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Labor Analgesia and Infant Brain Development

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GOLUB, M. S. *Labor analgesia and infant brain development.* PHARMACOL BIOCHEM BEHAV **55**(4) 619–628, 1996.—A large percentage of newborns are exposed to pharmacological agents that affect the brain in connection with pain management during labor. The two most commonly used agents are meperidine, administered intravenously or intramuscularly, and bupivacaine, administered by the epidural route. Over the years, infant behavioral assessments have been used in the neonatal nursery to identify labor analgesia regimens with minimal impact on neonatal status. However, considerable controversy has centered on the general issue of possible harm to the neonate from use of analgesia and anesthesia in obstetrics. Due to limitations on experiments in the obstetric situation and a lack of suitable animal models, the broader issues concerning the effects of these agents on the developing brain and possible long-term consequences for infant adaptive functioning have received little attention. A series of studies has recently been completed using a rhesus monkey model for administration of labor analgesia under controlled experimental conditions and long-term behavioral evaluation of infants. Most of the assessments, including those of cognitive function, were not influenced by perinatal analgesia. However, these studies have confirmed the neonatal depressant effects of meperidine and have suggested that the course of behavioral maturation during certain periods of infancy is influenced by both meperidine and bupivacaine administration at birth. These effects could occur as a result of effects on vulnerable brain processes during a sensitive period, interference with programming of brain development by endogenous agents, or alteration in early experiences.

Obstetrics Analgesics Opiate Anesthesia Bupivacaine Neonate Infant Behavior Rhesus monkey

PROBABLY the most widespread exposure of the developing brain to central nervous system active agents occurs at birth. Understanding how obstetric analgesics interact with brain development is a potentially important topic in behavioral pharmacology. Laboring women need access to the most effective and safest form of pain relief that can be provided through scientific understanding of this research problem. More broadly, this research topic can further our understanding of the vulnerability of the brain at the stages of development that occur in the late fetal and early neonatal periods.

This paper focuses on the two most commonly used obstetric analgesics, the opiate analgesic meperidine, typically administered intravenously or intramuscularly, and the local anesthetic bupivacaine, administered by the epidural route. Human clinical and epidemiological studies and experimental work conducted by our group in the rhesus monkey are reviewed.

EXPOSURE OF THE FETUS/NEONATE TO OBSTETRIC ANALGESICS

It is clear that obstetric analgesics are transferred to the fetus, where they exert pharmacological effects. Meperidine and related opiate analgesics are highly lipid soluble and readily distribute to the fetus. When bupivacaine is administered for epidural anesthesia, it is applied directly onto the external surface of the dura of the spinal cord, whence it diffuses into the cerebrospinal fluid, enters the venous circulation and is distributed via systemic circulation to the fetus. An important factor determining fetal exposure in the human clinical situation is drug-delivery interval; the longer the infant remains in utero after drug administration to the mother, the greater the cumulative exposure to drug. Numerous studies have demonstrated that effects of meperidine on the newborn are much more pronounced if drug-delivery intervals exceed 1 h (8,55,74,83).

A commonly used measure of distribution to the fetus is the fetal:maternal ratio or the concentration in serum from the umbilical cord divided by the concentrations of the drug in maternal serum at birth. The fetal:maternal ratio, however, provides only a point estimate. Animal models, particularly sheep and rabbits, are commonly used for maternal–fetal pharmacokinetic studies and determination of tissue concentrations (17,50). Typically, drugs are administered by intravenous or epidural routes during late pregnancy; studies that actually simulate the obstetric situation by administering drug during

labor have not been performed in sheep or rabbit models. We have recently undertaken studies in guinea pigs that use intrapartum administration and have confirmed that epidural bupivacaine reaches the fetal brain when administered during labor (36).

With regard to pharmacological effects, commonly used doses of meperidine (50 mg, i.v.) reduce the frequency and duration of fetal movements and fetal heart rate variability and oxygenation (7,95). Depending on dose, neonatal respiratory depression can be observed at birth (8,83). Shortly after birth, spontaneous nursing behavior is depressed or absent (73). Depression is usually not observable by 6 h after birth but can be detected with neurobehavioral testing as long as 3 days after birth (55). Although analgesia has not been evaluated, opiate agents undoubtedly provide pain relief to the fetus as well as to the mother during labor. Epidural anesthetics also transfer to the neonate and affect physiological function as indexed by changes in the fetal heart rate (56), blood gases (6), electrocardiogram (71), incidence of bradycardia (84) and neonatal hypotonia (78). Mepivacaine, etidocaine and lidocaine can produce a "floppy infant," an alert neonate with poor muscle tone (78). Although obstetric analgesics reach the fetus, fetal effects could be mediated via the maternal system as well as by direct pharmacological action on the fetus. In the case of meperidine, naloxone reversal of neonatal effects indicates a direct pharmacological effect (18,43,91).

