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Anesthetic Uptake—Of Mice and Men (and Whales)

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To test the hypothesis that anesthetic uptake varies with body size, the alveolar rates of uptake of subanesthetic concentrations of methane, cyclopropane, halothane, fluroxene, and ethyl ether were measured in rats, man, and one gray whale calf (weight 6,330 kg). Uptake was most rapid in rats, intermediate in man, and least rapid in the whale. Metabolic rate was unexpectedly high in the whale, leading to more rapid than anticipated alveolar uptake of anesthetics, which might have been still more rapid but for the effects of reduced ventilation and increased blood/gas partition coefficients. Nevertheless, the differences between the ratios of alveolar to inspired anesthetic concentrations (F_A/F_I) in the large and small animals were appreciable, particularly for soluble anesthetics: at 60 minutes F_A/F_I for halothane was 1.7 times greater in rats than in the whale, and F_A/F_I for ethyl ether was 2.7 times greater. The authors conclude that the rate of anesthetic uptake varies inversely with body size. (Key words: Pharmacokinetics: uptake: body size; Anesthesia, veterinary: whales.)

BOTH Salanitre and Rackow[1] and Eger *et al.*[2] have suggested that an increase in perfusion with a concomitant and proportional increase in ventilation should accelerate alveolar uptake of all anesthetics. This results from the more rapid saturation of body stores with anesthetics as flow to those stores is increased. The interest of these workers was directed principally to the effect of age on anesthetic uptake and distribution, but these concepts would appear to apply to any change in body size, since in general, a decrease in body size is associated with an increase in perfusion and ventilation per kilogram of weight. This follows from the regression of metabolic rate onto the 0.75 power of body weight.[3] Alveolar uptake of an anesthetic in a mouse or rat, then, should be far more rapid than its alveolar uptake in man; the uptake in man, in turn, should be faster than that in a larger animal such as an elephant or whale.

We measured rates of alveolar uptake of five gases in rats, man, and a California gray whale. Of the several possible interpretations of anesthetic "uptake," we use it to represent the rate of rise of anesthetic tension in end-tidal (alveolar) gas.[4]

Methods

Five rats, four men, and one immature gray whale were studied. Some of their physical characteristics are given in table 1. The whale had been captured in Scammon's Lagoon, Baja California, Mexico, in March 1971, at which time she was approximately 6 weeks old and weighed 1,970 kg. At the time of this study she was approximately 12 months old, weighed 6,330 kg, and had been kept during the intervening months in a local marine park.

End-tidal P_{CO_2} for the whale was determined with a CO_2 electrode (Radiometer BMS-3); for men and rats, we used an infrared CO_2 meter (Beckman LB-1). Values of oxygen consumption for man and rat were obtained from a standard text,[5] and oxygen consumption in the whale was measured from the volume and composition of expired gas collected for 5-minute periods on several occasions. Partition coefficients were determined in triplicate for the whale, in duplicate for each human subject, and from a single determination in each of three rats by the

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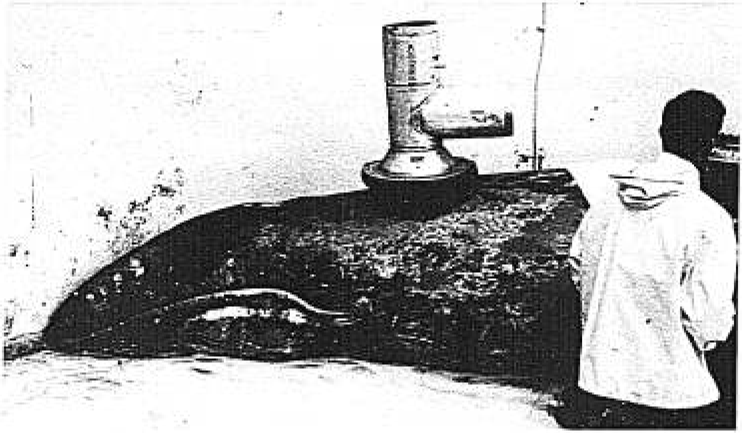

FIG. 1. California gray whale (*Eschrictius glaucus*) and nonrebreathing valve. Because the apneustic breathing pattern consists of an exhalation followed immediately by an inspiration, the valve was necessary to obtain alveolar gas samples. This photograph was taken shortly after capture, when the whale weighed only 2,950 kg. We studied anesthetic uptake just before her release, by which time she weighed 6,330 kg and was 8.15 meters long.

method of Theye.[6] Blood was drawn from a digital artery in the whale's flipper, and from cardiac punctures in the rats.

