Awakening Concentration of Desflurane Is Decreased in Patients with Obstructive Jaundice

Jian-Gang Song, M.D.,* Yun-Fei Cao, M.D.,† Li-Qun Yang, M.D.,‡ Wei-Feng Yu, M.D.,§ Quan Li, M.D.,|| Jin-Chao Song, M.D.,# Xiao-Yong Fu, Ph.D.,,** Qiang Fu, M.D.††

**Background:** Some studies suggest that behavioral complications of cholestasis, such as fatigue and pruritus, may be associated with altered neurotransmission in the brain. Because inhaled anesthetics primarily act on ion channels and receptors on the neuronal cell membrane and alter synaptic transmission in the central nervous system, it is possible that altered sensitivity to inhaled anesthetics may occur in cholestatic patients. Therefore, the authors compared the minimum alveolar concentration (MACawake) of desflurane in obstructive jaundiced patients with the MACawake in nonjaundiced patients.

**Methods:** Patients underwent inhalational induction of anesthesia with desflurane. MACawake was determined in each patient by observing the response to a verbal command (open eyes on request). An end-tidal anesthetic concentration was maintained at an initial target level of 1.4% for 15 min before a command. If a positive response was observed, the concentration of desflurane was increased by 0.1% and again kept constant for 15 min. The verbal command was then continued. This process was repeated until an end-tidal concentration was reached at which the patient did not respond to command. The anesthetic concentration midway between the value permitting the response and that just preventing the response was defined as MACawake for each patient.

**Results:** The MACawake of desflurane for patients with obstructive jaundice (1.78 ± 0.19%) was significantly less than those observed for the control group (2.17 ± 0.25%; P < 0.001) and correlated significantly with serum total bilirubin (r = −0.67, P = 0.004).

**Conclusions:** The MACawake of desflurane is reduced in obstructive jaundiced patients compared with nonjaundiced controls.

THAT there is a relation between the functional status of the liver and that of the brain has been known for centuries. The most widely recognized aspect of this relation is that hepatocellular failure may be complicated by the syndrome of hepatic encephalopathy, in which neurotransmission in the brain is altered. Recently, it has been suggested that some extremely common complaints among patients with cholestatic liver disease, such as fatigue and pruritus, might also be associated with altered neurotransmission in the brain. Because accumulating evidence has suggested that inhaled anesthetics exert their effects via acting on ion channels and receptors on the neuronal cell membrane and altering synaptic transmission in the central nervous system, this altered neurotransmission in the brain might affect the sensitivity of cholestatic patients to inhaled anesthetics. However, this hypothesis has not been confirmed in cholestatic patients.

For the inhaled anesthetics, the minimum alveolar concentration (MAC) for achieving a 50% probability of no response to a verbal command (MACawake) provides one measure of hypnotic potency. Accordingly, we designed this study to determine whether the MACawake of desflurane in patients with obstructive jaundice undergoing surgical treatment has been changed and to evaluate the relation between MACawake and serum concentrations of total bilirubin, bile acids, alanine transaminase, and albumin.

**Materials and Methods**

After receiving approval from our local ethics committee (Shanghai, China), informed consent was obtained from each patient undergoing elective surgery for hepatobiliary disease. Twenty-four patients with obstructive jaundice (serum total bilirubin > 20 μmol/L) caused by neoplasm of the bile duct or the head of the pancreas were included in the study. Twenty nonjaundiced patients who had chronic cholecystitis or liver hemangiomata served as controls. All patients had American Society of Anesthesiologists physical status I or II and were aged between 50 and 70 yr.

Exclusionary criteria were (1) age older than 70 yr or younger than 50 yr; (2) significant obesity (body mass index > 30 kg/m²); (3) a history of cardiovascular, respiratory, or renal disease; (4) hepatic encephalopathy, psychiatric illness, or neuropathy; (5) acid–base disturbance, blood electrolyte dysfunction, diabetes, sepsis, or obvious weight loss caused by carcinoma; (6) medications known to affect MACawake or a history of either alcohol or drug abuse; and (7) excitement with desflurane induction.

Each patient fasted for 12 h and did not receive any sedative or analgesic drugs before anesthesia. Intravenous access was established, and patients were monitored with electrocardiography, pulse oximetry, and nasopharyngeal temperature and invasive blood pressure.
measurement. Inspired and expired concentrations of desflurane, carbon dioxide, and oxygen were measured continuously using a Datex respiratory gas analyzer (Datex Instrumentarium Corp., Helsinki, Finland) calibrated by a standard gas mixture before anesthesia for each patient.

