Opisthotonus during Exposure to Isoflurane, Enflurane, and Halothane in Mice

Hisao Komatsu, M.D.,* Kenji Ogii, M.D.†

Some strains of mice, in whom anesthesia was induced with 1.2% isoflurane in air, developed episodes of intense opisthotonus, lasting 1–2 min. Occasionally, opisthotonus also occurred transiently on emergence from isoflurane anesthesia. The incidence of opisthotonus upon anesthetic induction varied with the strain of mice studied, and was particularly high (nearly 80%) in the ddN and YBR/Ki strains. A significantly lower incidence of opisthotonus was observed in all 14 strains studied when 2.0% enflurane was used. One percent halothane did not produce opisthotonus in any strain of mice except one animal of the YBR/Ki strain, and, in this situation, it occurred only on emergence. These results suggest that, in some strains of mice, induction of anesthesia with isoflurane may apparently excite (disinhibit) the central nervous system more intensely than does anesthesia with enflurane or halothane. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Brain: CNS excitation; disinhibition; electroencephalography; opisthotonus.)

Enflurane may cause seizures, especially when administered in high concentrations with hyperventilation. On the other hand, isoflurane, a stereoisomer of enflurane, does not cause convulsant activity but, rather, may exhibit anticonvulsant properties. During experimental and clinical studies of isoflurane in cats, dogs, and humans, spike waves with simultaneous slowing of the EEG have been observed, but seizure activity has not been reported. There have, however, been several case reports describing seizures with nitrous oxide-isoflurane and nitrous oxide-narcotic-isoflurane anesthesia.

In a specific species of mice, ddN, the authors observed an unexpectedly high incidence of opisthotonus (Fig. 1) during induction and, occasionally, during emergence from anesthesia with isoflurane. Opisthotonus occurs in cats in decerebrate rigidity, and can be described as a hyperextended posture of the neck, arching of the back, and extension of the tail. The etiology of this phenomenon is thought to be a hyperactive state of the stretch reflexes due to interruption of the inhibitory process of the CNS (disinhibition).

The current report describes the incidence of opisthotonus induced by isoflurane, enflurane, and halothane in ddN and 13 other strains of mice. Also described is the EEG activity of one ddN mouse during opisthotonus while anesthetized with isoflurane.

Materials and Methods

One hundred and twenty-four mice of the ddN strain and five to ten mice of each of 13 other strains (total 80) were studied (Table 1). All mice were 10 ± 2-week-old males weighing 25–32 grams. Their quarters were maintained at 24 ± 1°C with light present from 0600–1800 h, and the mice were fed a standard laboratory animal diet and tap water ad libitum until the experiment was started. No mouse displayed opisthotonus prior to anesthetic exposure. All experiments were performed during the same period of day, from 1300–1800 h.

A gas mixture of 1.2% isoflurane, 2.0% enflurane, or 1.0% halothane in air was administered into a 12-l plastic chamber using 5 l/min gas flow through a vaporizer. These concentrations were considered to be close to that of MAC for mice. The concentrations, measured at the gas outlet using gas chromatography, showed the delivered concentrations to be within 5% of the vaporizer settings.

Ten minutes or greater after gas flow was established, mice were transferred to the chamber and anesthetized. Room temperature was maintained at 24 ± 2°C throughout the experiment. The presence of opisthotonus was established by the criteria that head and tail were both bent backward more than about 30° from the horizontal plane. The observer was not blind to which anesthetic treatment was used.

ddN Mice

Of the 124 ddN mice, 54 were exposed to 1.2% isoflurane, 46 to 2.0% enflurane, and 24 to 1.0% halothane. The order of application of various agents was randomized. The animals were observed for any occurrence of opisthotonus. Observation time was 5–10 min, because any case of opisthotonus almost always occurred within 5 min after exposure to an anesthetic agent. After 10 min, the anesthetic gas was discontinued and the mice were permitted to awaken. Significance of differences in the incidence of opisthotonus between the three anesthetic groups was calculated by a

* Instructor.
† Professor and Chairman.
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Address reprint requests to Dr. Komatsu: Department of Anesthesiology and Emergency Medicine, Kagawa Medical School, Miki-cho, Kita-gun, Kagawa 761-07, Japan.
each mouse was exposed first to isoflurane, second to enflurane, and lastly to halothane with intervals of more than a week between applications. The method of administration, the concentrations of each anesthetic, and the observation time were the same as for the ddN mice. Significance of differences between the three anesthetic groups was not calculated, because the number of mice from each strain was small.

**The EEG Study**

A single ddN mouse was used in the EEG study. Under diethyl ether anesthesia, using a sterile technique, four stainless steel electrodes (0.27 mm diameter) were implanted stereotaxically by the atlas of Sidman et al.\textsuperscript{11} Left and right frontal cortex electrodes were implanted into locations 2 mm lateral and 1 mm anterior to the bregma (1 mm depth). A right parietal cortex electrode was implanted 2 mm lateral and 2 mm caudal to the bregma (1 mm depth). A left hippocampal CA 3 area (Stratum Radiatum) electrode was implanted 2 mm lateral and 2 mm caudal to the bregma (2.5 mm depth). Electrodes were secured to the skull with acrylic resin.

Two weeks after implantation, the EEG was recorded while the mouse was freely moving by connecting the electrodes to a socket with cords to amplify the signals through an electroencephalograph (San-ei electroencephalograph 1A52, San-ei Instrument Co., Ltd, Japan). Signals were recorded continuously while the mouse was awake, during exposure to 1.2\% isoflurane, and throughout recovery.

**Results**

In a typical case in which opisthotonus occurred, the mouse's movements would stop within a few minutes after exposure to the anesthetic, and, a few minutes later, the mouse would exhibit the posture demonstrated in figure 1. One to two minutes later, the opisthotonus would fade and the mouse would again become flaccid and immobile. The incidence of opisthotonus associated with the three anesthetic agents is shown in table 1.

