THE EFFECT OF NISENTIL UPON THE INTRA-UTERINE RESPIRATORY MOVEMENTS OF THE RABBIT FETUS * † ‡

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NISENTIL has recently been introduced as an obstetric analgesic by Smith and Nagyfy (1). Nisentil is *d,l*-alpha-1,3,dimethyl-4-phenyl-propionoxypiperidine hydrochloride and had been referred to as NU 1196. Comments in clinical reports regarding fetal depression following its administration to the mother vary from the comment of Hapke and Barnes (2) of "little evidence of fetal respiratory depression" to that of Lund (3) of "some increase in neonatal asphyxia." The clinical estimation of the effect of analgesic and anesthetic drugs administered to the mother on the respiratory function of the newborn is difficult because of a number of uncontrollable factors present in clinical obstetrics. Thus valuable data can be secured by studies of the effects of such agents on the fetuses of pregnant rabbits near term.

EXPERIMENTAL PROCEDURES

The method reported by Snyder and Rosenfeld (4) and by Bonar and Blumenfeld (5) was used with minor modifications. This method is based upon the observation that regular rhythmic respiratory movements occur in fetuses during a period immediately before birth and that these movements are influenced by drugs administered to the maternal circulation.

Our procedure was as follows: An extract of pregnancy urine (antuitrin S, Parke-Davis), in a dose of 120 to 130 IU, was administered intravenously to a pregnant rabbit approximately seven days before delivery. The hormone retards uterine contractions by inhibiting the onset of labor (6) and it has been shown that the character and rate of the uterine movements have some effect on respiratory activity of the fetus close to the end of term (4). At the time of the experiment a spinal transection was done under local anesthesia at approximately

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the level of the tenth or eleventh thoracic segment. The rabbit was then placed in a large bath containing Ringer's solution at 37 C and arranged in such a way that the head and upper chest region were above the fluid level. A midline abdominal incision was made and the uterus, submerged under the Ringer's solution, was carefully withdrawn and laid upon a submerged shelf. The uterine wall opposite each placenta was incised, freeing the fetuses which were floated out enclosed in their membranes onto the submerged shelf.

The fetuses were numbered according to their position in the uterine horn and the respiratory movements of each fetus were counted by means of a series of numbered keys and signal magnets corresponding to the numbers of the fetuses. One key and signal magnet circuit was provided for each fetus. Maternal respirations were also recorded on the kymograph by means of a balloon pneumograph and a tambour. A time marker set at one minute intervals made it possible, after the experiment, to determine the rate of the respiratory movements of the fetuses and of the mother.

After a period of observation during which control rates were recorded the nisentil was given by a single injection into the marginal ear vein of the mother. The rates of respiration of each fetus were recorded at frequent intervals and of course the maternal respiration was a continuous recording. These rates were followed for at least four hours. At the conclusion of each experiment, each fetus was delivered to air, the cord tied and cut and note was taken of the strength of respiration, the cry if present and the general condition of the fetus.

EXPERIMENTAL RESULTS

Results of a typical experiment in which 7 mg. per kilogram of nisentil was administered intravenously to the mother are shown in table 1 and in figure 1. The variations in the fetal rates during the control period can be observed to range between 3 and 22 per minute. Snyder (4) also found similar variations of the rate of respiratory movements between the fetuses of a given experimental animal. It is, therefore, necessary in order to determine the effect of the nisentil to observe both the change of rate of each individual fetus and the change of arithmetic mean. These are both indicated in the table and the graph. As can be seen nisentil in this dose abolished fetal respiratory movements for almost fifteen minutes, after which restoration of activity began and at the end of about two and a half hours recovery was practically complete. The depression of the maternal respiration is approximately parallel to that of the fetuses.

Nine pregnant rabbits were used in these experiments. Doses ranged from 3 to 15 mg. per kilogram. Despite caution and care in injection, death of the mother occurred in 3 cases with doses of 11, 13 and 15 mg. per kilogram. A summary of these experiments is given in table 2. It will be seen that a dose of 3 mg. per kilogram produced very

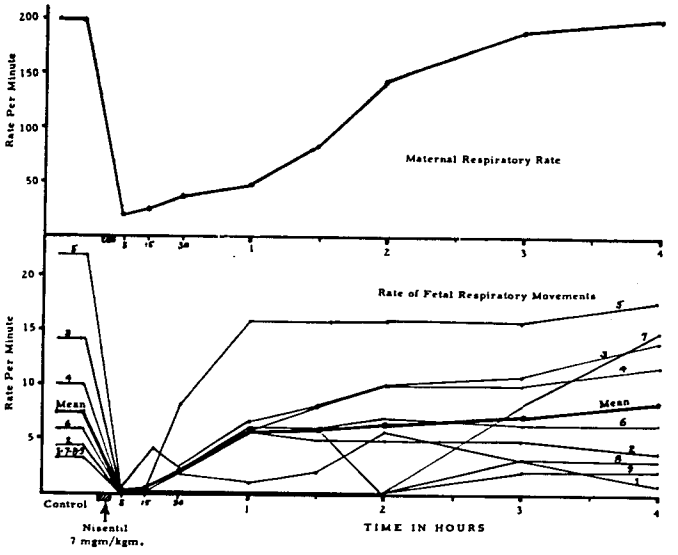

FIG. 1. Changes produced in the maternal respiratory rate and in the rate of the respiratory movements of 9 fetuses after the intravenous administration of 7 mg. per kilogram of nisentil by the marginal ear vein of the mother.

