MODIFICATION OF ASPECTS OF THE ENDOCRINE RESPONSE TO TRACHEAL INTUBATION BY LIGNOCAINE, HALOTHANE AND THIOPENTONE

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SUMMARY

The effects of two different concentrations of halothane (0.5 or 1.5%) and two different doses of thiopentone (4.5 or 10 mg kg\textsuperscript{-1}) on the plasma concentrations of cortisol, growth hormone (GH) and prolactin (PRL) were studied in response to the stress of tracheal intubation. Additionally, the effect of the intratracheal administration of 4% lignocaine spray 2 ml was investigated. The study group included 48 healthy women. During a “light” level of halothane and thiopentone anaesthesia, the plasma concentration of cortisol increased in response to tracheal intubation in the patients who did not receive intratracheal analgesia. Topical analgesia with lignocaine prevented the increase in cortisol concentration and this would seem to indicate that the increase was caused by the stress of laryngoscopy and intubation. At a deeper level of halothane anaesthesia, and in association with the larger dose of thiopentone the increase in cortisol concentration was suppressed. GH did not change from the preanaesthetic value in any group and there were no differences between the control group and the study groups. PRL increased significantly in all groups. Increasing the dose of thiopentone caused a further increase in PRL concentration which indicated a direct stimulatory action of thiopentone on PRL release.

Mechanical stimulation of the respiratory tract provokes a sympathetic reflex (Tomori and Widdicombe, 1969) and an increase in the plasma concentration of noradrenaline after tracheal intubation (Russel et al., 1981). The usual circulatory responses to laryngoscopy and intubation in an anaesthetized patient (tachycardia and an increase in arterial pressure) (King et al., 1951; Prys-Robert et al., 1971) are diminished by fentanyl (Kautto, 1982) and by spraying the trachea with lignocaine (Denzinger, Ellison and Ominsky, 1974).

Although large doses of opiates can prevent the endocrine response to surgery and to the stress of tracheal intubation (George et al., 1974; Hall et al., 1978; Stanley et al., 1980), the effects of inhalation, anaesthesia and barbiturates on pituitary and adrenocortical function are unclear. The induction of anaesthesia with a combined thiopentone-nitrous oxide-oxygen sequence with or without halothane did not appear to have any effect on the plasma concentrations of cortisol (Virtue, Helmreich and Gainza, 1957; Clarke, Johnston and Sheridan, 1970) or growth hormone (Oyama and Takazawa, 1971). Oyama and Takiguchi (1970) observed an increase in the plasma ACTH and cortisol concentrations after the induction of halothane-nitrous oxide anaesthesia and this led the authors to suggest that halothane may exert a stimulatory action on adrenocortical function. However, this assumption was challenged by several authors (Clarke, Johnston and Sheridan, 1970; Clarke, 1973; Philbin and Coggins, 1978). Thus, the increase in hormone concentrations after the induction of halothane anaesthesia is seen merely as the physiological response to various stress factors attributed to the induction. It has been suggested that, when anaesthesia is deep enough, volatile anaesthetics may be able to prevent the endocrine and metabolic responses to surgically-induced stress (Hamelberg et al., 1960; Roizen et al., 1974; Philbin and Coggins, 1978). Recently, Roizen, Horrigan and Frazer (1981) demonstrated that halothane, enflurane and morphine can all prevent the noradrenaline response to skin incision.

The present study was designed to determine whether the depth of halothane or thiopentone anaesthesia had any influence on the changes in the concentrations of cortisol, growth hormone (GH) and prolactin (PRL) induced by intubation of the trachea. The effects of two different halothane concentrations (0.5 and 1.5%) and two different doses of thiopentone (4.5 and 10 mg kg\textsuperscript{-1}) on the plasma concentrations of these hormones were studied. In addition, the effect of the intratracheal administration of lignocaine (as a spray) was investigated to...
distinguish between the effects of anaesthesia, and
the stress of laryngoscopy and intubation.

