Appendix II

Guideline for Migraine Treatment by Valproic Acid (Provisional Edition)

Introduction

The Japanese Headache Society together with the Japanese Society of Neurology requested the Ministry of Health, Labour and Welfare to develop the use of sodium valproate for migraine. This issue was considered to qualify as medical and pharmaceutical data in the public domain at the "The Fifth Review Meeting on Non-approved Drugs and Off-label Drugs with High Need" held on October 6, 2010, and was accepted at the "Meeting of the First Committee on Drugs of the Pharmaceutical Affairs and Food Sanitation Council" on October 29, 2010. As a result, Depakene® for migraine was approved for health insurance coverage from October 29, 2010.

Regarding this health insurance coverage, attention has been called to the effect that users should be knowledgeable about the contents of the "Report Concerning the Qualification as Application Based on Public Domain Data", and use the drug with caution by adjusting dosage according to the conditions of individual patients.

Furthermore, instruction has been issued to publicize the following:

(1) Be well aware of the precautions for use of this drug. Strive to give prior explanations to patients regarding the treatment contents and possible adverse reactions, and obtain their informed consent.

(2) When a serious adverse effect is known, report to the relevant company or to the Ministry of Health, Labour and Welfare. Strive to obtain information of the cases in case of off-label use.

With this background, Board Director Sakai instructed the Treatment Promotion Committee to produce a guideline (provisional edition) urgently, in order that "migraine treatment by valproic acid" can be used effectively and safely. The guideline was produced jointly with the Committee for the Development of Diagnostic and Treatment Guidelines for Chronic Headache (Chairman: Nobuo Araki) which was inaugurated around the same time.

Committee for Guideline for Migraine Treatment by Valproic Acid (Provisional Edition):

The committee is composed of chairman: Kiyomi Yamane; vice-chairmen: Nobuo Araki and Takao Takeshima; members: Naoki Ando, Hisaka Igarashi, Keiko Imamura, Yasuo Ito, Yuji Kato, Kentaro Kuwabara, Tomokazu Shimazu, Hikaru Doi, Mitsue Fujita, Naoto Fujiki and Yuka Watanabe.

Production process and contents of guideline

The guideline was produced based on evidence and according to the "Diagnostic and Treatment Guidelines for Chronic Headache" compiled by the Japanese Headache Society. When there is insufficient evidence, the recommendation may be made according to expert opinion. The present guideline is provisional. The principle policy was to gather opinions from members of the Japanese Headache Society after publication of this provisional guideline and reflect the opinions in a subsequent revised edition.

The guideline contains the following clinical questions (CQ):

CQ 1. Is valproic acid effective for migraine prevention?
Is there international consensus for valproic acid as prophylactic medication for migraine?

CQ 2. What kinds of migraine patients are treated by valproic acid?

CQ 3. What doses of valproic acid are used for the treatment of migraine?
What are the precautions during administration of valproic acid?

CQ 4. What is the significance of measuring blood levels of valproic acid in the treatment of migraine?

CQ 5. Is valproic acid safe and effective in preventing migraine in children?

Conclusion

Hereafter, validation of the efficacy and safety of using valproic acid as prophylactic treatment for migraine attacks mainly by members of the Japanese Headache Society is necessary. Generation of new evidence is anticipated through this validation process.

On behalf of the authors of Guideline for Migraine Treatment by Valproic Acid (Provisional Edition)
Fumihiko Sakai, Board Director of the Japanese Headache Society
Nobuo Araki, Chair of Guideline Committee
Kiyomi Yamane, Chair of Guideline for Migraine Treatment by Valproic Acid (Provisional Edition) Committee

*This guideline was first published in Japanese Journal of Headache 2012; 38(3): 269-274.

CQ 1

Is valproic acid effective for migraine prevention? Is there international consensus for valproic acid as prophylactic medication for migraine?

Recommendation

Oral administration of valproic acid to migraine patients with headache attacks two or more times a month can be expected to reduce the number of attacks per month.

