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 intervention 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].

A dose of 0.5 mg CAB was administered orally to a number of 53 naïve 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 (MRM).

Cabergoline detection - tandem HPLC-MS/MS method:
Mass spectrometer: Applied Biosystems-Sciex model API 4000, triple-quadrupole, 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 HS F 5 (50x2.1 mm, with 5 μm particles);
Isocratic conditions;
Internal standard – Nisergoline (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

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.