Chapter 56

Calcium Antagonists in Migraine Prophylaxis

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Calcium antagonists have been introduced in migraine prophylaxis because of two effects considered to be of potential benefit (3):

1. Their vasodilatory effect on cerebral vessels (e.g., nimodipine and verapamil), which inhibits vasospasm of the cerebral arteries (22,64)
2. Their protective action (e.g., flunarizine) against cerebral hypoxia, which is thought to be present during migraine attacks (2).

Cerebral blood flow and transcranial Doppler studies have made it unlikely, however, that either of these phenomena occur during a migraine attack (see Chapter 35). Thus, as with many other drugs used in migraine therapy, the original rationale is equivocal. Herein two calcium antagonists, verapamil with possible efficacy and flunarizine with proven efficacy in migraine prophylaxis, are reviewed and their therapeutic use described briefly. The results of 11 trials of the use of nimodipine, which is not registered for migraine prophylaxis, and the results of using other calcium antagonists are reviewed briefly.

PHARMACOLOGIC BACKGROUND

A common feature of Ca^{2+} antagonists is to block the transmembrane influx of Ca^{2+} across cell membranes through slow, voltage-dependent channels, of which several types exist in cardiac muscle and vascular smooth muscle (21,33,76). Therefore, the antagonists are also called *slow channel inhibitors*, or Ca^{2+-} *entry blockers,* which are more accurate terms because they characterize the nature of the drug. For historical reasons, however, *calcium antagonist* is still the preferred term (76). Most of the antagonists in concentrations sufficient to inhibit the vascular and cardiac functions do not impair the Ca^{2+} influx in peripheral neural and vascular endothelial cells (21,73), but flunarizine cildipine and α-eudesmol, a P/Q-type Ca^{2+} channel antagonist, act prejunctionally on adrenergic nerves (6,28) or the release of substance P and calcitonin gene-related peptide (CGRP) from sensory nerves (5). The calcium antagonists are a heterogenous group of drugs (Fig. 56-1) with several subtypes blocking different types of Ca^{2+} channels (76).

The calcium antagonists have relatively selective effects on cerebral arteries compared with that on peripheral arteries (8,54,59,75). One reason may be that they are highly dependent on extracellular calcium for their activation; however, results from in vitro studies of this selectivity vary considerably among species. Thus, for nimodipine, the difference in potency for inhibiting the contraction of cerebral and peripheral arteries in animal studies was of the order of several thousand-fold (54,75), whereas in humans this difference was recently reported to be only about 10-fold (30). A novel Ca^{2+} antagonist dotarizine that also has antiserotonergic property diminished the vasoconstrictory of hyperventilation on cerebral vessels, suggesting it to be useful as a prophylactic medication in migraine therapy (34,35).

The other pharmacologic property of calcium antagonists considered possibly beneficial in migraine is the cytoprotective effect, that is, protection against excessive Ca^{2+} influx/release during cerebral ischemia. This cytoprotective effect has been demonstrated convincingly in animal studies for both flunarizine and nimodipine (36). It has also been suggested that calcium antagonists may be effective in migraine prophylaxis by inhibiting cortical spreading depression (CSD) (see Chapter 22). In one study in rats using a high dose of flunarizine (40 mg/kg intraperitoneally), flunarizine increased the threshold for CSD (77). A later study with the same dose but a modified technique failed to reproduce this result (44). In another study, an oral dose of 20 mg/kg flunarizine had no effect on CSD (24).