PATIENTS AND METHODS

Patients
Forty-eight women between the ages of 23 and 42 yr were included in the study. All were in good
general health (ASA I) and none was receiving
medication or hormone therapy. The patients were
selected from patients scheduled for gynaecological
laparotomy or laparoscopy: all had a history of
regular menstrual periods and none was pregnant.
Patients with malignant or infectious diseases were
excluded from the study. All had been informed as
to the exact nature of the study and all had agreed to
participate. The study was approved by the Ethics
Committee of the hospital.

Details of the patients are presented in table I.

Study groups
The patients were divided in sequential order into
four groups. In the patients in the control group
(group I) the trachea was intubated without intra-
tracheal analgesia and the patients anaesthetized
with thiopentone 4.5 mg kg\(^{-1}\), 0.5% halothane and
70% nitrous oxide. The patients in group II received
a spray of 4% lignocaine 2 ml topically to the larynx
and trachea before intubation and were anaesthet-
ized as in group I. The patients in group III received
thiopentone 4.5 mg kg\(^{-1}\), 1.5% halothane and 70%
nitrous oxide, but no intratracheal analgesia. In
group IV, anaesthesia was induced with thiopentone
10 mg kg\(^{-1}\) and maintained with 0.5% halothane and
70% nitrous oxide. No topical analgesia was used in
this group.

Blood sampling and stages of the study
Thirty to forty minutes before arrival at the
operating theatre the patients were premedicated
with diazepam 10 mg by mouth and atropine
0.01 mg kg\(^{-1}\) i.m. In all patients, anaesthesia was
induced between 8.00 and 10.00 a.m. and the inves-
tigation was performed before the surgical incision.

On arrival in the anaesthetic room, a cannula
(Viggo) was inserted to a peripheral vein. A control
blood sample (BA) was taken for hormone analyses
and an i.v. infusion of electrolyte solution (Fysiosol;
Leiras, Turku) 10 mg kg\(^{-1}\) h\(^{-1}\) started.

Anaesthesia was induced by injecting thiopentone
4.5 mg kg\(^{-1}\) (groups I–III) or 10 mg kg\(^{-1}\) (group
IV). Ventilation was controlled manually via a
face-mask and 100% oxygen administered. When
the patient no longer responded to requests to open
her eyes, and as soon as the loss of eyelid reflex was
noted, suxamethonium 1.5 mg kg\(^{-1}\) was given to
facilitate tracheal intubation. Laryngoscopy was
performed with a Mackintosh blade (No. 3). Ten
patients in group II received a spray of 4% ligno-
caine 2 ml topically in the larynx and trachea be-
fore intubation. In the rest of the patients (groups
I, III and IV) the trachea was intubated without
topical analgesia. An endotracheal tube (Mallin-
krodt; Endotrol i.d. 8 mm) was inserted to the
trachea in each patient. The cuff pressure was con-
trolled with a soft-seal cuff pressure indicator (Por-
tex) to maintain the cuff pressure at 50 cm H\(_2\)O
during the study.

Immediately after intubation, the tracheal tube
was connected to a Servo respirator, with a non-
rebreathing system, and mechanical ventilation
commenced. A gas mixture consisting of 30% oxy-
gen, 70% nitrous oxide and 0.5% halothane (groups I, II and IV) or 1.5% halothane (group III),
was administered. Halothane was vaporized in a
Fluotec Mark III vaporizer. The end-tidal carbon
dioxide and oxygen concentrations were monitored
continuously using a carbon dioxide and oxygen
analyser (Datex Normocap, Instrumentarium, Hel-
sinki) to keep the carbon dioxide within the range of
5.5±0.5% and the mean oxygen concentration
within 30±1%. During anaesthesia, alcuronium
was administered to provide neuromuscular block-
ade of about 80% (ulnar nerve stimulation through
needle electrodes: visual assessment).

A central venous catheter was inserted via an
antecubital vein and further blood samples were

<table>
<thead>
<tr>
<th>TABLE I. Data for 48 patients (means± SEM)</th>
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<tbody>
<tr>
<td>Group I</td>
</tr>
<tr>
<td>No. patients</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<td>Height (cm)</td>
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</table>
collected 10, 20 and 30 min after the induction of anaesthesia.