STUDIES OF OBSTETRIC ANALGESIA AND INFANT OUTCOME IN THE HUMAN CLINICAL SETTING

Human Clinical Studies of Neonatal Status

Human clinical studies have helped reduce the use of agents and doses of obstetric analgesics with the most serious impact on neonatal status, but they have provided little information concerning the interaction between individual agents and brain development. The initial study using the Apgar score (4) provided quantitative documentation of newborn depression and poor oxygenation ("blue babies") and led to a decline in use of general anesthesia, which was a common practice in obstetrics at that time. Analgesics such as morphine replaced general anesthesia. Meperidine came into widespread use after it was found to produce less neonatal respiratory depression than did morphine (89). Subsequently, techniques were developed for routine use of epidural anesthesia in labor, which further reduced the occurrence of neonatal depression. However, standardized neurobehavioral assessments [Scanlon Early Neonatal Neurobehavioral Scale (ENNS) and Amiel–Tison Neurological and Adaptive Capacity Scoring System (NACSS)] introduced by anesthesiologists in the 1970s demonstrated neonatal effects other than respiratory depression and poor oxygenation (2,78). The ENNS measured muscle tone and response to different sensory stimuli and emphasized evaluation of response decrement with repeated stimulus presentation. The NACSS focused on muscle tone. Both tests elicited typical newborn reflexes like rooting, sucking and grasp and provided a single overall summary score. These tests required less than 10 min to administer and could be conducted in the neonatal nursery. Using the ENNS, bupivacaine was reported to influence the neonate less than did lidocaine and mepivacaine (78,79) and became the standard agent for epidural analgesia. When bupivacaine was compared with meperidine, less neonatal depression but more prolonged effects on muscle tone were observed (91). The Apgar, ENNS and NACSS tests continue to be widely used to evaluate the neonatal effects of obstetric analgesics. For instance, the Apgar and NACSS tests were used to evaluate neonates during clinical trials for a new bupivacaine analog, ropivacaine (86).

Apart from guiding clinical choice of agents, characteristics of these studies seriously limit the conclusions that can be reached. Most studies of neonatal effects of obstetric analgesia compare one agent with another rather than with a nontreated control. Random assignment to a "no analgesia" control group is seldom feasible; we were able to locate only one early study in the United States and one study performed outside the United States that used random group assignment. If mothers receiving analgesia are compared with self-selected controls (women who do not need or choose not to use analgesia), factors like primiparity, long labor, use of oxytocin and instrumental delivery are almost inevitably more prevalent in the drug-treated group (52,53). Matching for most of these factors can only be done retrospectively, and multiple regression and covariance techniques have limited success in separating highly correlated variables. The same problem with confounding occurs when dose-response studies are attempted without random assignment.

From the point of view of the behavioral scientist, little is revealed by neonatal status exams concerning particular brain processes or systems affected and the impact on adaptive function. In addition, neonates are only evaluated during the first few days of life while they are in the hospital. Thus, it is not possible to determine whether neonatal effects persist and cause problems in older infants, indicating an effect on brain development rather than a transient pharmacological effect.

Human Studies with Behavioral and Psychological Endpoints

In addition to examining neonatal status, early studies also evaluated more complex aspects of brain function. In 1964, Stechler reported in *Science* that labor medication influenced the amount of attention 2–4-day-old babies directed at three pictures that were shown to them (85). Subsequently, investigators began to apply a broader range of behavioral and psychological tests and examine longer postbirth intervals. Many of these studies were more focused on possible long-term or permanent effects. In the most of the early studies, all the mothers had received different amounts and types of obstetric analgesia and/or anesthesia (there were no untreated controls). The independent variable was either the overall amount or "potency" of the drugs or the absence/presence of an individual drug used with other drugs (12,13,23,43). For instance, Brackbill et al. (12) reported that in a group of 25 infants, all of whom received prilocaine epidural anesthesia and 75% of whom had instrumental deliveries, 11 neonates whose mothers received meperidine (50–150 mg) habituated less rapidly to an auditory stimulus (white noise) than did 14 neonates who received only the prilocaine. This was a very striking finding; the prilocaine + meperidine group habituated half as fast as the prilocaine-only group, an effect that accounted for 73% of the variability. Other studies have also found slower habituation in meperidine-exposed infants against a background of multidrug deliveries. One study found that infants given meperidine followed by naloxone habituated more rapidly than did those given meperidine without naloxone (90). However, this study did not contain no-naloxone or no-analgesia controls. Thus, little could be discerned about possible agent-specific effects. In contrast with studies of neonatal status, these results were very controversial (51,53,65). Interpretation

of causal relationships between perinatal drug and infant outcome was complicated by confounding factors. In addition, the meaning and significance of the behavioral effects were disputed.

