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## Effect of Immunoactive Drugs on Postresuscitation Processes in the Brain and Steroid Hormones

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**Objective:** to evaluate the effects of the immunostimulants panavir and derinate on a postresuscitation process in animals of different sexes. **Material and methods.** The investigation was made on 200–250-g albino rats of both sexes in winter. Circulation was stopped by intrathoracic ligation of the cardiac vascular bundle in ether-anesthetized rats for 10 min. Functional recovery of the central nervous system and changes in sex steroid hormones were assessed in the postresuscitation period. The investigation used two immunoactive drugs: panavir 0.02 mg/kg and derinate 150 µg/kg. Either agent was intramuscularly injected twice: at 30 minutes after resuscitation and on the following day. **Results.** The injected drugs were ascertained to have a positive effect on functional recovery of the brain. Their use was shown to modify the sex steroid hormone profiles in both males and females in the early postresuscitation period. **Conclusion.** The findings suggest that the immunoactive agents are able to affect the nervous and endocrine systems in critical conditions. **Key words:** ischemia, central nervous system, immunoactive drugs, steroid hormones, sex differences.

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## Introduction

Clarifying the role of CNS in pathogenesis of critical illness remains an actual problems in anesthesiology-reanimatology [1–4]. Temporary cessation of blood circulation in the body and subsequent successful resuscitation are known triggers for the development of systemic reaction due to microcirculatory dysfunction and damage to endothelial cells. Pathological mechanisms of this reaction are related to immunologic and endothelial dysfunctions [5–7]. There are also sex differences of this reaction in humans and animals in terminal state [8–13]. Since steroid hormones affect the CNS recovery in postresuscitation period [14–16] and the immune responses are critical for the critical illness [9, 10], the objective of this study was assessing the influence of panavir and derinat (agents with immunostimulatory properties) on the course of postresuscitation period in animals of different sexes.

## Materials and methods

The work was carried out on 235 white rats of both sexes in winter season. The temporarily blood flow cessation was modeled by clamping the vascular bundle of the heart [17]. Time of circulatory arrest was 10 minutes. Resuscitation of rats was performed using mechanical ventilation apparatus UIDG-1 (Russia) in a hyperventilation mode and external cardiac massage along with intratracheal administration of epinephrine at the dose of 0.1 mg/kg.

Two immunomodulatory drugs, panavir and derinat, were employed in the study. Panavir represents a purified extract of plant shoots of *Solanum tuberosum*. Its main active substances include hexose glycosides composed of glucose, rhamnose, arabinose, mannose, xylose, galactose, uronic acids. Panavir is used in clinics as an antiviral drug. Panavir increases nonspecific resistance to various infections and facilitates the induction of interferon. It also has anti-parkinsonism activity [18].

Derinat is a sodium salt of the native low molecular weight DNA. The drug activates the processes of cellular and humoral immunity. It possesses high pro-reparative and pro-regenerative activities, has cardio- and neuroprotective properties, promotes of apoptosis of damaged cells, and enhances the recovery of immune system cells. The effects of derinat are explained by its antioxidant properties and membrane stabilizing capability. The most likely mechanism of derinat action is nonspecific biostimulation of organs and tissues [19].

Panavir or derinat were administered intramuscularly twice a day, on 30th minute and 24 hours after resuscitation. The dose of derinat was 150 micrograms per kg, the dose of panavir was 0.02 mg per kg.

Resuscitated animals were stratified into several groups by gender: control group (separately for males and females) who were administered saline solution and the group (male or female) who were administered panavir and derinat.

Sex steroid hormones pregnenolone (ng/ml), progesterone (ng/ml), 17OH-progesterone (ng/ml), androstenedione (ng/ml), testosterone (ng/ml), dihydrotestosterone (ng/ml), estradiol (pg/ml) and estrone (pg/ml) in blood were determined by enzyme-linked immunosorbent assay using hormone-specific kits (BSL, USA) and ELISA reader Stat Fax 2100 (USA). Functional state of resuscitated animals was assessed by size and intensity of decrease in neurological deficit (ND) by scores, as well as the total value of the ND, defined as the sum of the daily assessment scores until complete neurological recovery [17, 20]. Mean values, standard errors of the mean and standard deviations of the data sets were calculated during analysis of the results. To reveal the differences between groups parametric (Student's t-test) and nonparametric (Mann-Whitney and Fisher tests) criteria of the differences between groups were used after testing the groups for normality by Kolmogorov-Smirnov test.

## Results and discussion

Daily value of neurological deficit was determined in order to investigate the influence of panavir and derinat on the nervous system and general condition of the animals after systemic circulatory arrest. It was found that males who were administered derinat had the lower values of neurological deficit (ND) during first five days after resuscitation as well as the total value of ND, and the rate of its decrease compared with the control group (Table 1). In male rats administered with panavir the lower values of ND in three to five days after resuscitation and the total value of the LP were also observed, whereas the intensity of decrease in ND was higher compared to the control group. According to the above-noted parameters of restoration and dynamics of neurological status, there were no differences between males receiving panavir or derinat (Table 1).

