Experimental and Clinical Pharmacokinetics of Amitryptiline: Comparative Analysis

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Pharmacokinetics of two amitriptyline tablets, Amitryptiline Nycomed and Amitryptiline, was investigated clinically and experimentally after a single oral dose of 50 mg. A statistically significant correlation between amitryptiline serum concentrations in dogs and healthy humans (r=0.683, p<0.006) was established. In humans, standartized values of peak concentration and area under the concentration curve were significantly higher, specific volume of distribution and total clearance were lower, and half-life and mean retention time were significantly higher than in dogs. Characteristics of apparent bioavailability in dogs and healthy people did not statistically differ.

Key Words: *amitriptyline; pharmacokinetics; serum concentration; apparent bioavailability*

The development of new antidepressant drugs did not lead to substantial progress in mental disorder treatment [2,6]. Newly synthesized compounds with psychotropic activity are still compared in clinical studies with etalon (original) drugs, marketed several decades ago [3,6]. In case of antidepressants, such drug is amitriptyline, which remains to be the metric scale of antidepressant power, despite numerous adverse reactions. Amitryptiline is the most common antidepressant administered by psychiatrists in Russia.

The results obtained in studies on animals serve as a starting point for evaluation of medical product safety in clinical use. However, extrapolation of the data obtained in experiments on animals to humans is the most complex problem for evaluation of the safety of a new or generic drug. Most studies are focused on investigation of the toxicity of new or generic products [4,8,12]. However, knowledge of some pharmacokinetics principles is essential for clinicians.

In this study, the comparative analysis of pharmacokinetics and apparent bioavailability of amitryptiline was carried out using the data obtained in experiments on dogs and in clinical studies. To exclude the influence of various factors (different methods, patient's age, concomitant illness) amitryptiline pharmacokinetic was studied in experiments on animals and on young healthy individuals, using the same medicinal products, methods of quantitative determination of drug serum concentration and calculations of pharmacokinetic parameters.

MATERIALS AND METHODS

Amitryptiline pharmacokinetics was investigated in experiment on 12 nonpedigree dogs (6 females and 6 males, mean body weight 14.0±0.6 kg) and in 18 apparently healthy individuals (8 women and 10 men, age 19-40 years, mean body weight 73.7±1.6 kg) after single oral fasting dose of Amitryptiline

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Nycomed (Nycomed) or Amitryptiline (ALSI Farma) of 50 mg (2 tablets). The product was administered to dogs with small amount of curd cheese. It was a study with randomized, open, crossover design to exclude periodic effects and interspecific variability. The preparations were administered with an interval of 10 days.

The study was carried out with accordance to principles of Declaration of World Medical Association (Edinburgh, 2000). Written informed consent was obtained from all participants of clinical study before any procedures.

Blood for analysis was sampled into heparinized vials before dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after the dose in dogs and 1, 2, 3, 4, 6, 8, 10, 24, 30, 32, 36 hours after the dose in humans. Amitryptiline serum concentration in animals and humans was determined using HPLC. In total, 744 samples were analyzed (312 from dogs and 432 from volunteers).

The data of Amitryptiline serum distribution in dogs and healthy volunteers was analyzed using M-IND software [1]; the model independent parameters were calculated: peak concentration (C_{max}), time to peak concentration (T_{max}), area under the concentration—time curve ($AUC_{0-\infty}$), total clearance (Cl_t), mean retention time (MRT), half-life ($T_{1/2}$) and distribution volume (V_Z). The ratio $C_{max}/AUC_{0-\infty}$ (characterizing absorption rate), apparent bioavailability (f), and ratio of Amitryptiline and Amitryptiline Nycomed peak concentrations (f^{II}) were also determined.

The obtained results were analyzed using InStat software. The differences were significant at $p<0.05$. Correlation analysis of mean Amitryptiline serum concentrations in dogs and apparently healthy volunteers was also carried out. The following parameters were calculated for this purpose: parametric characteristics of the relationship (coefficient of correlation, r), test of significance (error probability, p), and coefficients in equation of linear regression $y=ax+b$, where x is serum concentration in dogs, y is serum concentration in volunteers.

RESULTS

Dynamics of averaged amitryptiline plasma concentrations in dogs and apparently healthy humans after single dose of Amitryptiline Nycomed and Amitryptiline (Fig. 1) and standartized pharmacokinetic curves for each product (Fig. 2) are presented.

Plasma levels of Amitryptiline in dogs and volunteers differed dramatically: much higher compound concentrations were detected in animals.