Guidelines in European and American countries also recommend valproic acid as the first choice of prophylactic medication for migraine. **Grade A**

Background and Objective

Valproic acid increases GABA level in the brain by activating glutamic acid decarboxylase and inhibiting GABA aminotransferase, and suppresses neuron excitability. Therefore, the effect of valproic acid on migraine and refractory chronic headache has been investigated. Approximately 20 years of use experience for migraine has been accumulated, and in European and American countries, valproic acid together with beta blockers and amitriptyline are listed among the first-choice drugs for migraine prevention.

Comments and Evidence

Prospective studies of valproic acid for migraine prevention include two studies on sodium valproate and four on divalproex sodium (compound of valproic acid and sodium valproate in 1:1 ratio). The results of these studies were subjected to systematic review in a Cochrane review, which concludes that sodium valproate/divalproex sodium reduces the frequency of headache attacks and increases the number of patients in whom migraine frequency is reduced by 50% or more.[1)]

Shaygannejad et al.[2)] reported that by taking oral sodium valproate 400 mg/day for 8 weeks, the frequency of headache attacks was reduced from 5.4 to 4.0 per month, headache severity from visual analog scale (VAS) score 7.7 to 5.8, and headache duration from 21.3 hours to 12.3 hours. While some reports indicate that valproic acid reduces headache frequency as well as attenuates headache intensity and shortens headache duration,[2)3)] other reports show that valproic acid reduces headache frequency but does not improve headache intensity or headache duration.[4)]

When compared with other drugs, valproic acid shows equivalent effectiveness as flunarizine,[5)] propranolol,[6)] and topiramate.

In overseas countries, the European Federation of Neurological Science (EFNS) migraine treatment guideline recommends valproic acid 500 to 1,800 mg/day for migraine prophylaxis at level A.[7)] The American Academy of Neurology migraine guideline also recommends valproic acid at grade A.[8)] Therefore, international consensus has been obtained for valproic acid as a prophylactic medication for migraine.

• References

1) Mulleners WM, Chronicle EP: Anticonvulsants in migraine prophylaxis: a Cochrane review. Cephalalgia 2008; 28(6): 585-597.
2) Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V: Comparison of the effect of topiramate and sodium valproate in migraine prevention: a randomized blinded crossover study. Headache 2006; 46(4): 642-648.
3) Hering R, Kuritzky A: Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 1992; 12(2): 81-84.
4) Jensen R, Brinck T, Olesen J: Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology 1994; 44(4): 647-651.
5) Mitsikostas DD, Polychronidis I: Valproate versus flunarizine in migraine prophylaxis: a randomized, double-open, clinical trial. Funct Neurol 1997; 12(5): 267-276.
6) Kaniecki RG: A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. Arch Neurol 1997; 54(9): 1141-1145.
7) Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sndor PS; European Federation of Neurological Societies: EFNS guideline on the drug

treatment of migraine—revised report of an EFNS task force. Eur J Neurol 2009; 16(9): 968-981.
8) Silberstein SD: Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000; 55(6): 754-762.

• Search terms

- PubMed search (2010/12/30)

(migraine) and ((preventive) or (prophylactic) or (prophylaxis)) and ((valproate) or (valproic acid)) 225

CQ 2

What kind of migraine patients are treated by valproic acid?

Recommendation

Valproic acid can be expected to reduce headache attacks in patients who have migraine attacks two times or more a month. In addition, valproic acid prophylactic therapy is recommended when migraine-induced disability in daily living is not adequately resolved with acute treatment alone; when acute treatment drugs are contraindicated, ineffective or resulted in overuse; and for special types of migraine with a risk of causing permanent neurological defects. **Grade A**

Background and Objective

The effect of valproic acid was investigated in patients with migraine or refractory chronic headache. Valproic acid significantly improved migraine compared with placebo, and the clinical trial results consistently showed that valproic acid is an effective prophylactic drug for migraine.[1)-5)]

The goals of valproic acid prophylactic therapy are:

(1) to reduce headache frequency, severity and duration

(2) to improve response to acute treatment

(3) to improve function and reduce disability in daily living.

