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Effects of total intravenous anesthesia with propofol on immuno-endocrine changes during surgical stress

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Abstract: Endocrine factors and cytokines are crucial to host responses to stress and infection. Because surgery is a major stressful condition, it is necessary to understand the influence of specific anesthetic procedures on immune-endocrine responses. The purpose of this study was to compare total intravenous anesthesia with propofol with conventional inhalational anesthesia on circulating cortisol, adrenocorticotropic hormone (ACTH), prolactin, alpha-melanocyte-stimulating hormone (αMSH), and the cytokine, interleukin-6 (IL-6) in healthy patients undergoing tubal ligation. The results show that circulating cortisol was significantly suppressed by propofol during induction of anesthesia. Likewise, continuous propofol completely abolished the response of circulating cortisol to surgery. Because ACTH responses to surgery were similar in the two groups, the inhibition likely occurred directly on the adrenal glands. This study is the first to report the effects of anesthesia on circulating αMSH, which was decreased significantly after induction with both anesthetic techniques and was still depressed at 90 min in the propofol patients. Other aspects of immune-endocrine responses to surgery were similar irrespective of anesthetic type, which further suggests a specific suppression of adrenal function by propofol.

Key words: Total intravenous anesthesia, Propofol, Stress response, Cytokines, Alpha-melanocyte stimulating hormone

Introduction

The endocrine response to stress has a central role in the maintenance of homeostasis through regulation of fluid and electrolyte balance and of metabolic and immune responses. Increased plasma cortisol concentration is used as a measure of stress in clinical medicine. Stimulation of the adrenal glands that occurs during stress is mediated via the release of adrenocorticotropic hormone (ACTH) which, in turn, is released by hypothalamic corticotropin-releasing hormone (CRH). Other endocrine responses to stress include the release of additional pituitary hormones such as prolactin and growth hormone, and of catecholamines and insulin. Further, a recent study showed that adrenaline releases the cytokine IL-6 which, therefore, may be included among the stress-induced factors [1]. Recent research also indicates that bidirectional communication exists between the endocrine and the immune systems that may be important in modulation of the host response to stress infection. For example, cytokines, including IL-1, IL-6, and tumor necrosis factor (TNF) released in infection and injury, activate the hypothalamic-pituitary adrenal (HPA) axis and release adrenal corticosteroids. Glucocorticosteroids can likewise modulate the production of such cytokines [2–8]. Surgery is a powerful stimulus of the immune-endocrine axis which must be distinguished from the influence of specific anesthetic procedures on host responses [9]. Previous investigations have demonstrated perioperative stimulation of the HPA axis, the renin-angiotensin axis, and the sympathetic nervous system [10,11]. The vast majority of these reports, however, were based on perioperative hormone data from heterogeneous groups of patients undergoing a variety of operations with many different anesthetic agents [12–18].

Propofol is a sterically hindered phenol that has anesthetic properties [19]. A large volume of distribution and a short elimination half-life (4 hours) give intravenous propofol potential advantages for induction of anesthesia in outpatients and as a maintenance hypnotic agent [20–22].

Reports on the endocrine effects of propofol have focused on the consequences of induction with this drug with the subsequent addition of an inhalational agent or nitrous oxide for maintenance whereas the in vivo effects of total intravenous anesthesia with propofol alone on release of glucocorticoids, other stress hormones, and on cytokines are unknown [23]. The purpose of this

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study was to compare the effects of continuous propofol with those of conventional inhalational anesthesia on these endocrine and immune stress variables in a group of healthy patients undergoing similar operations. The hormone response was assessed by measuring plasma ACTH, cortisol, prolactin and alpha-melanocyte-stimulating hormone (αMSH). The cytokine IL-6, which plays an important role in immune-endocrine communication, was also measured.

