The rationale for uncomplicated therapeutic regimens is that successful treatment requires patient compliance, and compliance increases as the number of daily doses decrease. This has been demonstrated in migraine patients taking prophylactic medications once, twice, or 3 times daily. The compliance rates decreased from 80% to 60% to 54% with increasing dosages. So, if once-daily dosing improves compliance, it should also improve treatment outcomes.

Pharmacokinetics is also an important consideration with once-daily dosing. Conventional drug release (ie, a drug administered every few hours) often gives rise to extremes of plasma drug concentrations to achieve an overall average effective dose over a certain period of time. At high concentrations, there is a risk of toxicity. Controlled-release formulations are able to maintain plasma concentrations within an effective plasma concentration range so that undertreatment and toxicity are not a problem.

Several formulations of the antiepileptic drug valproic acid have shown efficacy in treating people with migraine and other headache disorders. Valproic acid as oral tablets, extended-release oral tablets, and sprinkle capsules is absorbed in the intestines. As a syrup, it is absorbed in the stomach and intestine.

Studies have shown that valproic acid in the extended-release tablet formulation offers reduced fluctuation in plasma concentrations. As a consequence, there are potentially fewer peak-related side effects and potentially better efficacy with subtherapeutic serum concentrations (Unpublished data).

Evidence suggesting that less frequent dosing with valproic acid leads to improved compliance was used as the rationale for conducting a randomized, double-blind, multicenter, placebo-controlled study to assess the safety and efficacy of divalproex sodium in the extended release formulation (DVS-ER). Divalproex sodium is a 1:1 molar ratio of valproic acid and valproate sodium.

For the study, 237 migraine patients 12 years or older were recruited. There was a 14-day washout period, followed by a 28-day baseline period. DVS-ER 500 mg once daily or placebo was administered for 7 days, then titrated up to 1000 mg for an additional 7 days. After 14 days of treatment, the dosage for some patients was reduced back to 500 mg. During the next 70 days, 98 patients took 1000 mg DVS-ER, 16 patients took 500 mg DVS-ER, 100 patients were in the placebo group for the higher dose, and 10 patients were in the placebo group for the lower dose. After a total of 84 days of treatment, all patients were reduced to 500 mg, and at 91 days all medication was stopped.

Patient demographics in the DVS-ER and placebo groups were similar. Most patients were about 40 years of age, with females comprising approximately 80% of each group. Most patients had had migraine for
approximately 20 years, and the overwhelming majority of patients with headaches (95%) were treated with acute pharmacotherapy during the baseline period.

The results showed a significant reduction in the mean reduction from baseline in the 4-week headache rate in patients taking DVS-ER vs placebo (1.2 vs 0.6, \( P = 0.006 \)). This was the primary efficacy measure.

The secondary efficacy measure was the reduction in the number of migraine headache days from baseline, which also showed a significant benefit for patients in the DVS-ER group compared with patients taking placebo (1.7 vs 0.7, \( P = 0.009 \)).

Patients in the DVS-ER group also showed a substantial decrease in the number of headache days during the first 4 weeks of the study (1.2 days vs 0.6 days). This was significant in the second 4 weeks, and the treatment difference continued to increase in the third 4-week period.

For those patients who completed the study, the reduction in 4-week migraine rate during the last 4 weeks was greater in the DVS-ER group than in the placebo group (2.0 vs 0.7, \( P = 0.001 \)). The percentage of patients with a 50% or greater reduction in the number of headache days was substantially greater for patients in the treatment groups than in the placebo groups (41% vs 28%, \( P = 0.024 \)).

DVS-ER was well tolerated. Placebo patients reported more asthenia, but there was more dyspepsia, nausea, vomiting, tremor, and rash in the DVS-ER group. However, none of the differences were significant. There was no difference in premature discontinuation and abdominal pain between the 2 groups.

In summary, DVS-ER appears to have twice the efficacy in 4-week headache rate, and produces a reduction in the number of 4-week headache days. There were decreases in migraine headache rate, migraine headache days, and patients with a 50% or greater reduction in migraine headache rate among patients who completed the study. DVS-ER seems safe and well tolerated at doses up to 1000 mg once daily as studied in this 90-day clinical trial. – –MG

REFERENCES

1. Mulleners WM, Whitmarsh TE, Steinert TJ. Noncompliance may render migraine prophylaxis useless, but once-daily regimens are better. Cephalalgia 1996;16:52-56.