THE DOMPERIDONE TEST IN HYPER-PROLACTINEMIA STATES

G. BAVIERA, F. ABATE, A. OLIVA, P. MARTINO, M. CAMINITI, L. DE MEO

Obstetric and Gynecological Clinic, University of Messina

SUMMARY

The Authors report their experience regarding the use of Domperidone for the differentiation of hyper prolactinemias in tumoral and functional types. The criterion utilized was the total area found under the percent stimulation curve obtained after domperidone administration (4 mg i.v.). The results indicate that domperidone causes significant ($p<0.001$) increase in prolactin secretion in the puerperium as to those patients having prolactinoma.

The major part of hyper prolactinemia syndromes can be produced either by presence of basophilic adenoma either by a functional alteration of the hypothalamic control of the prolactin secretion.

In order to distinguish between those two hyper prolactinemia states, medecines capable of affecting the function and/or the metabolism of neurotransmitters that follow an important role in the control of hypothalamic neurones and therefore in the regulation of hormonal secretion of the front hypophysis, have been used during the last years. The precursory or the simulated substance of Dopamina like L-DOPA and Bromocriptina have failed because the precise place of the Catecholamine defect in patients with prolactinoma is not situated at the level of dopaminergic receptors of the HPR secerning cell (Welsech and others in 1971, McLeod and Lehmeyer, 1974). The insufficient discriminative power of medecines blocking the dopaminergic receptors as Chloropromazine, Metoclopramide and Sulpiride is probably due to the integration necessity or CNS and Hypophysis as well, because such compounds can exert their action discharging prolactin (Anden and others, 1970; Kleinberg and others, 1971; Honda and others, 1977). Recently Müller and others proposed the use of Domperidone, antidopaminergic compound that exerts its action at the level of peripheral receptors of dopamina (Reyntjens and others, 1978), in the differential diagnosis of hyper prolactinemias.

MATERIAL AND METHODS

We have, in order to verify its validity, performed the test on ten voluntary women at the second day of delivery, on 15 patients with radiological, biochemical and hystological signs of prolactinoma, on 4 patients with hyperprolactinemias with uncertain ethiology and for control in six women with normal menstrual cycle in folliculin phase. The test has been performed between 8.30-9 after two basic drawings (−15.0) injecting 4 mg of Domperidone i.v., and drawing subsequently samples every 15′ for two hours.

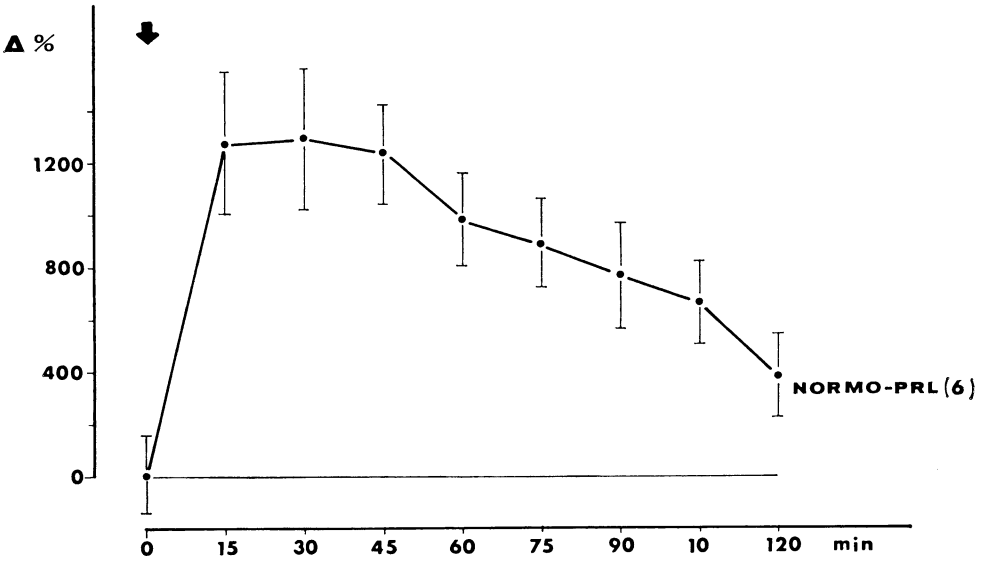

Fig. 1. — Percentage variations as to the basis of prolactin values after Domperidone (4 mg i.v.) in normo prolactinemia patients (M ± ES).

