Thiopental Prevents A Beta-Endorphin Response to Cardiopulmonary Bypass

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Introduction

Physiologic stresses such as surgery and hemorrhagic or septic shock induce various endocrine responses. Beta-endorphin, one of the major endogenous opioids, is derived from pro-opiomelanocortin, a precursor of adrenocorticotropic hormone (ACTH) (Akil et al., 1984). The activation of the endorphin system is linked to the activation of the hypothalamic-pituitary-adrenal (HPA) axis, as revealed by parallel variations in ACTH, cortisol, and plasma beta-endorphin in response to nociceptive stimuli or hemodynamic insult (Carr and Murphy, 1988). Recent experimental studies reveal that the endogenous opioid system is mobilized during cardiovascular impairment, such as congestive heart failure (Kawashima et al., 1991), acute myocardial ischemia (Oldroyd et al., 1992), or in preoperative hemodynamic insufficiency in cardiac surgical patients with coronary artery or valvular heart disease (Carr et al., 1989).

Marked increases in plasma beta-endorphin levels influence the cardiovascular system via both central and peripheral mechanisms (Holaday, 1983).

Cardiopulmonary bypass (CPB) is an extremely non-physiologic state using non-pulsatile flow, hemodilution and hypothermia, and provokes marked stress responses with increases in numerous hormones including beta-endorphin (Yamashita et al., 1984; Cork et al., 1985; Hynynen et al., 1986; Lacoumenta et al., 1987; Anand and Hickey, 1992). As the patients are weaned from bypass, released endocrine substances might alter hemodynamics. These stress hormone responses could be reduced or blunted by various anesthetic agents (Cork et al., 1985; Hynynen et al., 1986; Lacoumenta et al., 1987; Anand and Hickey, 1992; Stanley et al., 1980; Sebel et al., 1981).

The aim of the current study was to examine whether thiopental, a commonly used anesthetic agent that has been the focus of
controversy concerning cerebral protection during CPB (Slogoff et al., 1982; Nussmeier et al., 1986; Metz and Slogoff, 1990), may blunt CPB-induced beta-endorphin responses.

Materials and Methods

The study was performed after approval by the institution's clinical research committee and after obtaining informed consent from each patient. Exclusion criteria were patients with severe cardiovascular deterioration (stroke index below 30 ml/beat/m²) or in emergency operation. Patients were randomly allocated into two groups; a thiopental treated pre-CPB group (T-group) or an untreated control group (C-group). All patients were maintained on their preoperative cardiac medications until the morning of surgery. All received premedication at 7 AM with intramuscular morphine sulfate (0.1 mg/kg), scopolamine (0.4 mg) and oral lorazepam (1-2 mg). Radial and pulmonary artery catheters were placed using local anesthesia before surgery. Electrocardiogram leads II and V4, and hemodynamic measurements which included mean arterial (MAP), pulmonary arterial (PAP), pulmonary capillary wedge (PCWP) and right atrial (RAP) pressures were monitored and recorded throughout the operation. Cardiac output (CO) was measured by thermodilution technique before and after CPB, and was replaced by nonpulsatile pump flow during bypass. Systemic vascular resistance (SVR) was calculated by standard formulae, and body temperature (BT) was measured in the nasopharynx.

All patients received a uniform anesthetic induction regimen with fentanyl (3 ug/kg), vecuronium (0.1 mg/kg) and isoflurane (1-2 vol%), and had similar anesthetic regimens for maintenance including continuous infusion of low dose fentanyl (2 ug/kg/hr), isoflurane (0.5-1 vol%) and N₂O(30%) intraoperatively. The compositions of the CPB prime, membrane oxygenator, perfusion flow rates (2.2 L/min/m²) and cooling procedure for hypothermia (cooled systemically to 28 °C) during CPB were also standardized in all patients.

Just prior to the declamping of venous cannula to initiate CPB, patients in the T-group received sodium thiopental (500 mg), and patients in the C-group received normal saline (20 ml) bolus into the central venous line by assistants to adhere to the double blind test.

In all patients, hemodynamic measurements including MAP, CO and SVR were performed and arterial blood samples were obtained a baseline prior to the bypass, at 30 min and at 60 min after the initiation of the bypass. Blood samples were centrifuged immediately and the plasma was stored at -70 °C until assay. The total beta-endorphin immunoreactivity (IBE) was measured using a radioimmunoassay technique described previously in detail (Carr et al., 1981). Such methods reflect plasma levels of beta-lipoprotein, a precursor, and result in normal
iBE values of less than 50 pg/ml. Assays for iBE were blindly performed on coded specimens.