The blood samples for the hormone analyses were collected into 10-ml EDTA tubes and centrifuged immediately after collection. Plasma was separated, divided into 2-ml aliquots, placed in polypropylene tubes, frozen and stored at −20°C until analysis.

**Radioimmunoassays**

Cortisol analyses were carried out by radioimmunoassay with reagents obtained from Farmos Group Ltd, Turku, Finland. The normal range for cortisol concentration in adults was 200–800 nmol litre⁻¹ at 8.00–9.00 a.m. (Farmos Diagnostica 125I-Cortisol Kit). The inter-assay coefficient of variation was 7.5% and the intra-assay coefficient of variation as calculated on three pooled samples was 7.3–8.2%.

The plasma growth hormone concentration was measured using a double-antibody radioimmunoassay technique with reagents obtained from International CIS, St Quentin, France. Using this method, Molinatti and colleagues (1969) found basal GH concentrations in adult plasma ranging from 0 to 6.5 μg litre⁻¹. The inter-assay coefficients of variation calculated from assays carried out on two pooled samples were 4.5 and 11.7%, respectively.

The radioimmunoassays for prolactin concentration were performed with reagents obtained from Biodata, Hypolab S.A., Coinsins, Switzerland. The lower limit of sensitivity of the method was 0.5–1.0 μg litre⁻¹. The upper normal value of prolactin concentration in fertile women was 20 μg litre⁻¹. The inter-assay coefficients of variation as calculated on two pooled samples were 6.4 and 8.1%, The intra-assay coefficient of variation was 3.7%.

**Statistical analysis**

As the distributions of the cortisol, GH and PRL concentrations were found to be skewed, a logarithmic transformation was performed before analysis of the data (Armitage, 1971). The statistical significance between the preanaesthetic (BA) values and each anaesthesia value (10, 20 and 30 min) was calculated by paired t test. The changes from the BA values between each treatment were calculated in the same way and compared using the t test for grouped data. The statistical significance of the differences are indicated as follows:

*P* < 0.05, **P** < 0.01 and ***P*** < 0.001.

**RESULTS**

The means for the estimated hormonal concentrations during the study are shown in table II.

**Preanaesthetic hormone concentrations**

The plasma cortisol concentration before the induction of anaesthesia (BA) was significantly smaller in group IV than in groups II and III (*P* < 0.05)

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**Table II. Plasma concentrations of cortisol, GH and PRL during the study (means ± SEM). BA = before anaesthesia**

<table>
<thead>
<tr>
<th></th>
<th>BA</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
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</thead>
<tbody>
<tr>
<td><strong>Cortisol (nmol litre⁻¹)</strong></td>
<td></td>
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<tr>
<td>Group I</td>
<td>419 ± 34</td>
<td>430 ± 41</td>
<td>587 ± 29</td>
<td>530 ± 37</td>
</tr>
<tr>
<td>Group II</td>
<td>467 ± 42</td>
<td>440 ± 37</td>
<td>479 ± 51</td>
<td>428 ± 42</td>
</tr>
<tr>
<td>Group III</td>
<td>513 ± 41</td>
<td>554 ± 57</td>
<td>584 ± 55</td>
<td>486 ± 42</td>
</tr>
<tr>
<td>Group IV</td>
<td>359 ± 24</td>
<td>299 ± 20</td>
<td>277 ± 18</td>
<td>237 ± 12</td>
</tr>
<tr>
<td><strong>GH (μg litre⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group I</td>
<td>1.77 ± 0.76</td>
<td>1.48 ± 0.66</td>
<td>1.51 ± 0.59</td>
<td>1.46 ± 0.57</td>
</tr>
<tr>
<td>Group II</td>
<td>0.73 ± 0.23</td>
<td>0.75 ± 0.18</td>
<td>0.73 ± 0.12</td>
<td>0.81 ± 0.13</td>
</tr>
<tr>
<td>Group III</td>
<td>0.52 ± 0.10</td>
<td>0.69 ± 0.14</td>
<td>1.21 ± 0.34</td>
<td>1.31 ± 0.46</td>
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<tr>
<td>Group IV</td>
<td>0.31 ± 0.08</td>
<td>0.40 ± 0.06</td>
<td>0.45 ± 0.15</td>
<td>0.76 ± 0.32</td>
</tr>
<tr>
<td><strong>PRL (μg litre⁻¹)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Group I</td>
<td>12.1 ± 1.7</td>
<td>38.5 ± 6.1</td>
<td>37.4 ± 5.1</td>
<td>32.5 ± 4.5</td>
</tr>
<tr>
<td>Group II</td>
<td>11.5 ± 1.6</td>
<td>28.7 ± 4.8</td>
<td>30.4 ± 4.2</td>
<td>24.5 ± 4.0</td>
</tr>
<tr>
<td>Group III</td>
<td>12.2 ± 2.1</td>
<td>32.4 ± 6.0</td>
<td>38.4 ± 6.4</td>
<td>33.6 ± 6.0</td>
</tr>
<tr>
<td>Group IV</td>
<td>6.9 ± 0.5</td>
<td>33.8 ± 4.0</td>
<td>48.7 ± 8.3</td>
<td>44.7 ± 7.9</td>
</tr>
</tbody>
</table>
and \( P<0.01 \), respectively). The preanaesthetic concentrations (BA) of plasma growth hormone were similar in all groups. The basal PRL concentration (BA) was significantly less in group IV than in groups I and II \((P<0.05)\).

