Anesthesiology
59:421–424, 1983

Anesthetic Requirements for Halothane in Young Children 0–1 Month and 1–6 Months of Age

J. Lerman, M.D., F.R.C.P.(C), S. Robinson, M.D.,† M. M. Willis, B.S.,‡ G. A. Gregory, M.D.*

In a previous study, the authors found that infants, in the first 6 months of life, required the highest minimum alveolar concentration (MAC) of any age group (1.09% halothane). Because only two neonates (0–31 days of age) were included in the original study and because profound depression of blood pressure and heart rate have been reported in neonates, the authors determined 1) whether the MAC of halothane in neonates (n = 12) differs from that in infants (1–6 months of age) (n = 12) and 2) whether the blood pressure and heart rate responses in neonates differ from those in infants at approximately 1 MAC. The authors found that the MAC of halothane in neonates, 0.87% ± 0.03 SEM, was significantly lower ($P < 0.01$) than that in infants, 1.20% ± 0.06 SEM. With induction of anesthesia, the systolic blood pressure decreased 23% in neonates ($P < 0.05$) and 34% in infants ($P < 0.005$) from awake values. Similarly, the heart rate decreased 12% in neonates and 22% in infants ($P < 0.05$). The incidence of hypotension (>30% decrease in systolic blood pressure from awake) in neonates, 33%, was not significantly different from that in infants, 44%. The authors conclude that the MAC of halothane in neonates is 25% less than that in infants and significantly less than was thought previously. The MAC in infants is the highest of any age group. The decrease in blood pressure and the incidence of hypotension in neonates are similar to those in infants at approximately 1 MAC of halothane. (Key words: Anesthesia: neonatal, pediatrics. Anesthetics, volatile: halothane. Blood pressure: drug effects. Heart: pulse rate. Potency, anesthetic: MAC).

MAC, AN ESTIMATE of anesthetic requirement, is that alveolar concentration of anesthetic at which 50% of the patients move in response to a single stimulus (skin incision). Of the many factors known to influence MAC, age is one of the most important. As age increases from the newborn to the elderly, MAC steadily decreases.[1–4] Although we previously demonstrated that infants in the first 6 months of life had the highest MAC, we included only two neonates in our original study.[2] Furthermore, we recently reported that the MAC of term fetal lambs was only one fourth that of 12-h-old lambs.[5] Because of these two observations, we suspected that the MAC of neonates had been overestimated.

The relationship between age and anesthetic requirement is of concern because of the relationship between anesthetic dose and the depression of vital signs. Several investigators compared the depression of blood pressure and heart rate in neonates and infants at equal anesthetic concentrations and clearly demonstrated more circulatory depression in neonates than in infants.[3,6,7] Based on these studies, investigators have concluded that at MAC, neonates are more prone to circulatory depression than older infants. However, it is possible that the MAC of halothane in neonates is lower than was thought previously. Because of this and because of the significant concern over circulatory depression in neonates under anesthesia, we determined whether the MAC of neonates is the same as that of infants and whether the blood pressure and heart rate responses in neonates and infants differ at equipotent concentrations of halothane.

Materials and Methods

Twenty-four unmedicated patients, ASA 1 and 2, were divided equally into two groups according to age: neonates 0–31 days of age and infants 1–6 months of age. The neonates were at least of 37 weeks gestation at the time of admission into this study. All patients were NPO for approximately 4 h preoperatively. None of the patients, nor their mothers, were receiving medications at the time of this study.

The operating theater was warmed to approximately 25°C before each patient arrived. Patients were monitored in the routine fashion, including arterial blood pressure (doppler), electrocardiogram, and temperature. Blood pressure and heart rate measurements were recorded at three times: 1) before induction of anesthesia, 2) at a steady state end-tidal halothane concentration before skin incision, and 3) at the maximum heart rate during the 2 min following skin incision. After endotracheal intubation, either awake or with halothane and oxygen, a steady state end-tidal halothane concentration was established and maintained for approximately 10–15 min.[3] For neonates of less than 42 weeks gestation age, a mixture of air and oxygen[8] was used as the carrier gas. The end-tidal halothane concentration was sampled through an 8-in 19-ga catheter, whose tip was placed at

* Fellow, Department of Anesthesia and The Cardiovascular Research Institute, University of California.

