LA TERAPIA FARMACOLOGICA DEGLI ADENOMI IPOFISARI

AGONISTI DOPAMINERGICI

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TERAPIA MEDICA DELL'ADENOMA PRL SECERNENTE

- G02CB
- 1. BROMOCRIPTINA
- Bromocriptina Dorom 2,5 mg
- Parlodel 2,5 5 o 10 mg
- 2. CABERGOLINA
- Dostinex 0,5 mg 2 o 8 cp
- Actualene 0,5 mg 8 cp
- Cabergolina Ratiopharm e Teva 0,5mg 2 o 8 cp
- Cabaser 1 mg e 2 mg off label
- 3. METERGOLINA
- Liserdol 4 mg

- N04BC
- 1. BROMOCRIPTINA
- Bromocriptina Dorom 5 o 10 mg
- Parlodel 5 o 10 mg
- 3. PERGOLIDE
- Pergolide EG 1 mg (PT 6 mesi)
- 4. CABERGOLINA
- Cabaser 1 e 2 mg

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Roma,
9-11 novembre 2012

SPECIAL FEATURE

Clinical Practice Guideline

Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline

Shlomo Melmed, Felipe F. Casanueva, Andrew R. Hoffman, David L. Kleinberg, Victor M. Montori, Janet A. Schlechte, and John A. H. Wass

4.0. Management of prolactinoma

Recommendation

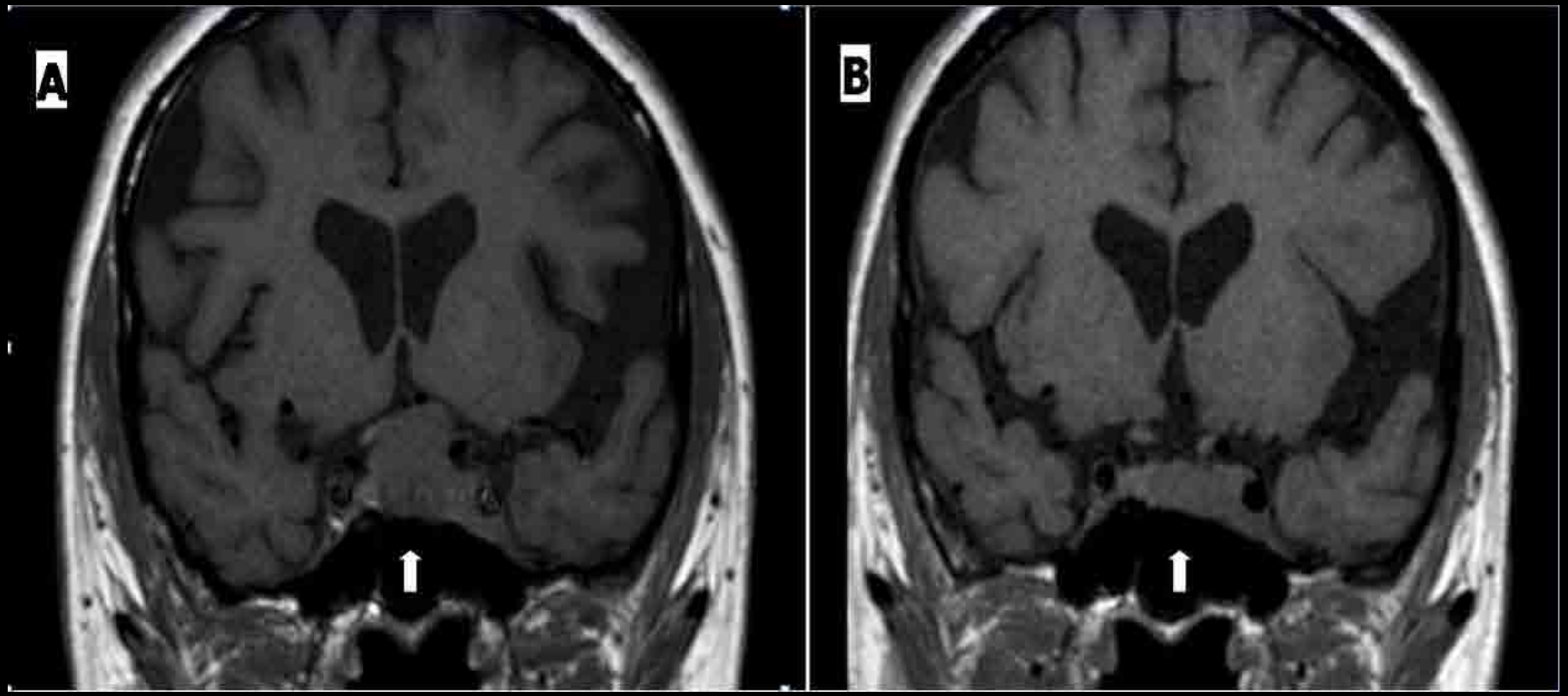
4.1. We recommend dopamine agonist therapy to lower prolactin levels, decrease tumor size, and restore gonadal function for patients harboring symptomatic prolactin-secreting microadenomas or macroadenomas (1|⊕⊕⊕⊕). We recommend using cabergoline in preference to other dopamine agonists because it has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage (1|⊕⊕⊕⊕).