All results were reported as mean ± standard deviation (SD). Repeat measures ANOVA test and Sheffe's test were applied to compare the statistical differences of the changes in iBE levels. Unpaired t-tests for age and weight, and Chi-square tests for sex and the type of operation were applied for the differences between the groups. P values less than 0.05 were considered statistically significant.

Results

Thirty patients were entered in this study. One patient in the T-group and one in the C-group were excluded due to extremely high prebypass iBE levels. Twenty-eight of thirty

Table 1. Demographic data

<table>
<thead>
<tr>
<th></th>
<th>T group</th>
<th>C group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Type of Operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Valvular</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Age (yr)*</td>
<td>59.5 ± 7.5</td>
<td>61.8 ± 6.8</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>9/5</td>
<td>10/4</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>78.8 ± 8.2</td>
<td>79.6 ± 7.9</td>
</tr>
</tbody>
</table>

* All values are mean ± SD. CABG; coronary artery bypass grafting.

Table 2. Change in plasma beta-endorphin level (pg/ml)

<table>
<thead>
<tr>
<th></th>
<th>T group</th>
<th>C group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prebypass</td>
<td>42.4 ± 17.6</td>
<td>29.4 ± 14.0*</td>
</tr>
<tr>
<td>30 min CPB</td>
<td>41.0 ± 14.1</td>
<td>38.7 ± 18.2*</td>
</tr>
<tr>
<td>60 min CPB</td>
<td>41.4 ± 15.3</td>
<td>41.2 ± 20.6*</td>
</tr>
</tbody>
</table>

All values are mean ± SD.
* P=0.04; compared to prebypass value in the thiopental (T-) group.
# P=0.006, 1 P=0.004; compared to prebypass value in control (C-) group.

Table 3. Hemodynamic indices and body temperature

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MAP (mmHg)</th>
<th>CO* (L/min)</th>
<th>SVR* (dynes.sec.cm⁻²)</th>
<th>BT (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T - group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebypass</td>
<td>79.0 ± 16.4</td>
<td>3.8 ± 1.4</td>
<td>1653.7 ± 475.3</td>
<td>32.8 ± 2.3</td>
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<tr>
<td>30 min CPB</td>
<td>78.4 ± 13.1</td>
<td>3.9 ± 1.2</td>
<td>1456.6 ± 303.4</td>
<td>28.7 ± 1.7</td>
</tr>
<tr>
<td>60 min CPB</td>
<td>75.8 ± 18.5</td>
<td>4.0 ± 1.4</td>
<td>1435.2 ± 231.3</td>
<td>29.8 ± 2.1</td>
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<tr>
<td>C - group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebypass</td>
<td>83.2 ± 13.3</td>
<td>3.6 ± 1.7</td>
<td>1738.3 ± 498.1</td>
<td>32.9 ± 2.9</td>
</tr>
<tr>
<td>30 min CPB</td>
<td>82.2 ± 13.3</td>
<td>3.8 ± 1.6</td>
<td>1603.3 ± 401.9</td>
<td>28.6 ± 1.8</td>
</tr>
<tr>
<td>60 min CPB</td>
<td>76.8 ± 15.0</td>
<td>3.8 ± 1.4</td>
<td>1511.3 ± 302.4</td>
<td>28.9 ± 1.7</td>
</tr>
</tbody>
</table>

All values are mean ± SD. MAP; mean arterial pressure, CO; cardiac output, SVR; systemic vascular resistance, BT; body temperature. * replaced pump flow during bypass.
* SVR = [(MAP - RAP)/CO or pump flow] x 80. 1 P<0.05; compared to prebypass values in each group.
Fig. 1. The changes measured as a percentage of the plasma beta-endorphin (iBE) levels. The bars indicate mean ± SD. During the bypass, plasma iBE levels significantly increased in the control group (F=10.9, P=0.006 at 30 min, F=12.3, P=0.004 at 60 min), but did not change in the thiopental group (F=0.6, P=0.5; F=0.2, P=0.6). The overall differences in the iBE levels were statistically significant between the times and the groups (F=8.7, P=0.001). (* P<0.05; compared to prebypass value in the control group, † P<0.05; compared to the values in the thiopental group)

Patients completed the study; 14 in the T-group, 14 in the C-group. The T and the C groups did not differ as to the type of operation, age, sex or weight (Table 1).