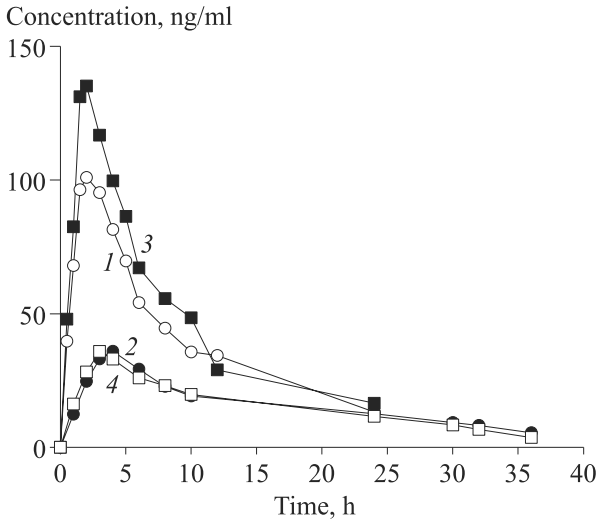

Fig. 1. Averaged pharmacokinetics curves for Amitryptiline (*1*, *2*) and Amitryptiline Nycomed (*3*, *4*) in dogs (*1*, *3*) and healthy volunteers (*2*, *4*).

Amitryptiline peak concentration was reached in dogs after 2 hours and was 135.2±14.2 and 101.0±10.1 ng/ml for Amitriptyline Nycomed and Amitriptyline, respectively. In humans, peak concentration was reached after 3 hours for Amitryptiline Nycomed and after 4 hours for Amitryptiline (35.9±4.6 and 36.0±4.0 ng/ml, respectively). Pharmacokinetic curves for the studied drugs were identical in dogs and humans. The range of individual values of amitryptiline plasma concentrations in dogs (coefficient of variation, CV was 32-77% and in volunteers 42-78%).

Profiles of averaged standartized pharmacokinetic curves for dogs and humans were the same,

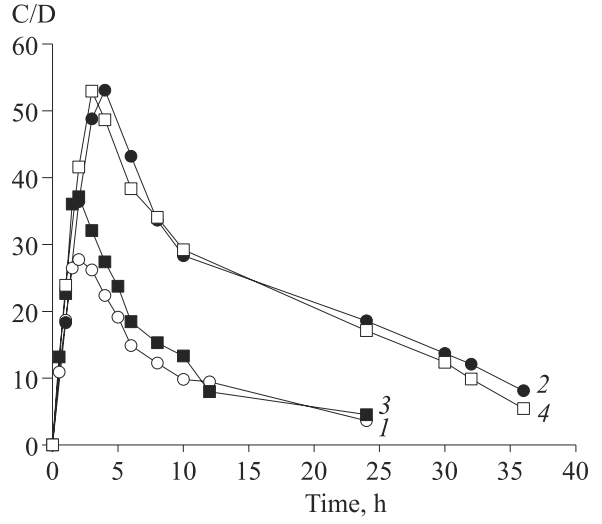

Fig. 2. Standartized pharmacokinetics curves for Amitryptiline (*1*, *2*) and Amitryptiline Nycomed (*3*, *4*) in dogs (*1*, *3*) and healthy volunteers (*2*, *4*).

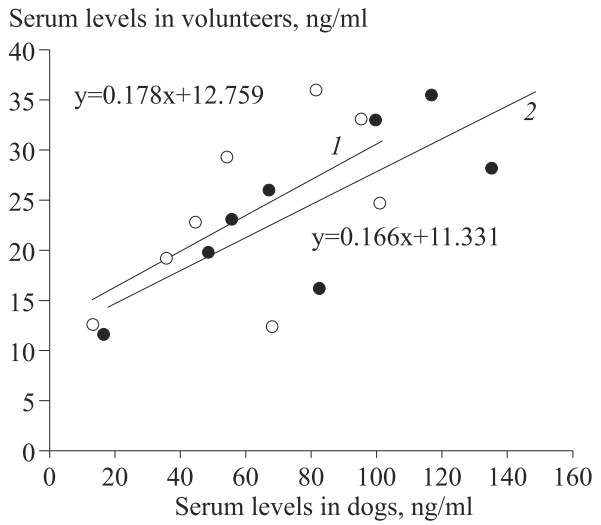

Fig. 3. Diagrams of regressional relationship between amitriptyline plasma concentrations in dogs and humans after single oral dose of Amitryptiline Nycomed (dark marks) and Amitryptiline (open marks). *1*) Amitryptiline trend line, *2*) Amitryptiline Nycomed trend line.

but plasma levels in volunteers were significantly higher: 52.9±6.8 and 53.1±5.9 ng×kg/ml×mg compared to 37.1±3.9 and 27.7±2.8 ng×kg/ml×mg in dogs for Amitryptiline Nycomed and Amitryptiline, respectively.

