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BROMOCRIPTINE INHIBITION OF HYPERPROLACTINEMIA DURING SURGERY

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Abstract. The material included two groups of 10 women undergoing diagnostic laparoscopy. General anesthesia was administered by injection of 0.1 mg fentanyl followed by infusion of propanidide-succinylcholine. The control group received no medication prior to surgery, whereas patients in the experimental group were given 5 mg bromocriptine per os. Blood samples for prolactin determinations were drawn as the patients were placed on the operating table and immediately following surgery. The association of anesthesia and surgery caused prolactin levels to rise from 10.9±3.5 to 168±18.7 ng.ml^{-1} in the control group ($p \ll 0.001$) and from 3.5±0.5 to 7.5±1.1 ng.ml^{-1} in the test group ($p < 0.001$). A significant difference was noted between the two groups for their pre- and postoperative levels and prolactin response ($p < 0.05$, $p \ll 0.001$ and $p \ll 0.001$, respectively). The proposed protocol successfully suppresses prolactin increase during surgery and constitutes a useful tool for investigating hyperprolactinemia and its consequences during this same time. Possible applications include *in vitro* fertilization and studies on prolactin receptor-bearing tumors.

Key words: Prolactin, bromocriptine, pituitary, dopamine

Hyperprolactinemia during surgery is a well-established phenomenon (7, 13, 17) and has been shown to be due to several factors such as surgical stress (1, 17) and anesthesia using either inhalational anesthetics (9) or pure analgesic compounds (9, 10) and neuroleptic-analgesic mixtures (7). Prolactinemia during surgery is considerably increased and rivals that encountered in pituitary adenoma (7, 9, 17). Although the action of prolactin is far from being completely understood (1, 2) it still remains of interest to study the effects of suppressing this hyperprolactinemia during surgery. Clinically relevant applications include *in vitro* fertilization and studies on prolactin-receptor bearing tumors, as reviewed in the Discussion.

The purpose of the present study was to establish a protocol for anesthesia which would prevent prolactin from rising during surgery — or at least maintain if within physiological limits.

PATIENTS AND METHODS

Twenty women scheduled for diagnostic laparoscopy for tubal infertility were randomized into two groups, based on their file number. Even-numbered patients were assigned to the control group, while odd numbers received bromocriptine. Age, weight and height were statistically comparable for both patient populations. All patients were healthy and had received no medication during the 3 months prior to laparoscopy. All patients demonstrated a normal endocrine profile.

At 9 p.m. on the day preceding surgery, the experimental group received 5 mg bromocriptine per os. Control patients received no medication. Preanesthesia was administered one hour before surgery and consisted of 20 mg diazepam and 0.5 mg atropine i.m. Anesthesia was begun between 8 and 9 a.m. by an anesthesiologist informed of the study but unware as to which group each patient belonged. It consisted of 0.1 mg of fentanyl injected i.v. followed by a drip (500 ml) of 5% glucose containing 3 g propanidid (Epontol^{R}; Laboratoire Théraplix, Paris) and 100 mg succinylcholine (Succicurarium^{R}; Laboratoire Robert & Carrière, Paris) started at the rate of 20 ml.min^{-1}. The patient was intubated when the corneal reflex was no longer evident. Ventilation consisted of a 50/100 nitrous oxide – oxygen mixture and was based on a tidal volume of 10 ml.kg^{-1} and 12 inspirations.min^{-1}. Anesthetic flow was subsequently reduced to approximately 8 ml.min^{-1}.

Two samples of peripheral venous blood were drawn: a preoperative sample when the patient was placed on the operating table, and another at completion of surgery, approximately 30 min later. Only one preoperative control blood sample was taken for reference, since previous studies have already established that under such conditions prolactin levels are often above normal values. Moreover, the objective of the present study was merely to investigate the rise in prolactin during surgery. All samples were centrifugated immediately and plasma removed and stored frozen. Prolactin levels were determined using unmodified C.E.A.-I.R.E. SORIN radioimmune assay (PROL-RIA 200; C.E.A.-I.R.E., Gif sur Yvette). Each sample was evaluated in triplicate. The inter-assay coefficient of variation on normal pooled female serum was 7.5% (15 determinations) with an intra-assay coefficient of variation of 5.9% under the same conditions. All determinations were carried out using the same reagents. The lower limit of sensitivity was 0.5 ng.ml^{-1} and the normal plasma prolactin level was 3 to 13 ng.ml^{-1}.