AGONISTI DOPAMINERGICI

EFFICACIA DELLA TERAPIA DOPAMINERGICA (REVISIONE LETTERATURA)

- 68% (40-100%) NORMALIZZAZIONE DELLA PRLemia
- 86% (33-100%) RISOLUZIONE DELLA GALATTORREA
- 67% (6-100%) MIGLIORAMENTO FUNZIONE SESSUALE
- 53% (10-100%) RISOLUZIONE INFERTILITA'
- 67% (40-100%) RISOLUZIONE DIFETTI CAMPIMETRICI
- 62% (20-100% RIDUZIONE VOLUMETRICA ADENOMA

MACROADENOMA PRL SECERNENTE PRIMA (A) E DOPO 1 ANNO DI TERAPIA CON CAB (B)



AGONISTI DOPAMINERGICI

Eur J Endocrinol. 2012 Nov;167(5):651-62. doi: 10.1530/EJE-12-0236. Epub 2012 Aug 23.

Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92 patients.

Vroonen L, Jaffrain-Rea ML, Petrossians P, Tamagno G, Chanson P, Vilar L, Borson-Chazot F, Naves LA, Brue T, Gatta B, Delemer B, Ciccarelli E, Beck-Peccoz P, Caron P, Daly AF, Beckers A.

Department of Endocrinology, Centre Hospitalier Universitaire de Liège, University of Liège, Domaine Universitaire du Sart-Tilman, 4000 Liège, Belgium.

- 92 pazienti (50F,42M)
- 76 macro, 16 micro
- 12 portatori di alterazione genetica (AIP)
- Terapia solo farmacologica 36 pz (39,1%), chirurgica 56 pz (60,9%), radiante 13 pz (14,1%)
- Dose mediana CAB 3,5 mg/sett. (2-10,5)
- Normalizzazione PRL 28%, regressione tumorale 19,9%
- Sviluppo di tumore aggressivo 4 pz (4,3%), carcinoma 3 pz (3,3%)
- Deceduti 4,8%

Endocr Pract. 2011 May-Jun;17(3):e55-8.

Positive prolactin response to bromocriptine in 2 patients with cabergoline-resistant prolactinomas.

Iyer P, Molitch ME.

Department of Pediatrics, Diabetes, and Metabolism, University of South Florida, Tampa, FL, USA. iyerp@allkids.org

