Median Effective Doses (ED50) of Halothane in Adults and Children

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Median effective doses of halothane (ED50), determined in 73 pediatric subjects and 31 adults grouped according to age, were: 1.20 per cent at 0 to 6 months; 1.16 per cent at 6 to 24 months; 1.07 per cent at 24 to 48 months; and 0.9 per cent in adults. The dose–response curves for all groups did not deviate significantly from parallelism. Halothane was 1.28 and 1.12 times more potent in producing anesthesia in adults than in the 0-to-6-months and 6-to-24-months group. Potency in the 24-to-48-months group did not differ significantly from potency in adults or in younger children. In contrast, taking hypotension as a measure of circulatory effect, halothane is a less potent cardiovascular depressant in adults than in young children. (Key words: Halothane; Children; ED50.)

CLINICIANS have long believed that infants and children require higher inspired tensions of inhalation anesthetics for a given effect than adults. In 1952, Deming showed that infants had higher concentrations of cyclopropane in the blood than older children at clinically comparable depths of anesthesia. Adults under similar conditions had even lower concentrations.[1] However, the clinical signs varied from patient to patient in Deming's small group of subjects. The present study was designed to determine if the effective anesthetic concentration of halothane for children differs from that for the adult.

The median effective dose (ED50) method of Litchfield and Wilcoxon[2] permits comparison of the potencies of drugs in different groups of subjects, converting the dose–response curve to a straight line by a log dose–probit transformation. In addition, the method provides a test for goodness of fit, checks for parallelism of two dose–responses and (most important) estimates the confidence limits of the ED50 before calculating potency ratios. Using this method, we determined the median effective end-tidal concentration of halothane, defined as that concentration which abolishes muscular movement in response to initial skin incision in 50 per cent of subjects. Eger and his colleagues described a similar end-point in the determination of MAC.[3] ED50 was chosen in preference to MAC because of consideration of efficiency of experimental design.

Methods

Seventy-three healthy infants and children in age groups 0 to 6 months, 6 to 24 months, and 24 to 48 months, and 31 adults, all of physical status 1 or 2, were studied. We had planned to give five concentrations of halothane in oxygen: 0.63, 0.79, 1.0, 1.26 and 1.58, selected in logarithmic progression to cover the expected range of ED50. Equal distribution of numbers for each dose was also planned, for ease of calculations. Early experience showed that the lowest dose selected, 0.63 per cent, was not useful because children of all ages invariably moved with incision. In

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the adult group, study of 0.63 per cent halothane was eliminated entirely.

Preanesthetic medication consisted of atropine, 0.02 mg/kg body weight, for children, and 0.4 to 0.6 mg atropine for adults. Induction of anesthesia was accomplished by wafting cyclopropane over the faces of the children and by giving the adults either cyclopropane or nitrous oxide by mask and circle system until loss of consciousness occurred. We then discontinued nitrous oxide or cyclopropane and administered halothane and oxygen, delivered from a Fluotec® vaporizer in a nonrebreathing system at flows exceeding respiratory minute volumes. A concentration of 2.5 per cent halothane was given until tracheal intubation could be accomplished without the use of muscle relaxant or topical anesthetic. After tracheal intubation, the selected end-tidal halothane ($F_{ET_{Hal}}$) was reached by decreasing inspired halothane ($F_{I_{Hal}}$). We kept $F_{ET_{Hal}}$ constant for at least 15 minutes prior to incision in children; 20 minutes in adults. $F_{ET_{Hal}}$ could be changed rapidly after alteration in $F_{I_{Hal}}$ because of the nonrebreathing system used. Respiration was controlled in all patients. A rectal thermistor probe was used to monitor body temperature, and circulating water pads held the temperature constant at 36.5 ± 1 C. A stethoscope taped to the chest provided continuous monitoring of heart sounds. Blood pressure was measured every two minutes by oscillotonometry. At the time of incision, limb movements or facial grimace indicated a lack of effective anesthesia.

A Beckman LB-1 infrared halothane analyzer continuously sampled gas at 500 ml/minute through a 15-gauge plastic catheter whose tip lay 1 cm from the tracheal end of the tube. The end-tidal plateau was improved by placing a spring-loaded valve between the reservoir bag and the endotracheal tube (fig. 1). The inspiratory valve required a pressure of 2 torr to open. Criteria for satisfactory recording included a stable end-tidal plateau for 15 to 20 minutes and small $F_{I_{Hal}}$–$F_{ET_{Hal}}$ differences during slow respiration or long expiration. If slow respiration or pressure on the chest during expiration caused no further change in the end-tidal plateau, the end-tidal

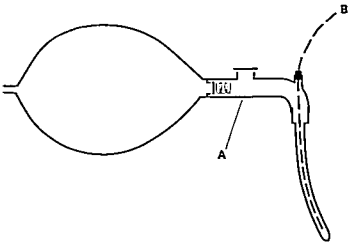

FIG. 1. Nonrebreathing system. *A*, spring-loaded valve with 2-torr opening pressure. *B*, sampling catheter.

sample was accepted as satisfactory. We discarded records that did not satisfy the criteria and repeated the study of that concentration in another patient. The calibrating gases, prepared by the method of Hill,[4] were analyzed by gas chromatography against standard mixtures.* When the detector case was pressurized with 100 per cent carbon dioxide, the analyzer showed no response to 8 per cent CO_2. We recorded the data on a Grass polygraph.

