Cabergoline test as a predictor for long term therapy management of hyperprolactinemia

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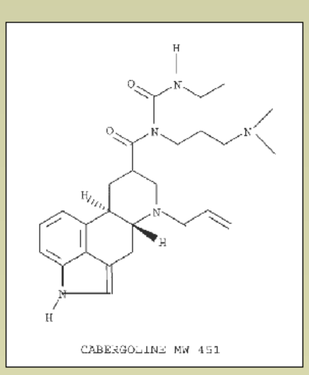
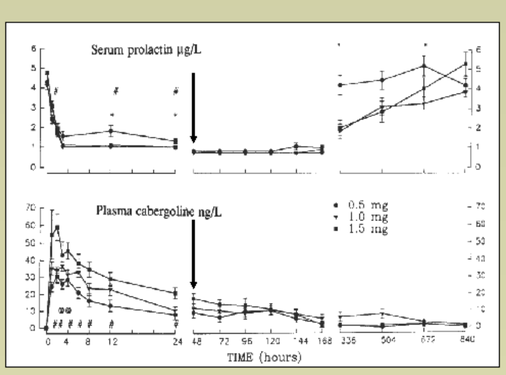
Prolactinoma (PRM) treatment is based upon dopamine agonists, cabergoline (CAB) being one of the most used in the last decade. Sensitivity to CAB varies in terms of tumour volume and PRL secretion, up to 8–15% of PRM being defined as resistant. Since it is known that increasing the dosage improves the response rate, we aimed to measure plasma CAB levels in PRM patients under this treatment in a prospective interventional study.

Cabergoline is a synthetic ergoline dopamine agonist with a high affinity for D2 receptors indicated for use in HPRL disorders. Following oral administration, peak plasma concentrations of cabergoline are reached within 2–3 hours. Over the 0.5–7 mg dose range, cabergoline shows linear pharmacokinetics in healthy adult volunteers with a half time between 60 and 110 h [1].



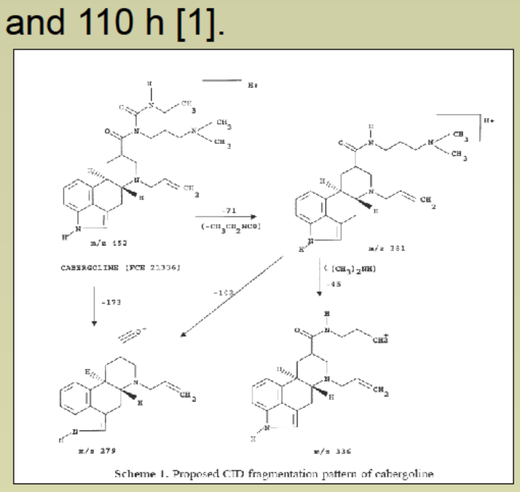


Up to 8% of PRMs are resistant to DA treatment

True resistance or incomplete absorption?

How to measure Cab

- Lack of commercial kits and antibodies
- Extraction & Chromatografic methods
- Spectroscopy methods
- LC - MS: sensitive to ionization, accurate standards



Scheme 1. Proposed CID fragmentation pattern of cabergoline

Protocol

A dose of 0.5 mg CAB was administered orally to a number of 53 naive patients, in a prospective interventional study. Based on hyperprolactinemia 2 groups were selected: the first group of 38 patients with prolactinoma and a second group of 15 patients with other causes of hyperprolactinemia, who served as control. In the prolactinoma group all cases were prospectively evaluated, starting a maintenance phase with 2-3 mg cabergoline twice a week for at least 6 months.

This second phase allowed us to divide the prolactinoma group into sensitive and resistant cases: 31 proved to be sensitive and 7 resistant to CAB, when comparing the results of serum prolactin dosage and tumor shrinkage on CT/MRI scan. The main test consists of a first phase when a single dose of CAB is administered and the serum prolactin is measured at basal, 12h and 48h comparing these results. For a more complete understanding and analysis of linkage mechanism the plasma CAB levels were also measured using a mass-spectrometry based method. The instrumental analysis was performed on a HPLC tandem mass-spectrometer in the multiple-reaction monitoring method (MRM).

Materials & Methods

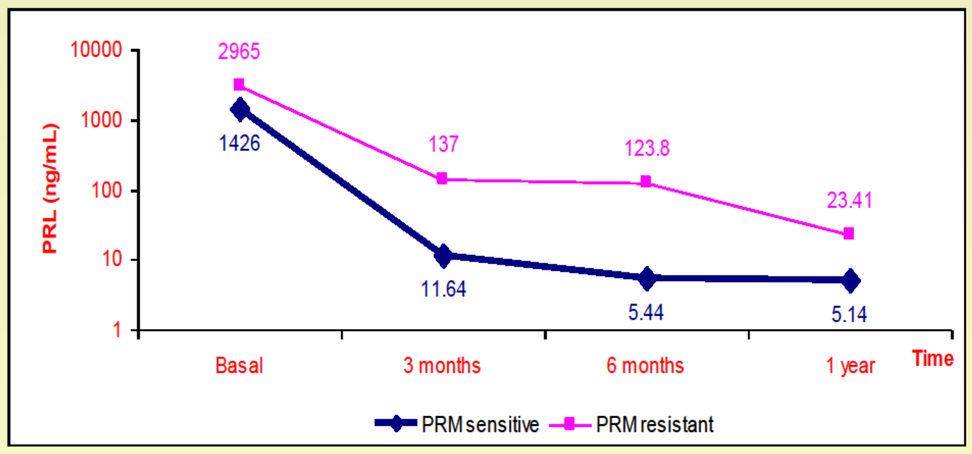
Cabergoline detection - tandem HPLC-MS/MS method:

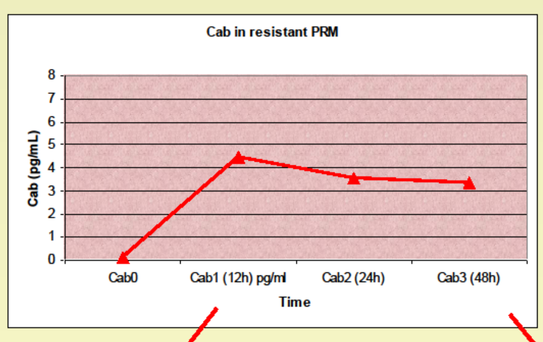
Mass spectrometer: Applied Biosystems-Sciex model API 4000, triple-quadropole, equipped with an atmospheric pressure electrospray ionization interface (Applied Biosystems model turboionspray), operating in positive-ion mode; the system include an Agilent 1200 pump and an autosampler CTC Pal.

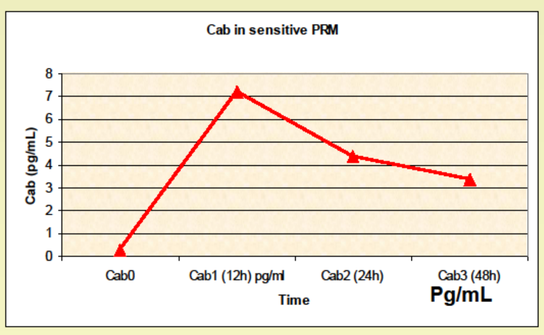
HPLC system

Reverse phase column Discovery HSF 5 (50x2.1 mm, with 5 µm particles);
Isocratic conditions;
Internal standard – Nicergoline (1 pg/ml in methanol)
Cabergoline Calibration points: 0; 1; 10; 100; 1000 pg/ml
A quantitative calibration with every batch of samples was performed.
Sensitivity – 1 pg/mL, linear signal.

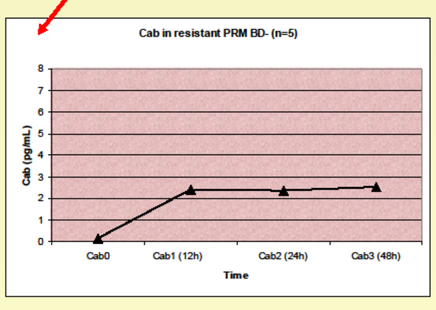
Results

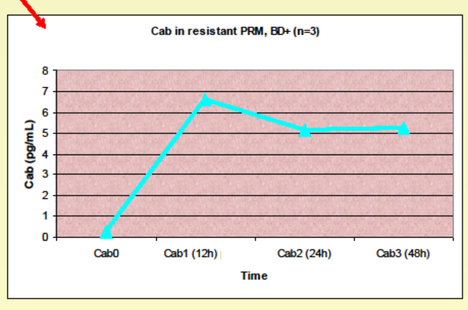






Cab 0,1 4,4 3,5 3,3 **Pg/mL** **Cab** 0,3 7,2 4,3 3,3





CAB determined prolactin decrease in both sensitive and resistant cases but with a significant difference. In sensitive prolactinoma the decrease showed to be from 2781ng/ml to 1099ng/ml at 12h (which means almost with 60%, p=0.001), 1075.1 ng/ml at 24h and 843.63 at 48h. The highest decrease was registered at 12h after CAB administration.

In resistant prolactinomas, the decrease went from 3675.7ng/ml basal value to 2043ng/ml at 12h, 1679.71 at 24h and 1586.6 ng/ml at 48h (which means lower than 45% in the first 12h). In the control group the decrease was also much smaller. In the follow up time: one patient with small response at CAB test proved to be long-time therapy responsive and another one with prolactin decrease on CAB test, proved to develop partial response in long time treatment. Meanwhile, CAB pharmacokinetics showed the highest value at 12h, which was 9.50pg/ml, with 6.44pg/ml at 24h and 4.73pg/ml at 48h.

Discussion

- In sensitive PRM, PRL values decrease on average at 48h to a level 30% from baseline. In resistant PRM, the decrease is similar but at higher values.
- Therapeutic CAB levels are above 6 pg/mL. Lower values at 12 h might suggest lack of appropriate absorption.
- Timing of administration (twice/thrice) per week
- Reliability / predictive value of suppression test
- Sensitive / resistant status of PRM
- Resistance or lack of absorption?
- Cabergoline metabolites and their action on PRL

Conclusions: CAB test can provide information about the sensitivity to treatment for a better future management and good results, which is allowing patients to receive personalized therapy in adapted method and time duration. Anyway, further studies with larger study population should be done in order to completely understand all possible determinants of a better or a more accurate therapy response.

1. Andreotti et al. Pharmacokinetics, pharmacodynamics, and tolerability of cabergoline, a prolactin-lowering drug, after administration of increasing oral doses (0.5, 1.0, and 1.5 milligrams) in healthy male volunteers. J Clin Endocrinol Metab 1995;80:841-845.

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