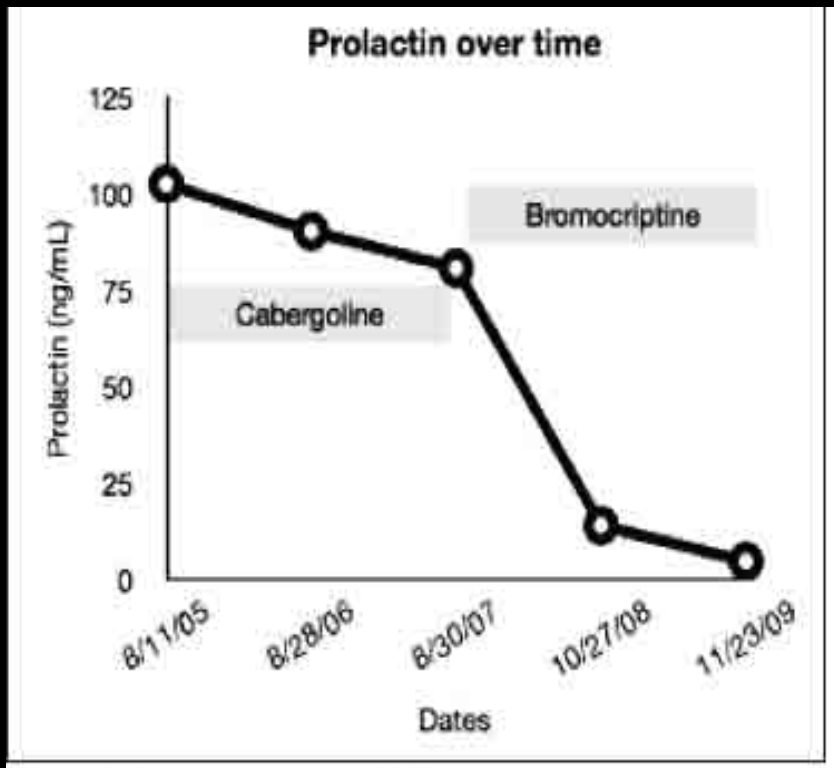


Fig. 1. Change in serum prolactin in Patient 1 after initial treatment with cabergoline followed by bromocriptine.

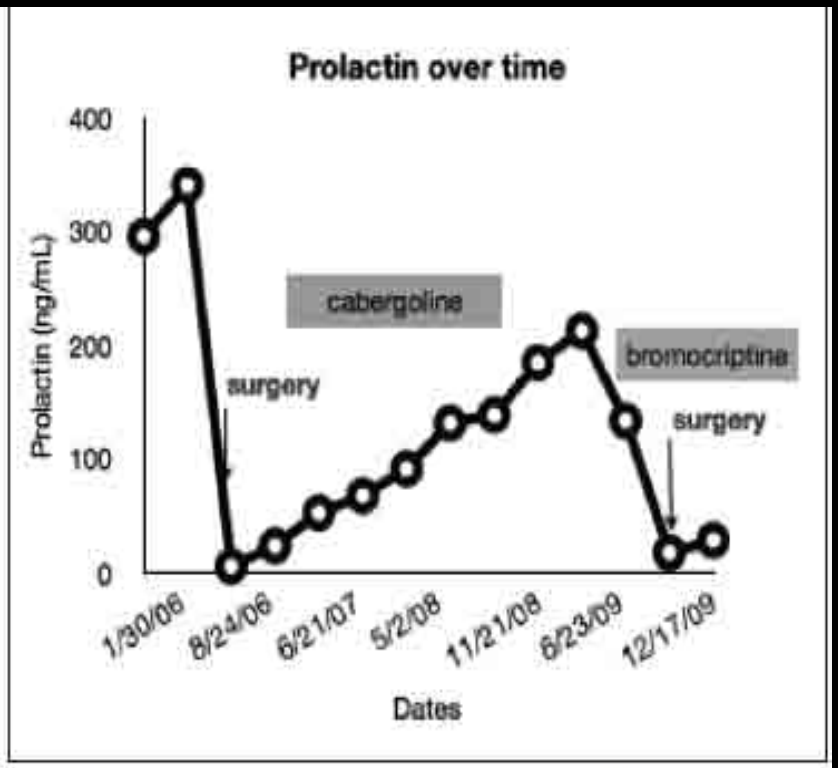


Fig. 2. Change in serum prolactin in Patient 2 after initial treatment with cabergoline followed by bromocriptine.

AGONISTI DOPAMINERGICI

Pituitary. 2011 Dec;14(4):362-9.

Secondary resistance to cabergoline therapy in a macroprolactinoma: a case report and literature review.

Behan LA, Draman MS, Moran C, King T, Crowley RK, O'Sullivan EP, Smith D, Thompson CJ, Agha A.

Department of Academic Endocrinology and Diabetes, Beaumont Hospital and RCSI Medical School, Dublin 9, Ireland. lucyannbehan@beaumont.i.e

Paziente femmina di 57 anni, con macroprolattinoma, responsiva alla CAB per 8 anni (normalizzazione della PRL e srinkage dell'adenoma); in seguito progressivo incremento della PRLemia e dell'adenoma senza risposta a dosi fino a 6 mg/w (paziente sottoposta ad intervento NCH+RT)

FIBROSI VALVOLARE E CABERGOLINA

- Serotonina importante nello sviluppo cardiaco (effetto mediato da 5HT(2B)R)
- Stimolazione di 5HT(2B)R causa eccessiva stimolazione di fibromioblasti, con ispessimento e restrizione dell'ostio valvolare
- Cabergolina: potente agonista 5HT(2B)R
- Bromocriptina: debole agonista 5HT(2B)R
- Correlazione degli effetti patologici con dose e durata della terapia?
- Prevalenza di valvulopatie nei soggetti normali?