What types of neurobehavioral effects have been described as a consequence of obstetric analgesia? Many of these studies, conducted in the 1970s and early 1980s, used the Brazelton Neonatal Behavioral Assessment Scale (BNBAS). The BNBAS determined the presence and vigor of neonatal reflexes and assessed responsiveness and response decrement like the ENNS and NACSS. However, it was a longer test (49 items), included factors such as state regulation and was intended for use by a trained examiner. The BNBAS was usually analyzed in clusters of items thought to represent discrete brain functions such as habituation, orientation, motor performance, regulation of state, autonomic regulation and occurrence of abnormal reflexes. The clusters could be conceptually linked to biological substrates and later function. As summarized in reviews by Brackbill et al. (13) and Sepkoski (81), all seven of the commonly used clusters, as well as other behavioral evaluations reflecting similar functions, have been affected in some of the 40–50 studies of different agents conducted prior to 1985. The most commonly affected cluster was motor performance, followed by habituation and orientation (81). No two studies had similar enough designs to provide a replication of a particular result, and many used high doses, and/or multiple drug treatments, and did not have unmedicated controls.

A large-scale study using the BNBAS compared groups receiving meperidine, bupivacaine or no labor analgesia with a 42-day postnatal evaluation period (9,59,75). The analysis of the resulting data sets revealed few significant differences between the drug and control infants, and most of these were seen immediately after birth. However, a number of relationships emerged from regression analyses using dose of drug. This finding points out the problems associated with forming a single exposure group made up of women who had received over a fivefold difference in dose. Variability is inevitably large in the drug-exposed group, and drug effects that are not linear or that occur in a restricted dose range will not appear. In this report, the investigators suggested that the drug had a biphasic effect, improving behavioral endpoints at low doses and adversely affecting them at higher doses.

Two well-controlled studies comparing a single agent to a control no-analgesia† group have detected effects up to about 1–1.5 month of age (the oldest age tested) for both meperidine and bupivacaine (55,82). Findings are described here in detail to illustrate the kind of information that results from this type of study. The first study compared neonates exposed to a low dose of meperidine with no-analgesia controls (55). BNBAS testing was conducted at less than 12 h and at 3 days after birth. Gravidity (number of previous pregnancies) and parity (number of previous deliveries) were significantly lower in the drug-exposed group and labor was longer. Parity was correlated with BNBAS scores and so was used as a covariate in the analysis. There were no main effects of drug, but interactions between drug and test time were noted; for the state-regulation cluster, the drug group had a lower score than did controls at 3 days, and for the abnormal reflex cluster, the drug group had a lower score than did controls less than 12 h after birth. Drug delivery interval was correlated with the abnormal reflex cluster on both days. The investigators concluded that neurobehavioral effects of meperidine were seen but that they were subtle and, in the case of state regulation, too small to be considered meaningful by accepted norms. No particular interpretation of the meaning of the abnormal reflex score was provided.

The second study compared epidural bupivacaine with no-analgesia controls (82). The BNBAS was administered 3 h after birth and 3, 7 and 28 days after birth. The groups were matched for parity and, as closely as possible, for labor length; however, they differed significantly in amount of oxytocin used and frequency of instrumental deliveries, both of which were greater in the drug group and were used with labor length in covariate and multiple regression analyses. A significant drug effect was identified for the orientation and motor clusters. Both clusters were also influenced by test time, but there was no interaction with drug in either case. In regression analyses, which included oxytocin, instrumental delivery and labor length, dose of bupivacaine was associated with poorer scores for the orientation and motor clusters. The investigators suggested that the longer term effects could be a consequence of the influence of early behavioral differences in the neonates on later mother–infant interaction. Despite attempts to control for confounding, this study has also proved to be provocative and controversial (3).