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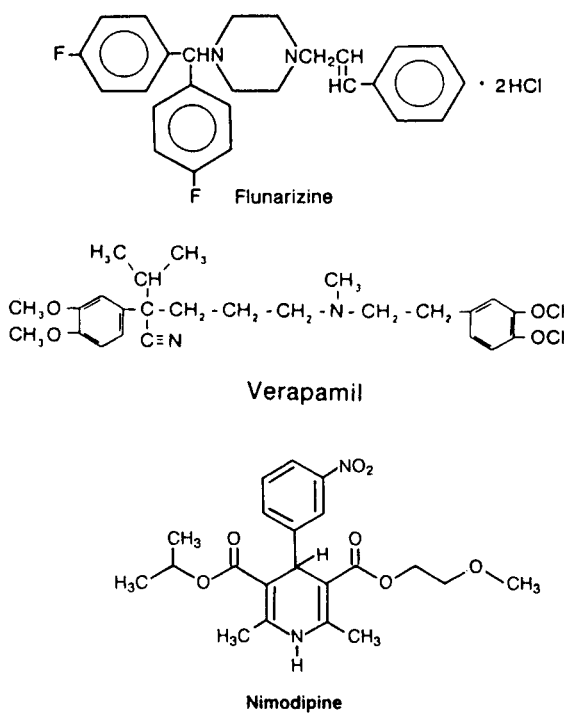

FIGURE 56-1. Chemical structures of flunarizine (*Flun*), a difluorinated piperazine derivative, verapamil (*Ver*), a synthetic papaverine derivative, and nimodipine (*Nim*), a 1,4-dihyropyridine derivative, with proven (*Flun*) or possible (*Ver*, *Nim*) efficacy in migraine prophylaxis.

The brain contains a high density of binding sites for calcium antagonists (22), and the drugs have central nervous system (CNS) effects that could be relevant for their effect in migraine. In humans, experimental evidence has been found that nimodipine can affect neurotransmission (29), and flunarizine has proven efficacy as an add-on drug for epilepsy (53,74). In addition, the side effects of flunarizine, such as sedation, weight gain, Parkinsonism, and depression, strongly suggest interaction with CNS neurotransmitters. In addition, flunarizine has antihistaminic effects (74).

POSSIBLE MODE OF ACTION IN MIGRAINE

Cerebral arterial vasospasm is unlikely to occur in migraine, and flunarizine, the best proven calcium antagonist for migraine, exerts minimal calcium antagonistic effect on cerebral vessels in therapeutic doses (30). This drug does, however, appear to impair the synthesis and release of nitric oxide, a substance possibly responsible for migraine pain (see Chapter 40), from perivascular nerves (6) and possibly endothelium in cerebral vasculatures. Interferences with the release of sensory transmitters, substance P and CGRP, by α-eudesmol may also be involved in migraine prophylaxis (5). On the other hand, nimodipine in doses used in migraine prophylaxis can exert an effect on cerebral vessels (30), but it has only minor or no prophylactic effect (*vide infra*). The cytoprotective effect of calcium antagonists is probably irrelevant, because the most convincing effect of calcium antagonists is in migraine without aura (69), in which cerebral blood flow is normal during attacks (see Chapter 35). The mechanism of action of calcium antagonists in migraine prophylaxis is most likely through their interaction with CNS neurotransmission.

PHARMACOKINETICS

The half-life of verapamil is 3 to 7 hours (27), and the drug is given in three daily doses. Sustained-release preparations of verapamil can be given once or twice daily. Flunarizine has a terminal elimination half-life of 18 days (74) and is given once daily.

RESULTS OF CONTROLLED CLINICAL TRIALS WITH VERAPAMIL

Verapamil has been evaluated for migraine prophylaxis in three small, double-blind, crossover trials (43,63,64). In total, only 41 patients were evaluable in these trials; therefore, the results cannot be applied directly to the general migraine population.

In two trials, verapamil (240 and 320 mg daily) was better than placebo (43,64), and in one study verapamil (320 mg) had an effect that was similar to that of long-acting propranolol (120 mg daily) but also similar to that of placebo (63). In two double-blind trials, probably performed simultaneously, 320 mg/d of verapamil had better results than 240 mg daily compared with placebo control (62), but the lack of randomization precludes drawing any conclusions.