Patients and methods

Healthy patients (ASA physical status I or II) who were scheduled for laparoscopic tubal ligation performed in the morning gave written informed consent to participate in this institutionally approved study. Patients with a known endocrine abnormality or previous adverse reaction to general anesthesia or to the study drugs, as well as anyone chronically or acutely taking steroids, were excluded. On arrival in the operating room, the unpremedicated patients were randomly assigned to one of two study groups. All patients then received fentanyl 1.0 μg/kg intravenously 5 min before the commencement of induction. Anesthesia was induced with either propofol 2 mg/kg (n = 24) or thiopental 4 mg/kg (n = 21) over 20 s, and an additional 20 or 25 mg, respectively, was administered at 10-s intervals, if necessary, until loss of verbal contact. Tracheal intubation was facilitated by the administration of 0.1 mg/kg vecuronium and anesthesia was maintained with the immediate commencement of either a continuous infusion of propofol or 1.00%–1.25% end-tidal isoflurane added to a 50:50 mixture of N_2O and O_2. After the loading dose, the propofol infusion scheme consisted of an infusion of 10 mg/kg/h for the first 10 min, 8 mg/kg/h for the next 10 min, and 6 mg/kg/h rate thereafter until the end of surgery, using an Ohmeda 9000 syringe pump Liberty corner, NJ, USA [24–26]. These infusion rates were predicted to maintain a target propofol concentration of 3–5 μg/ml which would ensure approximate anesthetic equi-potency with the isoflurane group (Nimmo WS, International Anesthesia Research Society, review course lectures, 1990, written communication). In a further attempt to achieve comparable anesthetic adequacy, the propofol infusion rate and the isoflurane concentration were adjusted to keep the heart rate within 15% of the preinduction values if the hemodynamic variables suggested inadequate anesthesia after the initial stepwise infusion regime had been completed. The propofol group was ventilated with an air-oxygen mixture. Ventilation was assisted to maintain end-tidal CO_2 between 35 and 40 mmHg and further relaxant was given on the appearance of evidence of return of neuromuscular function on ulnar nerve stimulation. Emergence and reversal were facilitated with neostigmine (20 μg/kg) and glycopyrrolate (4 μg/kg), and all patients received approximately 10 ml/kg of lactated Ringer's solution in the perioperative period.

Venous blood samples were obtained 10 min preinduction (−10 min), 30 (+30) and 90 min (+90) postinduction through a dedicated intravenous cannula inserted at the antecubital fossa of the arm opposite that used for drug and fluid administration. Surgery did not begin until 30 min after induction of anesthesia so that the effects of anesthesia alone could be observed. All anesthetic inductions began at essentially the same time of day to eliminate the potential contribution of circadian variations in hormone release.

Noninvasive measurements were made of systolic, mean, and diastolic arterial pressures and pulse rate. These readings were recorded immediately before fentanyl administration, 1 min prior to induction, 5 min post-induction, just prior to skin incision, and every 5 min thereafter for the duration of surgery. The cumulative volume of propofol infused displayed by the pump was recorded every 5 min.

Blood sample preparation and hormone assays

Blood samples were collected in prechilled vacuum tubes containing EDTA, placed on ice, and centrifuged (3000 rpm, 4°C, 30 min) within 20 min of sampling. Samples tubes for cytokine assays contained 100 μl of aprotinin (0.67 trypsin-inhibiting units per 1 μl of blood). The plasma samples were stored at −70°C. All samples from an individual patient were analyzed in a single assay to eliminate interassay variation. Radioimmunoassays for ACTH, cortisol, αMSH, prolactin, and IL-6 were performed in duplicate. Sensitivity and interassay coefficients of variation were 1 pg/ml and 3.2% for ACTH, 0.5 μg/dL and 5.7% for cortisol, 0.14 ng/ml and 4.6% for prolactin, and 5 pg/ml and 4.1% for αMSH, respectively. The quantitative enzyme-linked immunosorbent assay for IL-6 (Quantikine Immunoassay System, Minneapolis, MN, USA) had a sensitivity of <10 pg/ml and interassay coefficient of variation of <9.2%.

Statistical analysis

Age, height, and weight in the two groups were compared using an unpaired Student's t-test. For the hormone and the hemodynamic data, repeated measures analysis of variance was used to evaluate the significance of changes over time, differences between groups, and differential changes over time between groups. This analysis was performed using BMDP software, version 5. (Dallas, TX, USA) The results of statistical tests were considered significant when $P < 0.05$.