  Insufficienza tricuspidale 24-96%

  Insufficienza mitralica 10-80%

STUDI SUGLI EFFETTI CARDIACI DELLA CABERGOLINA

Bogazzi et al., 2008	100 pts	3-199 months	15-1327 mg	No VHD
Colao et al., 2008	50 ots	16-260 months	32-1938 mg	54% VHD
Walkil et al., 2008	44 pts	Mean 62 monthsB	311 mg	No VHD
Lancellotti et al., 2008	102 pts	12-228 months	18-1718 mg	No VHD
Kars et al., 2008	47 pts	8±0.6 yrs	24-1768 mg	17% VHD
Devin et al., 2008	45 pts	39±29 months	0.91±0.96 mg/w	No VHD
Herring et al., 2009	50 pts	1-13 yrs	443±53 mg	No VHD
Vallette et al., 2009	70 pts	55±22 months	282±271 mg	No VHD
Nachtigall et al., 2010	100 pts	6-200 months	15-2520 mg	gender
Tan et al., 2010	72 pts	26-96 months	126 (58-258) mg	No VHD

STUDI SUGLI EFFETTI CARDIACI DELLA CABERGOLINA (2012)

Roma,
9-11 novembre 2012

Yarman et al.	22 pts	Mean 61 months	155 mg	NO VHD
Halperin et al.	83 pts	12-765 weeks	217-306,6 mg	Lieve VHD 15pts con CD>180
Delgado et al.	45 pts	2° vs 1° year		Aortic valve calcif. 63%vs 38% untreated
Boguszewski et al.	51 pts	37,8±21,3 months	16-1286,8 mg	49,1vs 27,1% tr MI 45,1vs 20,3% trTRI 7,8 vs 0% m TRI
Studio AME	373pts	72.5 months (12-318)	272.5 mg (6-3360)	NO VHD 63%

Insufficienza tricuspidale moderata
(M.M donna a.64,CAB trt. 264 mesi, mg/sett 1,5 mg/w)

AGONISTI DOPAMINERGICI

Clin Neuropharmacol. 2011 Sep-Oct;34(5):179-81.

Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas.

Martinkova J, Trejbalova L, Sasikova M, Benetin J, Valkovic P.

2nd Department of Neurology, Comenius University, Bratislava, Slovakia.

Due pazienti con macroprolattinoma:

1 paziente ha sviluppato bulimia e dipendenza da gioco d'azzardo (cabergolina, bromocriptina, quinagolide)

1 paziente ha sviluppato ipersessualità (cabergolina)

Recurrence of Hyperprolactinemia after Withdrawal of Dopamine Agonists: Systematic Review and Meta-Analysis

Olaf M. Dekkers, Joep Lagro, Pia Burman, Jens Otto Jørgensen, Johannes A. Romijn, and Alberto M. Pereira

(*J Clin Endocrinol Metab* 95: 43–51, 2010)

Roma,
9-11 novembre 2012

TABLE 2. Persisting normoprolactinemia after withdrawal of dopamine agonists

	No. of studies	Fixed effects model (95% CI)	I^2	Random effects model (95% CI)
Overall effect	19	35% (31–39)	81%	21% (14–30)
Dopamine agonist				
Cabergoline	4	54% (47–60)	85%	35% (19–56)
Bromocriptine	12	20% (16–26)	20%	20% (14–28)
Cause of hyperprolactinemia				
Idiopathic hyperprolactinemia	3	53% (36–70)	85%	32% (5–80)
Microprolactinoma	13	40% (34–46)	84%	21% (10–37)
Macroprolactinoma	8	37% (29–46)	68%	16% (7–36)
Treatment duration				
<24 months	12	16% (11–22)	0%	16% (11–22)
>24 months	7	40% (35–45)	91%	34% (19–52)
Prespecified protocol				
Yes	9	45% (39–51)	84%	18% (9–31)
No	10	23% (19–28)	11%	24% (18–30)

AGONISTI DOPAMINERGICI

Clin Invest Med. 2012 Apr 1;35(2):E96-104.