Table I. *Pre and post operative levels of prolactin, and Δ PRL (Mean±SEM). Prolactin values significantly increase in both groups ($p \ll 0.001$ in control, $p < 0.001$ in experimental) but remain within physiological limits (3 – 13 ng.ml^{-1}) in experimental group.*

	Pre operative		**Post operative**		**Δ PRL**	
PRL ng.ml^{-1}	Mean±SEM	Range	Mean±SEM	Range	Mean±SEM	Range
Control	10.9±3.5	4.0 – 23.8	168 ±18.7	73 – 261	156±18.3	63 – 246
Experimental	3.5±0.5	1.4 – 7.6	7.5±1.1	2.6 – 13.4	4±0.8	1.2 – 9
p	<0.05	–	≪0.001	–	≪0.001	–

This study was performed under the guidelines set forth by the Helsinki Agreement and informed consent was obtained from all patients.

Statistical analysis was carried out using Student's *t*-test to compare intergroup mean values. Comparisons within the same group were based on paired Student's *t*-analysis. All results are expressed as means±standard error of the mean (mean±SE).

RESULTS

The calculation of mean values is given in Table I. Prolactin response in the bromocriptine-inhibited series (4 ng.ml^{-1}) was considerably lower than that of the control group (160 ng.ml^{-1}): ($p \ll 0.001$) even though prolactin levels significantly increased in both groups ($p < 0.001$ and $p \ll 0.001$, respectively). Pre- and postoperative levels in the bromocriptine group remained within physiological limits of 3 to 13 ng.ml^{-1}. Routine clinical follow-up did not reveal any adverse effects in patients who had received bromocriptine.

DISCUSSION

Prolactin is the only adenohypophyseal hormone under constant inhibition (1, 2) as opposed to other hormones for which secretion is induced by hypothalamic stimulation. Dopamine, with its strong inhibitory action, is the most powerful regulator of prolactin secretion (2, 11). In fact, dopamine antagonists give rise to considerably elevated levels of prolactin (1). Conversely, physiological (post-partum (2)) or pathological (tumor or functional disorders (6, 10)) hyperprolactinemia can be reduced by administration of dopamine agonists. As a result, bromocriptine — a dopamine agonist with few side effects — can effectively reduce hyperprolactinemia of various origins, thereby limiting its pathological consequences (6, 10). Oddly enough, the literature offers no help concerning the inhibition of hyperprolactinemia during surgery.

This protocol resulted in effective suppression of prolactin release during anesthesia and surgery. In all cases, measured prolactin levels were kept within or very close to the normal range as demonstrated by pre-and postoperative samples taken 30 min apart. This was considered adequate time to detect significant change, since prolactin has a plasma half-life of 20 to 30 min (1). Postoperative hyperprolactinemia in the control group was comparable to that in patients with prolactinadenoma. Bromocriptine was also shown to depress the preoperative level in the test group ($p < 0.05$).

Although these results cannot be extrapolated to more aggressive surgical procedures, this protocol would appear to imply some useful applications in short-term operations. One such application would be *in vitro* fertilization, for which postoperative luteal insufficiency has been suggested to explain re-insertion failures (16). *In vitro* studies have demonstrated that progesterone secretion by follicular cells is inversely proportional to rising prolactin levels (12). *In vivo*, both spontaneous and metoclopramide-induced hyperprolactinemia impair corpus luteum function (3, 8). In addition, postoperative luteal insufficiency, two-thirds of which is attended by metrorrhagia, has been reported after non-gynecological minor surgery (16). On the other hand, a minimal amount of prolactin is required *in vitro* to achieve adequate progesterone synthesis by follicular cells in culture (12). Although high dose, chronic administration of bromocriptine to women with normal menstrual cycles gradually induces decreased plasma progesterone during the luteal phase of the cycle (14), it is reasonable to assume that such a disturbance would not occur with a single dose because prolactin, though reduced, remains within the physiological range. Studies on human breast tumors may also benefit from this procedure. It is possible that prolactin binding sites could serve a therapeutic purpose (15). However, hyperprolactinemia not only leads to

receptor saturation which would impair the detection of these sites, but would also induce their prompt degradation by lysosomes (4, 5). It may therefore be of interest to prevent both of these phenomena *in vivo*. The two potential applications cited are presently under investigation.

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