Before the induction of anaesthesia (BA), all the individual cortisol concentrations were within the physiological range. The preanaesthetic growth hormone concentrations were outside the normal range in two patients in group I (6.6 and 9.7 \( \mu \)g litre\(^{-1} \)). In one patient in group I the preanaesthetic prolactin concentration was 30 \( \mu \)g litre\(^{-1} \) and in another patient in group III, it was 36 \( \mu \)g litre\(^{-1} \); both values being outside the upper limit of prolactin concentration in fertile women (20 \( \mu \)g litre\(^{-1} \)).

![Hormone changes during the study](image)

The hormonal changes during the study are presented in figures 1-3.

Since the hormone concentrations before anaesthesia were not normally distributed and because they also varied between the groups, individual values were not compared. The statistical differences presented in the text and in the figures relate to differences between the values for the hormones at different points of time during the study (10, 20 and 30 min after the induction of anaesthesia).

**Cortisol** (fig. 1). The plasma concentration of cortisol increased significantly in those patients anaesthetized with thiopentone 4.5 \( \text{mg kg}^{-1} \) and 0.5% halothane who received no intratracheal analgesia \((P<0.001 \text{ at 20 min and } P<0.05 \text{ at 30 min})\) (group I). There were no changes in the plasma cortisol concentrations in the patients receiving the same general anaesthetic along with lignocaine spray before intubation (group II). This group differed significantly from the patients receiving no intratracheal analgesia (group I) \((P<0.01 \text{ at 20 min and } P<0.05 \text{ at 30 min})\).

The cortisol concentration was similar to its preanaesthetic value in the patients anaesthetized with 1.5% halothane (group III), and a significant difference was observed between the patients anaesthetized with 0.5% (group I) and 1.5% (group III) halothane \((P<0.05 \text{ at 20 and 30 min})\).

The larger dose of thiopentone (10 \( \text{mg kg}^{-1} \)) led to marked \((P<0.001)\) decreases in cortisol concentrations after the induction of anaesthesia (10, 20 and 30 min) (group IV). The difference between these patients (group IV) and the patients receiving a small dose of thiopentone (4.5 \( \text{mg kg}^{-1} \)) (group I) was significant \((P<0.001 \text{ at 20 and 30 min})\).

**Growth hormone** (fig. 2). Growth hormone did not show any change from the preanaesthetic concentration in any of the groups and no differences appeared between the control group (group I) and the study groups (groups II, III and IV).

**Prolactin** (fig. 3). The prolactin concentration increased significantly \((P<0.001)\) in all groups. In patients receiving the larger dose of thiopentone \((10 \text{ mg kg}^{-1})\) (group IV) the increase in prolactin was significantly greater than in patients receiving the smaller dose of thiopentone \((4.5 \text{ mg kg}^{-1})\) (group I) \((P<0.01 \text{ at 20 min and } P<0.001 \text{ at 30 min})\).