Management of prolactinomas during pregnancy -- a survey of four Canadian provinces.

Almalki MH, Ur E, Johnson M, Clarke DB, Imran SA.

Division of Endocrinology and Metabolism, University of British Columbia, Vancouver, British Columbia, Canada.

- Micro: 94% sospende DAergici alla diagnosi di gravidanza
  79% sospende controlli di PRLemia
  94% non effettua RMN (tranne che in pz sintomatiche)
  32% effettua regolarmente CV
- Macro: 65% sospende DAergici alla diagnosi di gravidanza
  30% effettua regolari controlli di RMN e di PRL
  40% effettua regolarmente CV
- Grandi macro: 82% continua DAergici per l'intera gravidanza; 18% sceglie intervento NCH
  49% effettua regolari controlli RMN
  94% effettua regolarmente CV

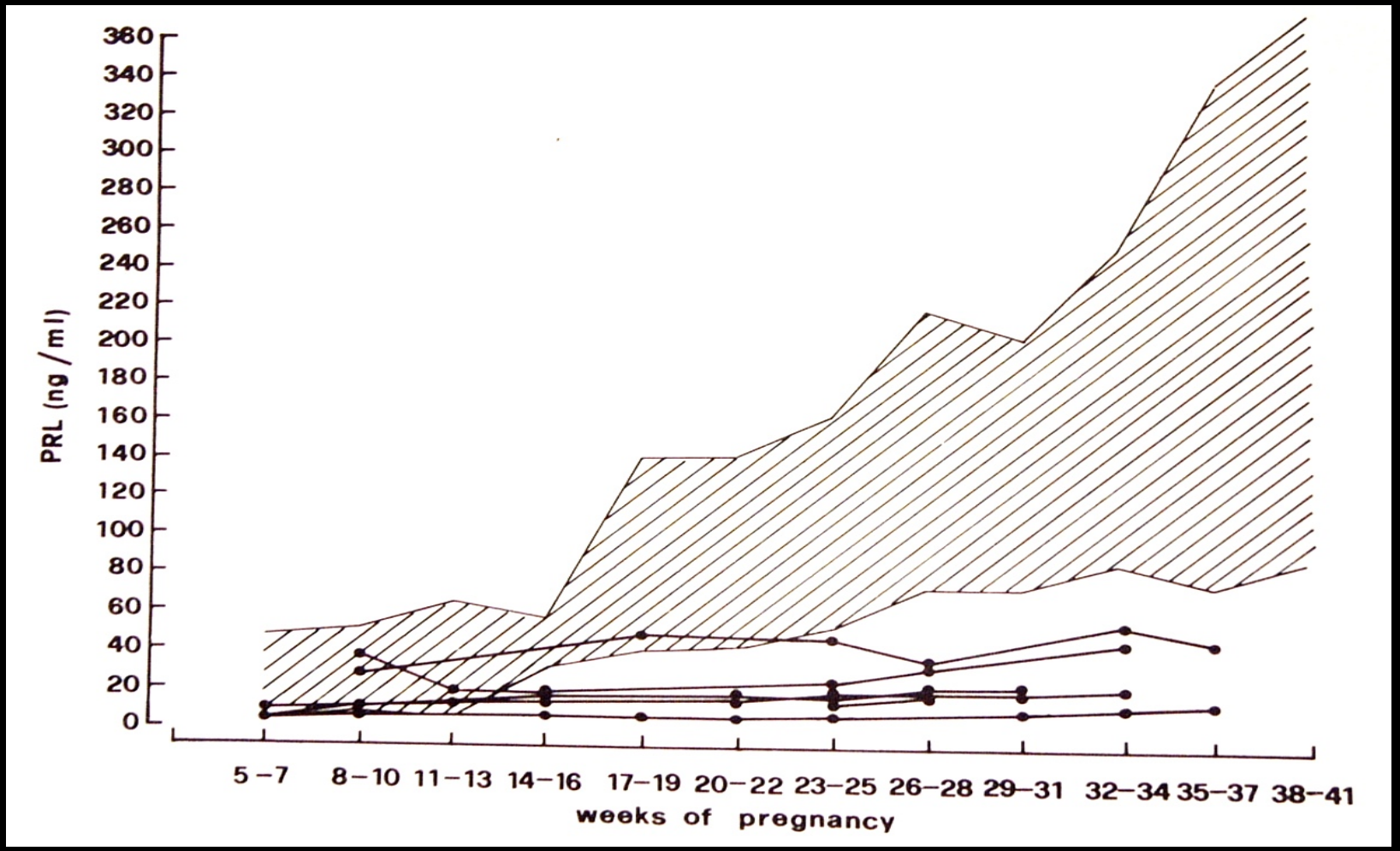
GRAVIDANZA IN MICROPROLATTINOMA

- 1. Pianificabile con terapia medica (bromocriptina o
- cabergolina) di dimostrata efficacia o chirurgica (in caso
- di intolleranza/ resistenza a terapia medica).
- 2. Dopo accertamento di gravidanza sospendere terapia.
- 3. Controlli in gravidanza: clinica. In caso di sintomi: CV, PRL e RMN (senza mdc)
- 4. In caso di espansione tumorale (assai rara) utilizzare
- bromocriptina.
- 5. Allattamento proponibile in assenza di complicanze
- 6. Dopo il parto o allattamento: PRL e RMN. Possibile
- normalizzazione della PRL

GRAVIDANZA IN MACROPROLATTINOMA