Among all groups of females no differences in size and total value of ND were observed. It should be noted that in

**Table 1**  
The value of neurological deficit (ND), summary ND and the rate of decrease in ND (points/day) in rats of both sexes in the control and treated group [Me, (25%, 75%)]

| Groups                                     | The value of neurological deficit (points) on the stages of the research, days |                 |                 |                 |                 | Summary ND (scores) | Rate of decrease in ND |
|--------------------------------------------|--------------------------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|---------------------|------------------------|
|                                            | 1 <sup>st</sup>                                                                | 2 <sup>nd</sup> | 3 <sup>rd</sup> | 4 <sup>th</sup> | 5 <sup>th</sup> |                     |                        |
| Males of the control group, <i>n</i> =20   | 12<br>(10; 16)                                                                 | 8<br>(7; 10)    | 6<br>(4; 7)     | 3<br>(2; 4)     | 1<br>(0; 2)     | 30<br>(25; 38)      | 0,33<br>(0,30; 0,39)   |
| Males of panavir group, <i>n</i> =13       | 12<br>(10; 14)                                                                 | 8<br>(6; 10)    | 4<br>(2; 6)*    | 2<br>(0; 2)*    | 0<br>(0; 0)*    | 26<br>(16; 32)*     | 0,40<br>(0,36; 0,50)*  |
| Males of derinat group, <i>n</i> =16       | 10<br>(8; 11)*                                                                 | 4<br>(4; 6)*    | 2<br>(2; 4)*    | 0<br>(0; 2)*    | 0<br>(0; 0)*    | 16<br>(14; 25)*     | 0,44<br>(0,40; 0,48)*  |
| Females of the control group, <i>n</i> =21 | 10<br>(8; 12)                                                                  | 6<br>(6; 8)#    | 4<br>(2; 4)     | 2<br>(0; 2)#    | 0<br>(0; 0)#    | 20<br>(18; 28)#     | 0,40<br>(0,36; 0,53)#  |
| Females of the panavir group, <i>n</i> =16 | 10<br>(8; 12)                                                                  | 6<br>(4; 6)     | 2<br>(2; 4)     | 0<br>(0; 2)     | 0<br>(0; 0)     | 18<br>(14; 25)      | 0,46±0,01*             |
| Females of derinate group, <i>n</i> =13    | 8<br>(8; 10)                                                                   | 4<br>(4; 6)     | 2<br>(2; 4)     | 0<br>(0; 2)     | 0<br>(0; 0)     | 15<br>(14; 21)      | 0,47±0,02*             |

**Note.** \* —  $p \leq 0.05$  compared with the control group of rats of the same sex; # —  $p \leq 0.05$  compared with the control group of male rats.

Table 2

| The blood concentration of hormones in intact, control and treated rats of both sexes ( $M \pm m$ ) |        |                  |                                                                                              |                    |
|-----------------------------------------------------------------------------------------------------|--------|------------------|----------------------------------------------------------------------------------------------|--------------------|
| Hormone threshold                                                                                   | Sex    | Intact           | The blood concentration of hormones in the 1 <sup>st</sup> day after resuscitation in groups |                    |
|                                                                                                     |        |                  | Control                                                                                      | Panavir+derinat    |
| Pregnenolone 0,054 ng/ml                                                                            | males  | 0,96±0,18 (13)   | 1,26±0,15 (8)                                                                                | 1,76±0,26 (15)     |
|                                                                                                     | female | 3,10±0,35 (16)** | 3,69±0,28 (9)**                                                                              | 2,59±0,24 (11)     |
| Progesterone 0.13 ng/ml                                                                             | males  | 3,86±0,73 (17)   | 9,70±1,77 (12)#                                                                              | 2,53±1,73 (14)*    |
|                                                                                                     | female | 32,3±4,45 (19)** | 61,1±6,36 (12)#,**                                                                           | 4,40±1,34 (10)*    |
| 17OH-progesterone 0,035 ng/ml                                                                       | males  | 0,38±0,06 (17)   | 0,39±0,05 (10)                                                                               | 0,69±0,54 (15)     |
|                                                                                                     | female | 5,24±1,04 (17)** | 15,50±2,52 (11)#,**                                                                          | 3,85±0,80 (10)*,** |
| Androstenedione 0,03 ng/ml                                                                          | males  | 0,60±0,10 (17)   | 0,15±0,06 (11)#                                                                              | 0,067±0,008 (14)*  |
|                                                                                                     | female | 0,22±0,06 (19)** | 1,0±0,33 (11)#,**                                                                            | 0,15±0,02 (11)*,** |
| Testosterone 0,04 ng/ml                                                                             | males  | 2,81±0,37 (17)   | 0,57±0,16 (11)#                                                                              | 1,35±1,09 (13)     |
|                                                                                                     | female | 0,05±0,03 (19)** | 0,20±0,13 (11)                                                                               | HO (10)            |
| Dihydrotestosterone 0,006 ng/ml                                                                     | males  | 0,5±0,06 (15)    | 0,14±0,02 (8)#                                                                               | 0,19±0,16 (15)     |
|                                                                                                     | female | 0,06±0,01 (16)** | 0,19±0,02 (9)#,**                                                                            | 0,05±0,008 (11)*   |
| Estradiol 16 pg/ml                                                                                  | males  | 26,35±1,63 (17)  | 37,23±1,85 (11)#                                                                             | 3,91±2,34 (15)*,#  |
|                                                                                                     | female | 32,95±3,04 (18)  | 33,22±4,22 (10)                                                                              | 11,25±4,88 (10)*,# |
| Estrone 10 pg/ml                                                                                    | males  | 17,88±4,07 (14)  | 24,08±8,71 (7)                                                                               | 7,10±2,40 (14)     |
|                                                                                                     | female | 23,60±2,44 (15)  | 77,42±12,13 (8)#,**                                                                          | 22,56±4,73 (9)*,** |

