PHARMACOLOGY AND TOXICOLOGY

Absolute Bioavailability of Himantane in Rabbits

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Pharmacokinetic parameters of himantane and its metabolites in the blood plasma of rabbits were compared after single administration of himantane solution in a dose of 25 mg intravenously and 100 mg orally. It was established that the original substance is characterized by low absolute bioavailability (7.95%). Himantane is subjected to first-pass effect and is extensively metabolized in the liver to metabolites with m/z 266 and 250.

Key Words: *himantane; pharmacokinetics; absolute bioavailability*

Potential antiparkinsonian drug himantane representing N-(2-adamantyl)-hexamethyleneimine hydrochloride was developed in V. V. Zakusov Institute of Pharmacology [1,3].

Here we studied pharmacokinetics of himantane in blood plasma of rabbits after intravenous and oral administration using the developed method of quantitative assay and determined its absolute bioavailability.

MATERIALS AND METHODS

Crossover study was conducted on 5 outbred male rabbits weighing 3.8±0.2 kg. The animals were kept under standard conditions in a vivarium of V. V. Zakusov Institute of Pharmacology under 12 h:12 h light:dark regimen and were deprived of food 12 h before the experiment. Himantane was administered as a single dose of aqueous solutions in a concentration of 25 mg/ml intravenously (into the marginal ear vein) and orally in a dose of 100 mg. After 2 weeks, administration of pharmaceutical forms of himantane was repeated in reverse order. Blood samples were taken at discrete time intervals before and 0.05, 0.1, 0.16, 0.25, 0.5, 1, 2, 3, 4, 6, 24 h after intravenous administration and before and 0.25, 0, 5, 1, 1.5, 2, 3, 4, 6, 24 h after oral administration. The test substances were extracted from the plasma after acetonitrile precipitation of proteins.

Blood plasma samples containing himantane and its metabolites were analyzed by HPLC using an Agilent 1200 Technologies chromatograph with a mass spectrometric detector on a Zorbax C18 column (150×4.6, 5 μ; Agilent). Mobile phase: solution A (25 ml 0.1 M ammonium acetate and 2.5 ml concentrated formic acid diluted in 500 ml water) and solution B (25 ml 0.1 M ammonium acetate and 2.5 ml concentrated formic acid dissolved in 500 ml acetonitrile) in a 1:1 ratio. The flow rate was 0.35 ml/min, nitrogen flow rate 12 liter/min, evaporator temperature 350°C. Detection was carried out in positive ionization mode for total ion current [2].

Quantitative determination of the drug was carried out by calibration with internal standard (tramadol). Correlation coefficient (r=0.998) demonstrated method linearity.

Pharmacokinetic parameters were calculated by model independent method.

The main pharmacokinetic parameters were area under the concentration curve ($AUC_{0-\infty}$), maximum concentration (C_{max}), elimination rate constant

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(K_{el}), and elimination half-life ($T_{1/2el}$). The absolute bioavailability (f_{abs}) was calculated by the formula: $f_{abs}=(AUC_{po0-\infty}\times D_{iv})/(AUC_{iv0-\infty}\times D_{po})\times 100\%$, where $AUC_{po0-\infty}$ and $AUC_{iv0-\infty}$ are AUC after oral and intravenous drug administration, respectively; D_{iv} and D_{po} are doses of the drug administered intravenously and orally, respectively.

RESULTS

After intravenous administration, himantane can be detected in rabbit plasma within 6 h (Fig. 1).

The calculated pharmacokinetic parameters are presented in Table 1.

Analysis of kinetics parameters allows us to conclude that himantane is rapidly excreted from the body, as is seen from mean $K_{el}=0.928\ h^{-1}$. The mean retention time MRT=0.92 h and half-elimination period $T_{1/2el}=0.88$ h also confirm rapid elimination of the drug from the body.

Pharmacokinetics of himantane after oral administration to rabbits differs significantly from that after intravenous injection, first of all by lower concentrations of unchanged drug (Fig. 1). Plasma levels of himantane rapidly increased ($C_{max}/AUC_{0-\infty}=0.49\ h^{-1}$) and peaked in 0.85 h. Then, a two-phase decrease in the concentration of unchanged himantane was observed. The mean half-elimination period was 3.39 h.