- 1. Pianificabile con terapia medica (bromocriptina o cabergolina) di dimostrata efficacia o chirurgica (in caso di intolleranza/ resistenza a terapia medica).
- 2. Dopo accertamento di gravidanza sospendere terapia.
- 3. Controlli in gravidanza: clinica, CV ogni 2 mesi, PRL in caso di sintomi, RMN (senza mdc) in caso di sintomi
- 4. In caso di espansione tumorale utilizzare bromocriptina.
- 5. Allattamento da discutere da caso a caso
- 6. Dopo il parto o allattamento: PRL e RMN. Possibile normalizzazione della PRL

LIVELLI DI PRLemia IN GRAVIDANZA
(Camanni et al., 1983)



European Journal of Endocrinology (2006) 155 717–723 ISSN 0804-4643

CLINICAL STUDY

Dopamine agonist therapy of clinically non-functioning pituitary macroadenomas. Is there a role for ^{123}I-epidepride dopamine D2 receptor imaging?

Wouter W de Herder[1], Ambroos E M Reijs[2], Richard A Feelders[1], Maarten O van Aken[1], Eric P Krenning[2], Hervé L J Tanghe[3], Aart-Jan van der Lely[1] and Dik J Kwekkeboom[2]

Departments of [1]Internal Medicine, Section of Endocrinology, [2]Nuclear Medicine and [3]Radiology, Erasmus MC, S Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

(Correspondence should be addressed to W W de Herder; Email: w.w.deherder@erasmusmc.nl)

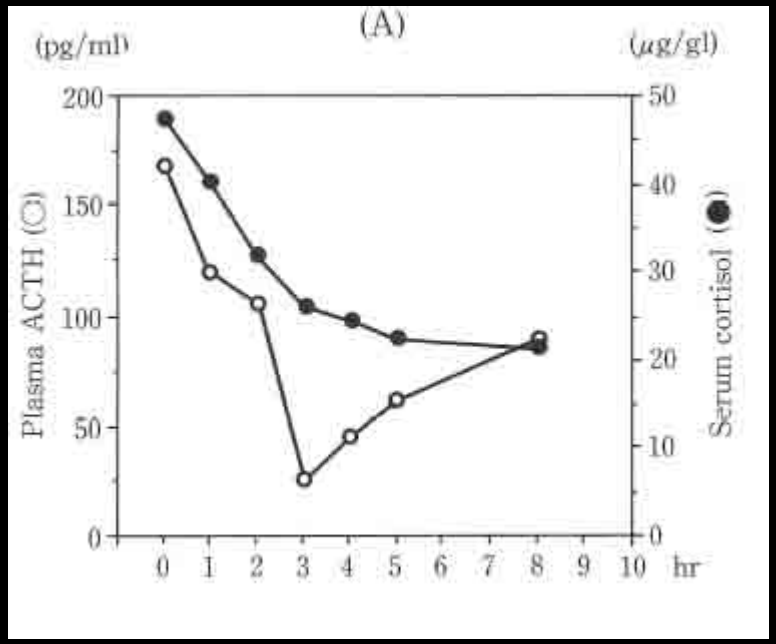
Table 2 Dopamine agonist therapy in 18 patients with clinically nonfunctioning pituitary macroadenomas who have also undergone ^{123}I-epidepride scintigraphy.

