EFFECT OF AMPICILLIN AND OXACILLIN ON FETAL AND NEONATAL DEVELOPMENT

V. V. Korzhova, N. T. Lisitsyna,
and E. G. Mikhailova

UDC 615.334.099:618.33+612.
647/.648.014.46:615.334

KEY WORDS: Ampicillin; oxacillin; heart; pregnancy; fetus; newborn infant.

An important problem in clinical medicine is the use of antibiotics to treat pregnant women with extragenital diseases. There is evidence in the literature that not all antibiotics are harmless to the developing embryo and fetus. For example, benzathine penicillin and antibiotics of the tetracycline series have a toxic action on the embryo, fetus, and newborn infant [2-4].

Clinical and experimental studies of penicillin and extensive experience of its use have shown that it has no adverse effect on the development of the embryo, fetus, and newborn infant or animal [3]. Meanwhile the semisynthetic penicillins, if used for therapeutic or prophylactic purposes in pregnant women with extragenital pathology (rheumatic heart diseases, diseases of the kidneys, lungs, etc.), have not been adequately studied. Accordingly it was considered important to study the effect of semisynthetic penicillins frequently used in obstetric practice for therapeutic purposes, namely ampicillin and oxacillin, on embryonic, fetal, and neonatal development.

EXPERIMENTAL METHOD

Experiments were carried out on 54 pregnant albino rats. Ampicillin was given to the animals of group 1 perorally in a dose of 250 mg/kg from the 4th to the 13th days of pregnancy, i.e., during the first half of pregnancy. Animals of group 2 received ampicillin from the 15th day of pregnancy to the end of parturition in a dose of 250 mg/kg.

The rats of group 3 received oxacillin from the 4th through the 13th days of pregnancy perorally in a dose of 40,000 units.

EXPERIMENTAL RESULTS

At autopsy on the animals of group 1 on the 20th day of pregnancy (end of gestation) it was found that ampicillin increased the overall-embryonic mortality a little (27.8 ± 4.2% compared with 16.6 ± 1.4% in the control; $P < 0.05$). In their external appearance the fetuses differed very little from the controls. Their size (29.0 ± 0.5 mm) was practically normal (30.0 ± 0.2 mm), although their weight was reduced somewhat (2.7 ± 0.1 g compared with 3.0 ± 0.1 g in the control; $P < 0.05$). The diameter of the placenta was the same as in the control group (13.0 ± 0.6 mm), but its thickness (3.5 ± 0.2 mm) and weight (390.0 ± 10.5 mg) were below normal (5.10 ± 0.15 mm and 640 ± 43 mg, respectively). Assessment of the state of the fetal viscera and bony structures by Wilson's method in Dyban's modification showed no difference from normal. Histological study of the fetal heart likewise revealed no abnormality.

Parturition in this group took place at term. The stillbirth rate was within normal limits (experiment 2.3 ± 0.4%, control 2.7 ± 0.5%). The postnatal mortality of the rats was nil. The newborn rats were lighter in weight (5.6 ± 0.1 g) than in the control (6.0 ± 0.1 g). Subsequently the differences in weight disappeared and after the 20th day of postnatal development the young rats weighed the same (32 ± 2 g) as in the control (34 ± 1 g; $P > 0.05$). Their physical development was indistinguishable from normal. Exposure to a strong acoustic stimulus (by Krushinskii's method) led to the development of CNS disturbances, in the form of increased motor activity and epileptiform fits, in rats from mothers receiving ampicillin in almost the same proportion of cases (13.5 ± 1.6%) as in the control group (8.9 ± 1.5%; $P > 0.05$).

Moscow Regional Research Institute of Obstetrics and Gynecology. (Presented by Academician of the Academy of Medical Sciences of the USSR P. A. Vershilova.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 2, pp. 184-185, February, 1981. Original article submitted December 9, 1979.

0007-4888/81/9102-0169$07.50 © 1981 Plenum Publishing Corporation

Analysis of data obtained in the animals of group 2 on the 20th day of pregnancy showed the same pattern as in group 1. A tendency was noted for the body weight of the fetuses (2.90 ± 0.97 g) and the thickness (4 ± 0.1 mm) and weight of the placenta (440 ± 21 mg) to be less than in the control. The heart of the experimental fetuses, on histological examination, was indistinguishable in all respects from the heart of the control fetuses.