Comments and Evidence

In a clinical trial conducted in migraine patients with a disease duration of two years or longer and migraine attacks of 4 times or more per month, attacks were reduced significantly during valproic acid treatment period compared with placebo period ($p < 0.001$). Valproic acid has been reported to be especially effective in treating refractory migraine.[6)7)] Even compared with other drugs, valproic acid shows equivalent effectiveness as propranolol[3)] and flunarizine.[8)]

The American College of Physician guideline, U.S. Headache Consortium guideline,[9)] and American Academy of Neurology guideline[10)] recommend valproic acid as one of the first-choice prophylactic therapies for migraine with the following indications:

(1) two or more disabling attacks (6 or more days) per month,

(2) contraindication or no response to acute treatments,

(3) use of acute medications two or more times per week,

(4) uncommon migraine conditions including hemiplegic migraine.

The guidelines also recommend to consider the adverse effects of acute treatments, patient preference, and the costs of both acute and prophylactic therapies.

Moreover, valproic acid is recommended as the first-choice medication especially in patients with comorbid conditions of epilepsy, mania, or bipolar disorder.[11)12)]

• References

1) Hering R, Kuritzky A: Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia 1992; 12(2): 81-84.

2) Jensen R, Brinck T, Olesen J: Sodium valproate has a prophylactic effect in migraine without aura: A triple-blind, placebo-controlled crossover study. Neurology 1994; 44(4): 647-651.

3) Kaniecki RG: A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. Arch Neurol 1997; 54(9): 1141-1145.

4) Klapper J: Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia 1997; 17(2): 103-108.

5) Mathew NT, Saper JR, Silberstein SD, Rankin L, Markley HG, Solomon S, Rapoport AM, Silber CJ, Deaton RL: Migraine prophylaxis with divalproex. Arch Neurol 1995; 52(3): 281-286.

6) Erdemoglu AK, Ozbakir S: Valproic acid in prophylaxis of refractory migraine. Acta Neurol Scand 2000; 102(6): 354-358.

7) Ghose K, Niven B: Prophylactic sodium valproate therapy in patients with drug-resistant migraine. Methods Find Exp Clin Pharmacol 1998; 20(4): 353-359.

8) Mitsikostas DD, Polychronidis I: Valproate versus flunarizine in migraine prophylaxis: a randomized, double-open, clinical trial. Funct Neurol

1997; 12(5): 267-276.
9) Snow V, Weiss K, Wall EM, Mottur-Pilson C: Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med 2002; 137(10): 840-849.
10) Silberstein SD: Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000; 55(6): 754-762.
11) Silberstein SD: Preventive migraine treatment. Neurol Clin 2009; 27(2): 429-443.
12) Finocchi C, Villani V, Casucci G: Therapeutic strategies in migraine patients with mood and anxiety disorders: clinical evidence. Neurol Sci 2010; 31(suppl 1): S95-98.

• Search terms

- PubMed search (2011/1/26)
  {migraine} 24041
  & {treat} 11630
  & {(preventive) or (prophylactic) or (prophylaxis)} 2888
  & {(valproate) or (valproic acid)} 210
  & {patient} 132

CQ 3

What doses of valproic acid are used for the treatment of migraine? What are the precautions during administration of valproic acid?

Recommendation

In adults, sodium valproate 400 to 600 mg/day taken orally is recommended for migraine prophylaxis.

Grade B

Valproic acid is contraindicated in women who are pregnant or has a possibility of being pregnant. When used in women of child-bearing potential, explain to the patients about adverse effects and teratogenicity, select sustained release formulation, and do not use in combination with other antiepileptic drugs. Considering the possibility of pregnancy, recommend the patient to check the menstruation period, basal temperature, and take folic acid 0.4 mg/day.