Patient no.	Sex	Age at baseline	^{123}I-epidepride scan	Hypo-pituitarism	Drug	Dose	Duration of therapy (months)	Tumor volume (mm^3)	% shrinkage
1	M	68	0	Yes	Quinagolide	300 μg/day	163	23 085	6
2	M	62	0	Yes	Quinagolide	300 μg/day	158	46 637	99
3	M	71	0	Yes	Quinagolide	150 μg/day	84	17 149	18
4	F	52	0	No	Quinagolide	150 μg/day	68	5081	0
5	M	79	1	No	Cabergoline	1 mg/week	57	24 417	5
6	F	65	1	Yes	Quinagolide	300 μg/day	110	27 231	58
7	F	66	1	Yes	Quinagolide	300 μg/day	84	904 320	27
8	M	75	2	Yes	Quinagolide	300 μg/day	34	76 451	27
9	F	86	2	Yes	Quinagolide	300 μg/day	48	73 585	25
10	M	54	2	Yes	Cabergoline	1 mg/week	34	91 906	32
11	M	32	2	No	Quinagolide	300 μg/day	96	407 513	74
12	M	75	2	Yes	Quinagolide	150 μg/day	39	19 383	27
13	M	59	2	Yes	Cabergoline	1 mg/week	84	31 846	5
14	F	77	2		Quinagolide	150 μg/day	68	137 189	35
15	M	50	2	Yes	Quinagolide	300 μg/day	101	31 846	97
16	M	67	2	No	Quinagolide	300 μg/day	115	588 679	42
17	M	78	2	Yes	Quinagolide	300 μg/day	187	95 227	0
18	F	76	3	Yes	Cabergoline	2 mg/week	72	164 553	0

AGONISTI DOPAMINERGICI

Cyclic Cushing's Disease in Long-Term Remission with a Daily Low Dose of Bromocriptine

Masahiro ADACHI, Ryoichi TAKAYANAGI, Toshihiko YANASE, Yoshiyuki SAKAI, Shoichiro IKUYAMA, Hiroyuki NAKAGAKI*, Yoshiyuki OSAMURA**, Naoko SANNO** and Hajime NAWATA



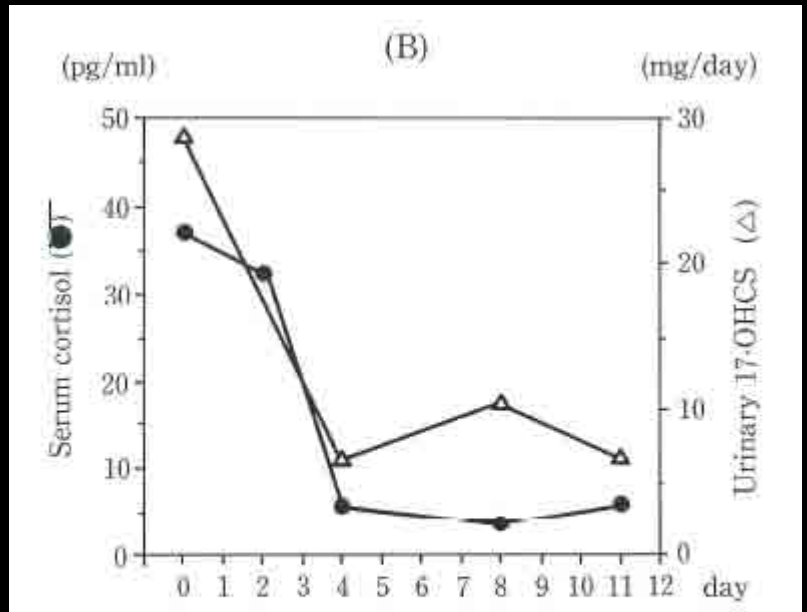


Figure 1. A) The short-term effect of bromocriptine (2.5 mg) on plasma ACTH (○–○) and serum cortisol (●–●). B) The effect of the daily treatment of bromocriptine (2.5 mg) on serum cortisol (●–●) and urinary 17-OHCS (△–△).