In conclusion, the scientific proof for a prophylactic effect of verapamil in migraine is almost nonexistent, and its use in migraine prophylaxis in some countries is based on open clinical studies that indicated some efficacy of the drug (61).

Therapeutic Use

Verapamil can be tried in migraine prophylaxis when other well-established drugs have not been effective (see Chapters 56, 57, 59, 60, and 61). The optimal daily dose is probably 240 to 320 mg given in divided doses of 80 mg or when available as sustained-release preparations.

- **Side effects:** constipation, hypotension, atrioventricular block, edema, headache, and nausea

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TABLE 56-1 Double-Blind, Placebo-Controlled Trials of Flunarizine in the Prophylaxis of Migraine

Trial	*Drug, Dosage (mg)*	*Study Design*	*No. of Patients (No. Evaluated, Type of Migraine)*	*Run-in (wk)*	*Duration of Treatment (mo)*	*Factors Evaluated*	*Investigators' Conclusion*
Louis (39)	Flun 10	Pa	58 MA, MO		3	Frequency, duration, severity	Flun > placebo (frequency)
Frenken and Nuijten (17)	Flun 10	Pa	35 MA, MO		3	Overall efficacy	Flun > Pl
Mendenopoulos et al. (46)	Flun 10	Pa	30 (20) MA	4	3	Frequency, duration, severity	Flun > Pl
Sorge and Marano (66)[a]	Flun 5	Pa	48 (42) MA, MO		3	Frequency, duration	Flun > Pl
Sørensen et al. (69)	Flun 10	CO	29 (27) MO	4	4 × 2	Frequency, duration, intensity	Flun > Pl (frequency)
Sorge et al. (65)[a]	Flun 5	CO	70 (63)	4 (4 wk washout)	3 × 2	Frequency, duration	Flun > Pl
Thomas et al. (72)	Flun 10	CO	29 (15) MO		3 × 2	Headache index	A trend in favor of Flun

[a] Children.
Abbreviations: Flun, flunarizine; Pl, placebo; Pa, parallel group design; CO, crossover design; MA, migraine with aura; MO, migraine without aura.
(Modified from Andersson K-E, Vinge E. β-adrenoceptor and calcium antagonists in the prophylaxis and treatment of migraine. *Drugs.* 1990;39:355–373.)

- **Contraindications:** bradycardia, second- and third-degree heart block, sick sinus syndrome, and β-blockers

RESULTS OF CONTROLLED CLINICAL TRIALS WITH FLUNARIZINE

For previous reviews of controlled trials with flunarizine, see the reports by Andersson and Vinge (3), Tfelt-Hansen et al. (71), and Todd and Benfield (74). A summary of seven placebo-controlled, double-blind, randomized trials that used flunarizine for migraine prophylaxis in both adults and children is presented in Table 56-1. In two trials, patients with migraine aura (46) or without aura (69) were studied. Both the parallel group (17,39,46,66) and the crossover (65,69,72) designs were used. A total of 299 patients were recruited for these trials, and 87% of the patients completing the trials were evaluable. The dropout rate of 13% is similar to the dropout rates found in other trials investigating migraine prophylaxis (see Chapters 56 and 57).

Flunarizine (10 mg daily in adults and 5 mg in children) produced better results than placebo in six studies (17,39,46,65,66,69) using both kinds of study designs, whereas there was only a trend in favor of the drug in one small trial (72). In one trial studying only migraine without aura, the efficacy of flunarizine in this form of migraine was confirmed (69) (Fig. 56-2), and one study indicated an effect in migraine with aura (46).

Based on the pooled raw data for frequency of attacks reported in six trials (17,39,46,65,66,69), one can, although with due acknowledgment to the pitfalls of doing so, calculate the mean frequency of attacks to be 1.9 during flunarizine treatment and 3.2 during placebo treatment. The calculated mean reduction of frequency during flunarizine treatment compared with placebo is thus 42%, a figure comparable to the effect of propranolol (see Chapter 56).