Although the incidence varied with the strain of mice, on the whole, it was highest in the isoflurane group and lowest in the halothane group (table 1). In ddN mice, the incidence of opisthotonus induced by isoflurane was significantly higher than that induced by enflurane ($P < 0.05$) or halothane ($P < 0.01$). Halothane did not produce opisthotonus in any strain of mice except in one of five YBR/Ki mice during emergence from anesthesia.

The EEG response to 1.2\% isoflurane recorded from right frontal and right occipital cortices in one ddN

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**Table 1. Percent of Mice Exhibiting Opisthotonus During Induction of Anesthesia with Isoflurane, Enflurane, and Halothane**

<table>
<thead>
<tr>
<th>Strain</th>
<th>Isoflurane 1.2</th>
<th>Isoflurane 2.0</th>
<th>Enflurane 2.0</th>
<th>Halothane 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddN</td>
<td>83 (54)*</td>
<td>13* (46)</td>
<td>0* (24)</td>
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</tr>
<tr>
<td>A/Ki</td>
<td>0* (10)</td>
<td>0 (10)</td>
<td>0 (10)</td>
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</tr>
<tr>
<td>AF/Biki</td>
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<td>0 (5)</td>
<td>0 (5)</td>
<td></td>
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<tr>
<td>AKR/Ki</td>
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<td>0 (5)</td>
<td>0 (5)</td>
<td></td>
</tr>
<tr>
<td>CSH/BifB/Ki</td>
<td>20 (10)</td>
<td>0 (10)</td>
<td>0 (10)</td>
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<tr>
<td>CSH/Biki</td>
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</tr>
<tr>
<td>C57BL/Ki</td>
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<td>0 (5)</td>
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<td>CBA/Ki</td>
<td>30 (10)</td>
<td>10 (10)</td>
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<td></td>
</tr>
<tr>
<td>CBA/Shiki</td>
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<td>0 (5)</td>
<td>0 (5)</td>
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<tr>
<td>DBA/2fKi</td>
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<td>0 (5)</td>
<td>0 (5)</td>
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</tr>
<tr>
<td>DBA/2Ki</td>
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<td>0 (5)</td>
<td>0 (5)</td>
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</tr>
<tr>
<td>FB/Ki</td>
<td>60 (5)</td>
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<td>0 (5)</td>
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<tr>
<td>RSA/Imr/Ki</td>
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<td>0 (5)</td>
<td>0 (5)</td>
<td></td>
</tr>
<tr>
<td>YBR/Ki</td>
<td>80 (5)</td>
<td>40 (5)</td>
<td>0 (5)</td>
<td></td>
</tr>
</tbody>
</table>

\* Numbers of animals are given in parentheses.
\*\* Significantly different from incidence in isoflurane group ($P < 0.05$).
\*\*\* Significantly different from incidence in isoflurane group ($P < 0.01$).
mouse is illustrated in figure 2. Spiking activity (single spikes) appeared during opisthotonus.

Discussion

It is well known that central nervous system (CNS) excitation occurs during induction of anesthesia with inhalational anesthetics. Transient pathologic neurologic signs during emergence from anesthesia have also been reported. Soliman and Gillies drew attention to the appearance of muscle spasticity in nearly all patients during recovery from general anesthesia. Rosenberg et al. reported that the incidence of hyperreflexia and myoclonus during awakening from anesthesia was greater following enflurane-nitrous oxide and less following halothane-nitrous oxide. These investigators indicated that muscle spasticity or hyperreflexia during recovery from anesthesia might be related to depression of supraspinal inhibitory pathways, thereby leading to increased activity of descending facilitatory tracts. Although there has been no previous report linking opisthotonus with clinically used anesthetics, our observations may be similar to those above because opisthotonus is a broadly facilitated state of muscle stretch reflexes.

It is particularly interesting that the incidence of opisthotonus was greatest with isoflurane and least with halothane. Shimoji et al. reported that more frequent occurrence of disinhibition of midbrain reticular neuron responses during light anesthesia might be related to the excitatory signs sometimes observed in clinical anesthesia. Their data also suggested that isoflurane blocked the inhibitory responses more frequently than halothane.

A possible mechanism of opisthotonus during induction of anesthesia in mice is that the higher centers are more rapidly inhibited than the facilitatory cells of the reticular formation (RF), which elicits stretch reflexes, thereby resulting in opisthotonus. As anesthesia deepens, the activity of the facilitatory cells of the RF may decrease and opisthotonus then disappears.

Halothane did not produce opisthotonus. This agent may inhibit the higher centers more slowly than isoflurane or enflurane, so that there is no lag between depression of each kind of cell, thus preventing the facilitatory cells of the RF from eliciting opisthotonus. A relatively long time lag after depression of the higher centers (or inhibitory cells of the RF) before the depression of the facilitatory cells of the RF might be a required condition for opisthotonus.

The effects of isoflurane on the EEG have been determined in cats, dogs, and humans, but not in mice. The spiking activity and increased EEG amplitude in the present report are consistent with the results of previous studies, although associated abnormal movement or tone have not been previously reported. This discrepancy may be due to species differences. The reason why opisthotonus occurs only in mice is unknown, but these animals may be more excitable. Some strains of mice are used as models for epilepsy. In summary, a high incidence of opisthotonus in ddN mouse was observed during induction of anesthesia with isoflurane. A lower incidence was observed with 2.0% enflurane, where it was not observed when 1.0% halothane was used. This phenomenon may occur when the inhibitory cells of the higher centers and/or RF are rapidly depressed before the facilitatory cells of the RF are depressed.

References