TERAPIA MEDICA PER SD. DI CUSHING

Medication Name	Dose (Range)	Mechanism of Action	Effectiveness #	Side Effects	Additional Comments
Ketoconazole	200-1,800 mg orally daily (in divided doses, bid – tid)	Inhibits several steroidogenic steps in adrenal cortex and gonads	70% (CD); 50% (ectopic ACTH)	Gastrointestinal symptoms, reversible transaminitis, severe hepatotoxicity, gynecomastia, low libido, erectile dysfunction, rash, sedation	It might be preferred over metyrapone in women
Metyrapone	750-6,000 mg orally daily (in divided doses, tid – qid)	Inhibits 11-beta hydroxylase in adrenal cortex	Up to 75% (CD)	Gastrointestinal symptoms, rash, dizziness, hirsutism (women), edema, hypertension	It might be preferred over ketoconazole in men; most commonly used medication in pregnancy (non FDA-approved use)
Mitotane	1-12 g orally daily	Inhibits several steroidogenic steps in adrenal cortex; adrenolytic	83% (CD)	Nausea, diarrhea, dizziness, other neurologic symptoms (ataxia, vertigo, decreased memory, confusion), dyslipidemia	To be avoided in women desiring pregnancy in the next 5 years
Etomidate	<0.1 mg/kg/hr iv	Inhibits 11-beta hydroxylase and 17,20-lyase in adrenal cortex	100% (short-term)	Excessive sedation, anesthesia	Especially useful when rapid control of hypercortisolism is desirable; evaluation and monitoring by anesthesiologist needed
Cabergoline	1-7 mg/week orally (taken biw – daily)	D2 receptor agonist	50-75% (short-term); 30-40% (2-3 years) in CD	Nausea/vomiting, dizziness, psychiatric manifestations, possible risk of valvulopathy	Possibly more effective in combination with ketoconazole and/or pasireotide; effective in some patients with Nelson's syndrome
Octreotide	Immediate release octreotide 200-1000 mcg sc tid; sustained release octreotide 10-30 mg im every 4 weeks	Somatostatin receptor agonist (mainly isoform 2)	Effective in some patients with ectopic ACTH-secreting tumors as well as some patients with Nelson's syndrome	Gastrointestinal side-effects, gallstones or biliary sludge, hyperglycemia, hypoglycemia, sinus bradycardia, hair loss	N/A
Pasireotide	600-900 mcg sc bid	Somatostatin receptor agonist (isoforms 1, 2, 3, and 5)	76-88% (CD)	Gastrointestinal toxicity, gallstones or biliary sludge, hyperglycemia, sinus bradycardia	Investigational

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- GRAZIE PER L'ATTENZIONE

STUDIO AME CAB-CUORE
CENTRI PARTECIPANTI

Roma,
9-11 novembre 2012

- Torino (Mazza)
- Torino (Limone)
- Torino (Ciccarelli)
- Cuneo (Borretta)
- Genova (Dal Monte)
- Genova (Cesarone)
- Milano (Ambrosi)
- Milano (Arosio)
- Milano (Beck Pecoz)
- Milano (Cozzi)
- Verona (Francia)
- Ferrara (Scannelli)
- Trieste (Bernardi)
- Udine (Grimaldi)
- Pisa (Manzani)
- Urbino (Vasta)
- Perugia (Angeletti)
- Bologna (Meringolo)
- Ceprano (Annese)
- Roma (DeFeudis)
- Roma (Pastone Mentuccia)
- Roma (Romanelli)
- L'Aquila (Jaffrain Rea)
- Frosinone (Vallalba)
- Caserta (DelBuono)
- Catania (DeGeronimo)
- Trapani (Ungaro)
- Bari (Giagulli)
- Bari (Guastamacchia)
- Bari (Rosco)
- Cagliari (Congiu)
- Grecia (Boikos)

STUDIO CAB-CUORE

Arruolati 373 pazienti (263 F, 110 M)

PRL media 316, 35 (21-25.000 ng/ml)

ETA' media 34 yrs (14-82)

Dose media 1,625 mg/w (0,125-7)

Durata media 72,5 m. (12-318)

Dose cumulativa 272,5 mg(6-3360)

Ecocardio Normale: 235 (63%)