Methane, cyclopropane, halothane, fluroxene, and ethyl ether were each added to each of four size G cylinders pressurized to 2,000 psi with air. The resulting concentrations were well below anesthetic range, and equalled 1, 1, 14, 6, and 3 per cent $\times 10^{-3}$, respectively. The same gases were breathed by all animals, and in all cases gases were administered by a nonrebreathing system. To study the whale required that the water level in her tank be lowered so as to immobilize her in about 2 feet of water, and she tolerated this for many hours without evidence of respiratory impediment. A whale nonrebreathing valve was fabricated of 8-inch

TABLE 1. Physical and Metabolic Characteristics of the Subjects*

	Rat	Man	Whale
Weight, g	3.5×10^2	7.2×10^4	6.3×10^6
$P_{A_{CO_2}}$, torr	39.6 ± 6.9	41.5 ± 2.0	56.7 ± 6.7
O_2 consumption, ml/min/kg	16.6	3.6	3.0
Blood/gas partition coefficients			
Methane	0.06 ± 0.02	0.05 ± 0.01	0.07 ± 0.01
Cyclopropane	0.84 ± 0.12	0.53 ± 0.15	0.77 ± 0.02
Fluroxene	3.33 ± 0.52	1.64 ± 0.35	2.32 ± 0.26
Halothane	6.56 ± 0.17	2.80 ± 0.61	5.50 ± 0.50
Ethyl ether	19.0 ± 2.5	11.9 ± 4.1	11.5 ± 1.4

* Values given are means ± SD. Blood lipid concentration in the whale was remarkably high, ranging from 800 to 1,200 mg cholesterol per 100 ml whole blood.

TABLE 2. Ratios of End-tidal-to-inspired Gas Compositions*

	Time, Minutes						
	1	2	4	8	16	32	64
Methane							
Rat			99+				
Man	77.4 ±9.2	92.3 ±4.5	95.3 ±5.4	104.4 ±8.7	98.0	97.5	97.9
Whale	90.4	91.0	94.4	98.9	100.1	—	—
Cyclopropane							
Rat	78.3 ±6.3	83.5 ±4.5	91.5 ±7.9	90.3 ±3.8	91.2 ±3.2	94.5 ±2.3	97.2 ±2.2
Man	51.9 ±3.7	65.2 ±0.6	72.7 ±1.4	78.0 ±1.9	82.5 ±2.1	86.9 ±2.0	90.6 ±1.3
Whale	54.3	60.8	66.2	76.0	78.1	83.7	88.1
Fluroxene							
Rat	55.4 ±5.6	57.1 ±6.6	63.4 ±6.6	65.5 ±5.5	66.6 ±6.0	69.3 ±4.1	74.1 ±4.3
Man	34.5 ±1.5	43.3 ±2.1	45.1 ±1.6	47.5 ±1.8	49.8 ±3.0	53.2 ±2.3	58.6 ±2.8
Whale	25.3	36.0	33.7	42.7	46.3	42.5	50.0
Halothane							
Rat	41.6 ±6.7	44.3 ±6.4	50.1 ±6.6	54.9 ±5.8	56.1 ±6.3	63.0 ±5.1	68.4 ±4.9
Man	25.7 ±0.8	31.2 —	32.6 ±2.0	35.8 ±2.9	39.4 ±4.1	44.3 ±3.8	50.4 ±4.2
Whale	11.9	23.7	16.4	28.2	25.2	33.5	40.6
Ethyl ether							
Rat	24.8 ±4.2	27.3 ±6.1	32.8 ±5.5	35.4 ±4.7	36.9 ±5.8	41.7 ±4.1	47.8 ±4.9
Man	12.7 ±2.0	14.9 ±2.5	14.4 ±0.4	16.2 ±1.2	18.4 ±0.9	20.1 ±1.0	23.9 ±1.8
Whale	5.3	—	7.9	13.1	12.6	12.6	16.9

* Values given are ratios of alveolar to inspired concentrations of indicated gases, expressed as mean per cent ± SD; except for whale values, which were selected at suitable intervals from measurements from each breath.

stovepipe (fig. 1) and seated over the blowhole on a foam cushion. (Whales do not normally breathe through their mouths). A 3,600-l meteorologic balloon served as an inspired gas reservoir. Expired gas was collected in 800-l balloons.