† Assistant Professor of Anesthesia.

‡ Research Assistant.

§ Professor of Anesthesia and Pediatrics.

Received from the Departments of Anesthesia and Pediatrics and the Cardiovascular Research Institute, University of California, San Francisco, California. Accepted four publication May 6, 1983. This work was supported, in part, with grants from NIH #1 PO1 AG 03104-01 and Ohio Medical Anesthetics. Presented in part at the annual meeting of the American Society of Anesthesiologists, October 1983.

Dr. Lerman is the recipient of a Fellowship in Anesthesia and Pharmacology, from The Hospital for Sick Children Foundation, Toronto, Ontario, Canada. His present address is the Department of Anesthesia, Hospital for Sick Children, Toronto, Canada.

Address reprint requests to Dr. Gregory: Department of Anesthesia, S436, Univesity of California, San Francisco, California 94143.

TABLE 1. Demographic Data for Neonates (n = 12) and Infants (n = 12)

Group	Mean Age (mos)	Weight (kg)	Hematocrit (vol %)	Temperature* (°C)
Neonates	.32 ± .3	3.4 ± .9	44 ± 9	36.6 ± 0.6
Infants	3.3 ± 1.3	4.8 ± 1.2	34 ± 4	36.6 ± 0.7

Data are means ± SD.
* The temperatures were measured at the time of MAC measurements.

the tracheal end of the endotracheal tube. The dead space of the collection system was flushed repeatedly before collecting each sample. The gas samples were obtained by aspirating 1-ml aliquots of end-tidal gas per breath. The gas was collected in a glass syringe fitted with a nylon stopcock and analyzed immediately by a mass spectrometer (Chemetron, Med-Spec II).[9] In those patients receiving halothane in 100% oxygen, the concentrationn of nitrogen in each gas sample was determined to preclude air contamination. Samples containing >1.0% nitrogen were repeated. Continuous end-tidal carbon dioxide concentrations were measured. End-tidal carbon dioxide concentrations ranged from 30–50 mm Hg during the study period. To achieve adequate end-tidal volumes for sampling, each patient was ventilated manually or mechanically.

The technique used to determine MAC is adapted from the "Up and Down Technique" by Dixon.[10] The objective of this technique is to bracket an end-tidal concentration that is MAC for the anesthetic being studied.

The first patient in each group was anesthetized to an arbitrarily selected end-tidal halothane concentration. The patient's response to the initial skin incision was reported as an all-or-none response–movement or no movement. Movement was considered to have occurred only when there was movement of the extremities. We did not include breath holding, coughing, or grimacing as positive responses. The halothane concentration selected for each subsequent patient was based on the response observed in the preceding patient (*i.e.*, if the preceding patient moved, the end-tidal halothane concentration for the subsequent patient was increased 0.2%; if the preceding patient did not move, the end-tidal halothane concentration was decreased 0.2%). The first pair of patients with unlike responses (move–no move) to skin incision constituted the first two patients in that group. Patients studied before the first pair of unlike responses were not included in the group analysis.

We calculated MAC to be the mean anesthetic concentration of the 12 patients in each group. To determine the standard error of MAC, we divided each group into three subgroups of four patients each¶ and calculated

¶ The patients in each subgroup consisted of four consecutively studied patients.

