The Effects of Age and Anesthetic Solubility on Anesthetic-induced Opisthotonus in Mice

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In our previous report which indicated volatile anesthetics-induced opisthotonus in mice, we hypothesized that opisthotonus might relate with the rapidity of anesthetic induction, i.e., the blood/gas partition coefficient of the agent. To confirm this, we determined the incidence of opisthotonus induced by four different halogenated ethers (2.0% sevoflurane, 1.3% isoflurane, 2.0% enflurane, and 0.5% methoxyflurane) and 1.0% halothane, a haloalkane, in male ddN mice. The effect of age on opisthotonus was also evaluated by using young (10 ± 2 weeks), middle-aged (6 ± 1 months), and elderly (12 ± 1 months) groups of male ddN mice. In each age group, the incidence of opisthotonus occurred in the following order: sevoflurane > isoflurane > enflurane > methoxyflurane > halothane. This partly supports our hypothesis as far as halogenated ethers are concerned. Halothane rarely produced opisthotonus. In the sevoflurane, isoflurane, and methoxyflurane groups, incidence was lower in middle-aged than in young or elderly mice, while incidence increased with age in the enflurane group. (Key words: anesthetic-induced opisthotonus, age factors, volatile anesthetics, blood/gas partition coefficient)

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Isoflurane, a structural isomer of enflurane, is not thought to stimulate the central nervous system (CNS)[1–4]. In our previous study, however, we found that isoflurane produces opisthotonus during induction of anesthesia in some strains of mice, and its order of incidence was: isoflurane > enflurane > halothane[5]. This order inversely correlates with the blood/gas partition coefficients, i.e., the rapidity of anesthetic induction. From this, we speculated that opisthotonus might require a relatively long time lag after depression of the inhibitory higher centers (and/or inhibitory cells of the midbrain reticular formation (MRF)) before the depression of the facilitatory cells of the MRF[5]. To confirm the finding that the incidence of opisthotonus correlates with the blood/gas partition coefficient of the anesthetic, the present study examined the incidence of opisthotonus caused by four halogenated ethers (sevoflurane, isoflurane, enflurane, and methoxyflurane) and halothane, a haloalkane, in male ddN mice. In our previous study, we only used young male mice (10 ± 2 weeks old). In aged animals, the brain tissue levels of catecholamine and acetylcholine, cerebral blood flow, cerebral oxygen consumption, and glucose utilization are all decreased[6,7]. To determine whether age has any effect on opisthotonus, we examined three different age groups of mice.

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Table 1. Percent incidence of Opisthotonus, and blood/gas and brain/blood partition coefficients of each anesthetic

Anesthetic %	A/B@	Age		
		10 ± 2 weeks	6 ± 1 months	12 ± 1 months
Haloether				
Sevoflurane 2.0	0.69/	94(34)	76(72) *	93(45) *
Isoflurane 1.3	1.37/1.65	83(76)	64(72) **	80(117) *
Enflurane 2.0	1.91/1.28	27(91) ##	44(85) *,#	71(98) **
Methoxyflurane 0.5	15.5/1.36	13(32)	1(67) *,##	23(80) **,##
Haloalkane				
Halothane 1.0	2.51/1.92	0(57)	0(85) #	3(88) ##

( ) = n

@ A: blood/gas partition coefficient in human middle-aged adults[16,22]

B: brain/blood partition coefficient in human middle-aged adults[22]

*significant difference from younger age group ($P < 0.05$)

**significant difference from younger age group ($P < 0.01$)

#significant difference from agent group in upper column ($P < 0.05$)

##significant difference from agent group in upper column ($P < 0.01$)

Materials and Methods

Young adult (10 ± 2 week), middle-aged (6 ± 1 month), and elderly (12 ± 1 month) male ddN mice were used. Separate gas mixtures of 2.0% sevoflurane (n = 34, 72, 45, in young, middle-aged, and elderly group, respectively), 1.3% isoflurane (n = 76, 72, 117, respectively), 2.0% enflurane (n = 91, 85, 98, respectively), 1.0% halothane (n = 57, 85, 88, respectively), or 0.5% methoxyflurane (n = 32, 67, 80, respectively) in air were added to a 12-1 plastic chamber using a 5 l/min gas flow through a vaporizer. All anesthetic concentrations were continuously monitored using a infra-red detector (Normac, Datex). The sevoflurane concentration, using the gas chromatograph, was obtained by following formula:

sevoflurane concentration =
0.91 × Normac value
in methoxyflurane mode

After the anesthetic concentration leveled off, mice were placed in the chamber. Observation time was up to 30 min enough to determine whether or not opisthotonus would occur. Opisthotonus was defined as the case when both head and tail bent backward more than about 15° (30° in our previous study) from the horizontal plane. This modification was made in order to more precisely investigate a CNS stimulating effect of an agent. After observation, anesthetic application was stopped and all mice recovered from anesthesia within a few minutes. Every mouse was only once exposed to an anesthetic. The volatile agents were passed through the chamber during the entire experimental period. The chamber temperature was monitored and maintained at 24 ± 1°C by a circulating-water heat exchanger. Inter-anesthetic group or inter-age group differences in the incidences of opisthotonus were determined by the Chi-square test, and $P < 0.05$ was considered statistically significant.