Grade A

Background and Objective

Valproic acid preparations include sodium valproate used in Japan, and divalproex sodium (preparation of valproic acid and sodium valproate in 1:1 ratio, valproic acid content is almost equivalent to sodium valproate) used in overseas countries. In Japan, the use of Depakene® for migraine was approved for health insurance coverage on October 29, 2010, and was officially approved in September 2011. Since migraine commonly occurs in women of child-bearing potential, and because there is a possibility of pregnancy during treatment, it is important to know about adverse reactions and precautions in use, and administer with caution. The safe and effective dose for use in Japan has to be proposed.

Comments and Evidence

Double-blind parallel-group controlled study and double-blind cross-over controlled study conducted overseas have proven that valproic acid is effective for migraine prevention, and the doses used in those studies ranged from 400 to 2,000 mg/day.[1] In Japan, the reported doses were 800 mg/day according to a study on migraine prevention (open study) conducted by Oana et al.,[2] and ranged from 200 to 1,000 mg/day when case reports were included. In the US, use of divalproex sodium at 500 to 1,000 mg/day was approved. The European Federation of Neurological Societies (EFNS) guideline recommends doses of 500 to 1,800 mg/day.[3]

Regarding the relationship between dose and prophylactic effect, one study reported that compared with blood valproic acid level of 50 μg/mL or higher, blood level lower than 50 μg/mL was associated with less adverse effects, significant decreases in headache frequency and number of days with headache. This report thus recommended low-dose valproic acid of 500 to 600 mg/day for migraine prevention.[4] Furthermore, another report indicated that in migraine patients who did not respond to low-dose valproic acid, dose increase did not improve response.[5] From the above findings, the recommended dose range of sodium valproate is 400 to 600 mg/day.

According to a survey on the use of valproic acid in Japanese patients with mania or with a manic state of bipolar disease, the major adverse effects include drowsiness, hyperammonemia, vertigo, hepatic function impairment, elevated creatine phosphokinase, and anemia.[6] Special attention is required when using valproic acid in women of child-bearing age. Regarding the relationship of valproic acid with congenital malformation, combined data from 8 cohort studies identified 118 cases of malformations in a total of 1565 pregnancies in which the women were exposed to valproic acid, showing a significantly higher incidence than in women not exposed to the drug.[7] In addition, the rate of malformation increased as the dose of valproic acid exceeded 1,000 to 1,500 mg/day,[8)-11)] suggesting that the rate of teratogenicity increases depending on the dose and blood level. In a prospective study of pregnant women with epilepsy receiving monotherapy with antiepileptic drug (carbamazepine, lamotrigine, phenytoin or valproic acid), cognitive function test conducted in three year-old children showed significantly lower IQ in children exposed to valproic acid treatment exceeding 1,000 mg/day in the fetal stage compared with other antiepileptic drugs.[12] From the above data, it was concluded that taking valproic acid during

pregnancy is associated with teratogenicity and impaired cognitive function in fetus. In May 2013, FDA advised that different from epilepsy treatment, use of valproic acid for migraine prevention is contraindicated in pregnant women and women who may be pregnant, because the risk outweighs the benefit. When used in women of child-bearing potential, the patients should be given prior explanations of adverse effects and teratogenicity, and sustained release formulation should be chosen so that blood level increases gradually. Since the frequency of teratogenicity is increased with multi-drug antiepileptic therapy,[8)9)] combined use of valproic acid with other antiepileptic drugs should be avoided. Patients should be instructed to check the menstrual cycle and basal temperature, and to stop taking valproic acid and contact the attending doctor when pregnancy is suspected. To reduce the risk of neural tube defect, patients should be advised to take folic acid 0.4 mg/day.[13)]

