EFFECT OF DIAZEPAM ON DEVELOPMENT OF THE OFFSPRING

B. I. Lyubimov, N. M. Smol'nikova, and S. N. Strekalova

UDC 618.3-085.216.5-07:616-053.31-07

Experiments on rats showed that diazepam, in a dose of 10 mg/kg by mouth throughout pregnancy, affects the development of the offspring. Changes observed in the behavior of the young rats are evidently due to the activating action of the compound in small doses on the fetus after passing through the placental barrier.

KEY WORDS: diazepam; development of the offspring.

The study of the effect of diazepam (Seduxen) on the development of the offspring is particularly important because of the wide use of this substance in clinical practice for the treatment of neuroses and psychoneuroses, as well as in obstetrics and gynecology for the treatment of some forms of pathological pregnancy, dysmenorrhea, and eclampsia, for the facilitation and quickening of labor, and so on [1, 7, 12]. Diazepam is also frequently used by clinically healthy persons for the prevention and relief of states of fear, anxiety, and tension, and for that reason it may often be taken without medical supervision.

Considering the facts mentioned above, and also the experimental and clinical data to show that diazepam penetrates easily through the placental barrier and is found in the fetal blood plasma and tissues [8, 10, 11], the study of the effect of this drug on the fetus and offspring is extremely necessary.

It is reported in the literature that diazepam, if administered to the mother, affects the cardiac activity of the fetus [11]. The author cited considers that this is due to the action of diazepam on the reflex centers of the brain. According to Jorgensen [9], benzodiazepines do not cause injury to the fetus if given in the early stages of pregnancy.

The object of this investigation was to study the effect of diazepam, when given during pregnancy, on the development of the progeny.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats weighing 180-230 g. Diazepam was given by mouth in a dose of 10 mg/kg once a day throughout pregnancy. Before delivery the females were placed in single cages. The offspring (125 young rats) were weighed periodically and a record was kept of the time when they opened their ears and eyes, they grew hair, opened the vagina, and so on. At certain age periods the behavioral responses of the animals were studied. Starting from the age of 3 weeks and until sexual maturity, the spontaneous motor activity was recorded once a week by an actometer. The orienting reaction was tested on the 20th, 30th, 40th, and 60th days of life by the "net climbing test." After the age of 2 months a conditioned-defensive avoidance reflex was formed in a maze. The method of training was described earlier [5]. In some animals, not trained in the maze, behavior was investigated in the "open field" [4]. Motor activity was judged from the number of squares crossed, the emotional state from the number of acts of defecation and micturition, and the intensity of the investigative instinct from the number

Laboratory of General Pharmacology, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 78, No. 10, pp. 64-66, October, 1974. Original article submitted December 28, 1973.

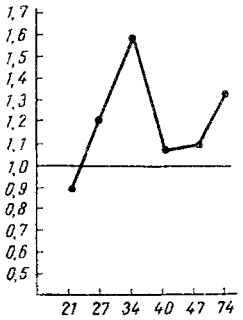

Fig. 1

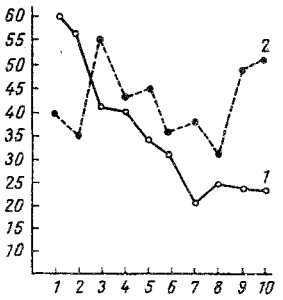

Fig. 2

Fig. 1. Spontaneous motor activity of rats whose mothers had received diazepam during pregnancy. Abscissa, age of rats (in days); ordinate, degree of change in motor activity compared with control, taken as 1.

Fig. 2. Formation of conditioned defensive avoidance reflex in rats whose mothers had received diazepam during pregnancy: 1) control; 2) diazepam 10 mg/kg. Abscissa, number of trainings; ordinate, time taken to run through the maze (in sec).

