The removal of chemotherapeutic preparations from the organism by hemosorption can be used successfully in the treatment of cancer patients with increased doses of antineoplastic agents or in the case of their overdosing.

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EFFECTS OF HEXAMIDINE AND CORTISONE ON THE EMBRYOTROPIC ACTIVITY OF DIOXIDINE

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Dioxidine (I) is a broad-spectrum antibacterial preparation, used in the treatment of suppurative infections, when other antibacterial agents are ineffective. The average clinical daily dose of the drug is 10 mg/kg. Earlier it was established in experiments on animals that when I is injected subcutaneously throughout pregnancy it has an embryolethal effect, and after a single injection it has teratogenic effect [1]. It is also known that in definite doses it induces pathological changes in the adrenal cortex of rats, and its combined use with cortisone (II) substantially reduces the adrenal toxicity of the drug [2]. Moreover, there are data on the fact that I gives a mutagenic effect [3]. The combined use of I with hexamidine (III) leads to a reduction of its mutagenic activity [4].

Considering these effects of I, we were interested in determining whether its embryolethal and teratogenic effects are associated with the indicated properties. In connection with this we investigated the effects of the combined use of I with II and III on embryogenesis.

EXPERIMENTAL METHOD

The experiments were conducted on 85 rats. A dated pregnancy was produced by the usual method [5].

Treatment with I in combination with II or III was performed at the periods of pregnancy when the injurious action on embryogenesis was the most pronounced. As a control, the animals of other groups received only I, only II, or only III at the same periods, while intact animals received water in the corresponding volume.

All the drugs were used in the form of the substance. When I and II were combined, I was administered throughout the pregnancy in a dose of 100 mg/kg subcutaneously, since the maximum embryolethal effect of I was manifested precisely in this dose and with this mode of administration. Lowering the dose to 50 mg/kg reduced the injurious effect [1]. At the same time, II was injected intramuscularly in a dose of 6 mg/kg, since in this dose in experiments on intact animals it reduced the adrenal toxicity of I and promoted survival of rats [2].

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TABLE 1. Effects of I, II, and Their Combined Use on the Embryogenesis of Rats during Prolonged Administration of the Drugs

Drug	No. of animals in group	Mode of administration of drug and dose, mg/kg	No. of corpora lutea	No. of resorbed and dead fetuses	No. of live fetuses	Embryonic deaths, %		Size, mm	Weight, g
						before implantation	after implantation		
I	16	Subcutaneous 100	183	166	—	9,3 (8,7—9,9)	100		
II	5	Intramuscular 6	54	1	50	5,6 (2,1—9,1)	2 (0,5—3,5)	38,2 (37,0—39,4)	4 (3,3—4,5)
I+II	7	Subcutaneous 100 + intramuscular	68	61	—	13,2 (10,1—16,3)	100		
Control	6		61	4	52	8,2 (6,5—9,9)	7,1 (6,2—8,2)	38,4 (37,3—39,5)	4,1 (3,7—4,5)

Note. Here and in Table 2 the confidence interval at P = 0.05 is indicated in parentheses.

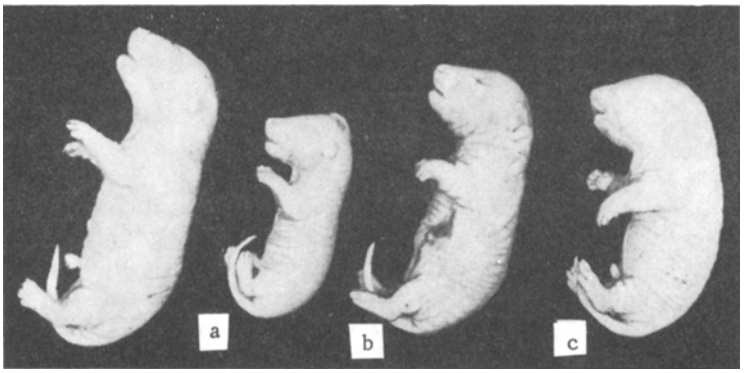

Fig. 1. Twenty-one-day rat embryos after administration of dioxidine (a), hexamidine (b), or combinations of dioxidine with hexamidine (c) to the females on the 10th day of pregnancy; on the left: 21-day embryos of control animals.

In a study of the effects of a combination of I and III on embryogenesis, the drugs I in a dose of 300 mg/kg and III in a dose of 100 mg/kg were administered simultaneously on the 10th day of pregnancy. This is due to the fact that precisely after a single injection of I on this day is the maximum teratogenic effect observed [6]. The antimutagenic action of III with respect to I is most pronounced in a dose of 100 mg/kg [4].