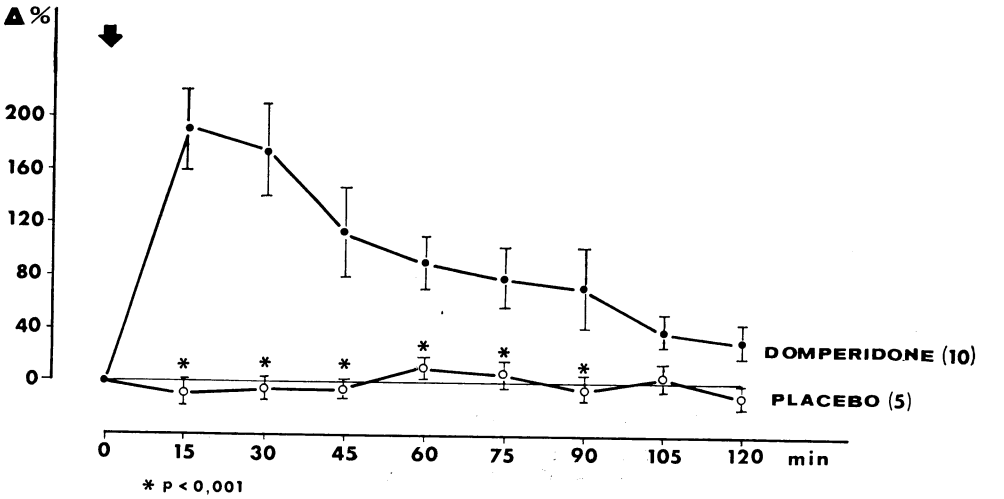

Fig. 2. — Percentage variations of prolactin secretion referred to the basis, after injection of Domperidone and placebo in 15 post delivery women (M ± ES).

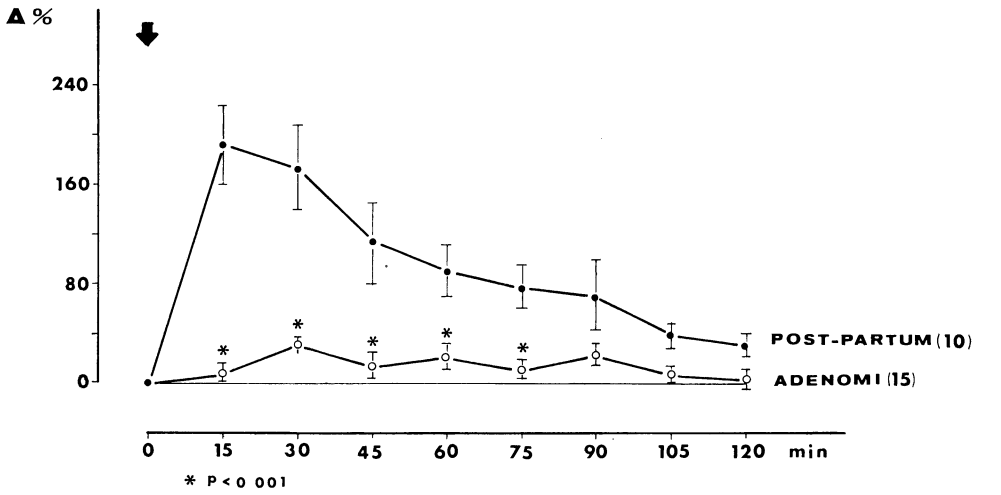

Fig. 3. — Percentage variations as to the basic levels of prolactin after DOM injection in 15 women with prolactinemias (M ± ES).

The plasma has been separated and freezed up to −20° C until dosage. Prolactin has been evaluated by the RIA method and 1 ng of the used standard, was equal to 29 WHO 75/504 and to 1 ng NHI F-I. The sensibility of the exam was equal to 1.5 ng/ml. The maximum limit in our laboratory is equal to 18 ng/ml. Obtained results were expressed as an increased percentage of prolactin values as to the basis and valued with the T of Student.

