Interspecies Pharmacokinetics of Xymedon

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Pharmacokinetics of immunomodulator xymedon at different modes of the drug administration was studied in humans, dogs, and rats. The main parameters of xymedon pharmacokinetics varied in different animal species. The results confirmed the efficiency and correctness of using allometrical method for extrapolation of pharmacokinetic data for tentative evaluation of drug parameters in humans by the results of preclinical trials on animals.

Key Words: *xymedon pharmacokinetics; allometrical method*

Extensive introduction of new drugs into medical practice necessitates comprehensive studies of the effects of xenobiotics on human body. Experimental preclinical studies of new drugs are usually carried out on laboratory animals. The development of new reliable and correct methods for extrapolation of pharmacological data from animals to humans is one of the priority problems of experimental biology and medicine [1,5,6].

Modern methodology of pharmacokinetic data extrapolation is based on the theory of physiological similarity of animal species. Approaches united by the "allometrical method of pharmacokinetic data extrapolation" are used. This method is based on the theoretically validated concept of pharmacokinetic time [8,11,12].

The physiological life span of small and large animals is of about the same duration measured by appropriate physical units of time [7]. Hence, when analyzing pharmacokinetic data, it is desirable to use a scale for measuring time characteristics, which would make it possible to compare the results for different animal species receiving different doses. Analysis of the known data on drug pharmacokinetics showed that total drug clearance and distribution volumes (kinetic, stationary, initial) depend on physiological parameters of animals and correlate with body weight [5,7]. Therefore animal body weight can be used as a component of the coordinate system for transition to a new scale for measuring physiological time [9,10, 13] — to pharmacokinetic time, representing a pseudodimensionless complex. Its concrete expression will be determined by the type of interspecies relationship between pharmacokinetic parameters.

When analyzing the available pharmacokinetic data obtained on several animal species, it is possible to evaluate the constants of species-to-species extrapolation and then estimate the pharmacokinetic parameters for each animal species and predict the values for humans. Parallel processing of the data for animals and humans (in clinical studies) will show more accurately the relationships between the species-specific parameters of the studied drug distribution in animals and man.

Xymedon is a new pyrimidine drug [4]. It accelerates healing of burns, improves take of bone autotransplants, and effectively modulates the immune system [2]. In gastroduodenal ulcerative defect the drug promotes healing of the ulcer and prolongs remission. Xymedon normalizes the ratio between fibrinogen content and fibrinolysis parameters, thus improving the total and local peripheral circulation [2,4].

We used the protocol of allometrical method of data extrapolation in the studies of xymedon pharmacokinetics.

MATERIALS AND METHODS

Xymedon pharmacokinetics was studied on rats and dogs and in volunteers at different drug doses and

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administration routes. Wistar rats were injected with the drug intraperitoneally in a dose of 10 mg (50 mg/kg). Dogs were injected with xymedon intravenously in a dose of 1200 mg (80 mg/kg, mean body weight of dogs 15 kg).

Volunteers received xymedon orally in doses from 500 to 2000 mg (7-30 mg/kg).

Xymedon concentrations in biological fluids (for evaluation of its pharmacokinetics) were measured by spectrophotometrically.

RESULTS

Xymedon distribution in animal and human blood was described by linear equations of linear chamber models [5]. Equation of a single-chamber model with first-order absorption adequately described xymedon kinetics in the blood of rats and humans, while for dogs xymedon elimination was adequately described by two-chamber model equation.

One-chamber model equation with first-order absorption:

$$C_p(t)=A\times(e^{-K_{el}\times t}-e^{-K_{abs}\times t}). \quad (1)$$

Two-chamber model equation:

$$C_p(t)=A_1\times e^{-K_{el}\times t}+A_2\times e^{-K_{abs}\times t}. \quad (2)$$

Statistical processing of pharmacokinetic data included evaluation of the model constants and integral pharmacokinetic values [3]. Xymedon distribution in humans at doses of 1000 and 2000 mg was characterized by close values of the kinetic constants of the models and integral pharmacokinetic parameters ($C_{L/f}$, MRT, V_1; Table 1). This fact leads to a conclusion about linear pharmacokinetics of xymedon in humans for the given dose range.

Comparison of the pharmacokinetic parameters in animals and humans led to a conclusion on species-specific differences in xymedon distribution. The rate of drug elimination decreased from rats to humans, the mean retention time (MRT_B) and specific distribution volume was higher in humans than in rats. Specific clearance of xymedon in animals and humans differed less. Xymedon is rapidly distributed in animal and human organs and tissues during the first minutes after administration. In rats the volume of initial distribution (V_1) 2-fold surpassed the blood volume, in dogs and humans it surpassed the blood volume 6- and 11-fold, respectively. If xymedon pharmacokinetics in the studied mammals is linear, we can use the allometrical method for pharmacokinetic data extrapolation [8,11, 12] in order to determine the interspecies relationships between xymedon distribution parameters in animals and man.