The results were evaluated by the methods generally used in teratological experiments [7]. On the 21st day of pregnancy the animals were sacrificed by decapitation, the abdominal cavity was opened, and the uterus and ovaries were extracted. The number of corpora lutea was counted in the ovaries, and the numbers of live and dead fetuses, as well as the number of resorptions were counted in the uterus. The fetuses were examined under an MBS-9 binocular microscope. Part of the fetuses were fixed in Bouin's fluid for study of the state of the internal organs. Preimplantation and postimplantation death and the percent of anomalous fetuses were calculated. The results obtained were treated by the methods of variation statistics.

RESULTS AND DISCUSSION

Influence of II on the Embryotoxic Effect of I. The influence of combined therapy with I and II on rat embryogenesis can be seen according to the results presented in Table 1. The administration of I alone to rats throughout the entire pregnancy led to 100% death of the fetuses, whereas II alone did not disturb embryogenesis. Embryonic death before and after implantation in the group of females that receive II did not exceed the control data. The craniocaudal size of the fetuses of the experimental group was equal to 38.2 mm, and that of the fetuses of the control group 38.4 mm.

TABLE 2. Effects of I, III and Their Combined Use on the Embryogenesis of Rats after a Single Injection on the 10th Day of Pregnancy

Drug	No. of animals in group	Mode of administration of drug and dose, mg/kg	No. of corpora lutea	No. of resorbed and dead fetuses	No. of live fetuses			Embryonic death, %		Size, mm	Weight, g
					total	anomalies		before implantation	after implantation		
						abs.	%				
I	14	Subcutaneous 300	162	127	24	16	66,7	5,2 (1,8—8,6)	84,1 (78,0—90,1)	32,7 (31,8—33,6)	2,6 (2,4—2,8)
III	11	Through a gastric probe 100	119	5	107	—	—	5,9 (2,3—9,5)	4,4 (1,1—7,7)	35,6 (34,6—36,4)	3,8 (3,6—4,0)
I+III	15	Subcutaneous 300 +gastric probe 100	173	24	131	18	13,7	9,2 (6,1—12,3)	16,9 (12,5—21,3)	34,1 (33,5—34,7)	3,3 (3,1—3,5)
Control	11		121	6	112	—	—	2,5 (1,3—3,7)	5,1 (2,5—7,7)	37,8 (37,5—38,1)	4 (3,8—4,2)

In the case of the combined use of I and II, the rat fetuses had died by the time of autopsy, just as when I alone was used. Thus, the embryolethal effect of I could not be reduced by its combined use with II.

Influence of III on the Embryotoxic and Teratogenic Effects of I. The results of these series of experiments are presented in Table 2. As it follows from its data, in the group of animals that received a single injection of I on the 10th day of pregnancy, a high level of death of the embryos is observed (84.1%). In 7 out of 14 females, all the fetuses died, while in each of the seven remaining females there were fetuses with developmental anomalies. Among the anomalies, cerebral hernias and cleft palate were most frequently encountered (see Fig. 1a). Pronounced inhibition of growth of the fetuses was noted. The average craniocaudal size of rat fetuses that received I was equal to 32.7 mm, weight 2.6 g, whereas in the control the values were 37.3 mm and 4 g, respectively.

The administration of III alone had no effect on the normal course of pregnancy and did not disrupt embryogenesis of the rats. The fetuses of females that received III showed virtually no difference from the fetuses of the control animals (see Fig. 1b). They had no developmental anomalies, and only a slight decrease in length was observed (35.6 mm in the experiment and 37.8 mm in the control); there were no significant differences of the body weight between the fetuses of the experimental and the control groups.

When I was administered in combination with III on the 10th day of pregnancy, a reduction of the embryotoxic and teratogenic effects was noted. Embryos with developmental anomalies in the form of cerebral hernia were detected in only 6 out of 15 females; this anomaly was substantially less pronounced than in the embryos that received I alone (see Fig. 1c). Among the remaining rats the embryos were normal. On the whole, the percentage of anomalous fetuses in the group that received I and III were 13.7, whereas in the group that received only I it reached 66.7. Death after implantation did not exceed 17% in the case of combined use of I and III. Just as in the case of the use of I alone, a reduction of the size and weight of the fetuses was observed, but to a substantially lesser degree. When the internal organs of the fetuses were examined, no developmental anomalies were detected in any of the groups. Thus, the use of I in combination with III significantly reduced the embryotoxicity and teratogenicity of I, although it did not entirely prevent the harmful effects of the drug on the development of the fetuses, as evidenced by the inhibiton of growth of the embryos, death of part of them, and developmental anomalies in certain cases.

The negative effects on the fetus may be direct or mediated through the maternal organism. The data obtained suggest that there is a direct influence of I on the fetus, which is supported by the absence of a positive effect when II is used as an agent for replacement therapy after the administration of I and the effect from the administration of I with III. It might be thought that the mechanism of the embryotoxic and teratogenic effects of I is associated with the mechanism of its mutagenic activity, since III, giving an antimutagenic effect, significantly reduces the injurious action of I on embryogenesis. However, this hypothesis does not exclude the presence of other mechanisms of injurious action of I on the fetus.

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