Eur J Clin Pharmacol (1987) 32: 525–527

**European Journal of Clinical Pharmacology**


*Short Communications*

# Effect of Flunarizine on Pituitary Secretion by Healthy Men and in Woman with Migraine

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**Summary.** Flunarizine is widely used in the prophylaxis of migraine. It is both a calcium blocker and a histamine antagonist at $H_1$-receptors and either of these effects could alter hormonal secretion. The effect of administration of flunarizine to 8 women with common migraine on pituitary secretion has been studied. The dopamine antagonist domperidone (10 mg) and gonadotropin releasing hormone (100 μg) were injected iv before and after one month of flunarizine therapy (10 mg orally at bedtime).

The basal prolactin level was significantly increased by the drug, and the peak induced by domperidone stimulation was reduced. Basal TSH concentrations were not affected, but the increase after domperidone was blunted.

After 90 days of therapy there were no significant differences from the baseline concentration. Neither basal nor gonadotropin releasing hormone - stimulated secretion of FSH and LH were affected by flunarizine. Twelve healthy men were given placebo and flunarizine (10 mg at bedtime) for 5 days in single-blind fashion. Flunarizine caused a significant increase in prolactin and TSH with no effect on basal gonadotropin and thyroid hormone levels.

These results can be accounted for by the calcium blocking effect of the drug, although weak interference with dopaminergic transmission is a further possibility explanation.

**Key words:** flunarizine, migraine; pituitary hormones, prolactin, TSH, gonadotropins, calcium blocking effect, dopaminergic blockade

Flunarizine is widely used in the prophylaxis of migraine [1]. Flunarizine has anti -histamine properties at $H_1$ receptors [2], but the therapeutic effects of the drug may be based upon interference with the calcium ion transport in vascular smooth muscle [3]. Both of these actions may have effects on the endocrine system, as has been described for other calcium blockers [4–6] and $H_1$ antagonists [7]. The calcium blocker verapamil decreased basal and gonadotropin releasing hormone (GnRH)-stimulated LH and FSH release and the TSH response to thyrotropin releasing hormone was also reduced [4]. In other studies verapamil has been shown to increase prolactin (PRL) levels [5, 6]. The $H_1$ anti-histamine chlorpheniramine decreased PRL secretion [7].

## Materials and methods

Eight women with common migraine (aged 22–41 years), with regular menses and no evidence of endocrine disease, volunteered for the study. All were studied on the 4th day of one menstrual cycle, on the 4th day of the following cycle, and 90 days after the start of therapy. During this period they took flunarizine 10 mg/day at bedtime. No other medication was allowed during the study.

At 8.30 a.m. an i.v. line was inserted into an antecubital vein and blood samples were collected 15 min before and immediately prior to i.v. injection of the dopamine receptor antagonist domperidone 10 mg and GnRH 100 μg at 9.00. Further Blood samples were collected after 20, 40 and 60 min. On the 90th day of therapy two basal samples were obtained at 8.45 and 9.00 a.m.

Twelve healthy men (aged 18–36 years), not affected by migraine, were also studied after giving their written informed consent. Two basal blood samples were taken at 8.45 and 9.00 a.m. On 3 different days first during basal conditions on no therapy, second after 5 days of placebo administration, and third after 5 days on flunarizine 10 mg p.o. at

**Table 1.** Effects of flunarizine (10 mg/day p.o. at bedtime for one menstrual cycle) on basal and domperidone - stimulated (10 mg i.v.) prolactin and TSH concentration in 8 women with common migraine. Median and (95% confidence limits)

| Prolactin (ng/ml) | Baseline | 20' | 40' | 60' |
|---|---|---|---|---|
| Before flunarizine (4th day of the cycle) | 11 (9-24) | 192[a] (105-221) | 188[a] (100-220) | 160[a] (14-200) |
| During flunarizine (4th day, successive cycle) | 19 (15-55) | 146 (95-228) | 140 (99-210) | 126 (70-208) |
| (90th day of treatment) | 10[c] (4-13) | | | |
| TSH (μIU/ml) Before flunarizine (4th day of the cycle) | 0.9 (0.7-1.3) | 1.8[a] (1.3-3.6) | 1.9[a] (1.7-2.3) | 1.7[b] (1.0-2.9) |
| During flunarizine (4th day, successive cycle) | 1.0 (0.5-2.1) | 1.4 (0.6-4.3) | 1.3 (0.8-1.9) | 1.0 (0.8-2.1) |
| (90th day of treatment) | 1.0 (0.8-2.0) | | | |