Baseline iBE levels just before CPB were slightly lower in the C-group (P=0.04). After the initiation of CPB, plasma iBE levels significantly increased in the C-group at 30 min (P=0.006), and remained elevated at 60 min (P=0.004). However, in the T-group, they did not change significantly during CPB (Table 2). The changes measured as a percent ([values at 30 min or 60 min minus baseline values] divided by baseline values X 100) of the iBE levels according to time variance were significantly greater in the C-group than those in the T-group (F=8.7, P=0.001) (Fig. 1).

Hemodynamic indices such as MAP, CO or required pump flow during CPB, SVR and the degree of hypothermia were similar in both groups (Table 3).

Discussion

In the present study, sodium thiopental administered just prior to the initiation of CPB, in combination with continuous low-
dose fentanyl infusion, completely blocked plasma iBE responses during CPB. In contrast, the control group that received the same fentanyl infusion but no thiopental, had significant increases in plasma iBE levels at 30 and 60 min during CPB (P=0.006, P=0.004 respectively). Thiopental prevented the increases of plasma beta-endorphin levels during CPB.

Our results in the control group agree with those of Yamashita et al. (1984) who reported a significant increase in plasma iBE (1.8 fold before CPB, 5.2 fold during CPB both compared to presurgical values) during CPB for open-heart surgery. The magnitude of the iBE increase, however, was less in our results (1.4 and 1.5 fold prebypass value, Fig. 1). Furthermore, our patients iBE levels increased only to within the upper normal range. An explanation for the attenuated iBE responses to CPB that we observed might be that we used continuous infusion of low-dose fentanyl as an anesthetic adjuvant throughout the operation in both the thiopental and the control groups. Conflicting results have been reported concerning the effectiveness of fentanyl alone in preventing hormonal responses to CPB (Cork et al., 1985), only partially blocking those responses (Stanley et al., 1980; Sebel et al., 1981), or having no effect (Hynynen et al., 1986). In the present study, the attenuated iBE responses in the control group reflects the partial blunting effect of fentanyl infusion. The totally blocked iBE response in the thiopental group presumably suggests supplementation by an additional inhibitory effect by the sodium thiopental.

In our results, prebypass iBE levels in the control group were significantly lower than those in the thiopental group. This may be related to the random selection of patients, however, lower prebypass levels were not important to compare the group differences. Because we analyzed the data with repeat measures - ANOVA tests to compare continuous variables, the differences in each discrete data, such as lower iBE levels between the groups could not affect the differences of the changes in iBE levels between the groups in this study.

Systemically administered beta-endorphin has effects on the cardiovascular system that include increased SVR, and a cardiodepressant effect with transient tachycardia followed by bradycardia (Holaday, 1983). Sodium thiopental also has a myocardial depressant effect, with initial transient hypertensive followed by hypotensive responses (Pauca and Roy, 1986). In this study, in spite of the changes in iBE levels or administration of thiopental, hemodynamic indices (MAP and CO) were similar in both groups, and SVRs were insignificantly higher in the control group. In a previous study with preoperative cardiac surgical patients (Carr et al., 1989), we observed significant correlations between iBE and hemodynamic indices (stroke volume, stroke index, cardiac output and cardiac index), especially in patients with a stroke index below 40 ml/beat/m². Kawashima et al.
(1991) likewise reported that beta-endorphin levels were negatively correlated with CO and positively with SVR (both P < 0.001) in patients with congestive heart failure. In the present study, we did not find any correlations between iBE levels and hemodynamic indices during CPB. While the earlier studies examined endogenous cardiovascular regulation in comparison with stress hormone regulation, in our study there were many confounding factors; pump flow, hemodilution, body temperature and vasoactive drugs affected hemodynamic indices during CPB; patients with stroke index below 30 ml/beat/m² were excluded to decrease variation from hypoperfusion (Kawashima et al., 1991; Carr et al., 1989), and therefore increases of iBE levels were modest.

