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## PHARMACOLOGY

## PHARMACOLOGICAL EFFECTS OF UKRAIN IN RATS AND RABBITS

MAŁGORZATA REMISZEWSKA, MARIA WUTKIEWICZ, ZENON JASTRZĘBSKI,  
HALINA CZYŻEWSKA-SZAFRAN and ANDRZEJ DANYSZ

Department of Pharmacology, Drug Institute,  
30/34 Chelmska Str., 00-725 Warsaw, Poland.

**Abstract:** The effect of Ukrain administered in various doses on mean blood pressure (MAP) and breathing rate in rats and rabbits was evaluated. It was found that MAP was reduced and breathing rate increased significantly in both animal species. Maximum tolerated dose (MTD) of Ukrain was 10-fold higher in rats than in rabbits, and it amounted to 3.5 mg·kg<sup>-1</sup> and 0.35 mg·kg<sup>-1</sup>, respectively. Possible clinical implications of these findings were discussed.

**Key words:** Ukrain, maximum tolerated dose.

Ukrain is a semisynthetic drug derived from *Chelidonium majus* L. alkaloids conjugated to thiophosphoric acid. This drug is selectively taken up by human tumor cells but not by normal cells. It was found that the components of Ukrain have apparent immunomodulatory effects. These properties make this drug a strong and valid candidate for cancer therapy (1,2).

Toxicology studies using rats gave an LD<sub>50</sub> value of 250 mg·kg<sup>-1</sup> i.v. (3). In practice however, the results of the LD<sub>50</sub> test are of rather limited significance for medical diagnosis and treatment (4). For full extrapolation of hazard to man, the informations obtained in the classical LD<sub>50</sub> test required usually considerable supplementation with findings from other toxicity tests. Important data could be obtained in preclinical experiments by determination of the maximum tolerated dose (MTD) in various animal species (5,6). MTD is the highest dose affecting neither the circulatory nor the respiratory system. The present study examined MTD in two animal species - rats and rabbits.

## EXPERIMENTAL

Male adult rats of the Wistar-Kyoto strain from our own breeding colony weighing 320-340 g and male albino rabbits of the New Zealand strain weighing 2-2.5 kg were used. The rats were kept in a thermoregulated room (22 ± 1°C) on a 12/12 h light/dark cycle. The rabbits were housed in individual cages in standard conditions. Animals had access to food and water ad libitum.

All animals were anaesthetised with in-

traperitoneal injections of urethane in saline (1.7 g·kg<sup>-1</sup>). The trachea, common carotid artery and external jugular vein were cannulated. Arterial blood pressure was measured using an elektrosphygmomanometer ASE-1. Breathing rate was recorded using Marey's tambour. Body temperature was maintained between 37°-39°C with a heating pad placed beneath the animal.

Ukrain preparation, a 3% aqueous solution obtained from Ukrainian Anti-Cancer Institute in Vienna was diluted with 0.9% saline and administered intravenously in 10 minutes intervals. The rats were injected with following doses: 0.035, 0.35, 1.75, 3.5, 7.0 and 14.0 mg·kg<sup>-1</sup> in a volume of 1 cm<sup>3</sup>·kg<sup>-1</sup>. The rabbits received Ukrain at the doses of 0.087, 0.175, 0.35, 0.70, 1.40 and 2.80 mg·kg<sup>-1</sup>. Data are expressed as means ± S.E.M. and analyzed for significance using Student's t test. Each animal served as its own control.

## RESULTS AND DISCUSSION

It was found in the pilot studies on rats that Ukrain administered at the doses of 0.035 and 0.35 mg·kg<sup>-1</sup> affected neither arterial blood pressure nor breathing rate, while the third investigated dose of 3.50 mg·kg<sup>-1</sup> did not influence breathing, but it produced a slight decrease in blood pressure (-Δ 7.3 ± 1.9 mm Hg). In further studies the dose of 3.5 mg·kg<sup>-1</sup> as well as three additional doses of the drug i.e. 1.75, 7.00, 14.00 mg·kg<sup>-1</sup> were used. It was demonstrated that the changes in blood pressure and breathing rate observed after Ukrain administration were dose-dependent. The lack of the depressor response of Uk-

