DRUGS EXPTL. CLIN. RES. XVIII (SUPPL.) 89-91 (1992)

EFFECT OF SINGLE AND PROLONGED ADMINISTRATION OF UKRAIN ON PROLACTIN CONCENTRATION IN RATS

JAGIEŁŁO-WÓJTOWICZ E.,[1*] KLEINROK Z.,[1] NOWICKY J.W.,[2] MATUSZEK B.,[1] BARAN E.,[1] SURMACZYNSKA B.[1]

1) Department of Pharmacology, Medical Academy, Jaczewskiego 8, 20-090 Lublin, Poland.
2) Ukrainian Anti-Cancer Institute, Margaretenstrasse 7, 1040 Vienna, Austria.

Summary: *The effect of single and prolonged administration of Ukrain on the serum prolactin concentrations in rats of both sexes was investigated. One hour after intraperitoneal (i.p.) administration of Ukrain in rats, in doses of 7, 14 and 28 mg/kg, the drug did not affect their serum prolactin concentration. Only in a dose of 28 mg/kg did this drug decrease serum prolactin in a group of female rats. Repeated i.p. treatment (once daily for three months) with 7, 14 and 28 mg/kg of Ukrain significantly increased the serum prolactin concentration in rats of both sexes. The most marked effect was observed in the group of female rats.*

Introduction

Previous studies (1) showed that the central action of Ukrain after i.p. administration in rodents involves the stimulation of the dopaminergic system and the inhibition of the serotoninergic system. Recently the authors found that application of Ukrain to mice and rats for 3 months significantly depressed the whole brain dopamine (DA) concentrations but did not affect the serotonin (5-HT) concentrations (2). The central dopaminergic and serotoninergic neurons are known to participate in the physiological regulation of prolactin secretion (3-7). It seemed interesting to investigate if observed changes in dopaminergic and serotoninergic activity after treatment with Ukrain result in changes of prolactin secretion.

The aim of this study was to determine the effects of a single and 3-month treatment with Ukrain on serum levels of prolactin in rats of both sexes.

*Author to whom correspondence should be addressed.

Materials and methods

Chemicals. High grade pure Ukrain (thiophosphoric acid alkaloid derivatives from *Chelidonium majus L.*) was received from Ukrainian Anti-Cancer Institute, Vienna, Austria. ^{125}J-Rat-Prolactin – RIA was supplied by DRG Instruments GmbH, (Marburg).

Animals. Two groups of Wistar rats (n = 160) of both sexes weighing initially 180–240 g were used in this study. They were kept in plastic cages, ten rats in one cage, in an air-conditioned room, with normal day – night cycle and received standard laboratory diet and water *ad libitum*.

Drug administration and blood collection. Ukrain was given i.p. in doses of 7, 14 and 28 mg/kg equivalent to 0.025, 0.05 and 0.1 of LD_{50}. The drug was administered in aqueous solutions in volumes of 0.5 ml/100 g. The control groups received i.p. identical volumes of distilled water.

0378-6501/92/0000089 + 3 $02.00/0

© 1992 Bioscience Ediprint Inc.

levels in the rats of both sexes. Changes are stronger in the female rats that in the male rats and are proportional to the dose.

An increase in the serum prolactin concentrations is probably connected with the depressive action of Ukrain on dopaminergic structures in rats. Previous reports (2) indicated that administration of Ukrain for 3 months to rats significantly decreased the brain DA concentrations but did not affect the 5-HT, but this speculation remains to be tested because Ukrain can interact with other monoaminergic systems (1, 2, 8).

It is suggested that the results of this study can be interesting and helpful in the clinical use of Ukrain which has been found to have immunomodulatory activity (9–11). Recently, prolactin has been shown to be a modulator of the immune response by stimulation expression of receptors on T lymphocytes (5).

References

(1) Kleinrok Z., Jagiełło-Wójtowicz E., Matuszek B., Chodkowska A. *Basic pharmacological properties of thiophosphoric acid alkaloid derivatives from* Chelidonium majus L. Pol. J. Pharmacol. Pharm., **44**, 227, 1992.

(2) Kleinrok Z., Jagiełło-Wójtowicz E., Nowicky J.W., Chodkowska A., Feldo M., Matuszek B. *Some pharmacological properties of prolonged administration of Ukrain in rodents.* Drugs Exptl. Clin. Res. **XVIII**, (Suppl.), 93, 1992.

(3) Boyd III A.E., Jordan R.M., Kohler P.O. *Disorders of the hypothalamus and anterior pituitary.* In: Kohler P.O., ed. "Clinical Endocrinology", John Wiley and Sons, London, 1986, p. 11.

(4) Jagiełło-Wójtowicz E., Załuska W., Szponar J., Surmaczyńska B., Wójcicki M., Kleinrok Z. *Effects of serotonin-active drugs on prolactin secretion in male rats.* Pol. J. Pharmacol. Pharm., **40**, 73, 1988.