**DISCUSSION**

The procedures of laryngoscopy and intubation are considerably less complex and traumatic than major
surgery. However, it is easier to standardize stress during intubation than during surgery. In the present study, care was taken to standardize the stress stimuli provoked by laryngoscopy and intubation, and the continuous irritation of the trachea caused by the tracheal tube.

Despite the fact that the study was undertaken during the unstable period during the development of halothane anaesthesia, the dose of the different halothane concentrations was regarded as being sufficient for the present study since the concentration of halothane in the inspired gas mixture, and the ventilation (Secher, 1982), were kept constant in each patient.

When given according to body weight the efficacy of thiopentone shows considerable variation in different individuals. However, the difference between the two doses of thiopentone was considered sufficient to minimize this bias. Moreover, no differences were found in age, weight or height (Christensen, Andreasen and Jansen, 1981) between the groups.

The present study showed that the anaesthetic technique used in the control group (thiopentone 4.5 mg kg\(^{-1}\), 0.5% halothane, 70% nitrous oxide in oxygen and no intratracheal analgesia), was not capable of preventing the adrenocortical response to the stress of laryngoscopy and intubation. However, a deeper level of halothane anaesthesia, an increase in the dose of thiopentone and the intratracheal administration of lignocaine were all able to suppress the adrenocortical response to intubation. The prompt decrease in the cortisol concentration noted in the patients receiving the larger dose of thiopentone may have been a result of downward trend associated with the diurnal rhythm of cortisol at 8–12 a.m. (De Lacerda, Kowarski and Migeon, 1973). However, we cannot exclude some supplementary direct depressant action of thiopentone, similar to that of opiates (McDonald et al., 1959; Stubbs et al., 1978) on adrenocortical function.

Our study did not show any difference in the growth hormone responses between the control group and the study groups. In the control group, disproportionately high growth hormone concentrations were obtained in some of the individual patients and these may have affected the interpretation of the results.

The increase in the plasma concentration of prolactin during surgery and other conditions of stress has been documented previously (Noel et al., 1972; Sowers et al., 1977; Adashi et al., 1980; Lehtinen, 1981). In all of these studies, a marked increase in prolactin concentration was found immediately after tracheal intubation. Our present data demonstrated a significant increase in plasma prolactin concentration during halothane anaesthesia. BA = before anaesthesia. **P < 0.01; ***P < 0.001.
concentration in each group. The depth of halothane anaesthesia did not have any influence on the prolactin concentration. Increasing the dose of thiopentone from 4.5 to 10 mg kg\(^{-1}\) caused a further increase in prolactin concentrations which indicated a direct stimulatory action of thiopentone on prolactin release. It is possible that the increase in prolactin concentration found in the other groups, was also induced by thiopentone. The intratracheal administration of lignocaine spray did not prevent the increase in prolactin concentration and this would seem to indicate that the prolactin response is not a result of the stress of intubation. On the other hand, the difference found between the adrenocortical and prolactin responses after the induction of anaesthesia may indicate a difference in the mechanisms by which ACTH and prolactin increase in response to this kind of stress.

In conclusion, our data identify the doses of halothane and thiopentone that prevent the increase in plasma cortisol concentration in response to tracheal intubation. However, from a practical standpoint, the haemodynamic effects of the higher concentrations of halothane and thiopentone are not easily tolerated by patients with unstable haemodynamics and heart disease. Furthermore, care must be taken in administering these doses to elderly patients and to the more seriously ill patients. On the other hand, the neuroendocrine response and the excessive increase in arterial pressure may be harmful in certain patients as, for example, those with coronary artery disease or a cerebral aneurysm (Fox et al., 1977; Kono et al., 1981). Our data demonstrated that the intratracheal administration of lignocaine spray was able to prevent the increase in the plasma concentration of cortisol after intubation. This, together with the beneficial circulatory effects of intratracheal lignocaine (Denlinger, Ellison, and Ominsky, 1974; Kautto and Heinonen, 1982), support the use of topical analgesia before intubation of the trachea. However, perhaps the most important message of our study was that even minor differences in anaesthetic technique may alter the endocrine response to stress and this highlights the importance of the standardization of stressful stimuli, and the depth of anaesthesia, when endocrine or metabolic changes are studied during anaesthesia and surgery.