Results

Mean ages for the four groups were 1.8 months, 14 months, 44.4 months and 35 years, respectively. The number of subjects moving on stimulation was expressed as a decimal fraction of the group tested at that concentration, (F_{moved}). Small standard deviations in the mean $F_{I_{Hal}}$ and $F_{ET_{Hal}}$ values indicated homogeneity of anesthetic concentration in each group (table 1). Log–probit plots of F_{moved} as a function of $F_{ET_{Hal}}$ provided ED50 values by interpolation. The ED50 taken from such plots decreased as age increased: 1.20 per cent halothane at 0 to 6 months; 1.16 per cent at 6 to 24 months; 1.07 per cent at 24 to 48 months; and 0.94 per cent in adults. Replotting the data on linear scales showed a family of dose–response curves (fig. 2) which do not deviate significantly from parallelism, so that potency ratios at 50 per cent effect

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may be calculated legitimately. The lines tend to converge at 1.50 per cent halothane, indicating that only a small number of any population would still be ineffectively anesthetized at that concentration.

If the ED50 for the 0-to-6-months group is taken as unity, then halothane is 1.28 times more potent in adults than in children. The ED50 assay of Litchfield and Wilcoxon gives 95 per cent confidence limits for such a potency ratio, enabling significance testing at the 5 per cent level. A ratio as large or larger than 1.28, comparing adults and the youngest children, is unlikely to arise as often as once in 20. Comparison of the adults with the 6-to-24-months group gives a potency ratio of 1.23, also significantly different from unity. Differences in potency among the groups of children were not significant, nor was that between the adults and the oldest children studied.

Four of the 24 youngest patients, two of the 24 in the 6-to-24-month group, and only one of the 31 adults developed hypotension 30 per cent or more below the pre-study systolic blood pressures. Four of the children became hypotensive at $F_{ET_{Hal}}$ values of 0.75 to 1.2 per cent, but the adult became hypotensive only above $F_{ET_{Hal}}$ 1.5 per cent.

Discussion

Depth of anesthesia is difficult to ascertain. We assume that the end-tidal halothane, $F_{ET_{Hal}}$, corresponds to alveolar and to arterial tensions when the $F_{I_{Hal}}$–$F_{ET_{Hal}}$ difference is small. If the arterial blood and brain are equilibrated with alveolar tension, the latter quantifies the depth of anesthesia. Depth may also be estimated from certain reproducible effects on the electroencephalogram [5] or in the H-reflex,[6] but precise and reproducible signs do not exist for specific levels of anesthesia. Muscular response to initial incision is a familiar sign, less subjective and more easily reproduced than EEG and clinical signs of anesthesia. Although this is the same end-point used for the determination of MAC,[7] we chose the ED50 assay because it provides an estimate of fiducial limits of calculated 50 per cent response. Such an estimate is necessary to test the significance of observed differences between age groups. Similar information can

TABLE 1. Halothane Concentrations, Fractions Moving at Incision, and Derived Median Effective Doses in Children and Adults

Age Group	Number of Patients	Halothane Concentration				Fraction Moving	Halothane Concentration		Potency Ratio
		Inspired		End-tidal			ED50 Per Cent	95 per cent Confidence Limits Per Cent	
		Per Cent	SD	Per Cent	SD				
0 to 6 months	6	0.81	0.23	0.73	0.7	1.0	1.20	1.10–1.30	1.00
	6	1.30	0.23	0.98	0.04	0.83			
	6	1.40	0.09	1.23	0.06	.67			
	6	1.59	0.05	1.50	0.04	0.0			
6 to 24 months	6	0.83	0.04	0.76	0.03	1.0	1.16	1.02–1.31	1.034
	5	1.14	0.13	0.97	0.07	1.0			
	7	1.40	0.09	1.24	0.03	0.43			
	6	1.56	0.10	1.45	0.05	0.17			
25 to 48 months	7	0.88	0.15	0.76	0.06	1.0	1.07	0.93–1.23	1.12
	6	1.24	0.10	1.03	0.05	0.5			
	6	1.55	0.11	1.27	0.02	0.33			
	6	1.75	0.20	1.51	0.06	0.0			
Adults, mean age 35 years	8	0.82	0.09	0.73	0.06	0.75	0.94	0.79–1.12	1.28
	11	1.14	0.08	1.01	0.04	0.55			
	7	1.40	0.01	1.25	0.10	0.14			
	5	1.65	0.05	1.47	0.07	0.00			