**Note.** \* –  $p \leq 0.05$  compared with the control; \*\* –  $p \leq 0.05$  when compared to the intact animals of the same sex; # –  $p \leq 0.05$  when compared between males and females in the same experimental group. ( ) – number of animals; BT – below the sensitivity threshold.

Table 3

### Plasma levels of corticosterone in intact and resuscitated rats the next day after resuscitation [Me (25%; 75%)]

| Groups                          | Corticosterone (pmol/l) |
|---------------------------------|-------------------------|
| Males, intact                   | 343.4 (206.4; 387.7)    |
| Males, resuscitation, control   | 315.5 (266.5; 340.0)    |
| Males, resuscitation, panavir   | 400.2 (354.9; 406.4)    |
| Males, resuscitation, derinat   | 395.0* (347.5; 439.2)   |
| Females, intact                 | 366.6 (327.1; 388.3)    |
| Females, resuscitation, control | 329.7 (294.3; 410.3)    |
| Females, resuscitation, panavir | 346.9 (325.3; 411.2)    |
| Females, resuscitation, derinat | 429.4* (402.0; 440.0)   |

**Note.** \* –  $p \leq 0.05$  when compared with the control group resuscitated rats of the same sex.

males of the control group compared with the corresponding group of females values of ND at the 2nd, 4th and 5th day after resuscitation were higher, as well as the cumulative value of total ND, while the rate of decrease in ND was lower (Table 1). Thus panavir and derivate were able to accelerate neurological recovery in animals of both sexes. The results showed that tested drugs possess immunoreactive properties that affect the recovery of the nervous system.

Investigation of sex steroid hormones after a day of resuscitation showed that (a) the blood level of pregnenolon and progesterone was increased in males and females in the control group compared to the respective group of intact rats. (b) the blood level of 17OH-progesterone and estrone was increased in females, and (c) the blood level of estradiol was increased in males. Changes of male sex steroids in males and females had multidirectional nature: blood concentrations of androstenedione, testosterone and dihydrotestosterone in males were decreased whereas in females these hormones except testosterone were increased (Table 2). In the same period of observation, quantitative profile of sex steroid hormones in control rates and those animals receiving panavir and derinat was significantly different. Therefore, in groups with administration of drugs, in contrast to control groups, the blood concentration of progesterone, 17OH-progesterone, androstenedione and testosterone in males,

and that of progesterone 17OH-progesterone, androstenedione and estrone in females remained the same in intact animals. However, the lower values of the blood levels of estradiol were observed in groups of males and females that received panavir and derinat versus intact animals (control) (Table 2). It is necessary to note that the blood levels of steroidal sex hormones remained the same as in intact animals or even decreased below norm in rats of both sexes when a drug was administered (Table 4). The above results indicated that the investigated immunostimulatory drugs significantly affected the profile of sex steroid hormones in rats in the early postoperative period.

It has been reported that after the injury combined with hemorrhage, hypoxemia or hypotension induced by bleeding, in the reperfusion period, inhibition of the immune system occurs in male mice, while in female mice immune system activity remains high. Study on the relationship of sex with immune system response to ischemia led researchers to conclusion about inhibitory effect of male steroid hormones and activating influence of female sex hormones or their ratio on the immune system [10–13].

The results obtained are not related to the influence of the trial drugs on the hypothalamo-pituitary-adrenal system as during their administration a slight increase of corticosterone compared with control groups of resuscitated

ed rats was observed only when using derinat. However, there was no difference in all groups of resuscitated rats by this index from intact groups (Table 3).

Thus, within the first two days after the resuscitation the effect of the drug on the blood levels of sex steroid hormones were not associated with activation of the hypothalamo-pituitary-adrenal system.

## Conclusion

Data demonstrate that panavir and derinat lead to a reduction of female hormones in males and females when

compared to the corresponding control. Earlier [it was found that the introduction of drugs had a positive effect on the structural changes in the brain [21, 22]. Administration of panavir reduced the structural changes associated with sexual characteristic of animals: application of panavir contributed to prevention of neuronal death in CA1 hippocampal sector in males, whereas in females the same effect was revealed in cerebellar Purkinje cells [23].

In summary, the obtained results demonstrate that immunostimulatory drugs panavir and derinat affects the nervous and endocrine systems in early postoperative period.

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