# EFFECT OF ANESTHESIA AND SURGICAL STRESS ON PROLACTIN LEVELS IN PREGNANCY

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SUMMARY

The Authors examine the variations of PRL plasma levels after the administration of Sodium Thiopentale 500 mg i.v. to ten patients undergoing voluntary pregnancy interruption between the 8th and the 14th gestational week; PRL levels which were already elevated due to estrogen action, as is physiological in pregnancy, further increased after the anaesthetic drug injection, confirming the ability of Sodium Thiopentale to increase prolactin levels even in estrogen-induced hyperprolactinemic conditions; the possible ways through which the drug may act are then discussed.

Surgical stress and anesthesia cause significant increases in prolactin (PRL) plasma levels.

The process through which sodium thiopentale raises PRL levels ([1, 2, 3]) is still unknown.

Among its possible actions there are: blockage of dopamine (DA) synthesis; depletion of catecholamine central stores; interferences in catecholamine synthesis; increase in DA turnover and competition towards hypothalamic and hypophyseal receptor sites.

The difficulty in identifying the action sites of many drugs stems from the existence of DA receptors both in the hypothalamus and the hypophysis ([4]).

Theoretically, it is possible to distinguish the effects on the two different action sites (hypophyseal and hypothalamic) by measuring reaction times after the administration of the drug.

In the case of short-reaction time drugs, a direct effect on galactothroph can be assumed (partially at least).

With regard to longer-reaction-time substances, the most likely hypothesis is that of an intermediate mechanism, probably acting on the hypothalamus.

Estrogens are the most important among substances causing prolactin increases. Their administration raises the number of mythoses in galactothrops and the estrogen-induced hypophyseal hyperplasia concerns almost exclusively this kind of cells ([5]).

Hypophysis is known to grow in size during pregnancy, doubling its weight by the end of it. This weight increase is almost exclusively due to the proliferation of galactophore cells.

PRL is the main secretion of pregnant women's hypophyses. Consequently, its plasma levels increase 10/20 fold in pregnancy ([6]).

This fact is generally ascribed to the increase of estrogen levels in pregnancy.

The administration of estrogens to non-pregnant women stimulates PRL secretion.



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Animals with low estrogen levels in pregnancy also show low PRL levels.

The foetus hypophysis too is affected by the action of placenta estrogens. PRL levels develop similarly to mother's ([7]).

Furthermore, there is a close correlation between PRL plasma levels at a given pregnancy stage and hypophysis weight at the same gestational age ([4]).

PRL is also present in amniotic fluid in a much higher concentration than in the mother's serum.

However, although the decidua is a possible source, amniotic PRL exact origin and control are still unknown.

Endovenous or endoamniotic administration of DHEA-S, an estrogen precursor, in pregnancy causes the increase of PRL amniotic levels, at least within six hours from administration, which could exclude any influence of mother's circulation on amniotic PRL control ([6]).

Our purpose is studying the development of PRL levels, after administration of sodium thiopentale, in an experimental pattern of estrogen-induced hyperprolactinemia, that is pregnancy.

## MATERIAL AND METHODS

This study concerns 10 patients, at the 8th/14th week of pregnancy, hospitalized at the Obstetric and Gynecological Clinic of Parma University for voluntary interruption of pregnancy (Act. No. 194, 22-5-1978).

In all cases the intervention was performed through aspiration of the uterine content, after dilatation of the cervix to Hegar No. 10.5, in general anesthesia by sodium thiopentale (500 mg e.v.).

Samples were taken according to the following protocol:

— 2 basal samples 24 and 3 hours before anesthesia,

— 4 samples 2, 4, 12, 24 hours after anesthesia, respectively.

Sampled blood was immediately centrifuged and stored at −30 °C until the moment of determination.

PRL levels were measured in double samples following the radioimmunologic method (kits " Biodata ", double antibody).