The experimental newborn rats were practically indistinguishable from the controls. However, just as after administration of ampicillin in the first half of pregnancy, no CNS disturbances were found in the fetuses (11.6 ± 2.3%; $P > 0.05$).

A sharp increase in the dose of ampicillin given to 2.5 g led only to prolongation of pregnancy by a few hours and to a greater decrease in weight of the fetuses.

At autopsy on the rats of group 3 on the 20th day of pregnancy an increase in the overall embryonic mortality to 37.5 ± 2.4% was observed. Oxacillin, injected in the early stages of embryogenesis, sharply inhibited development of the fetus and placenta: The mean weight of the fetuses was 1.7 ± 0.3 g (3.0 ± 0.1 g in the control) and their mean length was 25.4 ± 1.1 mm (30 ± 0.2 mm in the control). The diameter (12.0 ± 0.1 mm) and weight (420 ± 12 mg) of the placenta also were less than in the control. The weight and size of the fetuses varied only a little. Sometimes hemorrhages were present on the face and body.

Investigation by Wilson's method in Dyban's modification showed marked dilatation and congestion of the blood vessels of the brain, lungs, and heart. Hemorrhages were present into the pelvis, kidneys, and pericardium and beneath the pia mater in the temporal and occipital regions. Histological examination of the heart revealed areas of congestion of blood vessels in all layers of the myocardium. The course of parturition was disturbed. It took place 1-2 days later than in the control (on the 24th-25th and on the 23rd days, respectively), with profuse bleeding. At autopsy the uterine mucosa was blood-red in color, and large blood clots were seen at the sites of attachment. Stillbirths were observed in 13.0 ± 0.9% of cases (2.7 ± 0.5% in the control). The number of young in the litter was smaller (7-8) than in the control (9-10). The weight of the young rats and their physical development in the postnatal period showed considerable delay compared with these indices in the control. For instance, body weight by the 20th day of postnatal development was 26 ± 1.3 g in the experiment compared with 34 ± 1 g in the control ($P < 0.01$). No disturbances of CNS function could be found in the living young rats.

Administration of oxacillin in the same dose in the second half of pregnancy also led to increased fetal mortality (21.5 ± 1.3%). Hemorrhages were seen very often on the amnion and on the head and body of the fetus. The size (25.0 ± 0.8 mm) and weight (2.5 ± 0.2 g) of the fetuses also were smaller, although less so, than when the antibiotic was given in the first half of pregnancy. Development of the placenta was inhibited, as shown by a decrease in its diameter (12.0 ± 0.1 mm) and weight (490 ± 27 mg). Very often hemorrhages and congestion could be seen beneath the pia mater (in the region of the fontanel). Histological examination revealed congestion of the vessels of the myocardium in all layers in some places, and congestion was particularly marked in the outer and inner layers of the myocardium. Parturition also was delayed and prolonged, with profuse bleeding and a high stillbirth rate (10 ± 1%). A postnatal mortality was present (2.5 ± 0.3%), but not in the control.

The newborn rats weighed less at birth (5.0 ± 0.04 g) and the difference from the control continued for 20 days of the postnatal period, when it was 20.0 ± 1.7 g in the experiment and 34.0 ± 1.0 g in the control ($P < 0.01$). The physical development of the young rats was grossly retarded and in particular their eyes opened late (on the 19th day in the experiment and on the 15th day in the control).

Ampicillin thus has no teratogenic action on the developing embryo, fetus, or newborn rat. However, the weight of the fetus and of the newborn animal was reduced, in agreement with data obtained by other workers [5]. Oxacillin, injected into the mother at any time of pregnancy, had a deleterious effect: it disturbed the course of parturition, caused hemorrhages and bleeding, and led to an increased stillbirth rate and postnatal mortality and retarded the physical development of the progeny.