The comparability of flunarizine (10 mg daily) with propranolol (120 mg daily) was also indicated by three comparative multicenter trials (41,42) that had a parallel group

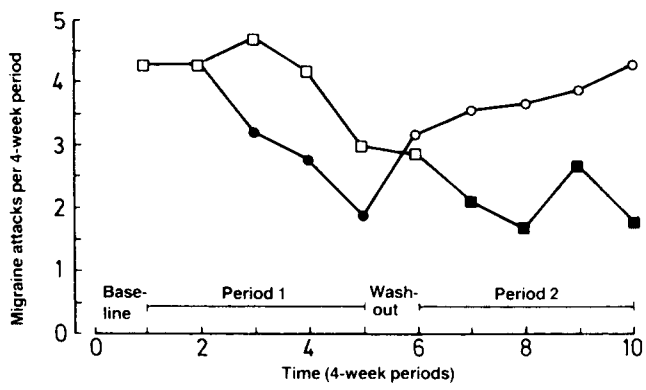

FIGURE 56-2. The effect of flunarizine on the frequency of attacks in a placebo-controlled crossover study in 27 patients with migraine without aura. (Reprinted with permission from Sørenson PS, Hansen H, Olesen J. A placebo-controlled, double-blind, crossover trial of flunarizine in common migraine. *Cephalalgia.* 1986;6:7–14.)

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design and included a total of 464 evaluable migraine patients in whom similar decreases in the frequency of attacks were observed. In one trial, flunarizine 10 mg was found to be comparable to 160 mg propranolol (18). In one very large trial ($n = 808$) 5 and 10 mg daily with a weekend drug holiday was comparable to slow-release propranolol 160 mg (15). Definite proof of comparability, however, cannot be deduced from these trials because they were not placebo controlled.

Flunarizine also was found to produce comparable results to metoprolol (200 mg daily) in two trials (23,70), pizotifen (1.5 to 3 mg daily) in four trials (13,40,56,78), cinnarizine (225 mg daily) in one trial (16), methysergide (2 mg daily) in one trial (67), and (-dihydroergocryptine in one trial (11). None of these trials was placebo controlled, however.

Side Effects

Taken together, the placebo-controlled trials indicate that sedation is associated with flunarizine treatment with a mean of 13% for all flunarizine-treated patients compared with 2% for patients on placebo (17,39,46,65,66,69,72). In addition, weight gain was reported in some trials, that is, in 22 (65) to 53% (72) of patients on flunarizine, whereas in another trial body weight was unchanged (46). In comparative trials, flunarizine seemed to induce sedation (mean 19%) and weight gain (mean 21%) with the same frequency as pizotifen (mean 17% and 27%, respectively) (13,40,56) and sedation in the same range as propranolol (mean, 11% and 8%, respectively) (41,42). In one large comparative trial (15), weight gain occurred more often during flunarizine 5 mg (10%) and 10 mg (7%) than during propranolol (3%) treatment. One study reported two cases of depression during or after flunarizine therapy (56). After reports of extrapyramidal symptoms and depression occurring during flunarizine treatment (for literature, see Micheli et al. [48]), attention has been drawn to depression during flunarizine used for migraine prophylaxis. In one comparative trial, depression occurred in 6 of 72 (8%, 95% confidence intervals [CI] 3 to 17%) treated with flunarizine and in 2 of 75 (3%, 95% CI 0 to 9%) treated with metoprolol (200 mg daily) (70). Depression during flunarizine therapy occurred with some latency (after 3 to 5 months of treatment) (70). An open crossover trial comparing 5 and 10 mg of flunarizine daily reported depression to occur more frequently with the higher dose of flunarizine (in 5 of 40 patients) (12). Long-term open trials of flunarizine for migraine prophylaxis (9,37), on the other hand, indicate an incidence below 1% per year.