(5) Klonoff D.C., Karam J.H. *Hypothalamic and pituitary hormones.* In: Katzung B.G., ed. "Basic and Clinical Pharmacology", Appleton and Lange, California, 1989, p. 451.

(6) Tuomisto J., Männistö P. *Neurotransmitter regulation of anterior pituitary hormones.* Pharmacol. Rev., **37**, 249, 1985.

(7) Van de Kar L.D., Urban J.H., Richardson K.D., Bethea C.L. *Pharmacological studies on the serotonergic and nonserotonin-mediated stimulation of prolactin and corticosterone secretion by fenfluramine.* Neuroendocrinology **41**, 283, 1985.

(8) Jagiełło-Wójtowicz E., Feldo M., Kleinrok Z. *Studies on the participation of the GABA-ergic system in the central effects of Ukrain* alkaloids from Chelidonium majus L. *in mice.* Pol. J. Pharmacol. Pharm. **44** (Suppl.), 143, 1992.

(9) Liepins A. *Enhancement of cell mediated lysis of tumor cells* by Chelidonium majus L. *alkaloids* (Ukrain). J. Cancer Res. Clin. Oncol. **116** (Suppl.), 436, 1990.

(10) Malter M., Süss R. *Preliminary report on Ukrain: studies of toxicity and immunomodulation (the effect on cytotoxicity).* German Cancer Research Centre, Heidelberg, pp. 1–6, 1988.

(11) Nowicky J.W., Staniszewski A., Zbroja-Sontag W., Ślęzak B., Nowicky W., Hiesmayr W. *Evaluation of thiophosphoric acid alkaloid derivatives from* Chelidonium majus L. *("Ukrain") as an immuno stimulant in patients with various carcinomas.* Drugs Exptl. Clin. Res. **XVII**, 139, 1991.

The rats of the first group (n = 80) were killed by decapitation one h after administration of Ukrain or placebo and blood was taken.

The rats of the second group (n = 80) which received Ukrain in doses of 7, 14 and 28 mg/kg or placebo, once daily for three months, were sacrificed 24 h after the last dose of the drug and blood was taken. The blood from each rat was allowed to clot and the serum was stored at −20°C until radioimmunoassays (RIA) were performed.

Prolactin radio-immunoassay. Serum prolactin was measured by RIA using the kit supplied by DRG Instruments GmbH (USA). The assays were performed according to the instructions supplied with the kit, and rat serum prolactin was expressed as ng/ml.

Statistical analysis. The statistical analysis was done according to Student's t-test, calculating the standard error of the mean (± s.e.).

Results

Table I shows that one h after administration of Ukrain (7, 14 or 28 mg/kg) there was no effect on the serum prolactin concentrations in rats. The exception was a decrease of serum prolactin in female rats receiving 28 mg/kg i.p. of Ukrain.

The prolonged experiments showed that the administration of Ukrain (7, 14 or 28 mg/kg i.p.) once daily for three months caused a significant increase of prolactin concentrations in the rat serum of both sexes (Table II). Serum prolactin concentrations in the three month experiment were higher in the groups of female rats in relation to controls and to groups of male rats.

Discussion

The results indicate that Ukrain modifies the prolactin secretion in rats of both sexes. It was found that a three month treatment with Ukrain elicited a greater response of prolactin than it did one h after its administration. It was demonstrated that one h after i.p. application of Ukrain in doses of 7, 14 and 28 mg/kg, the drug did not affect the serum concentration of prolactin. The exception was a decrease of serum prolactin in female rats treated with Ukrain in a dose of 28 mg/kg.

These results show that a 3-month treatment with Ukrain significantly increases the serum prolactin

Table I *Effect of Ukrain on serum prolactin concentrations in rats**

Treatment mg/kg i.p.	Sex	Prolactin ng/ml
Control group	Male	22.0 ± 0.12
	Female	24.1 ± 0.21
Ukrain – 7.0	Male	21.1 ± 0.23
	Female	23.8 ± 0.18
Ukrain – 14.0	Male	23.0 ± 0.11
	Female	24.2 ± 0.20
Ukrain – 28.0	Male	20.7 ± 0.31
	Female	22.1 ± 0.20**

* The rats were decapitated one h after injection of Ukrain. Values are means ± s.e.
**Differences statistically significant from control values.

Table II *Effect of a three month treatment with Ukrain on the serum prolactin concentrations in rats**

Treatment mg/kg i.p.	Sex	Prolactin ng/ml
Control group	Male	21.7 ± 0.13
	Female	24.2 ± 0.21
Ukrain – 7.0	Male	28.4 ± 0.17**
	Female	32.0 ± 0.31**
Ukrain – 14.0	Male	37.1 ± 0.22**
	Female	54.1 ± 0.26**
Ukrain – 28.0	Male	41.2 ± 0.19**
	Female	59.0 ± 0.31**

* Ukrain was given once daily for three months. The rats were decapitated 24 h after the last dose of the drug. Values are means ± s.e.
**Differences statistically significant from control values: $p < 0.001$.