The test of MACawake for each patient was determined using a modification of the method of Chortkoff et al.17 All patients spontaneously breathed 100% oxygen through a clear, plastic, tight-fitting facemask attached to a semiclosed anesthetic circuit used to protect the end-tidal samples from contamination by inspired gas. Anesthetic administration began with a single-step increase to the initial target end-tidal concentration of 1.4%. This and subsequent steps were maintained for 15 min to allow adequate time for alveolar and brain desflurane partial pressures to equilibrate. Then, a designated observer blinded to the patients’ clinical conditions, the patient group, and the anesthetists administered asked the patient in a normal tone to open his or her eyes, repeating the request not more than three times. If he or she made an appropriate response, the anesthetic concentration was increased by 0.1% and again kept constant for 15 min. The process was repeated until an end-tidal concentration was reached at which the patient did not respond appropriately to command. The MACawake for each patient was the concentration midway between the value permitting the response (opening eyes on request) and that just preventing the response. When MACawake had been determined, samples of arterial blood were collected for analysis of blood gas tensions, and samples of venous blood were collected for measurements of liver biochemistries. Then, anesthesia was deepened to a level appropriate for the surgical procedure.

Values are presented as mean ± SD. The Student unpaired t test was used for analysis of variance between the groups. Using SPSS 10.1.4 for Windows (SPSS Inc., Chicago, IL), multiple regression was used to determine whether total bilirubin, alanine transaminase, bile acids, or albumin correlated significantly with MACawake of obstructive jaundiced patients for desflurane. P < 0.05 was considered statistically significant. In addition, we had measured the MACawake of five jaundiced patients and five nonjaundiced patients in the preliminary trial. Consequently, based on the difference between two groups, the formula for normal theory, and assuming a two-sided type I error protection of 0.05 and a power of 0.80, 20 patients in each group were required to reveal a statistically significant difference.

### Results

There were no significant differences between the two groups with respect to age, weight, sex, or body temperature (table 1). No episodes of hypotension (systolic blood pressure < 90 mmHg), bradycardia (heart rate < 60 beats/min), hypoxemia, hyperthermia, depression of respiration, or acid–base disturbance occurred during the course of measurement of MACawake.

The MACawake of desflurane for patients with obstructive jaundice (1.78 ± 0.19%) was significantly less than that observed for the control group (2.17 ± 0.25%; P < 0.001). Multiple regression analysis showed that there was a high negative correlation between serum total bilirubin and MACawake, whereas alanine transaminase, bile acids, and albumin did not significantly correlate with MACawake (table 2). The equation of the regression line for desflurane was MACawake (%) = 2.041 − 0.00094 · total bilirubin (μM), with R² of 0.444 (fig. 1).

### Discussion

Our study showed that the MACawake of desflurane for patients with obstructive jaundice decreased significantly compared with that of nonjaundiced controls (P < 0.001); moreover, there was a high negative correlation be-

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obstructive Jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>10/10</td>
<td>13/11</td>
</tr>
<tr>
<td>Age, yr</td>
<td>57.4 ± 7.3</td>
<td>59.3 ± 5.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.2 ± 8.0</td>
<td>61.6 ± 7.0</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>36.0 ± 0.6</td>
<td>36.1 ± 0.5</td>
</tr>
<tr>
<td>Total bilirubin, μM</td>
<td>12.1 ± 5.1</td>
<td>273.8 ± 137.8</td>
</tr>
<tr>
<td>Bile acids, μM</td>
<td>5.8 ± 1.8</td>
<td>143.1 ± 65.3</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>42.1 ± 2.7</td>
<td>37.5 ± 4.7</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>41.2 ± 9.8</td>
<td>128.8 ± 111.3</td>
</tr>
</tbody>
</table>

All values except n and sex are expressed as mean ± SD.

### Table 2. Results of Regression Analysis for MACawake as the Dependent Variable

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Regression Coefficient (β)</th>
<th>SE</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1.749</td>
<td>0.334</td>
<td>1.049 to 2.448</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>-8.65 × 10⁻⁴</td>
<td>0.0003</td>
<td>-0.001 to -0.0003</td>
<td>0.004</td>
</tr>
<tr>
<td>Bile acids</td>
<td>-1.21 × 10⁻⁴</td>
<td>0.0003</td>
<td>-0.001 to 0.001</td>
<td>0.693</td>
</tr>
<tr>
<td>Albumin</td>
<td>6.86 × 10⁻³</td>
<td>0.008</td>
<td>-0.009 to 0.024</td>
<td>0.382</td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>2.08 × 10⁻⁴</td>
<td>0.001</td>
<td>-0.001 to 0.001</td>
<td>0.698</td>
</tr>
</tbody>
</table>