Results

Forty-five women underwent laparoscopic tubal ligation. The two groups were not significantly different with respect to age, height, weight, baseline (preinduction) cortisol, and IL-6 plasma levels (Table 1). The mean ± SD operative time and intraoperative fluid administration were 62.8 ± 4 min and 750 ± 59 ml, respectively, with no significant differences between the two groups. Mean propofol usage was 749.5 ± 36 mg. No blood transfusions were required, and none of the patients suffered a perioperative surgical complication. The pulse rate decreased in both groups after induction and prior to surgery but these differences within and between the groups did not reach statistical significance. The pulse rate did not differ between the groups or between preinduction and the commencement of surgery. Two patients (8%) in the propofol group required an upward adjustment of the maintenance infusion in response to an increase in pulse rate during surgery, with a resulting rapid return to baseline heart rate levels. Mean arterial blood pressure was significantly higher in the propofol group once surgery began.

Table 1. Demographic data (mean ± SE)

	TIVA	Inhalational
Patients (*n*)	24	21
Age (years)	22.3 ± 1.0	36 ± 2.8
Height (cm)	157.8 ± 0.8	156 ± 1.5
Weight (kg)	64.6 ± 1.6	65 ± 4.4
Cortisol (μg/dl)	23.2 ± 2.9	27.21 ± 4.3
IL-6 (pg/ml)	29.7 ± 3.9	25.1 ± 4.4

TIVA, total intravenous anesthesia; IL-6, interleukin-6.

The mean ± SD cortisol concentrations decreased significantly ($P < 0.001$) in propofol group, but not in the inhalation group ($P = 0.648$) 30 min post-induction (Fig. 1). The inhalation group had a highly significant ($P < 0.001$) elevation in coritisol concentrations after 90 min of surgery. In contrast, the mean cortisol level in the propofol group returned to the baseline ($P = 0.27$) only during this period. ACTH decreased significantly after induction similarly in both groups. After surgery, ACTH increased markedly and to the same extent in both groups ($P < 0.001$). A significant elevation in circulating prolactin was observed both at 30 ($P < 0.001$) and at 90 min ($P < 0.001$) irrespective of the anesthesia type. IL-6 levels increased significantly in both groups at 90 min ($P = 0.012$) but not postinduction.

Circulating αMSH decreased significantly at 30 min ($P = 0.0041$ for propofol, $P = 0.0165$ for isoflurane) in both groups. αMSH decreased from a preinduction mean ± SD of 17.77 ± 5.42 to 15.35 ± 4.13 pg/ml after 30 min of anesthesia with propofol and to 15.87 ± 4.21 pg/ml after 1 h of surgery; decreased from a preinduction mean of 16.67 ± 4.92 to 14.94 ± 3.52 pg/ml after 30 min of isoflurane anesthesia, and then increased to 17.12 ± 3.63 after 1 h of surgery ($P = 0.59$). αMSH

