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PRELIMINARY OF PHARMACOKINETIC STUDIES OF UKRAIN IN RATS

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Summary : Ukrain (thiophosphoric acid alkaloid derivatives from Chelidonium majus L.) was intraperitoneally (ip) administered in a dose of 28 mg/kg (equivalent to 0.1 LD_{50}) into the rat. A HPLC method for a rapid determination of Ukrain in plasma was described.

It was found that Ukrain rapidly penetrated into the plasma of rat and the elimination of drug from the plasma was slower. The results obtained were as follows: 1/ absorption rate constant ; k_a = 0.0432 [min^{-1}] , 2/ elimination rate

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constant : K = 0.0113 [min^{-1}] , 3/ time of the drug half-life : $t_{1/2}$ = 61.32 min , 4/ the actual Ukrain concentration in the plasma : $C = 33\ e^{-0.0113t} - 39\ e^{-0.0432t}$ [µg/ml] 5/ time of delaty of the drug absorption : T_0 = 5.23 min .

Introduction

Pharmacological studies showed that Ukrain (a semisynthetic malignotoxic drug) administered ip to rodents quickly penetrated the blood-brain barrier (1-4). The purpose of the present work was to estimation of the some pharmacokinetic parameters of Ukrain in the rat plasma after ip administration.

Materials and methods

Animals. The experiments were conducted on male Wistar rats (N=35), weighing 220-240 g. The animals were divided into seven groups, each consisting of 5 rats. They were kept in cologny cages in standard laboratory conditions with free access to food and tap water.

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

Treatment and blood collection.Each group of rats were given Ukrain in a dose of 28 mg/kg ip (equivalent to 0.1 LD_{50}) in a volume of 0.5 ml/100 g. The animals of the each group were killed by decapitation in different time after the drug administration : 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 were assayed by high-performance liquid chromatography (HPLC) type 302 (Techma-Robot, Poland) and the steel column (200 x 4 mm) filled with LiChrosorb RP-18.

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Detector UV- 254 was used at a sensitivity (80 : 15 : 5) at pH = 2.54. A 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 from the 5 determinations. The plots of relationship between the Ukrain concentration in the plasma and the time of blood collection were prepared on the semilogarithmic paper. The kinetic parameters were calculated as follows :

1) determination of rapidity constant for absorption and elimination processes of Ukrain

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

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

4) the actual drug concentration in the plasma : $C = B_e^{-Kt} - A_e^{-Kat}$

5) time of the half-life : $t_{1/2} = \frac{0.693}{K}$

6) time of delaty of the drug absorption : $T_o = \frac{\ln A - \ln B}{K_a - K}$

Results and discussion

Table 1 shows that Ukrain given in a dose of 28 mg/kg ip to rats rapidly penetrated into the plasma .The highest concentration of the drug in the plasma was observed after the 60 min of administration.

Figure 1 ilustrates the determination of rapidity constant for absorption and elimination processes of Ukrain. The so-called „ substraction technique „ was applied for calculation of the first-order elimination rate constants (K) and the first-order absorption rate constants (k_a). The kinetic parameters were :

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

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Table 1.

Plasma concentration-time profile of Ukrain following its administration (ip) in a dose of 28 mg/kg (i.e. 0.1 LD_{50}) to rats.

Time (t) in min	The observed concentration (C) in µg/ml	The extrapolated concentration (µg/ml)	Difference (C') in 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 from the 5 determinations