RESULTS

In 6 women under control with basic values of prolactin equal to 7.13 ± 0.17 ng/ml (M±ES), Domperidone provoked a maximal increase of prolactin equal to 10-15 times the basic values, 10-45 minutes after the administration of the medecine and even maintained a high level after 180′ (fig. 1).

In 10 women at their second day of delivery, with basic values of 79.42±6.37 ng/ml Domperidone has induced a maximum increase of PRL between the 70 and 400% of the basic values from 15′ up to 60′ after injection of the medecine and that variation was significantly different as to the other 5 patients with basic values of 127.87±20.30 ng/ml (M ± ES) who received placebo (fig. 2).

The administration of Domperidone in 15 patients with prolactinoma with basic

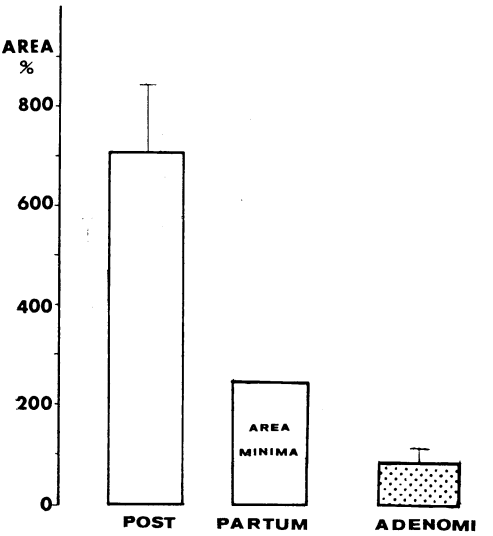

Fig. 4. – Total areas of percentage response of prolactin secretion after DOM (4 mg i.v.) in 10 women in post delivery and in 15 patients with adenoma (M ± ES).

values of 261.43±72.11 (M±ES) ng/ml did not lead to significant values of PRL secretion and a highly important difference from +15 to +90 has been observed as to patients with hyper puerperium PRL (fig. 3).

lactinoma, showed significantly lower as to the one obtained in puerperium (fig. 4).

Only one case showed a superior area to the minimum met in women with hyper PRL puerperium. Out of the 4 patients with hyper PRL with uncertain ethiology,

Case No.	Age years		Duration of symptoms		Sella turcica	Basilar levels hPRL ng/ml	LH ng/ml	FSH ng/ml	E_2 pg/ml	Δ max % hPRL	LH	FSH	Area %
1	29	−0	2	−	N	36,2	1,3	1,0	103	158	1150		972
2	24	+	2	+	N	36,9	1,3	2,0	49	52	1470	530	63
3	37	+	1	−	N	45,0	3,0	1,3	26	7	623	168	−130
4	34	−0	2	+	N	33,0	2,3	1,3	47	75	650	320	609

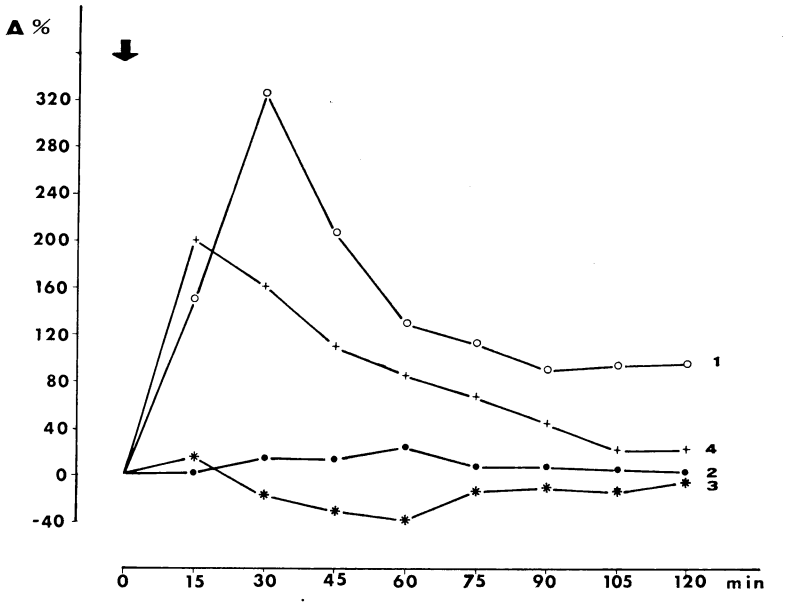

Fig. 5. — Variations of Prolactin secretion referred at the base after injection of DOM in 4 women with hyper prolactinemias and uncertain ethiology.