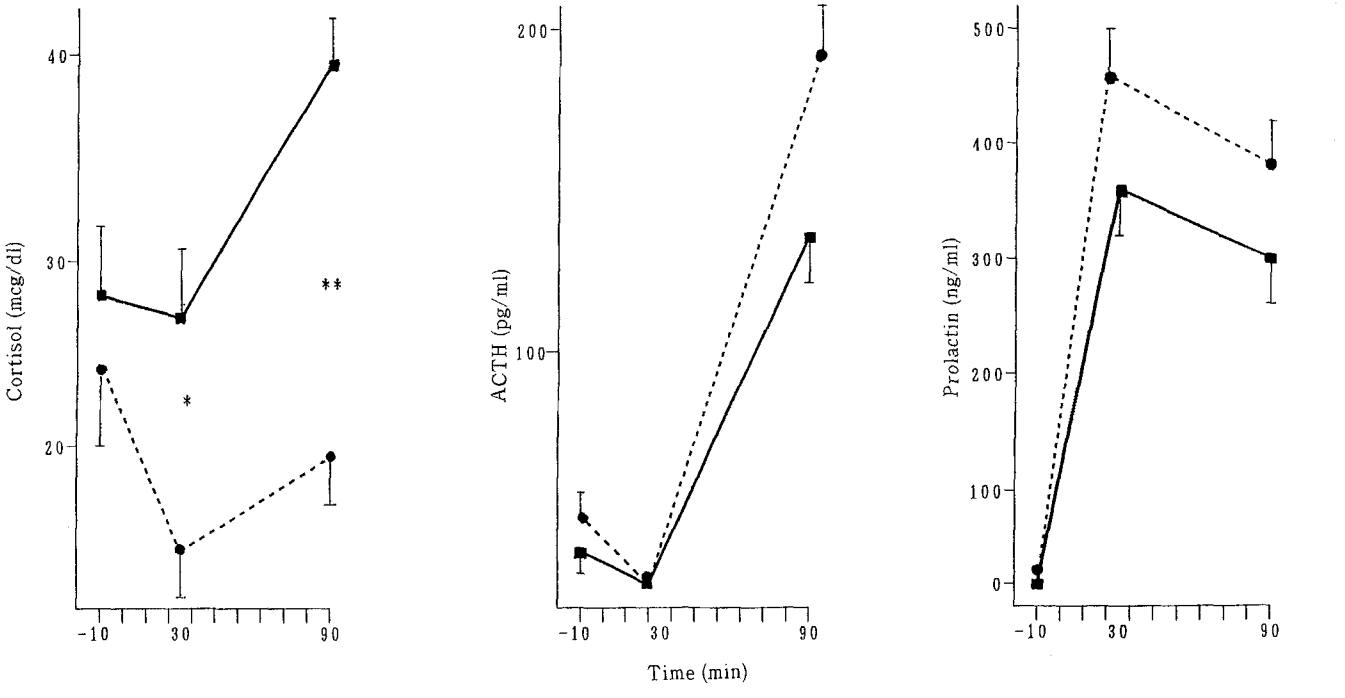

Fig. 1. Endocrine response (mean ± SE). *Solid line*, general anesthesia with isoflurane (GA); *dashed line*, total intravenous anesthesia (TIVA); *single asterisk*, $P < 0.05$; *double asterisk*, $P < 0.001$

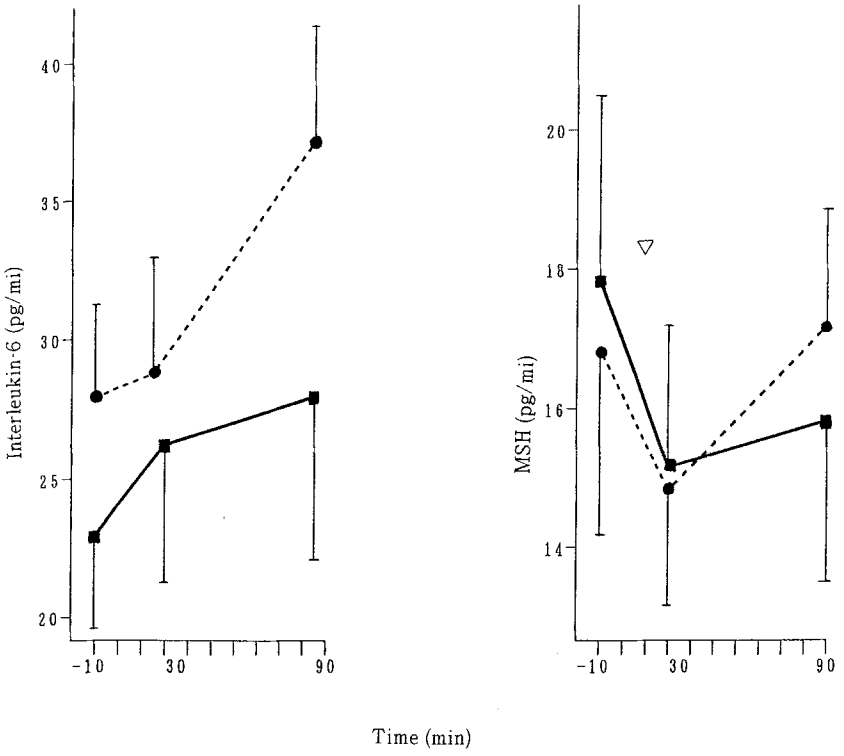

Fig. 2. Immuno-endocrine response (mean ± SE). *Solid line*, GA; *dashed line*, TIVA; *triangle*, $P < 0.05$

did not differ between the two groups at 30 ($P = 0.88$) or 90 ($P = 0.65$).

Adverse effects that occurred in more than one patient were nausea (3/21) after thiopental and pain on injection (2/24) after propofol. These adverse effects were transient and required no treatment.

