the index of postimplantation losses (L) in mice on the dose (D) in an analysis of the dominant lethality at the stage of mature sperm can be described by the equation $L = 6.0 + 94D/(D_{50} + D)$.

When fotrin is introduced with PVP, the dose leading to death of half of the embryos proves approximately twice as high ($D_{50} = 17.1$ mg/kg) as without PVP ($D_{50} = 8.6$ mg/kg), which agrees with the 2-3-fold decrease in the ability of fotrin to penetrate into the peripheral compartment and gonads.

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INFLUENCE OF DIOXIDINE ON THE CORTICOSTEROID FUNCTION OF THE ADRENALS

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UDC 615.281.015.4:616.45-008.6].07

Dioxidine (1,4-di-N-oxide of 2,3-dihydroxymethylquinoxaline, I) possesses high antibacterial activity in experiments on animals [1-6] and is now widely used in the treatment of infectious diseases, especially those caused by pathogens resistant to antibiotics and sulfanilamides [7-14]. And yet, I gives a number of side effects [15-17].

In an experiment on rats it was shown [18, 19] that I induces a pronounced stimulation of the adrenal cortex. The state of the adrenals was evaluated according to their weight and their ascorbic acid content. However, it was shown in [20] that I induces an increase in the weight of rat adrenals only at the first stage; then the weight of the glands decreases and atrophy of them develops.

In this work we studied the nature of the influence of I on rat adrenals and made an attempt to eliminate this undesirable action of the preparation.

EXPERIMENTAL

Dioxidine was administered to rats in the form of a 1% aqueous solution internally in doses of 50, 100, and 250 mg/kg (corresponds to approximately 1/15, 1/7.5, and 1/3 LD_{50}, respectively) for 1-4 weeks. The animals

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 10, pp. 1174-1177, October, 1983. Original article submitted March 29, 1983.

0091-150X/83/1710-0698$07.50

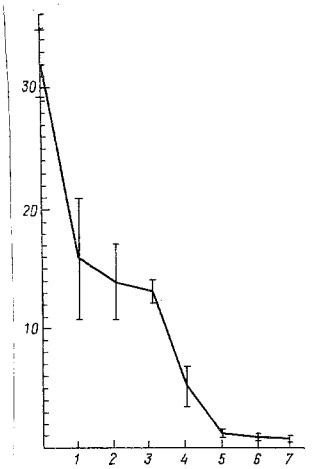

Fig. 1

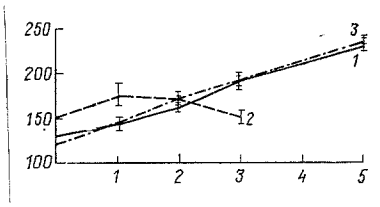

Fig. 2

Fig. 1. Corticosterone content in the blood of rats. Along x axis: day of administration of dioxidine; along y axis: corticosterone concentration (in μg%).

Fig. 2. Dynamics of the body weight of rats. Along x axis: period of observation of animals (in weeks); along y axis: body weight (in g). 1) Animals that received I + II; 2) animals that received I; 3) control.

were kept under observation for 12 weeks. A total of 360 noninbred male white rats weighing 120-150 g were used. The weight of the adrenals of the rats was determined, along with the corticosterone concentration in the blood serum by a radioimmune method and the content of ascorbic acid in the adrenals by a colorimetric method [21]; histological sections of the adrenal glands were stained with hematoxylin–eosin and with Sudan III. To correct the toxic action of I on the adrenals we used cortisone III, which was injected intramuscularly in doses of 5 and 2.5 mg/kg for 1-5 weeks. The results obtained were treated statistically [22].

RESULTS AND DISCUSSION

The investigations conducted showed that I in a dose of 250 mg/kg decreases the corticosterone content in the blood of rats (Fig. 1). After a single administration of I, the corticosterone concentration is halved; repeated introduction of I in the same dose leads to a stable decrease in the corticosterone content in the blood, which is also maintained after the preparation is discontinued. Moreover, the weight of the adrenals of the animals is substantially increased (by a factor of 1.5-2) during the administration of I, but after it is discontinued, the weight of the adrenals gradually decreases.