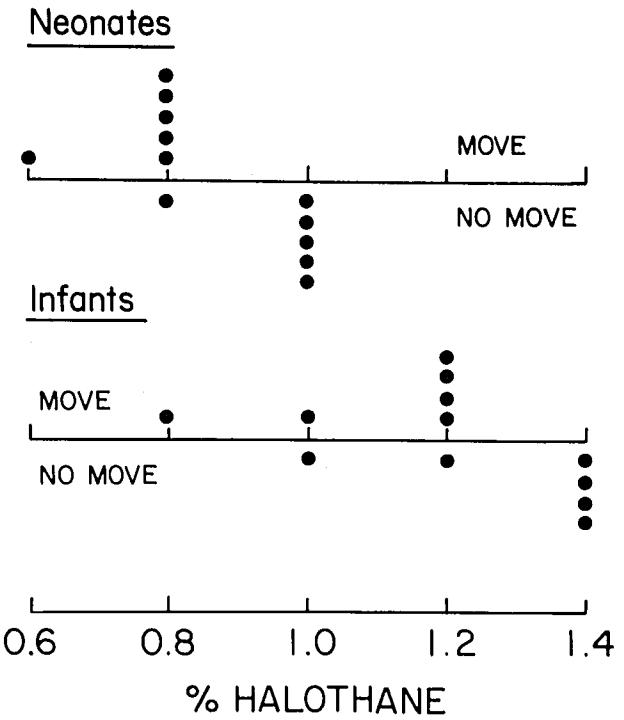

FIG. 1. Data for an individual patient are given as a filled circle. The position of the circle along the horizontal line indicates the end-tidal halothane concentration immediately before skin incision. The position of the circle above or below the line indicates whether the patient moved or failed to move respectively. The greater sensitivity of neonates to halothane is apparent.

the mean anesthetic concentration for each subgroup. The standard error was the variance of the mean halothane concentrations of these three subgroups.[10]

Statistical significance ($P < 0.05$) was determined using repeated-measures analysis of variance,[11] the Student-Newman-Keuls multiple range test, and the Fisher exact test, where appropriate.

This study was approved by the Committee on Human Research at the University of California Medical Center, San Francisco. Informed consent was obtained from the parents or guardian of each patient before surgery.

Results

The two groups of patients studied were appropriate for age-predicted weight and hematocrit (table 1).[12] The mean temperatures for the two groups were not significantly different.

Figure 1 shows the move–no move responses to skin incision at different end-tidal halothane concentrations. Using the Dixon analysis, we found that the MAC of halothane in neonates, 0.87% ± 0.03, was significantly less than that in infants, 1.20% ± 0.06 ($P < 0.01$). A Waud analysis of the data produced very similar MAC values.

The mean systolic blood pressure and heart rate responses for both groups are shown in table 2. Although

TABLE 2. The Hemodynamic Responses in Neonates and Infants at End-tidal Halothane Concentrations Bracketing MAC

Group	Systolic Blood Pressure (mmHg)			Heart Rate (beats/min)		
	Awake	Unstim.	Stim.	Awake	Unstim.	Stim.
Neonates	78 ± 11	59 ± 14*	64 ± 19*	161 ± 20	143 ± 18	146 ± 19
Infants	86 ± 17	57 ± 12†	66 ± 19†	156 ± 30	121 ± 15*	131 ± 20*

Data are means ± SD.

Systolic blood pressure decreased significantly from awake values in both neonates and infants. Heart rate did not differ from awake values in neonates but decreased significantly in infants.

Awake = preinduction; Unstim. = anesthetized at MAC prior to skin incision; Stim. = anesthetized at MAC after skin incision.

* Differ from awake values, $P < 0.05$.

† Differ from awake values, $P < 0.005$.

50% of the patients moved after surgical stimulation, we still were able to accurately measure blood pressure and heart rate. The awake systolic blood pressure and heart rate measurements (table 2) in neonates and infants were at the upper limits of normal for the respective age groups.[12] The systolic blood pressure decreased significantly from awake values, in both the anesthetized unstimulated and stimulated states for both neonates ($P < 0.05$) and infants ($P < 0.005$), at approximately 1 MAC halothane. Similarly, the heart rate decreased 12% from awake values in neonates and 22% in infants ($P < 0.05$). The incidence of hypotension (>30% decrease in systolic blood pressure from awake) at 1 MAC halothane in neonates, 33%, was not significantly different from that in infants, 44%. There was no significant change in the blood pressure and heart rate between the unstimulated and stimulated states for either group.

Discussion

Earlier studies reported that the anesthetic requirement in infants less than 6 months of age was greater than at any other time of life.[1-3] However, in our original work,[2] we studied only two neonates. In fact, the MAC of halothane in infants less than 6 months of age reported in our earlier work fell between the MAC values for neonates and infants in our present work. The present study demonstrates that at MAC, neonates require 25% less anesthetic than infants and that infants have a greater anesthetic requirement than at any other age. We recently reported a 71% lower anesthetic requirement in term fetal lambs when compared with newborn lambs who were older than 12 h of age.[5] Furthermore, we demonstrated a significant rise in the MAC of newborn lambs during the first 12 h of extrauterine life. The increase in MAC for newborn lambs is consistent with our findings of an increasing anesthetic requirement in humans during the first 6 months of extrauterine life.