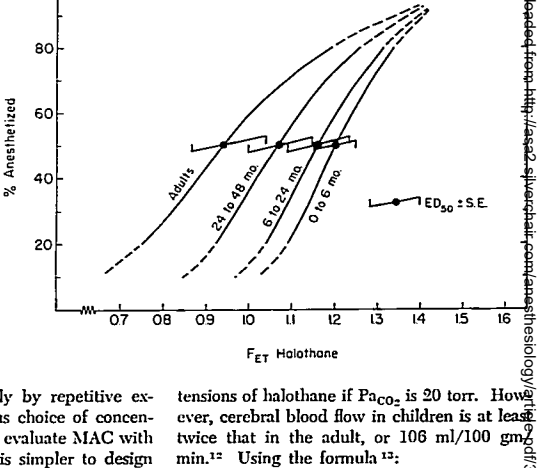

FIG. 2. Dose-response curves for halothane in different age groups replotted from log dose-probit analysis of Litchfield and Wilcoxon.

be obtained for MAC only by repetitive experiments. While judicious choice of concentrations may permit one to evaluate MAC with relatively few subjects, it is simpler to design an experiment with a fixed number of subjects than to utilize the open-end design of MAC. The experiment is more likely to be economical of subjects and time when ED50 is employed. Furthermore, ED50 is widely accepted in pharmacologic studies.[8, 9]

We eliminated some of the factors that could have influenced the results. Atropine as the only preanesthetic medication abolished the contribution of narcotics and barbiturates to anesthetic requirement.[10] The spring-loaded valve minimized contamination of the expirate with inspired gas, allowing a satisfactory end-tidal plateau. As an added precaution, $F_{I_{Hal}}$ was decreased slowly until it approached $F_{ET_{Hal}}$, so that the difference was small, decreasing the error from contamination of the sample with inspired gas. High $F_{ET_{Hal}}$ owing to the presence of alveoli with large ratios of ventilation to perfusion was also minimized by this maneuver.

We assumed that the concentration of anesthetic in the alveoli is indicative of the concentration in brain. In an analog analysis using data for adults, Munson [11] showed that at least 20 minutes are required to reach 95 per cent equilibration of arterial and cerebral tensions of halothane if Pa_{CO_2} is 20 torr. However, cerebral blood flow in children is at least twice that in the adult, or 106 ml/100 gm-min.[12] Using the formula [12]:

$$T = \frac{100 \text{ lambda}}{\text{CBF}} \cdot \ln 20,$$

where T is time in minutes, CBF 106 ml/100 gm/min, and lambda (blood–brain) 2.6,[13] the estimated time for 95 per cent equilibration of arterial and cerebral tensions is 7.5 minutes for children. It appears, therefore, that 15 minutes of constant $F_{ET_{Hal}}$ for children, and 20 minutes for adults to compensate for the smaller cerebral blood flow, are more than adequate to reach 95 per cent arterial–cerebral equilibrium.

The ED50 in adults was numerically higher than MAC (0.77 per cent) reported by Saidman and his associates,[7] although the stimuli and responses were similar in the two studies. Comparison of the two values may not be meaningful since the methods of determination of average dose were different. Halothane was 1.28 to 1.12 times as potent in adults as in children aged 0 to 6 months and 6 to 24 months, respectively.

Considering hypotension as an index of circulatory effect, the potency ratio is less than unity (adults compared with children), contrasting with the greater-than-unity potency

ratio for anesthetic effect. It is clear that, because higher concentrations of anesthetic are necessary to anesthetize children, the risks of hypotension greater, and changes more rapid, continuous attention is necessary.

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Drugs

SUCCINYLDICHOLINE The negative inotropic effect of barbiturates on the isolated heart of the guinea pig can be decreased by the positive inotropic effect of succinyldicholine. Succinyldicholine prevents cardiac arrest from barbiturate doses twice the usual arrest doses. The decrease of heart rate following the injection of barbiturates is less pronounced if succinyldicholine is added. These findings may help to explain the beneficial effect of succinyldicholine immediately following induction of anesthesia with barbiturates in cardiac patients. Possible explanations are the blocking action of barbiturates on the preganglionic synapses of the sympathetic and parasympathetic systems or that the depression of the myocardium by barbiturates prevents response to the cholinergic effect of succinyldicholine. (*Droh, R., and Horst, J.: The Influence of Succinyldicholine on Myocardial Insufficiency following Barbiturates, Der. Anaesthesist 17: 301 (Sept.) 1968.*)