Rats were anesthetized by intraperitoneal injection of pentobarbital, 35 mg/kg, and tracheotomies were performed. They then were paralyzed with gallamine and ventilated with a Bird respirator attached to the distal end of a T-piece.[7] The apparatus deadspace was 3 ml, and tidal volume was about 10 ml. Human subjects breathed spontaneously from a 9-l reservoir via a Collins J valve. Inspired and end-tidal samples were collected in glycerinized glass syringes, 50 ml for the whale and human subjects, and 5 ml for rats,

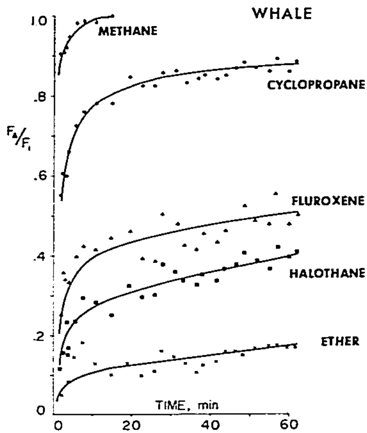

FIG. 2. Anesthetic uptake rate in the whale, expressed as the ratio of alveolar to inspired fractional concentration of gas. Each point represents the ratio determined from a single breath. The uptake of methane was complete within 20 minutes.

and analyzed for the test gases by gas chromatography using a Porapak T column and a hydrogen flame ionization detector. For the whale, each 50-ml end-tidal sample was taken from a single breath; for man, 10-ml samples were taken from each of five breaths; 1-ml samples were taken from each of five breaths for the rat. Similar samples were collected in acid-washed syringes for CO_2 analysis.

Results

End-tidal P_{CO_2} was greater in the whale than in man or rat (table 1), and varied considerably from breath to breath, according to the respiratory rate. Oxygen consumption varied with the whale's age and size: the value given was interpolated from a series of approximately monthly determinations.[8]

For all gases the alveolar uptake was most rapid in the rat, less rapid in man, and least rapid in the whale (table 2, figs. 2–4).

Discussion

Qualitatively, these results support the hypothesis that an increase in body size, and thus in ventilation and perfusion per kilogram, results in a more rapid alveolar uptake of anesthetic.[1,2] For example, the difference between the rates of alveolar uptake of halothane in man and rat is such that an eightfold increase in ventilation and perfusion in man would be necessary for the two rates to be equal.[2]

Differences between the rates of uptake in man and the whale were less than anticipated, and would have been smaller still had it not been for the lower blood/gas partition coefficients and higher ventilation (as reflected by the lower $P_{A_{CO_2}}$) in man. The closeness of human and whale curves derives from the unexpected near-identity of their metabolic

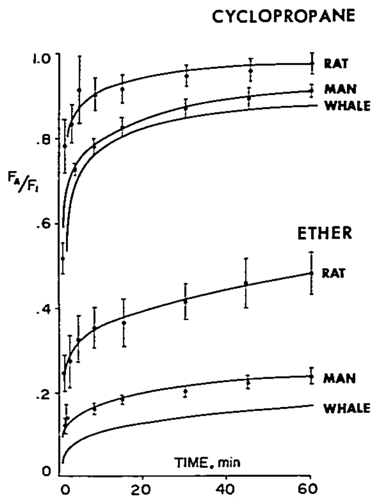

FIG. 3. Comparison of rates of uptake of cyclopropane and ethyl ether in the three species. The points represent mean values ± SD for rat and man, and are shown in figure 2 for the whale curves. Methane uptake (not shown) was complete in all species within 20 minutes.

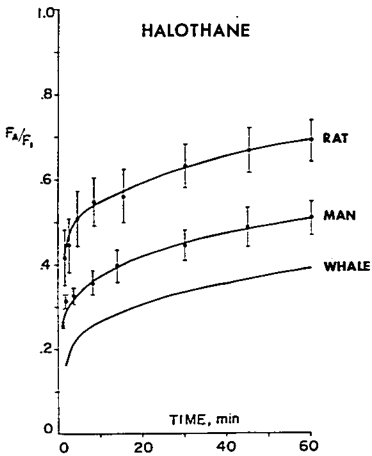

FIG. 4. Comparison of rates of halothane uptake in the three species. The points represent mean values ± SD for rat and man, and are shown in figure 2 for the whale curves.

rates despite the difference between their sizes. Immaturity and rapid growth in the whale led to a higher-than-predicted metabolic rate based on body size.

One important finding from this study is the lack of equilibration between alveolar and inspired concentrations in small animals when the inspired gas has an appreciable solubility in blood. Thus, the use of inspired concentrations as indicating or equalling alveolar concentrations for agents such as fluroxene, halothane, ether, or methoxyflurane is unwarranted in animals as small as rats. It may be that still greater increases in perfusion and ventilation, as would be obtained in still smaller animals such as mice or bats, would reduce the alveolar-to-inspired difference to relatively unimportant levels (*i.e.*, $F_A/F_I = 0.90$ or more. However, such data are not yet available.

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