48, 96, 144, 196, and 240 h after treatment. Total radioactivity was measured in samples of the liver, kidneys, lungs, spleen, myocardium, and brain.

Blood samples were placed in centrifuge tubes washed with heparin (500 IU/ml). The blood was centrifuged at 3000 rpm for 15 min. The plasma was placed in scintillation flasks.

The homogenate of organs (0.3 ml) was mixed with 15 ml toluene alcohol scintillation fluid and placed in flasks to measure total radioactivity. Total radioactivity of biological fluids was recorded on a TRI-CARB 2700 scintillation counter (Canberra-Packard).

RESULTS

Perorally administered amixin was characterized by high bioavailability. High concentrations of circulating amixin were detected in animals for a long time [6]. Amixin concentration in the plasma peaked

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0007-4888/05/1406-0708

by the 30th minute after treatment (Table 1). The concentration of ^{3}H-amixin and its metabolites in the plasma progressively decreased over 24 h and remained unchanged until the 10th day. Total radioactivity was maximum in the spleen, which is consistent with published data that 1-2% amixin is irreversibly bound in the spleen tissue after single administration [5]. The concentration of this drug was high in the liver, kidneys, and lungs. The peak of total radioactivity in the lungs, myocardium and spleen, liver, and brain was attained over 1, 4, and 24 h, respectively. The concentration of amixin and its metabolites decreased to a stationary level, which reflects a constant rate of drug elimination from all examined organs. Amixin concentration was minimum in the brain.

The main pharmacokinetic parameters were estimated by the method of linear regression due to slow elimination of amixin from organs and tissues [8].

The elimination constant was highest in the plasma (Table 2). Elimination of the substance involves a variety of processes in the kidneys, liver, lungs, and other organs. The rate of elimination from each organ was divided by drug concentration in the plasma to estimate the relative clearance in the examined organs. Drug clearance was highest in the plasma and spleen. Therefore, amixin is rapidly eliminated from these tissues. The elimination rate was lower in the liver, kidneys, and lungs. The elimination rate was minimum in the myocardium and brain. The distribution volume is the apparent volume of drug distribution when its concentration in the body does not differ from the concentration in the plasma. Moreover, the apparent distribution volume reflects accumulation of the circulating drug in tissues. The apparent distribution volume was maximum in the plasma and liver. The test parameter did not differ in the myocardium, kidneys, and brain. The distribution volume was minimum in the spleen (0.0002 ml/h). The AUC value is related to the distribution volume. When the drug has a linear distribution in the body, AUC is proportional to the total amount of the drug in the body and characterizes the total concentration of the radioactive drug in the organ. AUC was highest in the plasma, but lowest in the spleen and lungs. AUC did not differ in the kidneys and liver. AUC in the myocardium was 2-fold higher than in the brain. The estimated half-life of amixin was lowest in the brain (18 h), but highest in the myocardium (25 h). The half-life of amixin in the kidneys and lungs differed insignificantly (by 2 h). The half-life of amixin in the liver was 113 h. The theoretical half-life of amixin in mouse spleen corresponds to 1157 h.

TABLE 1. Concentration of Amixin and Its Metabolites in Mouse Organs and Tissues ($M\pm m$, n=6)

Time, h	cpm×g (ml)						
	blood plasma	liver	kidneys	lungs	spleen	myocardium	brain
0.25	676±249	596,125±28,842	488,651±58,843	1 249,580±801,858	3 678,580±520,695	362,750±47,466	70,602±9791
0.5	510±128	558,335±83,989	323,464±25,361	286,283±63,915	1 565,102±109,306	159,221±13,781	73,431±7710
1	445±81	592,177±169,682	947,375±506,767	969,829±283,337	4 101,777±848,976	328,531±47,066	78,264±5291
2	371±66	607,406±41,261	388,305±30,373	513,194±134,949	3 058,498±574,708	208,418±70,002	74,753±8461
4	226±33	664,176±39,477	504,582±16,671	474,778±63,474	4 152,446±815,786	379,636±74,524	87,369±12,371
24	136±56	137,657±12,683	753,397±57,150	328,295±22,074	1 296,475±143,008	1 560,571±172,208	717,790±55,998
48	395±153	25,470±9191	30,427±3066	62,256±31,237	357,855±114,028	21,620±3550	4978±557
96	603±224	246,359±14,735	126,482±10,526	202,426±44,263	1 101,994±167,997	94,634±9538	27,874±5859
144	292±48	98,435±34,333	75,899±28,150	123,399±42,105	818,670±291,522	67,661±23,852	28,381±10,388
192	420±63	263,659±29,000	163,990±13,958	182,577±90,226	1 174,749±193,166	430,347±246,990	30,260±7147
240	387±22	226,377±30,488	97,530±7735	218,918±107,798	1 186,714±516,493	64,168±17,781	30,385±10,282

TABLE 2. Elimination of Repeatedly Administered Amixin from Mouse Organs and Tissues

Parameter	Blood plasma	Liver	Kidneys	Lungs	Spleen	Brain	Myocardium
k	0.0006	0.0053	0.0069	0.0062	0.0039	0.0088	0.0088
LnC_0	5.82	13.15	12.98	12.91	14.48	11.55	12.59
C_0	332	496 163	416 190	389 959	18 561 162	100 293	282 740
$t_{1/2}$	187	113	63	65	1157	18	25
V	0.9374	0.0016	0.0009	0.0007	0.0002	0.0009	0.0007
Cl_T	253.6	0.2622	0.0929	0.0666	0.365	0.0238	0.026
$AUC_{0-\infty}$	72 156	25 407 366	26 934 422	33 251 129	1 909 652 215	6 822 023	12 479 875

Note. k, elimination constant, h^{-1}; LnC_0, logarithm of initial concentration of ^{3}H-amixin; $t_{1/2}$, half-time of drug clearance, h; V, apparent distribution volume, ml; Cl_T, drug clearance, ml/h; $AUC_{0-\infty}$, area under pharmacokinetic curve, cpm×g (ml).

The effect of repeated treatment with ^{3}H-amixin is similar to that observed in previous experiments [10]. After repeated administration of amixin, its bioavailability increases by several times (compared to single administration of the drug). The concentration of amixin in organs and tissues remains high over 10 days. These data indicate that repeated treatment with amixin holds much promise for the prevention and therapy of chronic diseases (particularly hepatitides).

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