LITERATURE CITED

1. A. P. Kiryushchenkov, "Transplacental passage of the antibiotics oxacillin, fusidin, and tetracycline and their effects on early stages of fetal development," Author's Abstract of Doctoral Dissertation, Moscow (1975).

2. A. P. Kiryushchenkov, M. F. Yankova, and M. A. Knyazeva, Akush. Gin., No. 12, 10 (1976).
3. V. V. Korzhova, N. T. Lisitsyna, E. I. Smirnova, et al., Byull. Eksp. Biol. Med., No. 7, 861 (1976).
4. V. M. Lotis and V.V. Korzhova, in: Abstracts of Proceedings of the 11th All-Union Congress of Obstetricians-Gynecologists [in Russian], Moscow (1963), pp. 94-96.
5. V. N. Solov'ev and L. P. Kovalenko, Antibiotiki, No. 9, 815 (1973).
6. J. S. Gordon and S. Y. Sbarra, Am. J. Obstet. Gynec., 126, 1023 (1976).
7. R. T. Hall, W. Barnes, L. Kreishnan, et al., Am. J. Obstet. Gynec., 124, 630 (1976).
8. A. Philipson, Am. J. Obstet. Gynec., 130, 674 (1978).
9. J. Simko, K. Barna, E. Barnova, et al., Csl. Gynek., 41, 598 (1976).

SOME BIOCHEMICAL AND BEHAVIORAL EFFECTS OF MORPHINE IN BENACTYZINE-TREATED RATS

A. L. Bandman, É. T. Vasilenko, and N. N. Pshenkina

UDC 615.212.7:547.943].015.2:615.217.34

KEY WORDS: benactyzine; motor excitation; morphine; dopamine; homovanillic acid.

Considerable importance in the regulation of spontaneous motor activity is attached to the nigrostriatal complex and, in particular, to interaction between antagonistic cholinergic and dopaminergic mediator systems in this brain structure. The state of equilibrium and balance between them is essential for normal functioning of the striatum and for the performance of physiological locomotor activity [15]. Central cholinolytics, by shifting the balance toward dopaminergic mechanisms, also induce behavioral disorders in the form of motor excitation, whereas drugs depressing dopaminergic activity may have a sedative or even a cataleptogenic action depending on their dose. Besides other pharmacological agents, the narcotic analgesics also give a hypokinetic effect and are able to modify dopamine (DA) metabolism in intact animals [9], but if the balance between the mediator systems is disturbed the character of their influence on dopaminergic transmission is still unexplained.

To study this influence the action of morphine was studied on behavior and on some indices of DA metabolism in the striatum of rats after preliminary injection of the central cholinolytic benactyzine.

EXPERIMENTAL METHOD

The behavioral effects of benactyzine were assessed by the spontaneous motor activity test, which is usually used to study the behavior of animals under the influence of drugs, including correlation between their action on cholinergic mediation processes and behavior [1, 7]. The biochemical studies included determination of the DA and homovanillic acid (HVA) concentrations in the caudate nucleus by modified methods in [10, 14]. Experiments were carried out on noninbred male rats weighing 180-250 g. The animals' motor activity was recorded throughout the experiments by the "Animex" apparatus (model DSE, sensitivity and tuning 40 μA), and the recording began 10 min after the animal was placed in the chamber. During the first hour motor activity of intact animals was recorded in all the experimental groups (background); activity of rats of group 1 (the control) was then recorded, physiological saline was injected, activity of the rats of group 2 was recorded, and they were given benactyzine in a dose of 40 mg/kg. The animals of groups 3 and 4 received injections of morphine 30 min after benactyzine in doses of 2 and 10 mg/kg, respectively. Rats of groups 5 and 6 received only morphine in doses of 2 and 10 mg/kg, respectively. Motor activity was recorded for 1 h after injection of morphine. The mean number of movements for the group was expressed as a percentage of the background value and compared with the control for similar time inter-

S. M. Kirov Military Medical Academy, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR V. K. Kulagin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 2, pp. 185-188, February, 1981. Original article submitted May 6, 1980.

0007-4888/81/9102-0171$07.50 © 1981 Plenum Publishing Corporation