Based on analysis of individual distributions of xymedon in humans and animals, we proposed the following ratios for pharmacokinetic parameters:

$$CL=a_1\times W^{n1} \quad (3)$$

$$V_1=a_2\times W^{n2} \quad (4)$$

Since pharmacokinetics of xymedon in two of the three biological species is adequately described by one-chamber model equations, the interspecies pharmacokinetic relationship can be analyzed on the basis of one-chamber model of substance elimination from animal and human body.

After transformation we have an expression of interspecies pharmacokinetic relationship, describing the elimination of xymedon in different animal species at different doses:

$$Y(T_{ph})=\frac{1}{a_2}\times e^{-a_1/a_2\times Tph}, \quad (5)$$

where $T_{ph}=t\times W^{(n_1-n_2)}$ is pharmacokinetic time; (6)

$$Y(T_{ph})=C_p\times\frac{t}{D_0/W^{n2}}, \quad (7)$$

where C_p is the drug concentration in the blood.

Interspecies constants of extrapolation $\{a_1, a_2\}$ and degree indexes n_1 and n_2 are unknown parameters of model **(5)**-**(7)**. In order to find these parameters, let us use the data on xymedon distribution in rats, dogs, and humans. Averaged data for a group of volunteers receiving the dose of 2000 mg, were used in estimation. Estimations were carried out using SCALE software developed by us and intended for plotting interspecies pharmacokinetic curves and predicting the parameters of substance distribution in other biological species. Based on estimated constants of interspecies extrapolation, correlation equations were derived, describing the relationship between the main pharmacokinetic parameters of xymedon distribution in animals and humans and body weight:

$$CL=62.11\times W^{1.12} \quad (8)$$

$$V=260.16\times W^{1.2784} \quad (9)$$

$$K_{el}=0.239\times W^{-0.159} \quad (10)$$

$$MRT=4.19\times W^{0.159} \quad (11)$$

The differences between estimated and experimentally measured xymedon constants in the blood during the elimination stage were negligible. Blood levels of xymedon during the elimination stage esti-

TABLE 1. Population Pharmacokinetic Parameters of Xymedon Distribution in Humans and Animals

Parameter, units	Rats (intraperitoneally)	Dogs (intravenously)	Humans (orally)	
	10 mg	1200 mg	1000 mg	2000 mg
A_1, mg/ml	0.592±0.148	0.244±0.008	0.041±0.008	0.047±0.004
α, 1/h		4.21±1.34		
A_2, mg/ml		0.086±0.007		
B, 1/h		0.122±0.019		
K_{el}, 1/h	0.50±0.14	0.434	0.224±0.067	0.137±0.012
K_{abs}, 1/h	3.02±0.85		2.77±0.74	1.92±0.21
MRT, h	2.78	6.0	11.9	8.64
CL/W, ml/h/kg	60.0	110.1	85.0	90.0
V/W. ml/kg	101.2	242.3	381	630
AUC, mg/h/ml	0.839	0.726	0.228	0.333
$T_{1/2}$, h	1.73	4.74	8.9	5.59

TABLE 2. Evaluation of Interspecies Relationships and Pharmacokinetic Parameters of Xymedon

Pharmacokinetic parameters	Individual profiles (*per os*)	Prediction by 3 species	Prediction by 2 species
K_{el}	0.104-0.224	0.122	0.167
MRT	7.5-11.9	8.2	6.0
CL/W	78.7-92.5	103.4	141.5
V_1/W	400-767	849.2	846.6
A/D_0	$(19\text{-}31)\times10^{-6}$	17×10^{-6}	17×10^{-6}

mated by the model and measured for the group of volunteers were also close.

Extrapolation (prediction of the drug distribution parameters in man from the data in animal experiments) is an interesting task. Interspecies relationship was plotted and pharmacokinetic parameters in man were predicted on the base of experimental findings in rats and dogs. Estimated values of pharmacokinetic parameters of xymedon distribution in man were close to evaluations based on interspecies curves for three biological species and derived by analysis of individual pharmacokinetic profiles (Table 2).

Hence, interspecies relationship between the main parameters of xymedon pharmacokinetics was detected; efficiency and correctness of using allometrical method for extrapolation of pharmacokinetic data for predicting the tentative drug values in man by the results of preclinical trials on animals was confirmed.

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