Table 1. — *Prolactin plasma levels (ng/ml) before and after sodium thiopentale (500 mg e.v.).*

| Week of pregn. | 1st Basal | 2nd Basal | After 2 h | After 4 h | After 12 h | After 24 h |
|---|---|---|---|---|---|---|
| 8th | 10.5 | 9.5 | 61.2 | 38.0 | 6.0 | 13.5 |
| 9th | 26.5 | 20.0 | 100.0 | 65.3 | 18.0 | 14.5 |
| 9th | 21.5 | 14.5 | 119.5 | 95.0 | 15.5 | 21.5 |
| 9th | 43.0 | 27.7 | 131.0 | 119.4 | 14.0 | 24.0 |
| 9th | 14.5 | 23.0 | 112.0 | 100.0 | 24.5 | 42.5 |
| 10th | 55.0 | 55.5 | 175.0 | 175.5 | 34.0 | 32.0 |
| 10th | 54.0 | 38.5 | 215.0 | 125.1 | 19.0 | 33.2 |
| 10th | 48.5 | 25.0 | 128.3 | 90.0 | 20.1 | 26.5 |
| 12th | 46.0 | 55.5 | 125.0 | 131.3 | 45.5 | 49.1 |
| 14th | 50.5 | 49.0 | 128.5 | 55.0 | 74.3 | 65.0 |
| Average | 37.0 | 31.82 | 129.5 | 99.45 | 27.04 | 32.13 |
| S.D. | 17.0 | 16.80 | 41.30 | 40.65 | 19.86 | 16.18 |

## RESULTS

The administration of sodium thiopentale causes an increase in PRL plasma levels (table 1). Levels remain high until 4 hours after administration. After 12 hours the patients' behaviour develops non-homogeneously: in 8 out of 10 cases levels decrease below base levels to reach them again at the 24th hour.

Considering the cumulative PRL response (total of PRL plasma levels of the four samples taken after the administration of sodium thiopentale) and the increases in percentage compared with the average of the two basal levels (table 2),

Table 2. — *Cumulat. prolactin reaction (ng) after sodium thiopentale (500 mg e.v.) and percentage increase compared with average basal levels.*

| Week of pregnancy | Mean basal values | Cumulative response | Increase % |
|---|---|---|---|
| 8th | 10 | 118.7 | 1080 |
| 9th | 23.5 | 197.8 | 741 |
| 9th | 18 | 250.5 | 1291.67 |
| 9th | 35.3 | 288.4 | 717.0 |
| 9th | 18.5 | 279 | 1408.11 |
| 10th | 55.2 | 416.5 | 654.53 |
| 10th | 46.25 | 392.3 | 748.22 |
| 10th | 36.75 | 264.9 | 620.82 |
| 12th | 50.75 | 350.4 | 590.44 |
| 14th | 49.76 | 322.8 | 548.84 |

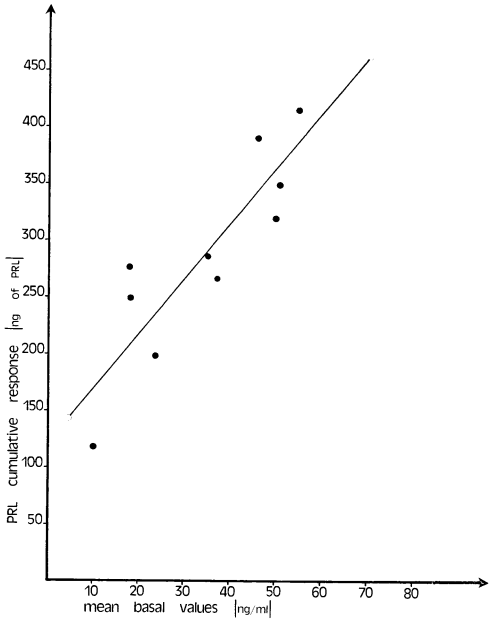


Fig. 1. — Correlation between PRL basal values (ng/ml) and cumulative PRL response (ng) after thiopentale (500 mg e.v.). $Y=4.87X+120.40$; $r=0.877$; $p<0.001$.

a progressive increase in cumulative response levels appears clearly.

As the basal level increases, the cumulative reaction increases too.

On the other hand, percentage increases compared with basal levels are progressively smaller as basal levels increase.

Correlation coefficients show a significant positive correlation between basal level and cumulative reaction ($r = 0.877$; $p<0.001$) (fig. 1), and an equally significant negative correlation between PRL basal level and percentage increase ($r = -0.797$; $p<0.01$) (fig.2).

The correlation between gestational age and PRL basal level ($r=0.727$; $p<0.01$) is also significant.