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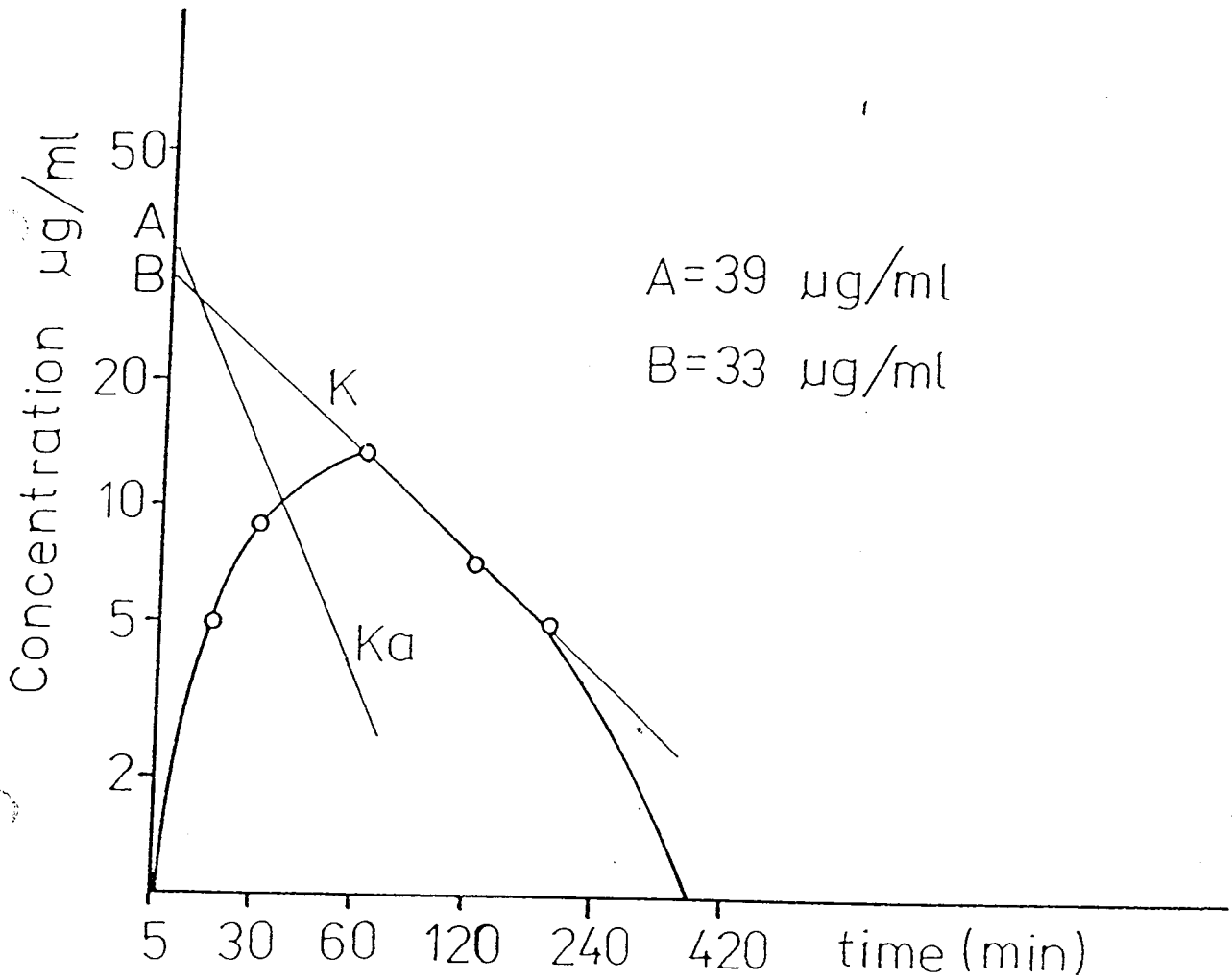
Fig.1 Determination of rapidity constant for absorption and elimination processes of Ukrain.



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The present study indicates that Ukrain given in a dose of 28 mg/kg ip to rats rapidly penetrated into the plasma. The absorption of the drug from the injection site begins with a delay of 5.23 min.(T_o) . It was found the actual Ukrain concentration in the plasma was : $C = 33\ e^{-0.0113t} - 39\ e^{-0.0432t}$ [µg/ml] . The time of the drug half-life was estimated : $t_{1/2} = 61.32$ min . The studies will be continued.

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