Possible impacts of altered neonate behavior on successful mother–infant interactions have long been a concern of behavioral scientists working in this area. Several early multiple-drug studies demonstrated effects on sucking and nursing behavior (14,44,53,72). One of the few studies with a randomly assigned no-analgesia control (54) found that parameters of sucking (rate, pressure, amount consumed) were reduced by secobarbital administration during labor. Mother–infant interaction was also briefly assessed as part of several studies with a no-analgesia control group. Lieberman et al. (59) found that bupivacaine-treated mothers spent less time talking to their infants, and Sepkoski et al. (82) found that mothers in a bupivacaine-treated group reported spending less time with their neonates than did the no-analgesia controls. In the most extensive and best controlled study of this type, Murray et al. (64) compared bupivacaine-exposed infants to no-analgesia controls by using standardized observation (hospital diary of feeding and crying, 10-min observation of feeding) and several standardized instruments [BNBAS, Neonatal Perception Inventory, Degree of Bother Inventory, Carey Infant Temperament Scale, Mother's Assessment of the Behavior of Her Infant (MABI)]. Labor length and frequency of instrumental delivery were greater in the bupivacaine group, and these variables were used as covariates in the analysis. One month after delivery, effects of epidural bupivacaine were observed on endpoints such as the total score on the Degree of Bother Inventory, the adaptability scale of the Carey Infant Temperament Scale and the Interactiveness Scale of the MABI. Of course, these effects could be due to drug action on either the infant or the mother. The investigators suggested that the effects could be mediated by a bias in maternal attitude and behavior due to the mother's early perceptions of the neonate.

† Mothers in nonmedicated or no-analgesia groups were not given systemic analgesia/anesthesia for pain relief during labor. However, they may have received local anesthetic for episiotomy or other medications with central nervous system effects such as antihistamines, antihypertensives, etc., during labor. The drug history of the mother during pregnancy or just prior to labor is unknown, so chronic or recent use of central nervous system active drugs is not taken into account.

Information concerning labor analgesic effects on infant behavior is missing in two areas, infant cognitive function and infant development. Paradigms for studying infant cognitive function, such as novelty preference, object permanence, associational learning and memory, were not available when the initial concern about neurobehavioral effects of obstetric analgesia were raised and have not subsequently been applied to this research problem. Studies of maturation rate by using sequential measures of behaviors that are known to mature during the evaluation period have also not been performed. Both types of studies require more extensive and controlled access to the infants.

Epidemiological Studies of Multiple-Risk Factors

A number of large retrospective studies have looked at perinatal risk factors and later childhood behavioral competence (15,39,62,68). These risk factors include low birth weight, prematurity, instrumental delivery, oxytocin-induced labor, neonatal status, type of delivery (vaginal/surgical) and obstetric analgesia. Obstetric analgesia is usually classified in broad categories such as general anesthesia, regional analgesia, number of agents or total dosage rather than by individual agent. School-age children are typically evaluated for IQ scores or other global functional measures. In these studies, obstetric anesthesia is frequently one of a number of cumulative risk factors defining neonates at high risk for later brain dysfunction (15,57). These studies, however, provide no specific information about individual agents or behavioral processes. Furthermore, retrospective identification of obstetric analgesia administration from medical documents is not always accurate (5).

A recent series of studies has examined obstetric analgesics as a risk factor for amphetamine and opiate addiction (45,46,66,67). Specifically, mechanistic considerations have suggested that nitrous oxide exposure might influence ontogeny and later responsiveness of the catecholamine systems and bias amphetamine addiction, whereas opiate analgesia exposure could similarly affect opiate addiction. Supporting evidence for the hypotheses has been reported, but interpretation of these studies has been difficult due to confounding factors such as socioeconomic status and hospital of birth.

STUDIES OF OBSTETRIC ANALGESIA AND INFANT OUTCOME IN MONKEYS

As described in the previous section, a major controversy has existed about the causal vs. associational nature of the relationship between obstetric analgesia and later infant behavior reported in the human clinical literature because of confounding between analgesia/anesthesia and other factors such as labor length and parity. In addition, adequate information to pursue pharmacological mechanisms is missing because there are no studies comparing individual agents at defined doses with randomly selected or matched controls who receive no medication. It is difficult to overstate the problems associated with performing and interpreting controlled studies in the human obstetric situation. However, this type of study can be performed in an animal model. By using laboratory animals, precise experimental control of age and parity, dose and time of dosing, maternal housing and nutrition and postnatal environments is possible. Rats and mice are not appropriate for this type of study because brain maturation is at a much earlier stage at birth than is the case in humans (19). These consideration led us to investigate this research problem in rhesus monkeys.