ACKNOWLEDGEMENTS
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MODIFICATIONS DU PROFIL DE REPONSE ENDOCRINE A L'INTUBATION TRACHEALE AVEC LA LIGNOCAIN, L'HALOTHANE ET LE PENTOTHAL

RESUME

Nous avons etudié les effets de deux concentrations différentes d’halothane (0,5 ou 1,5%) et de deux doses différentes de pentothal (4,5 ou 10 mg kg⁻¹) sur les concentrations plasmatiques de cortisol, d’hormone de croissance (STH) et de prolactine (PRL), en réponse à l’agression de l’intubation trachéale. De surcroît, nous avons observé l’effet de l’administration intratrachéale d’une vaporisation de lignocaine (2 ml à 4%). Le groupe étudié était constitué de 48 femmes en bonne santé. Au cours d’une anesthésie ‘légère’ à l’halothane et au pentothal, les concentrations plasmatiques de cortisol augmentaient en réponse à l’intubation trachéale chez les patients qui n’avaient pas reçu d’analgésie intratrachéale. L’analgésie topique à la lignocaine prévenait l’augmentation des concentrations de cortisol et ceci semblerait indiquer que cette augmentation répondait au stress de la laryngoscopie et de l’intubation. A des niveaux plus profonds d’anesthésie à l’halothane et en association avec la plus forte dose de thiopental, l’augmentation de la concentration de cortisol était supprimée. La STH restait inchangée par rapport à son niveau d’avant l’anesthésie et ceci dans tous les groupes, et il n’y avait aucune différence entre le groupe témoin et les groupes étudiés. La PRL augmentait significativement dans tous les groupes. L’augmentation de la dose de thiopental entraînait une nouvelle augmentation de la concentration de PRL qui indiquait une action stimulatrice directe du thiopental sur la libération de PRL.

MODIFIKATION DER ASPEKTE DER ENDOKRINEN REAKTION AUF ENDOTRACHEALE INTUBATION DURCH LIGNOCAINE, HALOTHANE UND THIOPENTAL

ZUSAMMENFASSUNG

MODIFICACION DE LOS ASPECTOS DE LA RESPUESTA ENDOCRINA A LA INTUBACION TRAQUEAL POR LIGNOCAINA, HALOTANO Y TIOPENTONA

SUMARIO
Se llevaron a cabo estudios de los efectos de dos concentraciones distintas de halotano (al 0,5 a al 1,5%) y de dos dosis diferentes de tiopentona (4,5 a 10 mg kg⁻¹) sobre las concentraciones en el plasma del cortisol, de la hormona de crecimiento (GH) y de la prolactina (PRL) en respuesta a la tensión de la intubación traqueal. Además, se averiguó el efecto de la administración intratraqueal de pulverización de lignocaina al 4% (2 ml). El grupo de estudio incluía a 48 mujeres sanas. Durante un nivel "ligero" de anestesia con tiopentona y halotano, las concentraciones en el plasma de cortisol aumentaron como respuesta a la intubación traqueal en las pacientes que no recibieron la analgesia intratraqueal. La analgesia tópica con lignocaina impidió el aumento de la concentración de cortisol y ello parece indicar que el aumento fue el resultado de la tensión debida a la laringoscopia y la intubación. Con niveles más elevados de halotano y en asociación con dosis mayores de tiopentona, el aumento de la concentración de cortisol fue eliminado. La GH no sufrió cambio alguno desde el valor antes de la anestesia en cualquiera de los grupos y no hubo diferencias entre el grupo de control y los grupos de estudio. La PRL aumentó de manera significante en todos los grupos. Al incrementar la dosis de tiopentona, se produjo un aumento adicional de la concentración de PRL, lo que indica una acción estimulante directa de la tiopentona sobre la liberación de PRL.