In conclusion, flunarizine has proven efficacy for migraine prophylaxis in both adults and children, and it seems comparable to other currently used drugs for migraine prophylaxis. Side effects, such as sedation, weight gain, and depression, can limit the use of flunarizine.

Therapeutic Use

Flunarizine can be used for migraine prophylaxis if the drugs of first choice, that is β-blockers, are either ineffective or contraindicated. The standard dose is 10 mg once daily, but 5 mg can be tried if side effects occur. Flunarizine probably should be tried for 2 months before deemed ineffective. The dose in children is 5 mg daily.

- **Side effects:** sedation, weight gain, depression, extrapyramidal symptoms (parkinsonism)
- **Contraindications:** pregnancy, parkinsonism, previous depression or excessive mood changes, first-degree relatives with a history of depression

RESULTS OF CONTROLLED CLINICAL TRIALS WITH NIMODIPINE

The possible prophylactic effect of nimodipine (120 mg daily) was investigated in six placebo-controlled, double-blind, randomized trials, including a total of 491 migraine patients (4,19,25,50,51,68). Nimodipine (120 mg daily) had superior results to placebo in the two first published trials (19,25). One trial (68) indicated some efficacy of nimodipine, but three later trials (4,50,51) found no significant difference between nimodipine and placebo.

In one placebo-controlled trial (7) in children, the efficacy of nimodipine was not demonstrated. Two doses of nimodipine, 60 mg and 120 mg daily, were compared in a crossover trial (47), and the higher dose seemed to reduce headache frequency more than the lower; however, both migraine and chronic cluster headache patients were investigated. In two small comparative crossover trials, nimodipine (120 mg daily) was found to have results comparable to those of pizotifen (1.5 mg daily) (26,49). Nimodipine also showed results comparable to those of flunarizine (20 mg daily) in one small parallel group trial (10). All these trials lack power and a placebo control, and therefore contribute little. In conclusion, some effect in migraine with aura cannot be excluded, but more than a minor effect in migraine without aura is unlikely. As a consequence, nimodipine has not been registered for migraine prophylaxis in any country.

OTHER CALCIUM ANTAGONISTS

Diltiazem (90 mg daily) was given to 15 patients in a pilot study; it decreased the number of attacks and the severity of attacks (57). In another pilot study, patients who did not respond to nadolol had significant benefit from diltiazem therapy (60). No double-blind, controlled trials have been performed using diltiazem.

In a double-blind, crossover trial that included eight patients with migraine associated with idiopathic Raynaud

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phenomenon, nifedipine (30 mg daily) showed better results than placebo (32). In an open study, about 70% of patients who had migraines reported benefit from nifedipine (31). In a randomized, open-label study, nifedipine (60 mg daily) had inferior results compared with propranolol (120 mg daily), and 9 of 20 patients treated with nifedipine withdrew from the study because of side effects (1). In a double-blind trial including 24 patients with migraine with aura, nifedipine (60 to 90 mg daily) achieved no better results than placebo (45). Thus, the limited trials do not support the use of nifedipine for migraine prophylaxis.

The atypical calcium antagonist cyclandelate (55) has been compared with propranolol and placebo. In one trial with parallel group design, cyclandelate (1,200 to 1,600 mg) was found to be comparable to propranolol (120 to 160 mg) in 62 evaluable patients (20), but the trial lacks placebo control, and the observed effects could be a result of the so-called time effect (52). In another trial, also with parallel group design, neither cyclandelate (1,200 mg) nor propranolol (120 mg) was statistically significantly superior to placebo in 214 patients (14). In contrast, cyclandelate (1,200 to 1,600 mg) was found to be superior to placebo in a small double-blind trial that included 15 and 10 patients in the two treatment groups, respectively (58). Thus, the scientific evidence for the use of cyclandelate in migraine prophylaxis remains to be established.

Finally, in a double-blind crossover from migraine without aura, nicardipine (40 mg daily) was superior to placebo (38). Based on only one published trial, however, nicardipine cannot be recommended for migraine prophylaxis.

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