## CONCLUSION

The results of our study confirm the hyperprolactin-inducing action of sodium thiopentale, even in the situation of hyperprolactinemia caused by pregnancy.

There is an immediate reaction: after five minutes there is an average increase of over 500% ([8]).

This rapid reaction suggests the existence of a direct influence of this substance on hypophyseal lactothrope, among the various possible processes. Sodium thiopentale might perform a competitive action on DA receptors in the anterior hypophysis.

This rapid action might also depend on a blockage of the inhibition mechanism, through the drug's action on hypothalamic dopaminergic neurons, rather than on a synthesis increase.

A further mechanism might play a major role. It concerns the GABAergic system.

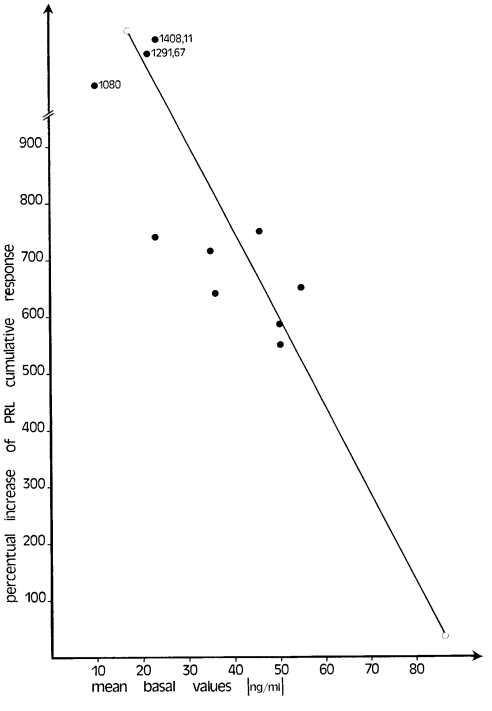


Fig. 2. — Correlation between PRL basal values (ng/ml) and percentage increase of PRL cumulative response after thiopentale (500 mg e.v.). $Y = -15.24X+1364$; $r = -0.797$; $p < 0.01$.

It has been proven for a while that the gamma-aminobutirric acid (GABA) causes general anesthesia both in man and in animals. Furthermore, it has been recently proven that the e.v. administration of gamma-idrossibutirric acid (a physiologic metabolite of GABA) can cause GH and PRL levels to increase significantly ([9]).

Therefore, sodium thiopentale action might be mediated by GABAergic neurons, that have an inhibiting influence on dopaminergic terminals of the tubero-infundibular system.

The tubero-infundibular dopaminergic system appears responsible for PRL secretion by the anterior hypophysis.

DA, released by terminal neurons of the tubero-infundibular system, is carried through the hypothalamic-hypophyseal portal system, to the anterior hypophysis where it performs its action, thus activating receptors inhibiting PRL release.

Apparently, tubero-infundibular neurons' activity is at least partly controlled by PRL levels ([10, 11]). The systemic injection of PRL selectively increases the average DA turnover.

The injection of neuroleptics and estrogens has similar effects.

When PRL levels rise, it enters the cephalo-rhachidian liquid and is carried to the IIIrd ventriculus where it can reach dopaminergic hypothalamic cells and alter the activitv of these neurons ([12]). In fact, direct PRL injection into the IIIrd ventriculus selectively increases DA turnover (in its maximum average) in the tubero-infundibular terminals but not in the dopaminergic terminal neurons of the striatum or the olfactory tuberculus ([13, 14]).

Therefore, PRL could exert a kind of feed-back control on its own secretion, by activating DA turnover in tubero-infundibular neurons' terminals ([15, 16]).

Increases clearly vary according to the different PRL basal levels. Reactions to the hyperprolactinemia-inducer stimulus, considered on a cumulative basis, are rather homogeneous: high reaction levels with high basal levels; lower reaction levels with lower basal levels, and a good correlation ($r=0.877$; $p<0.001$).

The percentage increases with respect to basal levels, which probably show a more accurate picture of lactothrope functional values, conversely show greater increase with the lower PRL basal levels, and a very significant negative correlation ($r=-0.797$; $p<0.01$).

A self inhibiting effect can be assumed to explain the behaviour highlighted in our study.

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