One day after the first, second, third, fourth, fifth, sixth, and seventh injections, the weight of the adrenals was (in mg): 42.2 (33.9-50.5), 39.8 (26.1-53.5), 42.0 (31.3-52.7), 55.4 (42.9-67.9), 65.0 (40.0-90.0), 77.0 (39.5-114.5), 57.0 (38.6-75.4), respectively, and one, two, three, and four weeks after the preparation was discontinued, the values of the weight were 34.0 (28.1-39.9), 32.4 (28.3-36.5), 28.8 (26.3-33.3), and 24.4 (20.8-28.0), respectively; in the control: 38.4 (29.5-47.3) mg.

Pathomorphological investigations of the adrenals showed that after a single injection of I in a dose of 250 mg/kg, the lipid content in the content in the cortex is reduced in comparison with the control, but when I is administered repeatedly, when there is an increase in the weight of the adrenals and a sharp decrease in the corticosterone content in the blood to 0.5 μg%, an accumulation of lipid inclusions is noted in the glands, accompanied by sharp destructive changes. After discontinuance of the preparation against a background of a progressive decrease in the weight of the adrenals and a low content of corticosterone in the blood, pathological processes continue to develop in the adrenals.

When I is administered in a dose of 100 mg/kg, substantially smaller changes are observed in the adrenals of rats, while at a dose of 50 mg/kg no pathomorphological changes are detected in the adrenals in the case of daily administration for a month.

The content of ascorbic acid in the adrenals of rats that received I internally in a dose of 250 mg/kg was substantially reduced.

The stable decrease in the corticosterone content in the blood of the animals with simultaneous hypertrophy of the adrenals is evidence of a direct action of the substance on the biosynthesis of corticosteroids, and not of an inhibition of ACTH secretion [23]. Since corticosterone is the natural secreted hormone in rats [24-26], on the basis of the data that we obtained, namely, the sharp decrease in the corticosterone content in the peripheral blood and pathological changes detected in the fascicular zone of the cortex, it can be concluded that I inhibits corticosterone synthesis in the adrenals. A corticosterone deficiency in the blood induces a disinhibition of the secretion of corticotropin releasing factor in the hypothalamus according to a feedback mechanism. This in turn leads to an intensification of ACTH formation, which stimulates steroidogenesis before the site of the blockage, as evidenced by the increase in the weight of the adrenal glands, decrease in their ascorbic acid content, and fatty infiltration of the fascicular zone of the adrenal cortex. Similar phenomena have been described in the literature in a study of amphenone, a known inhibitor of the function of the adrenal cortex [27]. The accumulation of lipids in the cortex may be a consequence of the fact that cholesterol is insufficiently utilized by the adrenals for the synthesis of corticosteroids.

In connection with the detected insufficiency of the adrenals in rats that received I, we studied the state of the adrenal glands in the case of simultaneous administration of I and II, which was taken as an agent for replacement therapy. The joint use of I and II ensured 100% survival of the rats in the group, whereas in the group of animals that received only I, 100% lethality was noted as a result of developing atrophy of the adrenals. Figure 2 presents the results of a determination of the body weight of animals that received only I daily in the same dose together with II in a dose of 2.5 mg/kg for one week, and then II alone for another four weeks. A pathomorphological investigation of the adrenals of the rats that received I in combination with II showed that they practically do not differ from the adrenals of intact animals. Consequently, II in a dose of 2.5 mg/kg is an effective agent of replacement therapy in the presence of a pathological state of the adrenals induced by internal administration of I in a dose of 250 mg/kg for one week. Under these experimental conditions, II in a dose of 5 mg/kg did not have a protective effect, and after the administration of II was stopped, all the animals died of the developing atrophy of the adrenals.

Thus, our investigations showed that I is an inhibitor of the function of the adrenal cortex and not a stimulator, as was described earlier [18, 19]. The degree of damage to the adrenals depends on the dose of the preparation. Since a dose of I of 250 mg/kg fits into the range of doses used as chemotherapeutic doses for the treatment of experimental infections induced by various pathogens [19, 28, 29], it may considered that I is a potentially hazardous drug with respect to its injurious action on the adrenals. In the clinic the use of I is limited to a dose of 10 mg/kg per day. Such a use of it evidently has no damaging effect on the adrenal cortex; however, it should be kept in mind that in the case of an overdose of the preparation its toxic action on the adrenals is possible. The use of II as an agent for replacement therapy significantly reduces the injurious effect of I on rat adrenals.

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