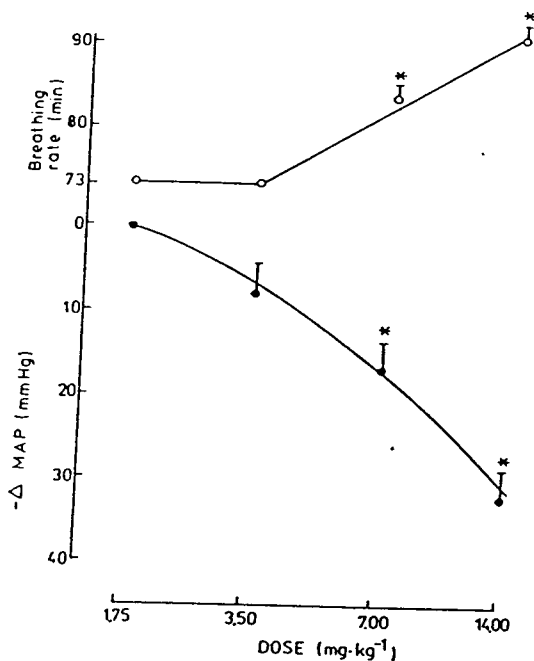


Figure 1. Effects of Ukrain on mean arterial pressure (MAP) and breathing rate in rats. The data are means  $\pm$  S.E.M. for 9 individuals. \*  $p < 0.05$

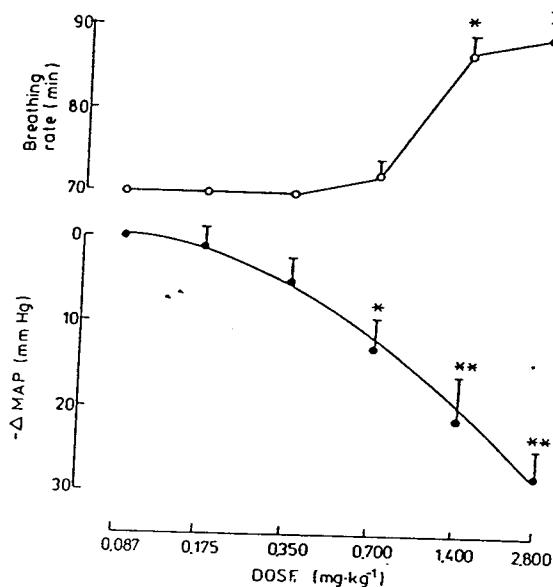


Figure 2. Effects of Ukrain on mean arterial pressure (MAP) and breathing rate in rabbits. The data are means  $\pm$  S.E.M. for 7 individuals. \*  $p < 0.05$  \*\*  $p < 0.01$

rain at the dose of  $3.5 \text{ mg}\cdot\text{kg}^{-1}$  was confirmed and this dose was accepted as the maximum tolerated dose in rats (Figure 1).

The profiles of arterial pressure and breathing rate for Ukrain-treated rabbits corresponded to those of

rats. Ukrain at the doses of  $0.875$ ,  $0.175$  and  $0.35 \text{ mg}\cdot\text{kg}^{-1}$  did not evoke any substantial changes in both parameters studied. The doses of  $0.70$ ,  $1.40$  and  $2.80 \text{ mg}\cdot\text{kg}^{-1}$  induced significant reduction of blood pressure. Breathing rate was significantly increased after administration of Ukrain at the doses of  $1.4$  and  $2.8 \text{ mg}\cdot\text{kg}^{-1}$ , whereas the doses of  $0.35$  and  $0.70 \text{ mg}\cdot\text{kg}^{-1}$  had no effect (Figure 2). We can conclude from the present study, that in rabbits the maximum tolerated dose not affecting the function of both circulatory and respiratory systems is  $3.5 \text{ mg}\cdot\text{kg}^{-1}$ .

Our experiments showed that rabbits are about 10 times more sensitive to toxic effect of Ukrain than rats. It is noteworthy, that the observed decrease in blood pressure was transient and lasted much longer in rabbits than in rats, that is 3.0 and 0.5 min, respectively.

The information obtained in the present study may indicate some consequences for proposed treatment of man with high doses of Ukrain. The possible reduction of arterial pressure during prolonged therapy with this drug should be taken into consideration. It has been shown that blood pressure reduction below the lower limit of cerebral blood flow autoregulation may cause unfavorable cerebral complications. Moreover, in hypertension the lower limit of autoregulation was found to shift to a significantly higher level. For that reason, severe hypertensive patients in whom the autoregulation is impaired may develop clinical signs of cerebral ischemia even after small decline in their blood pressure (7,8). The present study suggest that Ukrain should be introduced into therapy with a special caution in hypertensive humans. Furthermore, it is believed regarding the results of extensive toxicological and pharmacological studies that in most instances the factor of 10 can be used in extrapolating the data from rat to man (9,10). Thus, assuming that man is in general about 10 times more sensitive to poisoning than the rats the predicated maximum tolerated dose for man would amount to  $0.35 \text{ mg}\cdot\text{kg}^{-1}$ . It corresponds well with the maximum tolerated dose determined in rabbits. This results are consistent with the findings of other authors (10,11) demonstrating greater tolerance of rats to some undesired effects of drug than rabbits. The investigation of MTD in two animal species reported here provides guidance for the design of long-term studies in man and animal needed to obtain drug approvals.

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