Comparison of K_{el} constants after intravenous and oral administration of himantane revealed prolonged elimination of the drug after oral administration ($T_{1/2el}$ *per os* 3.9 times surpassed $T_{1/2el}$ *iv*). It is known that ideally these parameters in different administration routes of should not differ significantly in the same animal species. In our study, the difference between $T_{1/2el}$ values by 3.9 times can be explained by small sample (n=5) insufficient for more objective statistical evaluation. It should be remembered that in case of intravenous administration, the drug is only subjected to elimination, while in case of oral administration, the absorption phase proceeds simultaneously with the process of elimination, which ultimately affects the time of drug presence in animal organism.

TABLE 1. Pharmacokinetic Parameters of Himantane in Blood Plasma of Rabbits after Single Intravenous and Oral Administration (n=5; $\bar{x}\pm SD$)

Parameter	Administration route	
	intravenous (25 mg)	oral (100 mg)
$AUC_{0-\infty}$, ng/ml×h	413.16±130.17	137.87±96.83
C_0, ng/ml	3819.40±3404.69	-
K_{el}, h^{-1}	0.9278±0.5143	0.2549±0.1124
$T_{1/2el}$, h	0.88±0.33	3.39±1.98
MRT, h	0.92±0.51	5.04±3.18
T_{max}, h	-	0.85±0.84
C_{max}, ng/ml	-	68.04±42.11

Note. C_0, zero point concentration, *i.e.* theoretical concentration at the time of injection.

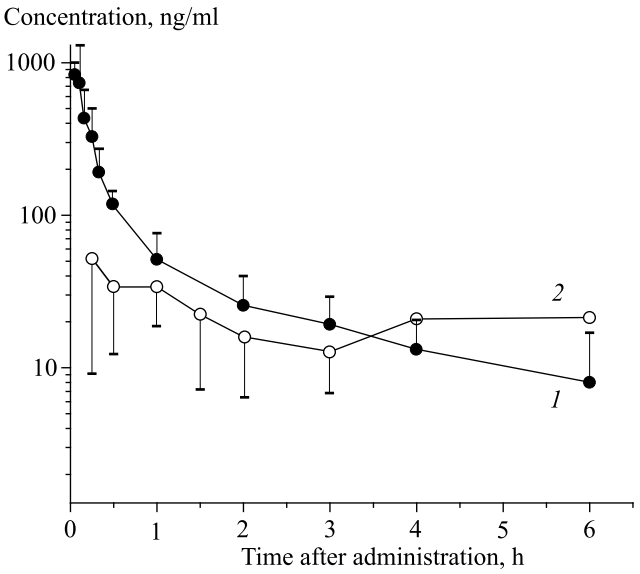

Fig. 1. Pharmacokinetic profiles of himantane in blood plasma of rabbits after a single intravenous (*1*) and oral (*2*) drug administration in doses of 25 and 100 mg, respectively (n=5; $\bar{x}\pm SD$).

Thus, the results of the study of himantane pharmacokinetics suggest that the drug is rapidly eliminated from the body and can be refered to the group of short-living agents.

After intravenous administration, the mean $AUC_{0-\infty}$ for himantane is 413.16 ng/ml×h and $AUC_{0-\infty}$ for its metabolite with m/z 266 is 152.59 ng/ml×h (*i.e.* lower by 2.7 times). However, after oral administration, $AUC_{0-\infty}$ for the metabolite with m/z 266 surpassed the corresponding parameter of himantane by 10 times. C_{max} of himantane and its metabolite with m/z 266 are 68.04 and 788.83 ng/ml, respectively. Thus, himantane after oral administration undergoes intensive biotransformation in the liver. The metabolite with m/z 250 is detected in minor amount after oral drug administration. The exact structure of the metabolites is not established. These are presumably dihydroxy derivative and N-oxide of himantane, respectively. Counter synthesis is necessary to determine their exact chemical structure.

Himantane and its metabolite are rapidly eliminated from the animal organism, as is seen from $T_{1/2el}$ values (Table 1). Only trace concentrations of the studied substances were detected in 24 h.

The mean absolute bioavailability of himantane after oral administration was 7.95±5.02%.

Hence, himantane after oral administration is fully absorbed from the gastrointestinal tract into portal circulation and due to first-pass effect less than 8% of the administered dose enters the systemic circulation.

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