• References

1) Vikelis M, Rapoport AM: Role of antiepileptic drugs as preventive agents for migraine. CNS Drugs 2010; 24(1): 21-33.
2) Oana K, Takemae N: Effectives of valproic acid for migraine and its evaluation. Japanese Journal of Headache 2007; 34(2): 179-184. (In Japanese)
3) Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sndor PS: EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. Eur J Neurol 2009; 16(9): 968-981.
4) Kinze S, Clauss M, Reuter U, Wolf T, Dreier JP, Einhupl KM, Arnold G: Valproic acid is effective in migraine prophylaxis at low serum levels: a prospective open-label study. Headache 2001; 41(8): 774-778.
5) Ghose K, Niven B: Prophylactic sodium valproate therapy in patients with drug-resistant migraine. Methods Find Exp Clin Pharmacol 1998; 20(4): 353-359.
6) Tezuka S, Nakame N, Sato F, Sasamoto T, Mikura M, Goto T: Special Investigation of sodium valproate for patients with mania or in a manic-depressive state of manic-depressive psychosis. Japanese Journal of Clinical Psychopharmacology 2008; 11(10): 1909-1920. (In Japanese)
7) Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, de Jong-van den Berg LT: Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med 2010; 362(23): 2185-2193.
8) Artama M, Auvinen A, Raudaskoski T, Isojrvi I, Isojrvi J: Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology 2005; 64(11): 1874-1878.
9) Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, McGivern RC, Morrison PJ, Craing J: Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2006; 77(2): 193-198.
10) Kaneko S, Battino D, Andermann E, Wada K, Kan R, Takeda A, Nakane Y, Ogawa Y, Avanzini G, Fumarola C, Granata T, Molteni F, Pardi G, Minotti L, Canger R, Dansky L, Oguni M, Lopes-Cendas I, Sherwin A, Andermann F, Seni MH, Okada M, Teranishi T: Congenital malformations due to antiepileptic drugs. Epilepsy Res 1999; 33(2-3): 145-158.
11) Vajda FJ, Hitchcock A, Graham J, Solinas C, O'Brien TJ, Lander CM, Eadie MJ: Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. Eur J Neurol 2006; 13(6): 645-654.
12) Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group: Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009; 360(16): 1597-1605.
13) Yerby MA: Management issues for women with epilepsy: neural tube defects and folic acid supplementation. Neurology 2003; 61(6 Suppl 2): S23-26.

• Search terms and secondary sources

- Search database: PubMed (2011/1/23)
  valproate
  and migraine 349
  and pregnancy and malformation 502
  and pregnancy and malformation and polytherapy 48
  and folic acid 134
- Search database: Ichushi Web for articles published in Japan (2006-2011) (2011/1/23)
  Valproate and migraine 68

CQ 4

What is the significance of measuring blood levels of valproic acid in the treatment of migraine?

Recommendation

When oral valproic acid therapy is used for the prevention of migraine attacks, the optimal blood level is considered to range from 21 to 50 μg/mL, and response does not improve even when the blood level increases to above 50 μg/mL. Therefore regular measurement of blood valproic acid level during prophylactic therapy and adjustment of the dose to maintain the optimal blood level are recommended. **Grade B**

Background and Objective

Although valproic acid has been reported to be effective for the prevention of migraine, there are large individual differences in absorption, and elevated blood level may cause serious adverse reactions such as disturbance of consciousness. Valproic acid is mainly used for the treatment of epilepsy, and the effective blood concentration range is considered to be 50 to 100 μg/mL. However, it remains unknown whether the same optimal blood level applies to migraine that has different pathophysiology from epilepsy. Therefore, setting the optimal effective blood level of valproic acid is desirable, also from the viewpoint of reducing adverse reactions.

Comments and Evidence

In general, due to the great individual differences in absorption of valproic acid and wide intraday variation of blood level, it is difficult to estimate the time to reach peak level. Therefore, trough level that is not affected by absorption is usually measured. When blood level exceeds 120 μg/mL, impaired blood coagulation, drowsiness, tremor, sedation, aggressiveness, hyperammonemia, and hyperglycemia appear. Drugs that increase blood valproic acid level include amitriptyline that is used as a prophylactic drug for migraine, and salicylic acid agents that are used during headache attacks. Long-term use of these drugs in combination with valproic acid requires caution.[1)] In elderly persons who have reduced albumin level, there is a risk of increase in blood level of the free drug.

