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The Duration of Effect of Maternally Administered Meperidine on Neonatal Neurobehavior

ROBERT HODGKINSON, M.A., M.D.,* AND FARKHANDA J. HUSAIN, M.D.†

The results of neonatal and infant neurobehavioral tests have been used as an argument against the use of anesthetic and analgesic drugs during labor and delivery. It has been claimed that changes persist for several years.[1,2] On the other hand, maternal pain and stress have been demonstrated to adversely affect the fetus[3,4] and relief by meperidine has been shown to be beneficial.[5] This study was designed to assess the effects of a single medication, meperidine, on neonatal neurobehavior and whether such effects persist in newborns up to the age of 5 days.

MATERIALS AND METHODS

The newborns were delivered by cesarean section indicated either by lack of progress in labor or malpresentation. A considerable number of women who had undergone previous cesarean sections were included since it is the policy of our Department of Obstetrics and Gynecology to allow such patients a trial of labor unless there is a contraindication. An investigator who took no part in the subsequent neonatal evaluations excluded patients who had been in labor more than 15 h, who had any perinatal risk factors, such as maternal disease (diabetes, gestational hypertension, marked obesity, etc.) or fetal distress. The patients ranged in age from 18 to 35 years. The neonates corresponded to the "clinically acceptable ideal group" of Crawford *et al.*[6] except that the mothers had been in labor.

The anesthetic used was an epidural injection of 20 ml 0.75 per cent bupivacaine at L3–4 which is adequate for 95 per cent of cesarean sections in our patient population. If the dose had to be augmented, the patient was excluded from the study. One liter of lactated Ringer's solution was administered prior to anesthesia, left uterine displacement using a wedge was employed, and all patients received 100 per cent oxygen fed through a wide corrugated tubing, a reservoir bag, and a close fitting mask.

Neonates were normal, term babies weighing more than 2,500 g. The Apgar score was above 6 at 1 min and 9 or above at 5 min. Neonates were placed in one of two groups: a meperidine group in which the mothers had received a mean dose of 105 ± 21 mg (mean ± SD) of meperidine and a non-meperidine group in which mothers had not received meperidine. No other narcotics were used during labor. Table 1 shows that there was little difference between groups in respect to birth weight, duration of labor, and the mother's age, weight, and height. There was a difference between groups in the percentage receiving epidural anesthesia for labor since this was a natural alternative to the use of meperidine.

Neonatal assessment was performed on the first day at 4 to 8 h of age and on subsequent days in the hour before the midday feeding. The evaluator was unaware of the anesthetic or analgesic management. Testing was performed in a quiet, constant temperature environment with the baby awake or in a light sleep. The Early Neonatal Neurobehavior Scale (E.N.N.S.) was modified to make it more sensitive by converting in into an eight-point scale. The order of administering the component tests to the neonate was kept constant. Details of the tests are given by Scanlon and associates in a previously published article.[7]

RESULTS

Since neurobehavioral scores are on a ranking (ordinal) scale, the score for each test was classified as being above or below the median score on each of the 5 days. Since the median score was a fraction, no scores fell on

TABLE 1. Patient Description (Mean ± SD) and Percentage Receiving Epidural Analgesia for Labor

	Meperidine Group	No Meperidine Group
Birth Weight (g)	3321 ± 391	3311 ± 407
Duration of Labor (h)	12.1 ± 3.5	11.6 ± 4.1
Mother's Age	21 ± 5.1	22 ± 6.3
Mother's Weight (kg)	71.7 ± 11.0	76.6 ± 8.7
Mother's Height (cm)	160 ± 4	161 ± 3
Meperidine Dosage (mg)	105 ± 21	0
Percentage Receiving Epidural Analgesia for labor	16	72

* Professor of Anesthesiology.
† Assistant Professor of Anesthesiology.

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Address reprint requests to Dr. Hodgkinson: Department of Anesthesiology, the University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, Texas 78284.

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TABLE 2. Percentage of Neonates with Low Scores in the Ten Constituent Assessments*

	Day				
	1	2	3	4	5
Overall	66§	62‡	60†	42	48
Pinprick	60†	58	48	44	50
Tone	64§	62‡	46	58	56
Rooting	58	60*	50	42	52
Sucking	60*	58	48	40†	52
Moro	58	58	50	56	58
Sound	50	56	52	46	42
Placing	62‡	52	42	50	56
Alertness	70¶	62	58	50	40‡
Decrement	62‡	64‡	60†	48	52

* Neonates were in the meperidine group; all scores were lower than the median; assessments were taken from the Early Neonatal Neurobehavorial Scale on the first five days after birth.
† $P < 0.05$.
‡ $P < 0.02$.
§ $P < 0.01$.
¶ $P < 0.001$.

the median itself. Table 2 shows the percentage of babies having a lower than median score (low score) in the meperidine group on days 1 through 5. The percentage of babies in the non-meperidine group having a score lower than the median can be obtained by subtracting the percentages in table 2 from 100. The scores were compared statistically by a non-parametric test (chi-square).

Table 2 shows that for overall assessment, tone, and alertness, the percentage of scores lower than the median (low scores) was greater in the meperidine group of neonates at a high level of statistical significance ($P < 0.01$ to < 0.001) while for response to pinprick, sucking, placing, and decrement score to pinprick, the percentage of low scores also was greater in the meperidine group but at a lower level of statistical significance ($P < 0.05$ to < 0.02). On day 2, the percentage of low scores was again greater for overall assessment, tone, and decrement score in the meperidine group at a statistical significant level of $P < 0.02$ and for rooting at a level of $P < 0.05$. By day 3, only overall assessment and decrement score had higher percentages of low scores at $P < 0.05$. On day 4, sucking showed a lower percentage of low scores in the meperidine group ($P < 0.05$) and on day 5, alertness ($P < 0.05$).

DISCUSSION

This study presents evidence derived from the use of the well-tested and widely used Early Neonatal Neurobehavioral Scale[7] (E.N.N.S.) that the effects of moderate doses (mean 105 ± 21 mg) of meperidine influence infant neurobehavior for 2 to 3 days but have no effect after the third day of life. It is possible that more sensitive tests might show a longer effect but the more sensitive the test, the less significance it probably has on infant well-being. E.N.N.S. scores have been shown to be unchanged following the use of bupivacaine for labor[8] and cesarean section[9] (mean dose 168 ± 7 mg). In addition, both groups received the same dose (150 mg) of bupivacaine so that it is reasonable to attribute any changes in neurobehavior to meperidine.

Objective evidence suggests that the pharmacologic effects of meperidine last about 3 days. The elimination half-life of meperidine is about 23 h[10] in the neonate compared to 3–5 h in the adult. Almost total elimination of the drug, including its principal and highly active metabolite nor-meperidine, takes place in 3 to 6 days.[11,12] Rosen and his colleages[13] have shown modification of the neonatal EEG within 2 min of maternal iv administration of meperidine and they and others[14] have demonstrated intermittent EEG changes lasting 3 days. It is concluded therefore that any pharmacologic effect of maternally administered meperidine on the neonate is limited to the first 3 days following birth.

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