Original Article

Magnesium sulfate inhibits sufentanil-induced cough during anesthetic induction

Li-Jun An1*, Bo Gui2*, Zhen Su1, Yang Zhang1, Hai-Lin Liu1

1Department of Anesthesiology, Huai’an First People’s Hospital, Nanjing Medical University, Huai’an, Jiangsu, China; 2Department of Anesthesiology, The 1st Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu, China. *Equal contributors.

Received August 7, 2015; Accepted August 10, 2015; Epub August 15, 2015; Published August 30, 2015

Abstract: Sufentanil-induced cough is a common phenomenon during the induction of anesthesia. This double-blind, randomized, and placebo-controlled study was designed to investigate the effects of prophylactic magnesium sulfate (MgSO4) on the incidence and severity of sufentanil-induced cough. A total of 165 patients who were scheduled for elective surgery under general anesthesia were allocated into three groups (I, II, and III; n = 55 each) that were injected with either 50 ml of normal saline, 30 or 50 mg/kg of MgSO4 (diluted with normal saline into 50 ml). One minute following the injection, all patients were injected with 1.0 μg/kg of sufentanil within 5 s. The incidence and severity of cough were recorded 30 s after the sufentanil injection. The hemodynamic parameters and plasma magnesium concentration of the patients were also noted. Three patients dropped out the study due to an obvious burning sensation during the injection of 50 mg/kg of MgSO4. Although the injection of 50 mg/kg of MgSO4 increased the plasma magnesium level, the increase remained within the therapeutic range (2-4 mmol/L). The incidence of cough was much higher in group I than in groups II and III (47.1% vs. 16.4% and 7.6%, respectively, P < 0.05). Compared with group I, group III had the lowest incidence of mild cough and both groups II and III had lower incidence of moderate and severe cough (P < 0.05). There were no differences in the hemodynamic data at three timepoints among the three groups. In conclusion, sufentanil-induced cough may be suppressed effectively and safely by prophylactic use of 30 mg/kg of MgSO4 during anesthetic induction.

Keywords: Anesthetic induction, cough, magnesium sulfate, sufentanil

Introduction

The clinical use of sufentanil, a thienyl analogue of fentanyl, during induction of general anesthesia, has become increasingly common because of its strong analgesic property. However, its injection often induces cough [1]. This pathological condition may specially threaten patients with a cerebral aneurysm, open eye injury, and asthma by increasing intracranial, intraocular and intraabdominal pressure. Although pretreatment with lidocaine, propofol, and dexmedetomidine effectively suppressed opioid-induced cough, they have some limits because of their side effects or slow onset time [2-4]. Therefore, research on this topic may have considerable clinical significance.

Magnesium plays a fundamental role in many cellular functions. It has a powerful relaxation effect on airway smooth muscles, so it is often used to treat the severe exacerbation of asthma [5]. Cough is similar to asthma in many aspects. In this double-blind, randomized, and placebo-controlled study, we investigated the effect of magnesium sulfate (MgSO4) on the incidence and severity of sufentanil-induced cough during anesthetic induction as a reference for future clinical application.

Materials and methods

Study design and study population

This study was approved by the Ethics Committee of Huai’an First People’s Hospital affiliated with the Nanjing Medical University, and written informed consent was obtained from eligible patients. A total of 165 patients, aged 18-65 years, classified as American Society of Anesthesiologists (ASA) physical sta-
Magnesium sulfate suppresses sufentanil-induced cough

Figure 1. CONSORT flow diagram.

Table 1. Demographic characteristics of the patients (n = 160)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I (n = 53)</th>
<th>Group II (n = 55)</th>
<th>Group III (n = 52)</th>
<th>P.Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40 ± 11</td>
<td>38 ± 10</td>
<td>41 ± 13</td>
<td>0.8126</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>33/20</td>
<td>31/24</td>
<td>34/18</td>
<td>0.8920</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.2 ± 11.2</td>
<td>51.9 ± 11.8</td>
<td>52.9 ± 12.1</td>
<td>0.5703</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>34/19</td>
<td>38/17</td>
<td>32/20</td>
<td>0.8246</td>
</tr>
</tbody>
</table>

Data are expressed as the number and mean ± SD. There are no statistically significant differences among the three groups with regard to age, gender, weight and ASA class. M: male. F: female. ASA: American Society of Anesthesiologists.