In order to assume objective evaluation criteria to the test response, we took the global PRL release into consideration after the medecine injection, evaluating the total area of the stimulation percentage curve. The obtained areas in patients with pro-

no. 1 and no. 4 showed a response to the test similar to the one met in puerperium, while in case no. 2 and no. 3, no significant variations were noted.

Case no. 2 showed furthermore normal response to GnRH and to TRH, and case

no. 3 replied absent to TRH (fig. 5). The global areas of response in the last two patients showed minimal levels met in puerperium, patients.

DISCUSSION AND COMMENTS

The data obtained in our laboratory show us that significant difference of the response to the test between patients with prolactinoma ($p < 0.001$). Through a comparative analysis between basic levels of prolactin and the answer to the test in all groups taken into consideration (data not published), and the presence of basic hormone levels in one case of adenoma (35.6 ng/ml), we can reject the hypothesis that this difference can be attributed to the different basic levels of PRL. The course of the test in women with good tumor joins the hypothesis that in these patients a defect of the dopaminergic neurotransmission (Fine and Frohman, 1978; Van Loon, 1978) and since Domperidone acts blocking a peripheral receptor under dopaminergic action, that leads to think that as a consequence of the adenoma development there should be an intrahypophysis trouble of the normal microvascular relations of the hypothalamic hypophisic system and so thus to a defect to DA-liberation through that way to the adenomastosis cells.

The non-response in the two cases of hyper PRL with uncertain ethiology can lead to think, that in those patients, a tumor at its initial stage is present, and so thus radiologically not evident. To our opinion, even if the response at the test cannot be taken as an absolute discriminant of the presence or less of an adenomastosis form (see false negatives), only a regular control of these hyper prolactinemia patients without any radiological sign of tumor, can verify the prognosis capacity of the medecine.

THANKS

The Authors would like to express their gratitude to Dr. A. M. Sabrie, Janssen Farmaceutici S.p.R. Rome for their supply of Domperidone.

BIBLIOGRAPHY

1) Anden N. E., Butcher S. C., Corrodi H., Fluxe K., Uncerstedt I.: *Europ. J. Pharmacol., 11*, 303, 1970.
2) Fine S. A., Frohman L. A.: *J. Clin. Invest., 61*, 973, 1978.
3) Honda F., Satoh Y., Shimomura K., Satoh H., Noguchi H., Uchida S., Kato R.: *Japan J. Pharmacol., 27*, 397, 1977.
4) Kleiberg D. L., Noel G. L., Frantz A. G.: *J. Clin. Endocrinol. Metab., 33*, 873, 1971.
5) MacLeod R. M., Lehemeyer J. E.: *Proc. Soc. Exp. Biol. Med., 145*, 1128, 1974.
6) Müller E. E., Genazzani A. R., Camanni F., Cocchi D., Massara F., Locatelli V., Molinatti G. M.: in Faglia, Giovannelli and MacLeod: " Pituitary microadenomas ", Academic Press, New York, pp. 347-365, 1980.
7) Reyntiens A. J., Niemegeers C. J. E., Nueten J. M., Laduron P., Heykants J., Schellekens K. H. L., Marsboom R., Jugenean A., Broekaert A., Janssen P. A. J.: *Arzeit. Foorsch. Drug Res., 28*, 1194, 1978.
8) Van Loon G. R.: *Lancet, 11*, 868, 1978.
9) Welsech C. W., Squiers M. D., Cassel E., Chen C. L., Martes J.: *Am. J. Physiol., 221*, 1714, 1971.