Although the present study did not evaluate clinical outcomes after CPB, the use of small doses of thiopental just prior to CPB could provide deeper anesthetic levels without significant hemodynamic changes and suppressed iBE responses. Hence the use of thiopental could be considered advantageous in the management of CPB. Accordingly, we should consider the benefits and risks for the use of sodium thiopental in CPB. The benefits include (1) prevention of catabolic stress responses to CPB, (2) prevention of awareness during high-dose opioid anesthesia, and (3) improvement of the neuropsychiatric outcome following the cardiac operation (Nussmeier et al., 1986; Metz and Slogoff, 1990; Prough and Mills, 1990). Risks are (1) potentially greater reliance on inotropic drugs for weaning from CPB, and (2) a longer recovery period for extubation. Because in the present study thiopental doses were much lower than those employed for "brain protection"; 15 mg/kg for bolus (Metz and Slogoff, 1990) or 39.5 mg/kg for infusion (Nussmeier et al., 1986), further studies are needed to reach conclusions concerning the use of thiopental in CPB with respect to the time course and dosage of thiopental, possible hemodynamic sequelae of such doses, effects on the weaning process such as the requirement for inotropics and postoperative surgical outcomes. In the absence of such study, our results are not sufficient enough to recommend routine use of thiopental before CPB.

However, the results of the present study, no changes of iBE levels in the thiopental group during CPB, suggest that the prophylactic use of sodium thiopental prior to the initiation of CPB could prevent CPB-induced beta-endorphin responses.

Summary

We studied the effects of adding a single bolus (500 mg) of sodium thiopental to a continuous infusion of low-dose fentanyl on plasma beta-endorphin immunoreactivity (iBE) responses to cardiopulmonary bypass (CPB) in 28 patients undergoing elective coronary artery bypass grafting or valve procedures.
Thiopental was injected just prior to the initiation of CPB. The iBE levels and the hemodynamic indices such as mean arterial pressure, cardiac output and systemic vascular resistance were measured before CPB, at 30 min and again at 60 min after the initiation of the bypass. The results were as follows.

After the initiation of CPB, iBE levels increased at 30 min and 60 min (P=0.006, P=0.004 respectively) in the control group, but not in the thiopental group. There were significant differences in the changes of iBE levels between the groups (F=8.7, G-G=0.002, P=0.001). The hemodynamic indices were similar in both groups.

In conclusion, pretreatment with thiopental just before the initiation of CPB prevents the stress-induced beta-endorphin response to CPB.

References


Lacoumenta S, Yeo TH, Paterson JL, Burrin JM, Hall GM: Hormonal and metabolic responses to cardiac surgery with sufentanil-oxygen anaesthesia. Acta Anaesthesiol Scand 31(3): 258-


체외순환전 투여된 Thiopental이 Beta-endorphin치 변화에 미치는 영향

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수술에 의해 발생되는 침해성 동중이나 혈역학적 변화 및 내분비계의 반응은 마취 방법에 따라 약화되거나 조정될 수 있다. 본 연구는 심장수술시 제외순환 직전에 sodium thiopental을 투여한 경우 beta-endorphin치 변화에 미치는 영향을 관찰하고자 시행되었다.

관상동맥 우회술과 판막치환술을 위한 제외순환 환자 28명을 대상으로 하였다. Isoflurane, N2O 및 fentanyl 지속 정주(2 ug/kg/hr)에 의한 전신마취 하에서 thiopental군(14명)은 sodium thiopental 500 mg을, 대조군(14명)은 생리식염수 20 ml를 제외순환 직전에 투여하였다. 제외순환 직전과 제외순환 개시 후 30분 및 60분에 beta-endorphin치와 평균동맥압, 심박출량 및 전신혈관 저항 등의 혈역학 지수를 각각 측정하였다.

Beta-endorphin치가 대조군에서는 제외순환 개시 후 30분 및 60분에 유의하게 증가하였으나(P=0.006, P=0.004) thiopental군에서는 변화가 없었다. Beta-endorphin치의 변화는 양군 사이에 두텁한 차이가 있었다(F=8.7, P=0.001). 혈역학적 변화는 양군 사이 차이가 없었다.

따라서 제외순환 개시 직전에 투여된 thiopental은 제외순환중의 beta-endorphin치 변화를 예방할 수 있는 것으로 사료된다.

중심 단어: Thiopental, Beta-endorphin, 제외순환