Table 2. Plasma magnesium levels (mmol/L, n = 160)

<table>
<thead>
<tr>
<th>Plasma magnesium</th>
<th>Group I (n = 53)</th>
<th>Group II (n = 55)</th>
<th>Group III (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.16 ± 0.3</td>
<td>1.17 ± 0.1</td>
<td>1.17 ± 0.3</td>
</tr>
<tr>
<td>After infusion</td>
<td>1.18 ± 0.4</td>
<td>2.50 ± 0.8</td>
<td>3.13 ± 0.6*</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD. *P < 0.05, group III vs group I.

The patients fasted for 8 h before administration of anesthetics. Upon arrival, monitoring was accomplished by electrocardiogram, non-inva-

tus I/II, and scheduled for elective surgery under general anesthesia were enrolled in this study. The exclusion criteria included a history of asthma; chronic administration of opioids, anti-cough medication or ACE-inhibitors; chronic cough; steroid therapy; upper respiratory tract infection in the previous four weeks; smoking; renal insufficiency; gastroesophageal reflux; hypermagnesemia; neuromuscular disease; morbid obesity; hypertension; and a cardiac disease, such as conduction block, bradycardia, arrhythmia or coronary artery disease. Patients with increased intracranial, intraabdominal or intraocular pressure were also excluded.
MgSO₄ suppresses sufentanil-induced cough

Table 3. Severity and incidence of sufentanil-induced cough (n = 160)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Severity of cough</th>
<th>Total</th>
<th>Incidence of cough (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>I (n = 53)</td>
<td>7 (13.2%)</td>
<td>13 (24.5%)</td>
<td>5 (9.4%)</td>
</tr>
<tr>
<td>II (n = 55)</td>
<td>4 (7.3%)</td>
<td>4 (7.3%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>III (n = 52)</td>
<td>2 (3.8%)</td>
<td>2 (3.8%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are expressed as numbers (percentages). *P < 0.05, groups II and III vs. group I.

Table 4. Hemodynamic data of the patients (n = 160)

<table>
<thead>
<tr>
<th>Group</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>I (n = 53)</td>
<td>81.7 ± 12.1</td>
<td>82.1 ± 12.9</td>
</tr>
<tr>
<td></td>
<td>II (n = 55)</td>
<td>79.9 ± 12.8</td>
<td>80.9 ± 13.4</td>
</tr>
<tr>
<td></td>
<td>III (n = 52)</td>
<td>79.3 ± 12.8</td>
<td>79.0 ± 13.9</td>
</tr>
</tbody>
</table>

| MAP (mmHg) | I (n = 53) | 88.1 ± 12.2 | 87.5 ± 12.4 | 87.9 ± 12.8 |
|            | II (n = 55) | 87.3 ± 11.8 | 86.7 ± 12.1 | 85.9 ± 11.9 |
|            | III (n = 52) | 88.2 ± 11.5 | 85.6 ± 11.8 | 85.1 ± 11.3 |

Data are expressed as the mean ± SD. There are no statistically significant differences among the three groups with regard to HR and MAP. HR: heart rate. MAP: mean arterial pressure.

Results

One-hundred-sixty-five patients were recruited into the study, with 160 included in the final analysis. The remaining patients were excluded.
Magnesium sulfate suppresses sufentanil-induced cough

due to the subsequent recognition of unexplained cough or obvious burning sensation during MgSO₄ infusion, as well as muscle rigidity after sufentanil infusion. Fifty-three patients were allocated into group I. Fifty-five and fifty-two patients received 30 and 50 mg/kg of MgSO₄, respectively (Figure 1). There were no significant differences among the three groups with regard to age, gender, weight, or ASA class (Table 1).

As shown in Table 2, group III (50 mg/kg of MgSO₄) showed increased plasma magnesium levels compared to group I (saline solution) (3.13 ± 0.6 vs. 1.18 ± 0.4 mmol/L, respectively); however, this increase remained within the therapeutic range (2-4 mmol/L). As shown in Table 3, the incidence of cough in group I was much higher than in groups II and III (47.1% vs. 16.4% and 7.6%, respectively; P < 0.05). Compared with group I, group III had the lowest incidence of mild cough and both groups II and III had a lower incidence of moderate and severe cough (P < 0.05). There were no differences in the hemodynamic data at three corresponding timepoints among the three groups with regard to HR and MAP (Table 4).