Monkeys are similar to humans in employing a reproductive strategy that includes single-offspring pregnancy, prolonged intrauterine development and an extensive period of dependency during the postnatal period. Labor and delivery in monkeys resembles that in humans in many ways including hormonal characteristics of late pregnancy (20) and uterine contraction patterns during labor (41). Monkeys differ from humans in that birth occurs according to a predictable diurnal schedule (infants are born 2–5 h after onset of the dark cycle) and locomotor abilities of neonates (standing and walking) mature within the first 2 weeks after birth. Newborn monkeys can be cared for in a neonatal nursery, where standardized neonatal assessments similar to the NACSS and BNBAS can be conducted (34).

We developed a methodology for administering analgesics during labor to conscious, minimally restrained rhesus monkeys. Pregnant monkeys were gradually adapted during pregnancy to a primate restraint chair (25). Labor readiness at term was evaluated with a modified Bishop score based on cervical length, consistency and dilation (27). Oxytocin-induced deliveries with administration of analgesic could then be conducted at term (60). Although the situation we used is not natural for rhesus monkeys, it is very similar to the human obstetric situation in terms of restricted movement and social interaction and the use of pharmacological analgesics and labor induction.

Doses at the high end of the human obstetric dose range were selected to produce pharmacological effects comparable to those reported in humans and compatible with the obstetric situation (i.e., alertness and mobility that allowed normal vaginal delivery). Administration was also modeled after the human obstetric situation. For example, the highest meperidine dose was administered in two portions 1 h apart. Bupivacaine was administered as a bolus followed by a 20-min infusion. The dose of meperidine used in our monkey studies, 2.0 mg/kg, was comparable to the highest dose of meperidine administered in a human study (55) of the effects of low doses of meperidine on neonatal behavior (100 mg or 1.4 mg/kg for a 70-kg parturient). The dose of bupivacaine used in the monkey studies, 1.2 mg/kg, was comparable to the mean dose of bupivacaine in a human study (82) of epidural aneshesia and infant behavior (112.7 mg or 1.61 mg/kg for a 70-kg parturient).

Meperidine and Alfentanil: Effects on the Neonate

The series of studies is outlined in Table 1. We first studied intravenous meperidine (2 mg/kg) and compared it with alfentanil (75 μg/kg), a more potent, shorter acting opiate agent that was coming into use in obstetrics, and with saline-injected controls. The doses were in the upper range of human therapeutic use in labor. Alfentanil had greater serum protein binding (97%) than did meperidine and so was anticipated to have a more limited transfer to the fetus. We found that fetal:maternal ratios of serum alfentanil at birth (0.20) were indeed lower than those of meperidine (0.46) but that plasma concentration of alfentanil increased rather than declined after birth so that the fetal:maternal ratio was 0.97 for alfentanil as opposed to 0.51 for meperidine at 2 h postnatal (31). Both meperidine and alfentanil produced respiratory depression as indicated by suboptimal respiratory rates on Apgar tests (overall Apgar scores were not affected). Both agents also produced a similar pattern of effects in the behavioral test battery (Table 1), which was conducted over the next 2 weeks (29). Drug-treated infants had greater elicited muscle tone (resistance of limbs to movement) and reduced responsiveness to aversive stimuli (pinprick, bell, bright light). In behavioral observations, male (but not female) drug-treated infants had