Our data indicate that the circulatory depression (estimated by systolic blood pressure and heart rate) at approximately 1 MAC halothane (table 2) is similar to that reported in lambs and sheep[13] but less than that reported in children.[3,6] In the sheep studies, we measured both MAC and circulatory responses for each age group[13]; however, in human studies reported by other investigators,[3,6] the MAC for neonates was assumed to be the same as that for infants. As a consequence, the circulatory responses in neonates were determined at anesthetic concentrations in excess of the MAC reported here. We found that the depression of blood pressure and heart rate in neonates was not different from that in infants at equipotent anesthetic concentrations of halothane (approximately 1 MAC).

Although the mean heart rate in neonates at approximately 1 MAC halothane was not different from that in the awake state, it was significantly ($P < 0.05$) lower in infants. Because infants cry more frequently on arrival in the operating room than neonates, we would expect them to have a higher sympathetic tone than neonates in this situation. Because anesthesia attenuates the sympathetic tone and because anesthesia depresses the baroresponse in proportion to MAC, *i.e.*, one-half MAC halothane causes the same depression of the baroresponse as does one-half MAC nitrous oxide,[14,15] we would expect the decrease in heart rate at 1 MAC halothane to be greater in infants than it is in neonates, as our data suggested.

The lower MAC for neonates reported in this article is relevant to previous concerns about cardiovascular stability during anesthesia for the very young patient. Compared with infants, neonates supposedly experience more myocardial depression[6] and are more prone to cardiac arrest[7] at a given level of anesthesia. However, based on our data, neonates are no more prone to hypotension and circulatory collapse at 1 MAC halothane than infants. Indeed, earlier studies either measured the circulatory responses at anesthetic concentrations far beyond MAC for that age group[6] or did not quantitate the alveolar anesthetic concentrations.[7] Earlier reports that neonates were more susceptible to circulatory depression during general anesthesia than infants were probably the result of a relative drug overdose.

The response of the newborn to nociceptive cutaneous stimuli is attenuated even in the awake state.[16,17] It would appear that the decreased sensitivity to pain during the first week of life reported by McGraw and Dargaisses, is attributable to an immature central nervous system. During the first few months of life, both the sensitivity to painful stimuli and the behavioral response to pain (lo-

calized withdrawal) rapidly mature in parallel to the ascent of MAC. Nevertheless, the accepted method of measuring the anesthetic requirement, a primitive reflex response to painful cutaneous stimulation, is probably sufficiently developed in the first week of life to use a response to nociception. We believe that by using both the reflex response to cutaneous stimulation and the changes in systolic blood pressure and heart rate under anesthesia, we are able to accurately measure the anesthetic depth (MAC) in neonates.

Progesterone and other hormones thought to decrease MAC, return to normal levels in both the mother and the neonate within 10 days of parturition.[18–20] Because the average age of neonates in this study was 0.3 months, progesterone may have affected the MAC of this group. Although we have shown a negative correlation between the serum concentration of progesterone and the MAC of halothane in newborn lambs,[5] no cause-and-effect relationship has been demonstrated.

Recent reports have demonstrated increased plasma peptide (β-endorphin and β-lipotropin) concentrations in newborns and the immediate postnatal period.[21,22] These peripheral endorphin concentrations decreased to adult levels by 24 days of age. Although peripheral β-endorphins do not cross the blood–brain barrier in adults,[23] this may not be the case in neonates. The studies of peptide concentrations in neonates did not include cerebrospinal fluid peptide determinations. If the high plasma β-endorphin and β-lipotropin concentrations detected in the neonatal period reflect an increased concentration of endorphins in the central nervous system, then this increase in central nervous system endorphin level may contribute to the elevated pain threshold reported by McGraw and the decreased response to pain we observed in the early neonatal period.

In summary, we determined the MAC of halothane in neonates 0–1 month of age and infants 1–6 months of age. Neonates require a 25% lower concentration of halothane at MAC than infants 1–6 months of age ($P < 0.01$) and a significantly lower concentration of halothane than was thought previously. The decrease in systolic blood pressure and the incidence of hypotension in neonates are similar to those in infants at approximately 1 MAC halothane.