Discussion

These data confirmed previous observations that propofol decreased cortisol during induction of anesthesia [27] and provide additional evidence that propofol abolishes the cortisol response to surgical stress. Activation of the HPA axis is crucial to the host response to injury and therefore this inhibitory effect could be detrimental during prolonged anesthetic and surgical stress. Because increases in circulating ACTH were similar in the two groups, the inhibitory activity of propofol is exerted directly on the adrenal glands rather than on the production or release of these triggering agents. Because all operations began at essentially the same time of day, diurnal variation could not have contributed to the differences between groups. Although anesthetic depth cannot be compared reliably, especially in the paralyzed patient, we strove to attain consistency in the two anesthetic regimens used so that the patients would be comparable as regards anesthesia.

Reports in the literature of the effects of propofol on adrenal steroidogenesis are conflicting. In vitro studies of guinea pig-dispersed adrenal cells showed that thiopental, propofol, and etomidate all inhibit ACTH-stimulated production of cortisol [20–21]. Thiopental and propofol were much less potent than etomidate in reducing cortisol secretion. Another in vitro study showed that propofol slightly decreased ACTH-stimulated cortisol synthesis in a concentration-dependent manner in isolated bovine adrenocortical cells [22]. Previous in vivo studies of the influence of propofol on glucocorticoid release were performed only during the induction of anesthesia. An induction dose of propofol can suppress cortisol but not block cortisol and aldosterone secretion in response to surgical stress or ACTH. In other research, on a small number of patients given an 8-h infusion of propofol for sedation, the drug had no effect on plasma cortisol levels, and the response to synthetic ACTH administration was normal [28].

The data demonstrate the first reported effects of anesthesia on circulating αMSH, which decreased significantly after induction with both anesthetic techniques.

Increases in circulatory prolactin are part of the typical response to stress [29,30]. Marked increase in prolactin concentrations were observed in all subjects independently of the anesthetic procedure. The increase started during the induction phase and reached a

plateau during surgery. The increase in prolactin during induction was likely due to a pharmacological action of the anesthetics. Thiopental has been shown to promote prolactin release possibly through a cholinergic mechanism [31]. Other anesthetic agents cause hyperprolactinemia and it may be that propofol has a similar effect. Alternatively, the opioid premedication with fentanyl may have been responsible for the increase in prolactin noted during induction.

The neuropeptide αMSH (1–13) is a propiomelanocortin derivative that shares the 1–13 amino acid sequence with ACTH. αMSH is a potent endogenous modulator of cytokine actions in models of fever and acute inflammation. It reduces fever and inflammation caused by endotoxin endogenous pyrogen and recombinant IL-1β, IL-6, and TNFα.

The basal average level of αMSH was within the normal range (15–20 pg/ml). Plasma levels of the neuropeptide significantly declined during induction of anesthesia ($P < 0.05$), consistent with the decrease in the parent molecule ACTH, but no increase was observed during surgery concomitant with the ACTH surge. A dissociation between the release of ACTH and that of αMSH already has been reported in previous experiments on animal models [32]. The present observation confirms that secretions of ACTH and αMSH are regulated independently.

IL-6 plays a crucial role in the induction of fever, in the acute phase response, and in immunoendocrine interactions. This cytokine is produced mainly by monocytes and macrophages, but several other sources have been identified including the anterior pituitary [33]. IL-6 has marked influences on the endocrine system; it promotes the release of several anterior pituitary hormones including ACTH, prolactin, growth hormone, and luteinizing hormone. IL-6 increases after surgery and the magnitude of the rise appears to be related to the duration of surgery. Because the cytokine was increased by adrenaline in the rat, one aim of this study was to determine whether anesthetic stress can induce IL-6 independently of surgical tissue damage. No increase in circulating IL-6 was observed after induction and before surgery in either group. Further, we did not observe any difference in the changes of circulating IL-6 in the two groups after surgery. These results indicate that anesthesia alone does not promote IL-6 release.

In conclusion, propofol suppresses cortisol release during anesthesia and surgery. Because inhibition of adrenal function contributes to hypotension, cortisol suppression may be important since propofol has a greater hypotensive effect than thiopental [34]. Although profound hypotension is more likely to be related to vasodilatation and negative intropism, further study is needed to establish the mechanism and reversibility of propofol's suppression of cortisol release during total intravenous anesthesia.

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