TABLE 1

STUDIES OF OBSTETRIC ANALGESIA AND INFANT OUTCOME IN ANIMAL MODELS

Agent	Evaluation Ages*	Drug dose and administration†	N/Group	Endpoints	Citation
meperidine hydrochloride	birth–14 wks postnatal	2mg/kg i.v. over 2 min during induced labor	5 monkeys	Plasma drug§ Neonatal status (Apgar)§ Neurobehavioral test battery§ Sleep wake patterns§ Fine motor ability Object constancy§ Observation of spontaneous behavior§ Growth and health	(28, 29)
alfentanil		2.4 μ/kg for 30 min, 1.2 μ/kg 10 min, then 0.6 μg/kg 10 min i.v. infusion during induced labor			
meperidine hydrochloride	3–12 mo postnatal	2 mg/kg i.v. over 2 min during induced labor	3–4 monkeys	Operant performance: discrimination reversal§ delayed alternation continuous performance§ Observation of spontaneous behavior§ Growth	(26)
meriperidine hydrochloride, high dose		2 mg/kg i.v. over 2 min followed 1 hr later by 1 mg/kg i.v. over 2 min during induced labor			
bupivacaine hydrochloride, 0.5%	birth–12 mo postnatal	0.6 mg/kg via epidural catheter over 2 min followed by 0.6 mg/kg over 20 min at term (165 days) or upon indication of imminent labor by cervical examination	8–11 monkeys	Neurobehavioral test battery§ Observation of spontaneous behavior§ Fine motor ability Visual novelty preference§ Object permanence Discrimination reversal Delayed nonmatch to sample Continuous performance Growth and health	(33)
meperidine hydrochloride	10/11 days postnatal	10–15 mg/kg 5 min prior to labor induction	6–10 male and 6–10 female guinea pigs	Vocalizations and cortisol in response to maternal separation§	(35)
meperidine hydrochloride	birth–14 wks postnatal	2 mg/kg i.v. over 2 min during induced labor	5–6 monkeys	Neonatal status (Apgar) Neurobehavioral test battery Sleep wake patterns§	(30)
meperidine + hypoxia		2 mg/kg i.v. over 2 min during induced labor+ 15 min hypoxia (12% O_2) on the day of birth		Fine motor ability Observation of spontaneous behavior§ Growth and health	

*Three months of postnatal development in rhesus infants is approximately equivalent to one year in human infants.
†Drug treated infants were compared to controls who underwent identical procedures but received saline rather than drug infusion.
§Significant group differences between control and drug exposed groups were found on some measures associated with this test. See Text.

a higher proportion of overnight sleep and a higher percentage of quiet sleep than did controls on the first night after birth. Both male and female infants demonstrated less active daytime behavior on the third day of life. Testing also suggested more favorable outcomes on some measures in the opiate-treated infants. The neonates exposed to meperidine and alfentanil regained their birthweight more rapidly than did controls and showed a more rapid maturation of prone progression (crawling, walking) and a higher percentage of mature postural patterns on the third day of life. General health evaluations indicated that formula intake, stool consistency and weight gain were similar in the two groups.

These evaluations demonstrated that meperidine and alfentanil had neurobehavioral effects that lasted up to 2 weeks of age. The indications of depression (more sleep, less responsiveness, lower daytime activity levels) during the first 3 days of life are consistent with the known pharmacological effects of opiates. The more rapid weight gain could be attributed to gastrointestinal effects of opiates, such as increased gastric emptying time. Furthermore, the increased muscle tone could be related to increased muscle rigidity seen with these agents. Because monkey infants have a much earlier onset of standing and walking than do human infants, the more rapid maturation of prone progression would not be noted in human infants. However, the increase in abnormal reflexes reported in human neonates exposed to meperidine may be related to these findings. Thus, the short-term effects of the drugs were in accord with previous reports in human neonates.

Meperidine and Alfentanil: Follow-up Evaluations through 14 Weeks of Age

Follow-up evaluations of this same group of meperidine- and alfentanil-treated infants were conducted by using standardized observational categories for spontaneous behavior and structured tests of fine motor behavior and cognitive abil-

ity (object permanence) from 2 to 14 weeks of age (28), which is equivalent to approximately 2 months to 1 year of age in children. In this age range, alfentanil-exposed infants seemed more affected than did meperidine-exposed infants. They showed a distinct drop in mature postural and locomotor behaviors (less standing and walking and more lying down) beginning at 6–7 weeks of age and poorer performance than did controls on object constancy testing that began at 6 weeks of age. Weight gain and fine motor maturation were similar in the drug-treated infants and controls, although the alfentanil-treated infants appeared to have a higher incidence of nonenteric infections.

Meperidine: Long-Term Evaluations through 1 Year of Age

Long-term evaluations were conducted from 3 to 12 months of age (equivalent to 1–4 years of age in children) (26). This study used a new cohort of meperidine-exposed infants and focused on cognitive function as evaluated with operant testing methodologies and observation of maturation of spontaneous behavior patterns. In discrimination reversal testing, drug-exposed infants demonstrated more balks and fewer correct choices after reversal. However, the treated group had fewer omission errors when tested on the Continuous Performance Test, a test of the vigilance aspect of attention. Toward the end of the evaluation period (6–12 months of age), differences in the maturation of spontaneous behavior patterns was noted. Control infants showed a decrease in motor activity (climbing, jumping, running) and an increase in quiet activities (manual exploration, visual surveillance) at this age, so that by 12 months of age they spent more time in quiet than in motor activities. This trend was not as apparent in the meperidine-treated infants, who continued to spend as much or more time in motor activities than in quiet activities. This study seemed to suggest that behavioral maturation patterns can be altered by perinatal analgesia and that some structured tests administered after the immediate neonatal period were also sensitive to exposure to opiate analgesics at birth.