TABLE 1. Behavior of Rats in an "Open Field" (M ± m)

Character of action	Number of squares crossed	Number of inspections of the hole	Number of defecations	Number of micturitions
Diazepam (10 mg/kg) during pregnancy	17,1±1,1	3,6±0,2	3,2±0,2	0,40±0,05
Control	10,5±0,7	2,7±0,2	2,7±0,2	0,17±0,03

of times the animals looked into holes in the corners of the squares in the floor. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS AND DISCUSSION

Diazepam slightly increased the length of pregnancy: in the experimental animals its mean duration was 23.5 ± 0.1 day compared with 22.9 ± 0.1 day in the control ($P < 0.05$). In general development and weight there was no difference between the offspring of the two groups, except for later opening of the vagina in the rats whose mothers had received diazepam. For instance, in 36 of 43 female rats of this group the vagina opened on the 49th-62nd day of life, and on the 46th day in only seven rats, whereas in the control group the vagina opened in 22 of 29 cases on the 45th-48th day, and only in seven cases on the 57th day after birth. This indicates delay in the sexual maturation of the female offspring of the experimental animals.

The degree of change in the spontaneous motor activity of the experimental young rats compared with the controls, taken as 1, is illustrated in Fig. 1. Clearly rats whose mothers had received diazepam were somewhat more mobile than the controls (on the 34th day; $P < 0.05$).

The increased motor activity of the offspring of the experimental animals also was observed when their behavior was studied in the "open field" (Table 1). The investigative instinct was stronger in young rats whose mothers had received diazepam, and they were rather more emotional than the young rats of the control group.

A study of orienting activity (net climbing) revealed no difference in the behavior of the offspring of the experimental and control animals. Only on the 10th day of life did more rats from the progeny of the

experimental animals hold on to the net compared with the control (67.3 ± 4.7 and 50.6 ± 5.6% respectively; $P < 0.05$). At this age, however, the young rats' eyes were still closed and the ability of the animals to hold on to the net reflected the muscle-relaxant action of the drug more than its effect on orienting activity.

In the course of 10 training exercises in rats whose mothers had received diazepam a conditioned-defensive avoidance reflex could not be formed, whereas in the control group six training exercises were sufficient to form this reflex (Fig. 2).

When administered during pregnancy diazepam thus had a definite effect on the development of the progeny: the rats showed increased spontaneous motor activity and motor activity in the "open field", they were more emotional, and they had a stronger investigative instinct; after 10 training exercises they were unable to form a conditioned-defensive avoidance reflex.

It can be concluded from the analysis of these results and data in the literature that changes in the behavior of the offspring were due mainly to the activating action of small doses of diazepam. In small doses this substance is known to facilitate the integrative ability of the nervous system [3], to activate the electrocorticogram [6], to increase motor activity, and to stimulate operant behavior [2]. The hypothesis that diazepam, in small doses, acts on the development of the offspring is also supported by the data showing that the compound can pass through the placental barrier [8, 10, 11].

LITERATURE CITED

1. Yu. A. Aleksandrovskii and V. N. Prokudin, Zh. Nevropat. i Psikhiat., No. 8, 12 (1969).
2. Yu. I. Vikhlyaev and T. A. Klygul', Farmakol. i Toksikol., No. 3, 268 (1973).
3. V. V. Zakusov, Farmakol. i Toksikol., No. 7, 7 (1971).
4. D. A. Kulagin and V. K. Fedorov, in: Genetics of Behavior [in Russian], Leningrad (1969), p. 35.
5. B. I. Lyubimov, N. M. Smol'nikova, and S. N. Strekalova, Farmakol. i Toksikol., No. 2, 165 (1973).
6. R. U. Ostrovskaya, Farmakol. i Toksikol., No. 1, 7 (1972).
7. J. Cohen, E. Harris, and H. Titus, South. Med. J. (Birmingham, Ala.), 54, 1271 (1961).
8. J. E. Idanpaan-Heikkila, P. I. Jonppila, et al., Am. J. Obstet. Gynecol., 109, 1011 (1971).
9. G. Jorgensen, Munch. med. Wschr., 114, 1151 (1972).
10. P. Sarteschi, G. V. Cassano, and G. F. Placidi, Pharmakopsychiat. Neuro-Psychopharmakol., 6, 50 (1973).
11. J. Scher, D. M. Hailey, and R. W. Beard, J. Obstet. Gynaecol. Brit. Common,, 79, 635 (1972).
12. Today's Drugs, Benzodiazepines, Brit. Med. J., 2, 36 (1967).