In migraine, adverse reactions occur less readily when the blood valproic acid level is maintained below 50 μg/mL, while significant reductions of headache frequency and days of attack are achieved. Consequently, a lower blood level goal is recommended when valproic acid is used for migraine prevention.[2)] Furthermore, in patients who do not respond to low doses of valproic acid, increasing the dose does not achieve response.[3)] The mean (SD) blood valproic acid level was 38.9 (37.3) μg/mL in an open-label extension trial administering divalproex sodium (a preparation of valproic acid and sodium valproate in 1:1 ratio) to migraine patients aged 12 to 17 years[4)] and was 44.8 (35.5) μg/mL in an open-label multicenter study,[5)] with significant decrease in migraine attacks. From the evidence so far, the recommended dosing regimen is oral administration of extended release sodium valproate preparation aiming at a blood level of 21 to 50 μg/mL.

In rat experiments, oral administration of sodium valproate immediately followed by oral administration of rizatriptan or sumatriptan resulted in significantly lower plasma levels of valproic acid compared with controls.[6)7)] This result suggests a possibility that even in humans, when valproic acid and triptan are used in combination in patients with coexisting epilepsy and migraine, epilepsy may be less well controlled (for migraine, since triptan is already being used, transient decrease in blood level of valproic acid may not affect migraine).

• References

1) Package insert for Depakene and Depakene R. (In Japanese)
2) Kinze S, Clauss M, Reuter U, Wolf T, Dreier JP, Einhupl KM, Arnold G: Valproic acid is effective in migraine prophylaxis at low serum levels: a prospective open-label study. Headache 2001; 41(8): 774-778.
3) Ghose K, Niven B: Prophylactic sodium valproate therapy in patients with drug-resistant migraine. Methods Find Exp Clin Pharmacol 1998; 20(4): 353-359.
4) Apostol G, Pakalnis A, Laforet GA, Robieson WZ, Olson E, Abi-Saab WM, Saltarelli M: Safety and tolerability of divalproex sodium extended-release in the prophylaxis of migraine headaches: results of an open-label extension trial in adolescents. Headache 2009; 49(1): 36-44.

5) Apostol G, Lewis DW, Laforet GA, Robieson WZ, Fugate JM, Abi-Saab WM, Saltarelli MD: Divalproex sodium extended-release for the prophylaxis of migraine headache in adolescents: results of a stand-alone, long-term open-label safety study. Headache 2009; 49(1): 45-53.
6) Hokama N, Hobara N, Kameya H, Ohshiro S, Hobara N, Sakanashi M: Investigation of low levels of plasma valproic acid concentration following simultaneous administration of sodium valproate and rizatriptan benzoate. J Pharm Pharmacol 2007; 59(3): 383-386.
7) Hobara N, Watanabe A, Kameya H, Hokama N, Ohshiro S, Hobara N, Sakanashi M: Effect of sumatriptan succinate, sumatriptan and succinic acid and on pharmacokinetics of valproic acid following oral administration of sodium valproate in rats. J Pharmacol Ther 2006; 34(11): 1157-1162.

• Search terms

- Search database: PubMed (2010/12/26)
  Migraine and Valproate 349
- Search database: Ichushi Web for articles published in Japan (2010/12/26)
  Migraine and Valproate 57

CQ 5

Is valproic acid safe and effective in preventing migraine in children?

Recommendation

For migraine in children, valproic acid should be restricted for patients with high-level disability not responding to other drugs, or patients with migraine while showing epileptic discharge on EEG (or epilepsies-related headache), and should be used with caution. **Grade B**

Background and Objective

Although valproic acid is also used in children as an anti-epileptic drug, adverse reactions such as liver dysfunction and hematocytopenia are sometimes encountered. Precautions are being undertaken, such as performing blood count and biochemical tests including ammonia level before starting treatment, and regularly performing blood test during treatment. In addition, the risk of teratogenicity in pregnant women has been reported. Therefore valproic acid is not the first choice as migraine prophylaxis for children including adolescent girls.