TABLE 1

THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF 7 MG. OF NISENTIL PER KILOGRAM INTO THE MATERNAL CIRCULATION ON RESPIRATORY RATES OF THE MOTHER AND OF THE FETUSES

	Control	5 min.	15 min.	30 min.	60 min.	90 min.	2 hr.	3 hr.	4 hr.
Maternal	200	14	22	30	44	80	140	190	200
Fetus:									
1	3	0	0	2	1	2	6	3	1
2	4	0	4	2	6	5	5	5	4
3	14	0	0	2	7	8	10	11	14
4	10	0	0	2	6	8	10	10	12
5	22	0	0	8	16	16	16	16	18
6	6	0	0	0	6	6	7	6	6
7	3	0	0	0	0	0	0	8	15
8	3	0	0	2	6	6	0	3	3
9	3	0	0	0	0	0	0	2	2
Mean of Fetal Rates	7.5	0	0.4	2	5.3	5.7	6	7.1	8.1

TABLE 2

SUMMARY OF THE EFFECT OF NISENTIL ADMINISTERED INTRAVENOUSLY INTO THE MATERNAL CIRCULATION ON THE RESPIRATORY RATE OF THE MOTHER AND ON THE MEAN RESPIRATORY RATE OF THE FETUSES

Dose, mg. per kg.	Respiratory Rate	Mean Respiratory Rate at the End of:								
		Control	5 min.	15 min.	30 min.	60 min.	90 min.	2 hr.	3 hr.	4 hr.
3	Maternal	200	30	44	160	172	184	200	196	
	Mean Fetal	12.6	7	6	11.6	11.2	10.4	11.4	13.4	
4	Maternal	184	30	40	48	55	64	72	135	196
	Mean Fetal	13.5	3.5	10	12.5	15	17	22.5	31	31
5	Maternal	160	5	13	20	28	37	42	42	50
	Mean Fetal	52.7	2	12.6	27.3	42.6	50	56	56.7	57.7
7	Maternal	200	14	22	30	44	80	140	190	200
	Mean Fetal	7.5	0	0.4	2	5.3	5.7	6	7.1	8.1
9	Maternal	200	18	18	23	25	26	35	63	100
	Mean Fetal	25.2	0	4.4	9.6	14	18.8	23.2	23.8	21.6
10	Maternal	196	5	22	26	30	34	40	50	52
	Mean Fetal	14.8	0	0	2.6	4.9	5	6.3	7.6	11.4
11	Maternal	184	12	Maternal death in 10 minutes						
	Mean Fetal	16.4	0							
13	Maternal	196	Maternal death in 5 minutes							
	Mean Fetal	38.6								
15	Maternal	200	Maternal death in 5 minutes							
	Mean Fetal	14.2								

little depression of the fetal respiratory rate which returned rapidly to a normal level. A dose of 5 mg. per kilogram produced marked depression of the fetal respiratory rate and also of the maternal respiratory rate which lasted as long as two hours. A dose of the 7 mg. per kilogram and higher produced stoppage of the fetal respiration for a short time and a period of three to four hours elapsed before both of these rates were restored to that of the control. In all cases the changes of the maternal respiratory rate showed a striking parallel to the changes in the rate of the fetal respiratory movements.

DISCUSSION

There are admitted limitations to the transference of laboratory findings on animals to clinical situations but in view of the usefulness of such investigations (7) these findings on nisentil are of some significance. The doses used for rabbits are higher than those which would be administered to pregnant mothers. This is a common finding and it is generally believed that while exact dose levels are not trans-

ferable, the basic conditions are similar in both situations. The experimental data also show a wide range in the rates of respiratory movements of the fetuses of a single rabbit. It would appear difficult to secure significant data from such a wide variation but in spite of this the effect of nisentil on the fetal rates was undeniable both when the rate of a single fetus or when the mean rate of all the fetuses was followed.

The experimental results establish the fact that nisentil passes freely across the placental barrier and excercises a depressant effect upon the rate of the respiratory movements of the fetuses. The degree of this effect is dependent upon the quantity of the agent administered to the maternal circulation. This effect on fetal respiratory movements is correlated with the decrease in respiratory rate of the mother. This leads to the suggestion that in obstetric analgesia, the maternal respiratory rate is an index of the effect of the agent on the fetal respiratory function. If this index is used it must be remembered that these findings show a greater effect on respiratory movements than on maternal respiration and that fetal respiratory movements were abolished while the maternal respiration was still present and sufficiently adequate to indicate that the mother was in no serious respiratory depression.

These observations lead to a question which can be answered only by clinical observation: can an obstetric analgesic agent such as nisentil produce a state of analgesia and amnesia in the mother without depression of maternal respiration? Such a question is almost impossible to answer by animal experimentation because of the inadequacy of analgesia testing methods. If this should be the case, it would then appear that such an agent would not depress the fetal respiratory function and would, therefore, be safe from the standpoint of risk to the fetus. Since this is not known it would appear advisable to recommend that nisentil be administered to the mother no closer than four hours before the expected delivery of the baby. This is good practice with most obstetric analgesics and is predicated on the expectation that four hours after administration the agent will largely be detoxified and its effects on the fetus minimal.

SUMMARY

Nisentil administered intravenously to the circulation of the pregnant rabbit near term produces depression of fetal respiratory movements in doses under 5 mg. per kilogram of body weight and abolition in doses of 5 mg. to 10 mg. per kilogram for a short period of time. Doses of over 10 mg. per kilogram produced death of the mother. Depression of the fetal respiratory movements was paralleled by depression of the maternal respiratory rate and this is suggested as an index of the effect of the analgesic agent upon the fetus.

The depression of the respiratory movements of the fetuses appeared to be parallel to the decrease in the respiratory rate of the mother and this is offered as a suggested clue, in the clinical use of nisentil for obstetric analgesia and amnesia, for determining the condition of the respiratory function of the "about-to-be-born" baby.

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