Discussion

Because injection of MgSO₄ can cause hypermagnesemia, which may lead to a serious inhibition of neuromuscular excitability, the plasma magnesium level must be closely monitored. Although injection with 50 mg/kg of MgSO₄ increased the plasma magnesium levels in our study, the increase remained within the therapeutic range (2-4 mmol/L). After administration of 30 and 50 mg/kg of MgSO₄, the incidence of sufentanil-induced cough declined from 47.1% to 16.4% and 7.6%, respectively. Three patients dropped out of the study due to an obvious burning sensation during injection with 50 mg/kg of MgSO₄. A relative high concentration might be attributed to this phenomenon.

Even small doses of sufentanil could produce violent coughing with an incidence of up to 31.9% [1, 7]. Considering the long time required for the surgery, we administered a bolus of sufentanil (1 μg/kg) during the anesthetic induction, which was higher than the former dose. Consequently, the incidence of sufentanil-induced cough was 45.8%. It seems that sufentanil-induced cough, such as by fentanyl, is also dose-related [6, 8]. Sufentanil-induced cough is mainly associated with reduced chest wall compliance, a phenomenon similar to chest wall rigidity, which often leads to difficult or impossible bag-mask ventilation because of vocal cord closure [7, 9]. Vocal cord activity is dominated by laryngeal muscles. Laryngeal muscle contraction causes glottis closure and the contraction of expiratory muscles, which may produce muscular rigidity or coughing. Other possible mechanisms have been proposed to explain this type of cough as follows: (a) inhibition of central sympathetic outflow causes vagal predominance and induces the cough reflex [10]; (b) excitation of pulmonary chemoreflex results from the stimulation of C-fiber receptors or irritant receptors, which are due to deformation of the trachea-bronchial wall by tracheal smooth muscle constriction [11]; (c) histamine is released from lung mast cells [10, 12]; (d) excitation of stretch receptors of the trachea and bronchial tree [13]; and (e) the central effect of opioids or dualism of opioid receptor [1, 14].

There are two possible explanations for the inhibitory effect of magnesium on sufentanil-induced cough. On the one hand, magnesium induces bronchodilation by inhibiting cholinergic neuromuscular transmission and attenuating calcium-induced muscle contraction [15, 16]. Evidence also showed that prostaglandin-mediated vascular smooth muscle relaxation might be magnesium-dependent, and magnesium possesses a mild sedative effect that helps achieve relaxation in acute bronchoconstriction [17]. On the other hand, magnesium acts as a calcium channel blocker at presynaptic nerve endings and decreases acetylcholine release at the motor endplate, which diminishes muscle fiber excitability and reduces the amplitude of the endplate potential [12]. Then, sudden vocal cord closure originating from sufentanil-induced laryngeal muscle rigidity can be suppressed.

There are some limitations that are relevant to our study. The severe cough was observed once in 0 cases, so larger samples might need to be involved. Furthermore, sufentanil infusion (0.2-0.3 μg/kg/hr) during emergence from desflurane anesthesia was reported to suppress coughing on extubation without delaying the extubation time [18]. Although it might be due
Magnesium sulfate suppresses sufentanil-induced cough

to the variance in timing the administration, more studies need to be performed to reveal the exact mechanism of sufentanil-induced cough during anesthetic induction.

In conclusion, due to several patients experiencing a burning sensation during the injection of 50 mg/kg of MgSO₄, pretreatment with 30 mg/kg of MgSO₄ can safely suppress the incidence and severity of cough induced by sufentanil (1 μg/kg) during anesthetic induction.

Acknowledgements

This study was funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions and grants from the National Natural Science Foundation of China (No. 81300937).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hai-Lin Liu, Department of Anesthesiology, Hua’ian First People’s Hospital, Nanjing Medical University, 6 Beijing Road West, Hua’ian 223300, Jiangsu, China. Tel: +86-13852346816; E-mail: liu hailin_1971@163.com

References