[a] $p<0.01$, [b] $p<0.05$, [c] $p<0.01$ vs pretreatment basal value

**Table 2.** Hormone concentrations during basal conditions and after 5 days of placebo or flunarizine (10 mg orally at bedtime) in 12 healthy men Median and (95% confidence limits)

| | Baseline | Placebo | Flunarizine |
|---|---|---|---|
| Prolactin (ng/ml) | 12 (10-18) | 14 (11-16) | 30[a] (21-35) |
| TSH (μIU/ml) | 2.4 (1.6-3.1) | 2.4 (1.8-3.0) | 6.6 (6.0-10.4) |
| T3 (ng/ml) | 114 (84-143) | 126 (110-131) | 119 (115-140) |
| T4 (ng/ml) | 81 (74-114) | 82 (73-106) | 86 (76-104) |
| FSH (mIU/ml) | 5 (3-10) | 6 (5-10) | 6 (4-9) |
| LH (mIU/ml) | 6 (4-10) | 6 (4-10) | 6 (3-9) |

[a] $p<0.01$ vs. Baseline and placebo

bedtime. Placebo was administered in single-blind (subject) fashion before flunarizine to control for any effect of the persistence of flunarizine in blood and tissues. LH, FSH, TSH, and PRL concentrations were assayed using commercial kits (Menarini Diagnostici, Florence, Italy). All the assays for the each hormone were performed in the same run. TSH and PRL were measured by IRMA (intra-assay CV 3.4% and 5.1%, respectively); LH and FSH were measured by RIA (intra-assay CV 6.1% and 4.9%, respectively); Thyroxine (T4) and 3,5,3'-triiodothyronine (T3) were measured by RIA (Medical Systems; intraassay CV 5.6 and 6.0%) in samples obtained from the healthy men.

Statistical analyse were performed with the matched pairs Wilcoxon test and by the Friedman two-way analysis of variance by ranks.

## Results

### *Migraine Patients*

The administration of flunarizine caused a significant increase in basal PRL concentrations ($p<0.01$), and the basal values of the other hormones were not affected (see Table 1). The response of TSH to domperidone was blunted, while the increase in PRL after dopamine receptor blockade was significantly reduced ($p<0.01$) by flunarizine. Treatment did not affect the basal or GnRH - stimulated concentrations LH and FSH (results not shown).

After 90 days of administration of flunarizine basal hormone concentrations were not significantly different from pretreatment values (see Table 1). The increase in basal PRL found after one month of therapy was no longer found.

### *Healthy Subjects*

PRL and TSH were significantly increased after flunarizine administration ($p<0.01$); Placebo did not induce any variation. The results are summarized in Table 2.

## Discussion

The results show that flunarizine caused a transient increase in circulating prolactin. Its calcium blocking action might explain the increase in basal PRL and TSH (in the short-term study in healthy subjects), since calcium ions are involved in the inhibitory action of dopamine on PRL and TSH producing cells (9, 10). As previously suggested for verapamil [5] the calcium blocking action of flunarizine might reduce the tonic dopamine receptor inhibition of PRL and TSH secretion.

Alternatively a direct weak dopamine receptor antagonist effect could account for the observed re-

sult and the reduced response to domperidone could also have been due to a direct dopamine receptor antagonist effect [8].

The return to normal of PRL concentrations during prolonged therapy is an important clinical observation, since menstrual irregularities and breast pain reported during the first week of treatment spontaneously subside exactly when the prophylactic effect on migraine becomes apparent [1].

The absence of an effect of flunarizine on FSH and LH secretion may have been one to relative independence of calcium of the GnRH-induced secretion, although this hypothesis is in contrast to the results of DeMarinis [4] using verapamil. The absence of a direct dopaminergic influence on LH and FSH producing cells could explain the lack of effect of flunarizine on LH and FSH, if a direct dopamine receptor antagonist action of the drug is accepted, an hypothesis which is consistent with the clinical observations of extrapyramidal effects in older patients treated with flunarizine.

The hyperprolactinaemia cannot be attributed to the antihistamine properties of flunarizine, since the administration of an $H_1$ histamine receptor antagonist should cause either a reduction in basal PRL concentrations or no effect at all [7].

In summary, the present investigation has shown that treatment with flunarizine in therapeutic doses can induce a mild and transient increase in PRL concentrations above the normal range. The calcium blocking activity of the drug and/or and its effect as a dopamine receptor antagonist could explain this action.

**Acknowledgements.** The authors are indebted to Mrs C. Benetti for her excellent technical and linguistic assistance and to Janssen Pharmaceuticals, Rome, for financial support.

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Received: July 18, 1986
accepted in revised form: March 5, 1987

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