Bupivacaine: Evaluations from Birth to 1 Year of Age

We have undertaken more recent long-term evaluations of monkey infants whose mothers received epidural anesthesia with bupivacaine (33). A bolus dose followed by an infusion (total dose 1.2 mg/kg bupivacaine) was given to simulate obstetric usage. The epidural anesthesia was not administered during labor but rather at full term (dams delivered an average of 3 days after bupivacaine treatment). Recent studies have suggested that bupivacaine itself prolongs labor in human parturients (77), and labor length has consistently been a confounder of bupivacaine use in obstetrics. If this is also the case in monkeys, it would be impossible to separate the effects of longer labor from the pharmacological effects of the drug.

Neonatal depression was not recorded in the bupivacaine-exposed animals, and object constancy, discrimination reversal and continuous performance tests were not affected, as had been the case for opiate exposed infants. In addition, as observed in opiate-treated infants, no behaviors indicative of hyperactivity or impulsiveness were seen. More rapid maturation of prone progression seen in the opiate-exposed infants may also have been reflected in the more mature prone progession scores of bupivacaine-exposed infants on the day of birth. More interestingly, differences in the time course of development of spontaneous behavior were observed at 6–8 weeks of age and at 6–12 months of age. Behavior at these ages was also affected in meperidine-exposed infants, but the pattern of effects was different. At 6–8 weeks of age, bupivacaine-exposed infants were not impaired in development of object constancy but did show delayed onset and frequency of manipulatory activities that normally occurs at this age. At 6–12 months of age, bupivacaine-exposed infants showed the age-appropriate increase in quiet activities and decrease in locomotor activity. However, another transition having to do with disturbance behaviors was altered. Disturbance behaviors typically occupied less than 3% of the total observation time and consisted primarily of infants sucking their fingers or toes. As the infants became older, they began to demonstrate motor disturbance such as repeated motor patterns such as climbing, flipping and cage shaking. Bupivacaine-treated infants showed less sucking during the earlier stages of infancy, and, as motor disturbance behaviors appeared, they showed exacerbated and prolonged amounts of time engaging in these behaviors.

Bupivacaine-exposed infants were also tested for visual novelty preference, a test developed by Fagan and Singer (22) and commonly used in human infants as an early indicator of intelligence. Novelty preference was normal in the bupivacaine-exposed group, but some differences were found in the duration of fixations. Bupivacaine-exposed infants directed more, shorter duration fixations at the stimuli than did controls.

Comparison of Bupivacaine and Opiate Agents

These studies have suggested that opiate agents differ from bupivacaine in their effects on infant behavior. Perhaps the more interesting conclusion suggested by the two studies is that effects of perinatal drug administration can emerge during major periods of transition in postnatal behavioral ontogeny, specifically at 2 months and 10–12 months of age, stages of maturation in monkeys that correspond to toddler and preschool ages in children. These are also important stages of maturation in the monkey. In early infancy, monkeys cling to their mothers with a prepotent involuntary clasp–grasp reflex. At around 2 months of age, voluntary control of grasp is achieved and infants are able to initiate departures from mother and engage in manipulation of the environment and peer play (11,40,47,61). During the later part of the first year, infants begin to spend less time in peer play and more time in typically adult activities such as foraging, grooming and maintaining visual surveillance of the environment (87). The exact nature and significance of the drug effects observed at these ages remains to be determined. They need to be confirmed in prospective studies and extended in experiments that test more specific hypotheses.

Meperidine and Maternal Separation in Guinea Pigs

One area we were not able to study in the infant monkeys was mother–infant interaction. To conduct the extensive behavioral evaluations in infant monkeys and avoid the stress of repeated separation from mother, the infants were raised in the primate nursery. However, mother–infant attachment is particularly relevant to meperidine because brain opiate systems have been implicated as mediators of separation-induced distress in different animal models including chicks (88), guinea pigs (69), rats (49) and monkeys (48). To address the question of whether an opiate agent such as meperidine, given at birth, could influence mother–infant attachment, a single dose of meperidine was administered to term pregnant guinea pigs just prior to labor induction and response to a 30-min

separation was measured on 11–12 days after birth by using a standardized protocol (42). The guinea pig was selected because brain maturation is advanced at birth, as is the case in monkeys and humans. The female guinea pig offspring that had been exposed to meperidine responded less to the separation, emitting about one-third the number of vocalizations as controls (35). There were no differences between corresponding groups of males, which generally vocalized less than did females during the separation. This result provides some indication that opiate agents can influence the response to maternal separation when given during delivery and not only at the time of separation, as has been previously demonstrated (48).

