Effect of Platinum-Containing Cytostatics on Rat Progeny

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Pathological changes in internal organs are seen in some offspring of intact females and males treated with platidiam 1 month before mating. One case of malformation was found in the progeny of cytostatic-treated females. High embryonal mortality is noted in animals treated with cytostatics 3 and 6 months before mating. Delayed ossification is observed in some animals of almost all experiments groups.

Key Words: *rat; platidiam; progeny*

Platinum complex compounds occupy a prominent place among modern antitumor drugs [2,4]. The use of these drugs improves prognosis in some oncologic diseases and allowed many oncological patients not only to survive but live a full life and have children. In light of this, delayed effects of platinoid toxicity in the normal (nontumor) tissues of the organism become an important problem. These effects partially derive from genetic disturbances in sex cells resulting in the appearance of abnormal progeny. Clinical observations are very contradictory. Some investigators have reported embryonal death, malformations, and high incidence of neoplasms in offspring of pairs where one of parents has been previously treated with cytostatics [5]. Others have shown that the incidence of congenital abnormalities is within expected limits [6].

The aim of the present study was to examine the offspring of rats treated with the platinum-containing cytostatic platidiam 1, 3, and 6 months before mating with intact mates.

MATERIALS AND METHODS

Experiments were carried out on 80 male and 180 female Wistar rats, 90 of which (30 males and 60 females) comprised a control group; 900 fetuses and 450 rat pups were examined. The rats received a single intravenous injection of platidiam (Lachema) in a dose of 4.0 mg/kg. This is a maximum permissible dose calculated by graphic probit-analysis over a 30-day observation period [1]. Treated males and females were caged with intact rats 1, 3, and 6 months postinjection. Mating was judged from vaginal smears. Some pregnant females (50%) were sacrificed on day 20 of gestation, and corpora lutea in the ovaries, implantation sites in the uterus, and live and dead fetuses were counted. Then the indexes of pre- and postimplantation mortality were calculated. The fetuses were removed, weighted, and their craniocaudal size was measured. Some fetuses were fixed in Bowen fluid followed by examination of internal organs by the Wilson method, while others were fixed in 96% alcohol and stained by the Dawson method in order to detect possible skeletal abnormalities [6]. Other pregnant females were maintained until delivery, and their offspring were observed for 2 months. The time of isolation of the conch, appearance of primary hairs, teething, eye and vagina opening, and testis descent were evaluated on days 5, 15, 30, and 60 after birth. The index of survival was calculated as the ratio of survivors by day 4 to live-born pups. We examined 6 groups of pups and fetuses obtained after two variants of mating:

1) males treated with platidiam 1, 3, and 6 month before mating and intact females;

2) platidiam-treated females (according to the same scheme) with intact males.

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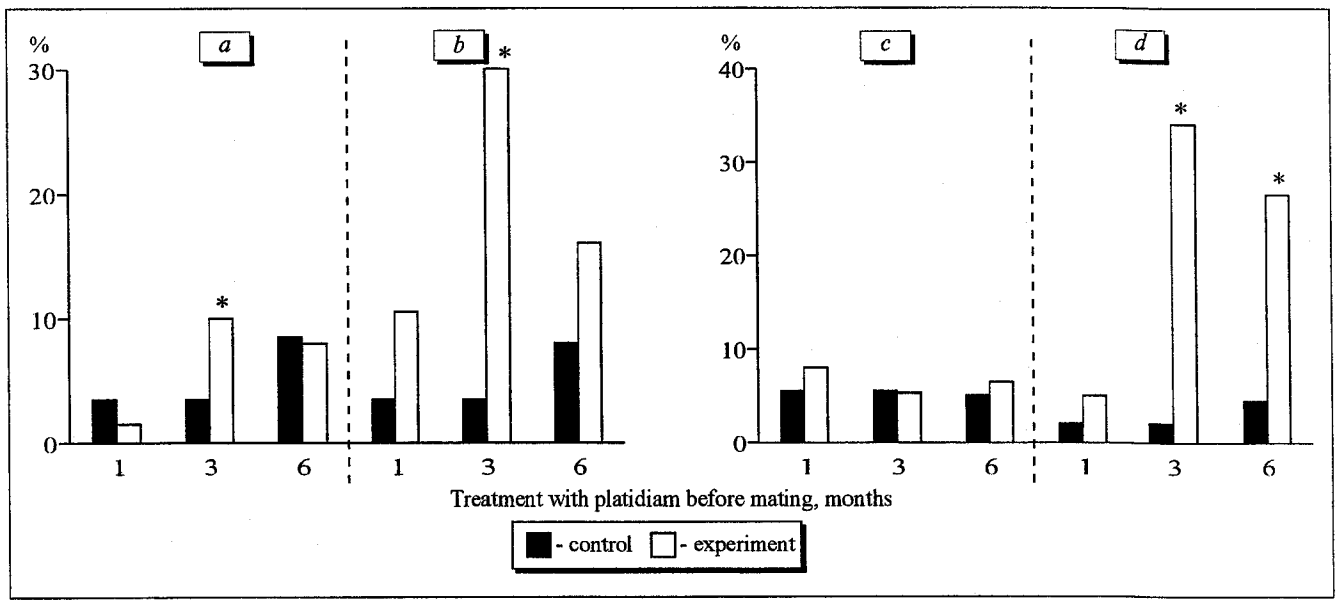

