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PRELIMINARY PHARMACOKINETIC STUDIES OF UKRAIN IN RATS

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Summary: *Ukrain (thiophosphoric acid derivative of* Chelidonium majus L. *alkaloids) was administered to rats i.p. at a dose of 28 mg/kg (equivalent to 0.1 LD_{50}). A high performance liquid chromatography (HPLC) method for rapid determination of Ukrain in plasma has been described. It was found that Ukrain rapidly penetrated into the plasma of the rats and the elimination of the drug from the plasma was slower. The results obtained were as follows: absorption rate constant k_a = 0.0432 [min $^{-1}$]; elimination rate constant K = 0.0113 [min $^{-1}$]; drug half-life $t_{1/2}$ = 61.32 min; actual concentration of Ukrain in the plasma C = 33 e $^{-0.0113t}$ - 39 e $^{-0.0432t}$ [μg/ml]; and delay in drug absorption T_0 = 5.23 min.*

Introduction

Pharmacological studies have shown that Ukrain (a semisynthetic malignotoxic drug) administered i.p. to rodents quickly penetrates the blood-brain barrier (1-4).

The purpose of the present study was to estimate some pharmacokinetic parameters of Ukrain in rat plasma after i.p. administration.

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Materials and methods

Animals. The experiments were conducted on male Wistar rats weighing 220-240 g (n=35) purchased from the Medical Academy breeding farm (Warsaw, Poland). The animals were divided into seven groups, each consisting of five rats. They were kept in colony cages under standard laboratory conditions with free access to food and water.

Drugs. Ukrain was received in its purest state from the Ukrainian Anticancer Institute (Vienna, Austria). All other chemicals were of analytical grade and were supplied by Merck (Darmstadt, Germany).

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Treatment and blood collection. Each group of rats was given Ukrain at a dose of 28 mg/kg i.p. (equivalent to 0.1 LD_{50}) in a volume of 0.5 ml/100 g. The animals in each group were killed by decapitation at different times after administration of the drug (5, 15, 30, 60, 120, 180, and 360 min). The blood from each rat was allowed to clot and the plasma was separated.

Experimental procedures. The concentration of Ukrain in rat plasma was assayed by high performance liquid chromatography (HPLC) type 302 (Techma-Robot, Poland) with the steel column (200 x 4 mm) filled with LiChrosorb RP-18. Detector UV-254 was used at a sensitivity of 80:15:5 at pH 2.54. The flow rate was 1.0 cm^3/min.

Mathematical evaluation. Pharmacokinetic analysis was carried out by a graphic method according to Wagner (5). The pharmacokinetic parameters were calculated as the mean of the five determinations. The plots of the relationship between the Ukrain concentration in the plasma and the time of blood collection were prepared on semilogarithmic paper. The kinetic parameters were calculated as follows:

(a) determination of rapidity constant for absorption and elimination processes of Ukrain:

absorption rate constant: $K_a = \frac{\ln C'_1 - \ln C'_2}{t_2 - t_1}$

elimination rate constant : $K = \frac{\ln C_1 - \ln C_2}{t_2 - t_1}$

(b) the actual concentration of the drug in the plasma:

$C = B_e^{-Kt} - A_e^{-Kat}$

(c) time of the half-life:

$t_{1/2} = \frac{0.693}{K}$

(d) time of delay of drug absorption:

$T_o = \frac{\ln A - \ln B}{K_a - K}$

Results and discussion

Table I shows that Ukrain, given at a dose of 28 mg/kg i.p. to rats, rapidly penetrated into the plasma. The highest concentration of the drug in the plasma was observed 1 h after administration.

Fig. 1 illustrates the determination of the rapidity constant for absorption and elimination processes of Ukrain. The 'subtraction technique' was used for calculation of first-order elimination rate constants (K) and first-order absorption rate constants (k_a). The kinetic parameters were:

$k_a = 0.0432\ [min^{-1}]$ and $K = 0.0113\ [min^{-1}]$

Table I *Ukrain concentration in plasma of male rats following its i.p. administration at a dose of 28 mg/kg (i.e., 0.1 LD_{50})*

Time (t), min	Real Ukrain plasma concentration (C), μg/ml	Extrapolated Ukrain concentration, μg/ml	Difference (C'), μg/ml
5	0	31.187	31.187
15	5	27.85	22.85
30	9	23.51	14.51
60	13.5	16.75	3.25
120	7.0	8.503	1.503
180	5.0	4.316	-
360	0.0	-	-

Each value is the mean of five determinations

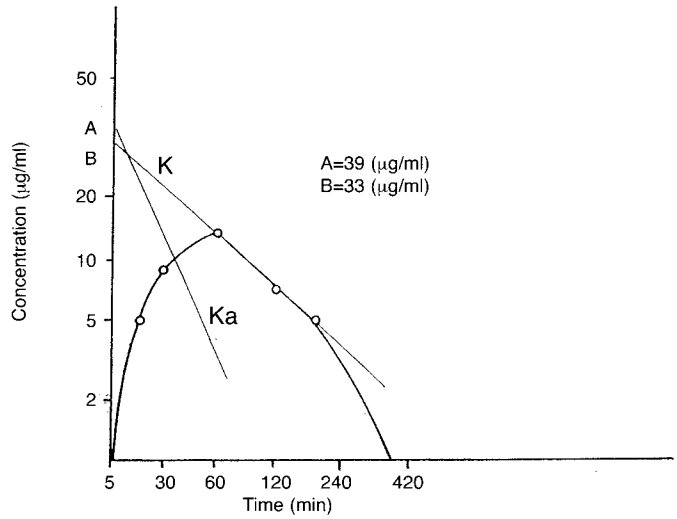

Fig. 1 Determination of rapidity constant for absorption and elimination processes of Ukrain.

The present study indicates that Ukrain given in a dose of 28 mg/kg i.p. to rats rapidly penetrates into the plasma. Absorption of the drug from the injection site begins after a delay of 5.23 min (T_o). The actual Ukrain concentration in the plasma was:

$$C = 33\ e^{-0.0113t} - 39\ e^{-0.0432t}\ [\mu g/ml]$$

The half-life of the drug was estimated as $t_{1/2}$ = 61.32 min.

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