CI = confidence interval; MAC = minimum alveolar concentration.
discrepancy. In this study, we determined MACawake investigator’s hands, which could also result in some et al. aged 21–30 yr reported previously by Chortkoff nonjaundiced patients aged 50–69 yr was smaller than crease the requirements of inhaled anesthetic. To hepatobiliary disease. It is reported that sepsis can decrease the requirements of inhaled anesthetic,18 To avoid the possible influences of sepsis and fluctuation of jaundice on MACawake, we excluded these patients from the study. Although neoplasm can induce obvious weight loss, which may also affect anesthetic requirements, these symptoms had not been present in patients we enrolled. The observer was blinded to the patients’ group, individual clinical conditions, and the anesthetics administered, but it was not feasible to blind the investigator as to whether the patient had obstructive jaundice because jaundiced patients show obviously yellow color. However, because the observer was not aware of our study design and our aim of determining the relation between obstructive jaundice and the sensitivity to inhaled anesthetic, we think that the physician bias was minimal. The MACawake value of 2.17 ± 0.25% desflurane for our nonjaundiced patients aged 50–69 yr was smaller than that of 2.60 ± 0.46% desflurane for healthy volunteers aged 21–30 yr reported previously by Chortkoff et al.17 using a similar method to determine the values of MACawake. Considering the influence of age on MACawake that each increasing decade of life is associated with a 6.7% decrease in MACawake, this discrepancy can be primarily attributed to the different ages of populations enrolled in the studies. In addition, we used the endpoint of eye opening, whereas Chortkoff et al. used the endpoint of response to the command to squeeze the investigator’s hands, which could also result in some discrepancy. In this study, we determined MACawake using ascending sequences of anesthetic concentrations. As guides to predicting relative times to awakening, data using descending sequences may seem more relevant. However, Jones et al.20 found no difference in values using ascending versus descending sequences of anesthetic concentrations for the endpoints of MACawake for desflurane. We maintained constant end-tidal concentrations of desflurane for 15 min. Theoretically, the time required for the brain to reach the same partial pressures as that in blood depends on the blood-brain partition coefficient. Based on laboratory investigation on tissue homogenates, 21 95% equilibration between arterial blood and brain partial pressures for halothane and enflurane should be completed in 14.4 and 7.9 min, respectively. Considering that desflurane has the lowest solubility of the modern clinically used volatile anesthetics, 15 min of steady state end-tidal concentrations of desflurane should allow adequate equilibration among the lung, the arterial blood, and the brain.

The mechanism of decreased awakening concentration of desflurane is unclear. Many pathophysiologic conditions can affect potency of inhaled anesthetics, including additional anesthetic drugs; differences in core temperature, age, hypotension, and acid–base status; and diseases such as hypothyroidism or hyperthyroidism.26 Diabetes,27 and sepsis,18 but these conditions did not occur in our patients. Because the elimination of inhaled anesthetics is predominately determined by the lung, rather than the liver, and desflurane possesses a relatively low solubility in blood and minimal metabolism in humans, its pharmacokinetic characteristics are unlikely to be changed significantly in patients with obstructive jaundice, even though liver function is impaired. Because it is known that anesthetic-induced hypnosis and amnesia are mediated primarily within the brain, changes in the functional status of the brain consequent to the obstructive jaundice seem to be more likely to increase hypnotic potency of desflurane.

Recently, it has been suggested that altered neurotransmission may occur in the brains of cholestatic patients. For example, some evidence suggests that pruritus and fatigue complicating cholestasis may be the consequence of a central mechanism, specifically increased opioidergic neurotransmission9–13 and defective serotoninergic neurotransmission.5–8 The latter is considered to be sensitive to inhaled anesthetics.9,30 Consequently, the altered neurotransmission in patients with obstructive jaundice may, at least in part, contribute to the reduction of anesthetic requirements. However, whether other neurotransmissions are also involved in the reduction of desflurane MACawake of jaundiced patients should be studied further, given the association of inhaled anesthetics with altered activity of a variety of neuronal ion channels, particularly the fast synaptic neurotransmitter receptors such as nicotinic acetylcholine, y-aminobutyric acid type, and glutamate receptors.51–53 Besides altered neurotransmission in the brain, the direct damage to the brain of obstructive jaundice may also play a role in decreasing the requirements of desflurane. An experimental observation in a well-characterized canine model of cholestasis secondary to bile duct

Fig. 1. Regression analysis reveals a significant correlation between serum total bilirubin and minimum alveolar concentration (MACawake) for desflurane (P < 0.01).

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resection provides histologic evidence that neurologic damage, such as simple atrophy and pyknosis of nerve cells, neurophagia, and ghost cells, was observed in the brain. Moreover, the range of neurologic damage spread from the basal ganglia, putamen, and red nucleus to the thalamus, cerebral cortex, and substantia nigra, with the duration of obstructive jaundice prolonged.34

In conclusion, our study demonstrates that the MACawake of desflurane was significantly reduced in obstructive jaundiced patients compared with nonjaundiced controls; moreover, there is a highly inverse relation between the concentration of serum total bilirubin and the MACawake of desflurane in jaundiced patients. Altered neurotransmission and neurotoxicity of jaundice in the brain may partly contribute to the reduction of anesthetic requirement.

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