Comments and Evidence

Reports have shown different results of oral valproic acid therapy for preventing migraine in children. While one article showed no difference compared to placebo[1] and another article showed equivalent effect as propranolol,[2] many articles reported its effectiveness.[3)-7)]

The drugs of first choice for preventing migraine in children are cyproheptadine, amitriptyline,[8)9)] and lomerizine (but all should be avoided for pregnant women and women who may be pregnant, and constant attention has to be given to the possibility of pregnancy). Use of valproic acid as a prophylactic medication for migraine in children is restricted to either I or II as shown below.

I. When disability is severe and patient does not respond to prophylactic drugs other than valproic acid:

Severe disability is indicated by:

1) although frequency is not high, each attack is accompanied by vomiting and severe headache requiring bed rest
2) high frequency (10 times or more a month, necessitating analgesic)

II. Migraine showing epileptic discharge on EEG (or epilepsy-related headache)

When using valproic acid for migraine in children, perform blood tests (blood count and biochemistry including ammonia level) before starting oral treatment, and perform the above tests and measure blood level of valproic acid at around 2 weeks after starting treatment. To assess the degree of improvement of migraine attacks by valproic acid, advise the patient to use a headache diary and always make an appointment for the next visit. Do not use aimlessly. Explain to adolescent female patient that use of the drug should be avoided if pregnancy is possible. Consider prescribing folic acid in combination with valproic acid as necessary.

When valproic acid is used for epilepsy in children, the maintenance dose is 15 to 50 mg/kg, dose escalation is 5 to 10 mg/kg for each step, and the blood level range is 50 to 100 μg/mL.[10)] When used for preventing migraine in children, response may be obtained with lower doses than above.

• References

1) Apostol G, Cady RK, Laforet GA, Robieson WZ, Olson E, Abi-Saab WM, Saltarelli M: Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. Headache 2008; 48(7): 1012-1025.
2) Ashrafi MR, Shabanian R, Zamani GR, Mahfelati F: Sodium Valproate versus Propranolol in paediatric migraine prophylaxis. Eur J Paediatr Neurol 2005; 9(5): 333-338.
3) Caruso JM, Brown WD, Exil G, Gascon GG: The efficacy of divalproex sodium in prophylactic treatment of children with migraine. Headache 2000; 40(8): 672-676.

4) Serdaroglu G, Erhan E, Tekgul H, Oksel F, Erermis S, Uyar M, Tutuncuoglu S: Sodium valproate prophylaxis in childhood migraine. Headache 2002; 42(8): 819-822.
5) Bidabadi E, Mashouf M: A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatr Drugs 2010; 12(4): 269-275.
6) Apostol G, Pakalnis A, Laforet GA, Robieson WZ, Olson E, Abi-Saab WM, Saltarelli M: Safety and tolerability of divalproex sodium extended-release in the prophylaxis of migraine headaches: results of an open-label extension trial in adolescents. Headache 2009; 49(1): 36-44.
7) Apostol G, Lewis DW, Laforet GA, Robieson WZ, Fugate JM, Abi-Saab WM, Saltarelli MD: Divalproex sodium extended-release for the prophylaxis of migraine headache in adolescents: results of a stand-alone, long-term open-label safety study. Headache 2009; 49(1): 45-53.
8) Lewis DW, Diamond S, Scott D, Jones V: Prophylactic treatment of pediatric migraine. Headache 2004; 44(3): 230-237.
9) Hershey AD, Powers SW, Bentti AL, Degrauw TJ: Effectiveness of amitriptyline in the prophylactic management of childhood headaches. Headache 2000; 40(7): 539-549.
10) Japanese Society of Neurology (ed.): Epilepsy Treatment Guideline 2010, Igakushoin 2010. (in Japanese)

• Search terms

#1 migraine
#2 valproic
#3 valproic acid
#4 #2 OR #3
#5 #1 AND #2
#6 #1 AND #2 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years
#7 #1 AND #2 Limits: Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Review, All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years