FUTURE DIRECTIONS: POTENTIAL MECHANISMS OF ACTION OF LABOR ANALGESICS ON DEVELOPING BRAIN

An appreciation of the effects of labor analgesia on brain development will require an understanding of the mechanisms by which these effects could occur. Several direct and indirect mechanisms need to be considered: (1) damage to a vulnerable process/area of the brain, (2) interference with "programming" of neural systems and (3) alteration of early postnatal interaction with the environment, including caretakers.

As for the first possibility, several brain areas could be seen as vulnerable due to a rapid rate of development at this time, primarily proliferation of cortical synapses (24) and myelination of subcortical structures (92). A general principle of neocortical development that has been derived from extensive work of Rakic et al. (70) is overproduction of synaptic connections ("cortical exuberance") during development. In rhesus monkeys, cortical exuberance begins in the perinatal period and reaches a peak at 2–4 months of age (94). During the same time periods, neurotransmitter receptor numbers peak in these cortical areas (58). Formation of synapses and the establishment of appropriate receptor types and numbers may be susceptible to disruption during this period of rapid development.

The second possibility is an important one for opiate agents. Opiate systems in the brain use different endogenous ligands such as growth and differentiation factors, and exogenous opiates can influence receptor regulation by these endogenous ligands (80). Endogenous opiates may have an organizational role in the brain around the time of birth due to the marked activation of these systems during labor and delivery in mothers and newborns (16,21,63). In addition, we have documented a rise in circulating beta-endorphin in monkeys in late pregnancy prior to the onset of labor (32). Attachment and bonding are processes that have been linked with opiate systems in the early postnatal period (10). Disruption of the normal ontogeny of the endogenous opiate system by perinatal meperidine is a mechanism for which some precedent has been established. Long-term effects on functioning of neurotransmitter systems have been demonstrated after brief exposures to exogenous receptor ligands (1,38,76,93). Not enough is known about the mechanism of bupivacaine action on brain to identify systems whose development could be "reprogrammed." Although bupivacaine and cocaine are similar in structure and pharmacology, bupivacaine does not affect dopamine reuptake and so is not likely to resemble cocaine in its developmental brain effects.

The third possibility, which is not well defined but is fascinating from the point of view of developmental psychology, is the role of early experience. Broadly, the experiences of early life that serve to "set" the operating characteristics of brain may be artificially altered. More specifically, labor analgesics might alter infant–caretaker interaction by a cognitively mediated effect (different evaluation by the mother of the drug vs. drug-free neonate).

It is also possible that labor analgesics could exacerbate the damaging effects of other interventions such as perinatal hypoxia. In fact, there is some evidence that analgesia lessens the occurrence and effects of hypoxia (37,65). We have shown that meperidine administered during labor alters the consequences of a 15-min period of oxygen deprivation on the day of birth, thus diminishing an increase in sleep the following night and also the pattern of change in exploratory and resting behaviors at 7 weeks of age (30).

SUMMARY

Our studies with perinatal administration of meperidine and epidural bupivacaine have produced both reassuring information and cautions that may be useful in improving the safety of obstetric analgesics. We have demonstrated, in detailed neonatal assessments, that meperidine-induced neonatal depression is limited in duration to the first few days after birth. We have also documented a lack of effect of either meperidine or bupivacaine on growth or on incidence of common infant health problems. Furthermore, our studies suggest a possible protective role of meperidine in offsetting the behavioral consequences of an hypoxic episode in the neonate. In addition, we have shown that the earliest infant cognitive abilities, object permanence and novelty preference, appear at the appropriate age in drug-exposed infants, although some aspects of performance may be affected. Our studies in older infants also indicate that complex cognitive processes such as learning, memory and attention are not substantially affected. No indication of hyperactivity or impulsivity was obtained.

However, studies in nonhuman primates indicate that the course of postnatal behavioral maturation may be altered by drug exposure at birth. This effect appears in connection with important milestones in brain development. The observation that different perinatal interventions affect the same developmental periods suggests that late gestation may be a "sensitive period" for organization of cortical areas important to maturation at these times. Substantiation of such a principle could be extremely valuable in understanding the potential vulnerability of the newborn brain to the different therapeutic interventions that are used in obstetrics and neonatology.

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