Correlation analysis showed a direct linear relationship between amitryptiline plasma levels in dogs and in humans both for Amitryptiline Nycomed (r=0.78, p<0.03), and Amitryptiline (r=0.62; p<0.1; Fig. 3). Trend lines for the test drugs were similar, and coefficients in equation of linear regression differed insignificantly, so the prediction of Amitryptiline plasma concentration in volunteers using the equation of linear regression for two compounds (a=0.1625; b=12.664; r=0.6831, p<0.006, n=16) seems to be useful.

Pharmacokinetic parameters of Amitryptiline Nycomed and Amitryptiline in dogs and healthy humans are presented in Table 1.

Mean C_{max} and $AUC_{0-\infty}$ in healthy humans were significantly lower than in dogs (by 3.4 and 1.8 times, respectively), and standartized values of these parameters in volunteers were higher (by 1.6 and 3.0 times, respectively). Time to peak concentration in volunteers was 1.9 times higher, and coefficients of absorption rate were 2.7 times lower. Specific distribution volume and total clearance in humans were by 1.9 and 3.7 time lower, and $T_{1/2}$ and MRT values were 2.6 and 2.9 times higher than in dogs. Significant differences in amitryptiline pharmacokinetics in dogs and humans were found. They seemed to be mainly determined by differences in metabolism and elimination of the compound. Amitryptiline metabolism in humans involves following cytochrome P-450 enzymes: CYP 2D6, CYP 1A2, CYP 3A4, CYP 2C9, CYP 2C19 [6,7,9,10]. Activity of CYP 2D15 enzyme, the main part of the cytochrome system in dogs, is similar to activity of CYP 2D6 enzyme in humans, therefore dogs are a good model for investigation of the metabolism mediated by CYP 2D6 enzyme. Activity of CYP 1A enzyme in dogs significantly

TABLE 1. Amitriptyline Nycomed and Amitryptiline Pharmacokinetic Parameters (M±m)

Parameter	Amitryptiline Nycomed		Amitryptiline	
	dogs	volunteers	dogs	volunteers
C_{max}, ng/ml	149.7±17.0	40.3±4.6	126.1±8.6	40.4±4.0
C_{max}/D	41.1±4.7	59.4±6.8	34.6±2.4	59.6±5.9
$AUC_{0-\infty}$/D, ng×h/ml	1345.1±171.2	660.5±74.1	1157.8±161.4	701.9±94.6
$AUC_{0-\infty}$/D	369.5±47.0	974.2±109.3	318.1±44.3	1035.3±139.5
T_{max}, h	1.9±0.2	3.7±0.4	1.9±0.2	3.7±0.4
$C_{max}/AUC_{0-\infty}$, 1/h	0.168±0.019	0.063±0.004	0.169±0.020	0.065±0.005
V_z, liter/kg	34.4±3.6	20.4±2.7	40.2±3.7	20.3±2.4
Cl_t, liter/h/kg	4.19±0.69	1.28±0.16	5.3±0.83	1.31±0.19
$T_{1/2}$, h	4.5±0.6	11.8±1.0	4.7±0.7	12.3±1.1
MRT, h	6.5±0.8	18.5±1.2	6.9±1.0	20.3±1.5
f, %	—	—	96.5±0.7	105.2±6.1
f^{II}, %	—	—	95.3±0.5	105.1±5.2
Relative absorption rate, %	—	—	99.7±2.8	104.1±6.1

Note. D: dose.

differs from activity of the corresponding enzymes in humans. There are no relevant data concerning other enzymes involved in metabolism in dogs [11].

Estimated values of relative bioavailability f, ratio of peak concentrations f^{II}, and relative absorption rate of Amitryptiline in comparison with Amitryptiline Nycomed indicated that these parameters in dogs and humans did not significantly different. The range of individual values in animals (CV=2-17%) was smaller, than in humans (CV=21-25%), and two-way confidence intervals (for f: 95.3-97.7 and 96.8-105.7% for dogs and volunteers, respectively; for f^{II}: 94.5-96.2 and 99.4-106.8%; for relative absorption rate: 93.8-104.8 and 96.8-105.7%, respectively) were within permissible limits [5]. The data obtained attest to bioequivalence of investigated products.

Thus, results of this study revealed a linear statistically significant correlation between amitryptiline plasma concentration in dogs and humans. Relative bioavailability of Amitryptiline and Amitryptiline Nycomed did not significantly differ in dogs and virtually healthy volunteers, therefore the use of dogs as an experimental model in pharmacokinetic studies, *i.e.* focused on investigation of relative bioavailability and bioequivalence of generic amitriptyline drugs, is reasonable.

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