Effects of the Standard and Endoliquor Injection of Estradurin on the Rat Prostate

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The effects of intramuscular and endoliquor routes of administration of water-soluble antiandrogenic drug estradurin on proliferative activity of the prostate were studied. Estradurin injection via both routes produced a suppressive effect on the prostate. The effect of the minimum estradurin dose injected into the liquor was most manifest and not paralleled by side effects.

Key Words: *estradurin; endoliquor administration; prostate; rats*

Prostatic cancer (PC) is the most prevalent malignant tumor in men [1]. It is a hormone-dependent tumor and hormone therapy is the first-line therapy for patients in whom radical intervention or radiotherapy is impossible. However, this obviously effective treatment is not free from side effects. The search for the most effective method for injection of drugs of this group causing the minimum effects is an important problem and the object of our research. Endoliquor injection of estrogens (diethylstilbestrol and sinestrol in oil solutions) exhibited the most pronounced inhibitory effect on prostate weight [2]. The efficiency of injection of sinestrol oil solution by lumbar puncture in patients with hormone-resistant PC has been demonstrated [3]. However, the use of this method is limited because of side effects of oil solution injection. Creation of estradurin, a water-soluble antiandrogen, prompted us to test its antiproliferative effects on PC tissue.

We studied the state of the prostate gland after intramuscular injection of estradurin in standard therapeutic dose (standard method) and after injection into the liquor in a dose reduced by 3 orders of magnitude.

MATERIALS AND METHODS

The study was carried out on outbred adult male rats (200-250 g). Group 1 (n=5; control) were intact rats. Group 2 (n=5) rats received an intramuscular injection of estradurin (1.5 mg per animal). Group 3 (n=10) animals received endoliquor estradurin in a dose of 0.002 mg per animal. The animals were decapitated 10 days after estradurin injection. The prostate was isolated and fixed in formalin and embedded in paraffin; microtome sections (4-5 μ) were stained with hematoxylin and eosin and examined under a microscope in transmitting light. The cell size was measured using a micrometer.

The data were statistically processed by Student's parametrical test, the results were considered significant at $p<0.05$.

RESULTS

The health status of animals of all experimental groups was satisfactory: the animals were active, normally gained weight, and exhibited no untoward reactions to drugs.

Intramuscular injection of estradurin caused a 3-fold reduction of prostatic weight in comparison with the control. Estradurin injection into the liquor caused a more significant organ weight loss: the weight of the prostate in these animals was 2.4 times lower than after intramuscular injection and 7-fold lower than in controls. Morphometry of prostatic cells showed a significant decrease of prostatic epithelium height (by more than 1.5 times from the control) after estradurin administration by both routes. On the other hand, none of the treatments modified the areas of the prostatic

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TABLE 1. Organ Wight, Epithelium Height, and Prostatic Cell Nuclei Size after Injection of Estradurin by Different Methods

Parameter	Control	Intramuscular injection	Endoliquor injection
Organ weight, mg	267.80±10.68	89.78±8.74*	38.00±8.21*+
Epithelium height, μ	88.03±3.62	57.82±6.54*	50.82±3.29*
Nucleus area, μ^2	13.97±0.43	13.54±0.58	12.83±0.58

Note. $p<0.05$ in comparison with *control, +intramuscular injection.

cell nuclei. Hence, treatment by both methods produced a suppressive effects on the prostate: the organ weight decreased, more so after endoliquor administration, and the epithelium height decreased in fact similarly in rats of both experimental groups.

Morphological studies showed destruction of the prostatic lobes, mainly at the organ periphery, in some animals 10 days after intramuscular estradurin. The epithelial cells in this zone were cubical. In the center of the organ the epithelial cell shape was almost cylindrical, indicating the onset of regenerative processes. Sites with chaotically scattered cells were often found. Numerous vacuoles were characteristic of the cytoplasm; they fused into one vacuole occupying virtually the entire cell space. There was virtually no connective tissue between the lobes. The epithelium extremely rarely protruded into the lobular lumen, this indicating the absence of secretion accumulation. The efferent ducts were slightly filled with secretion. Blood vessel walls were loosened but moderately filled with blood cells.

Overall destruction of the lobes was characteristic of the prostate in animals which received endoliquor estradurin. Intact lobes were rare, and the cells were chaotically scattered in them. Small sites with normal location of the epithelium, presented by cylindrical cells virtually devoid of secretory lumps, were sometimes found. Numerous vacuoles were well discernible in the cytoplasms of the efferent duct cells. Intact lobes formed no protrusions, and secretion was virtually always seen in them. The amount of connective tissue between the lobes was negligible in the entire organ. Vascular walls were also loosened, similarly as after intramuscular injection of estradurin, and slightly filled with blood cells.

Hence, estradurin administered by two routes inhibited the prostatic gland proliferation. The effect of endoliquor drug was more pronounced. This was shown by a greater organ weight loss and by the recovery of the prostatic tissue morphology, which started just 10 days after intramuscular injection of the drug. It seems that the efficiency of endoliquor estradurin was a result of the direct effect of the estrogen on the cerebral centers involved in regulation of the reproductive system. In contrast to endoliquor administration of oily solution of estrogens, no side effects were seen: the rats were active and gained weight normally.

Our experiments demonstrated the high efficiency of the endoliquor route of estradurin administration, reasulting in inhibition of the prostatic proliferative activity by the minimum doses without side effects. The results of our studies were patented: invention patent No. 2422915 of June 27, 2011 “A Method for Proliferative Process Inhibition in Prostatic Tissue in an Experimental Setting”.

REFERENCES

1. A. D. Kaprin and R. A. Gafanov, *Rus. Med. Zh.*, **15**, No. 14, 1105-1108 (2007).
2. V. N. Kuz’menko and Yu. N. Bordyushkov, *Probl. Endokrinol.*, No. 3, 45-48 (1984).
3. M. F. Polyanichko, L. I. Avtsina, and Yu. N. Bordyushkov, *Proceedings of Congress of Oncologists of the CIS Countries* [in Russian], Moscow, November 3-6, 1996, Pt. 2, P. 436-437.