The authors thank Dr. E. I. Eger for his guidance in preparing this manuscript and Drs. A. A. deLorimier and M. Harrison for their cooperation during surgery.

References

1. Deming M: Agents and techniques for induction of anesthesia in infants and younger children. Anesth Analg 31:113–117, 1952
2. Gregory GA, Eger EI II, Munson, ES: The relationship between age and halothane requirements in man. ANESTHESIOLOGY 30:488–491, 1969
3. Nicodemus HF, Nassiri-Rahimi C, Bachman L, Smith TC: Median effective doses (ED_{50}) of halothane in adults and children. ANESTHESIOLOGY 31:344–348, 1969
4. Cook DR, Brandom BW, Shiu G, Wolfson B: The inspired median effective dose, brain concentration at anesthesia, and cardiovascular index for halothane in young rats. Anesth Analg 60:182–185, 1981
5. Gregory GA, Wade JG, Beihl DR, Ong BY, Sitar DS: Fetal anesthetic requirement (MAC) for halothane. Anesth Analg 62:9–14, 1983
6. Diaz JH, Lockhart CH: Is halothane really safe in infancy? ANESTHESIOLOGY 51:A313, 1979
7. Rackow H, Salanitre E, Green LT: Frequency of cardiac arrest associated with anesthesia in infants and children. Pediatrics 28:697–704, 1961
8. Quinn GE, Betts EK, Diamond GR, Schaeffer DB: Neonatal age (human) at retinal maturation. ANESTHESIOLOGY 55:A326, 1980
9. Ozanne GM, Young WG, Mazzei WJ, Serveringhaus JW: Multipatient anaesthetic mass spectrometry. ANESTHESIOLOGY 55:62–70, 1981
10. Dixon WJ: Quantal response variable experimentation: The up and down method, Statistics in Endocrinology, Proceedings. Edited by McArthur JW, Colton T. Cambridge, MIT Press, 1970, pp 251–267
11. Glantz SA: Primer of Biostatistics. New York, McGraw-Hill, 1981, pp 87–8
12. Smith RM: Anesthesia for infants and children. Fourth edition, St. Louis, CV Mosby, 1980, pp 13–21
13. Robinson S, Gregory GA: Circulation effects of anesthesia in the developing sheep I. halothane. ANESTHESIOLOGY 53:S330, 1980
14. Ware R, Robinson S, Gregory GA: Effect of halothane on the baroreceptor response in newborn and adult rabbits. ANESTHESIOLOGY 56:188–191, 1982
15. Duncan P, Gregory GA, Wade JA: The effects of nitrous oxide on the baroreceptor response of newborn and adult rabbits. Anesth Soc J 28:339–341, 1981
16. McGraw MB: Some aspects of early sensory development, The Neuromuscular Maturation of the Human Infant. New York, Hafner Publications. 1963, pp 101–110
17. Saint-Anne Dargaisses S: Qualitative and quantitative analysis of each heading of the screening table, Neurological Development in the Full-Term and Premature Neonate. Amsterdam, Excerpta Medica 1977, pp 57–60
18. Ferris B, Green OC: Pregnanediol of Excretion by Newly Born Infants. Am J Dis Child 115:693–697, 1968
19. Conly PW, Morrison T, Sandberg DH, Cleveland WN: Plasma progesterone in the perinatal and neonatal period (abstract). Pediatr Res 2:308, 1968
20. Iffy L, Kaminetzky HA (eds): Principles and Practice of Obstetrics and Perinatology. Edited by New York, Wiley Medical Pubishers, 1981, pp 1670–1672
21. Moss IR, Conner H, Yee WFH, Iorio P, Scarpelli EM: Human β-endorphin in the neonatal period. J Pediatr 101:443–446, 1982
22. Bayon A, Shoemaker WJ, Bloom FE, Mauss A, Gullemin R: Perinatal development of the endorphin- and enkephalin-containing systems in rat brain. Brain Res 179:93, 1979
23. Oyama T, Matsuki A, Taneichi T, Ling N, Guillemin R: β-Endorphin in obstetric analgesia. Am J Obstet Gynecol 137:613–616, 1980