Fig. 1. Pre- (*a*, *b*) and postimplantation (*c*, *d*) embryonal mortality in platidiam-treated rats. *a*, *c*) intact females mated with males receiving platidiam 1, 3, and 6 months before mating; *b*, *d*) females receiving platidiam 1, 3, and 6 months before mating with intact males. Here and in Fig. 2: *significant differences from the control.

Three groups of fetuses and pups from intact parents served as the control. The data were processed statistically using the Student and Wilcoxon—Mann—Whitney tests and the Fischer *z*-transformation.

RESULTS

In females treated with platidiam 1 month before mating with intact males, the number of corpora lutea in the ovaries, of implantation sites in the uterus, and of live fetuses (per one female), as well as the indexes of embryonal mortality did not differ from the control. Platidiam injection to females 3 months before mating did not reduce the number of corpora lutea, while the numbers of implantation sites (8.56±0.91) and of live fetuses (5.11±0.77) considerably decreased in comparison with the control (10.77±0.55 and 10.15±0.55, respectively). This probably resulted in a marked rise of pre- and postimplantation mortality (Fig. 1). In females treated with platidiam 6 months before mating we noted only significantly decreased number of live fetuses (per female) and, consequently, a rise of postimplantation mortality. When intact females were mated with platidiam-treated males, increased embryonal mortality (reduced number of implantation sites and increased preimplantation mortality) was observed only if the treatment was performed 3 months prior to mating (Fig. 1).

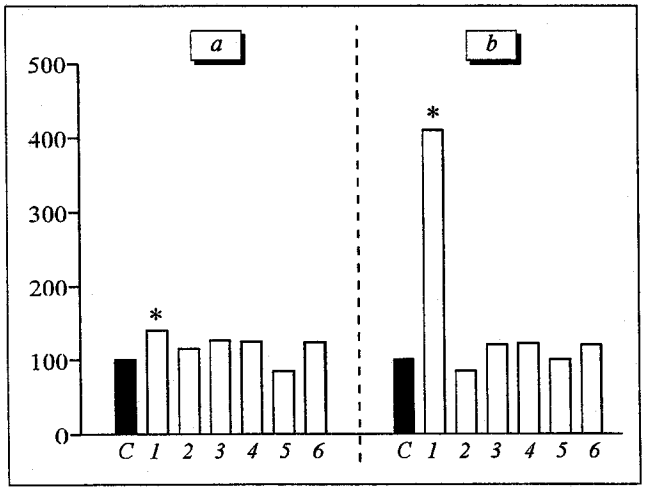

Fig. 2. Pathological changes in internal organs in fetuses from a platidiam-treated parents. Fetuses with hemorrhages (*a*) and cholestasis (*b*). *C*) control; *1-3*) fetuses from intact females and males treated with platidiam 1, 3, and 6 months before mating. *4-6*) fetuses from intact males and females treated with platidiam 1, 3, and 6 months before mating.