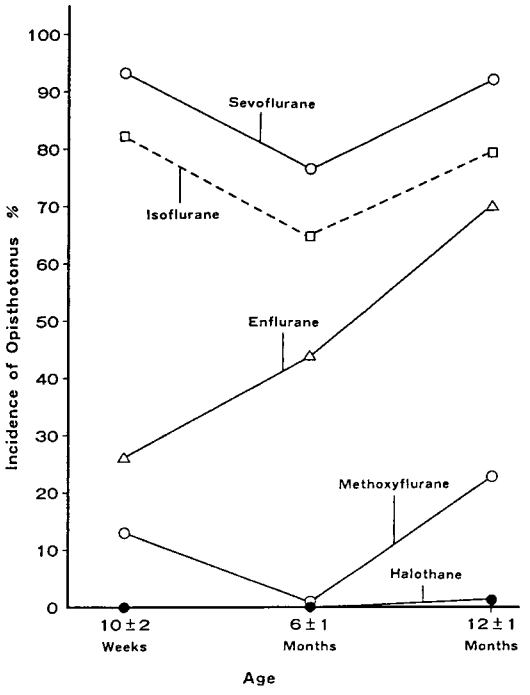

Fig. 1. Correlation between age of mice and the incidence of opisthotonus. Note that the incidence of opisthotonus in middle aged is lower than that for young or elderly mice. Note also that the incidence increases with age in the enflurane group.

Results

Opisthotonus usually occurred within 10 min after exposure to an anesthetic. A few occurred after over 20 min in the methoxyflurane group. The order of opisthotonic incidence in each age group was always sevoflurane > isoflurane > enflurane > methoxyflurane > halothane (table 1, fig. 1). The incidences in middle-aged mice were fewer than in young and elderly mice in the sevoflurane, isoflurane, and methoxyflurane groups. The incidence of opisthotonus in the enflurane group increased with age. Halothane rarely produced opisthotonus. The blood/gas and brain/blood partition coefficients of anesthetics, and the incidence of opisthotonus in the three age groups are shown in table 1.

Discussion

MAC values are reported to be 2.15% for sevoflurane (male mouse[8], 1.38% for isoflurane (rat)[9], 2.06% for enflurane (dog)[10], 0.27% for methoxyflurane (rat)[11], and 0.9% for halothane (male mouse)[8]. Although MAC for each anesthetic in ddN mice is unknown, anesthetic concentrations in this study, except for methoxyflurane[12], are close to those of MAC. In the present study, ddN mice required 0.5% methoxyflurane to be anesthetised. Koblin et al.[13] showed the nitrous oxide requirement decreases with age in mice. Halothane and isoflurane requirements also decrease with age in man[14,15]. Consequently, the elder mice might inhale a relatively higher concentration of anesthetics than 1 MAC.

In our previous study, we hypothesized that the rapidity of anesthetic induction might correlates positively with the induction of opisthotonus. Our present data may support our hypothesis so far as halogenated ether anesthetics are concerned since the incidence of opisthotonus is inversely proportional to the anesthetic. Sevoflurane (fluoromethyl-1,1,1, 3,3,3-hexafluoroisopropyl ether) is a rapid-acting, potent inhalation anesthetic whose rapid uptake and elimination are due to a low blood/gas partition coefficient[16], and this group had the highest incidence of opisthotonus. Ethers with the alpha carbon of the isopropyl group substituted by a halogen exhibit a strong convulsive component[17]. Although sevoflurane has not been clinically reported to induce a convulsion, the EEG pattern of high voltage slow rhythmic waves is seen in the case of fast induction at a concentration of 4%, which is thought to be a sign of CNS stimulation[18,19]. Our findings coincide with this description. Halothane rarely produced opisthotonus in any age group of mice. This agrees with our previous study[5] and with other studies demonstrating that halothane depresses CNS without seizure activity[20,21]. Methoxyflurane yielded a rather high incidence of opisthotonus despite having a slower anesthetic induction than halothane. This may be related to the general feature that haloethers' actions are more irritable to the CNS than haloalkanes'[17]. The incidence

of opisthotonus does not inversely correlate with the brain/blood partition coefficient (table 1) but rather with the blood/gas partition coefficient. This may be partly due to the fact that the brain was not equilibrated with the anesthetic during induction of anesthesia, while the blood/brain partition coefficient is measured under equilibrium state[22].

Two types of age-related differences in opisthotonic incidence were observed in this study. In one, the incidence in the middle age group was lower than that in the young and elderly groups, as shown in the sevoflurane, isoflurane, and methoxyflurane groups. Although the reason of this phenomenon is unknown, we believe that this is because the CNS of middle aged mice is more stable than that of young or elderly mice. The second type of age-related difference was that seen in the enflurane group, where the incidence of opisthotonus increased with age. Although the reason of this phenomenon is unknown too, this may be consistent with the observation that the occurrence of EEG seizures increases with increasing enflurane concentration from 2.0 to 3.5%[23] because the elderly mice may be expected to inhale a relatively high concentration of enflurane as compared with the younger mice (MAC of the elderly mice is expected to be lower than that of the younger mice).

In summary, anesthetic-induced opisthotonus might occur because of the increasing speed of anesthetic induction so far as haloether anesthetics are concerned. Halothane seldom caused opisthotonus. This may be due to the different general features (structure-activity relationships) between haloethers and haloalkanes that haloethers are more irritable to CNS than haloalkanes. The incidence of opisthotonus was lower in the middle age mice than in the young or elderly mice in the sevoflurane, isoflurane, and methoxyflurane groups, whereas it increased with age in the enflurane group.

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