Fetuses of all studied groups did not differ in their body weight and craniocaudal size. No marked abnormalities were found on gestation day 20. Examination of internal organs showed similar occurrence of hemorrhages in different organs and tissues, moderate dilation of lateral cerebral ventricles, cholestasis, and hepatic congestion in control and experimental groups. The only exception was the offspring from intact females and males receiving platidiam 1 month before mating. In this group, the number of fetuses with cholestasis and hemorrhages in different organs and tissues significantly surpassed that in the control group (Fig. 2). The presence of cholestasis

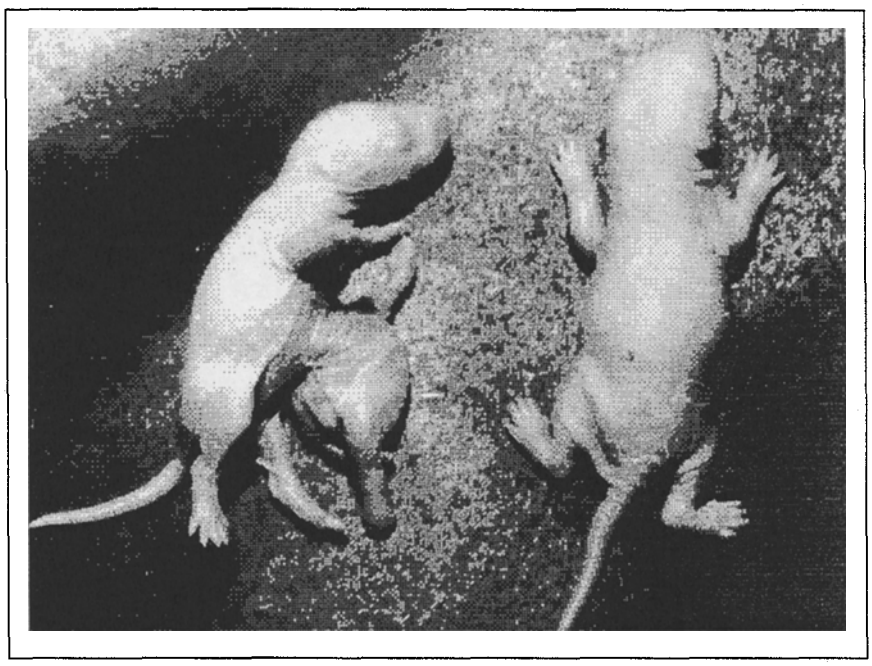

Fig. 3. Newborn rat obtained from a platidiam-treated female (1 month before mating) and an intact male (left) and control rat pup (right).

was morphologically verified: accumulation of bile pigments in hepatocytes and bile ducts was observed in liver specimens stained with hematoxylin and eosin. In addition, hydronephrosis and subcutaneous edema were found in 4 (6.1%) and 5 (7.7%) fetuses in this group, respectively.

Although no skeletal abnormalities were observed, the number of fetuses with a reduced number of ossification foci in the sternum, metacarpus, metatarsus, sacrum, and scull was significantly higher in all but one (females treated with platidiam 3 months before mating) experimental groups in comparison with the control ($p \leq 0.05$). This implies impairment of ossification processes in offspring from platidiam-treated animals.

Analysis of the postnatal ontogeny revealed the same survival rate in all studied group. The offspring of males injected with platidiam 1, 3, and 6 months before mating had no external defects and developmental abnormalities. In the offspring of platidiam-treated females we found a pup (platidiam injection 1 month before mating) with one head and two bodies (Fig. 3); one body had three extremities with 6 fingers on the forelimb. The pups in experimental groups did not differ from controls in physical development.

Thus, pathological changes were found in some fetuses obtained from intact females and males injected with the cytostatic 1 month before mating. In the offspring of platidiam-treated females we found a pup with crude external abnormalities. Mating 3 and 6 month after cytostatic treatment yielded high embryonal mortality. It should be noted that impaired ossification was noted in part of fetuses in almost all experimental groups regardless of the sex of treated parents.

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