CQ II-3-1

What kinds of patients requires prophylactic therapy?

Recommendation

For patients who have migraine attacks two times or more or 6 days or more a month, consideration of prophylactic therapy is recommended. Prophylactic therapy is recommended when migraine-induced disability in daily living remains with acute treatment alone, when acute treatment drugs cannot be used, and for special types of migraine with a risk of causing permanent neurological defects. **Grade B**

Background and Objective

Prophylactic therapy is needed if disability in daily living due to migraine is not adequately relieved by acute treatment alone. The goals of prophylactic therapy are to (1) reduce headache frequency, severity, and duration, (2) improve the response to treatment of acute attacks, and (3) improve function and reduce disability.

Since overuse of acute treatment drugs would induce medication-overuse headache, prophylactic therapy is also required in the case of excess use of acute medications.

Comments and Evidence

Some prophylactic therapies have been used empirically from the past. For some prophylactic therapies, scientific evidence has been obtained from randomized controlled trials (RCT). The effectiveness and usefulness of prophylactic medications are evaluated by the degrees of reduction in frequency, severity and duration of headache, and by the degrees of improvement in functioning and disability in daily living. Evaluation methods include the number of days with headache, duration of headache, quantity of acute medications used, QOL scales, and migraine severity scales. Scientific evaluation is possible, and significance of the difference versus placebo can be analyzed statistically.

However, the evidence regarding the degree of improvement that is deemed adequate is inadequate at present, and this issue has to be studied further.

In the migraine treatment guidelines published to date, expert consensus recommendations for the indication of prophylactic therapy are based on scientific evidence and use experience of prophylactic medications available in individual countries or regions at the time of guideline development.

In the guideline published in 1993 by the Italian Society for the Study of Headache,[1] prophylactic therapy is recommended when migraine with the same frequency persists after three months of symptomatic treatment in patients with two or more disabling migraine attacks per month or 4 or more days with headache per month.

In the Canadian guidelines,[2] prophylactic therapy is recommended if migraine attacks are severe enough to impair the patient's QOL or the patient has three or more attacks per month that fail to respond adequately to acute treatment.

In the Danish guideline,[3] prophylactic therapy is indicated when the patient has two or more attacks per months or persistent attacks that do not respond adequately to acute treatment.

The US Headache Consortium[4][5] recommends to decide indication of prophylactic therapy based on the needs of individual patients and other migraine characteristics. Prophylactic therapy is indicated when migraine interferes with daily living despite acute treatment; in the case of frequent headache attacks, or contraindication, failure or overuse of acute treatments; and when adverse events occur due to acute treatment. In addition, consideration of the costs of both acute and prophylactic treatments as well as patient preference is necessary. In the presence of uncommon migraine conditions with a risk of causing permanent neurological deficits, such as hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura, and migrainous infarction, prophylactic therapy for migraine is indicated to prevent neurologic damage.

In Japan, the headache treatment guideline was published in 2002 by the Japanese Society of Neurology.[6] In this guideline, an indication of prophylactic therapy is considered when migraine attacks occur at high frequency and do not respond adequately to acute treatment alone, when acute medications cannot be used due to contraindications or adverse effects, when abortive medications are not effective, and when overuse of acute medications occurs. Then the indication should be decided considering the health economic aspect (when prophylactic therapy is less costly) and patient's preference. In addition, prophylactic therapy is indicated in the case of special migraine conditions with a risk of causing serious neurological

damage, such as hemiplegic migraine, basilar-type migraine, migraine with prolonged aura, and migrainous infarction.

According to the guideline published in 2002 by the American Society of Internal Medicine,[7] for patients with two or more disabling attacks (6 or more days) per month, contraindication or no response to acute treatments, use of abortive medication two or more times per week, or the presence of uncommon migraine conditions including hemiplegic migraine, an indication of prophylactic therapy should be decided upon considering the adverse effects of acute treatments, patient preference, and the costs of both acute and prophylactic therapies.

In the French guideline,[8] prophylactic therapy is recommended when disability in activities of daily living (ADL) occurs due to the frequency and intensity of migraine attacks, and when the patient has taken acute migraine medication 6 to 8 times per month for three months or longer.

In the Taiwanese guideline,[9] prophylactic therapy is indicated in patients who have more than three to four migraine attacks per month with no response or contraindication to acute medications; in patients with special migraine conditions such as hemiplegic migraine, migraine with prolonged aura, and migrainous infarction; or in patients with migraine attacks that severely impair daily living.

In the 2009 revision of the European Federation of Neurological Societies (EFNS) guideline,[10] prophylactic therapy is recommended when daily living is severely impaired; when attacks occur two or more times per month; when migraine attacks do not respond to acute medications; and when frequent, prolonged, or uncomfortable auras occur.

A health insurance database analysis conducted in the US by Silberstein et al.[11] found that implementing prophylactic therapy in migraine patients reduced the use of acute migraine medications, decreased visits to medical facilities, and decreased the frequency of utilization of brain CT and MRI scans. The study concluded that prophylactic therapy is beneficial also from the medico-economic point of view.

Furthermore, research on comorbid conditions in migraine patients has advanced. In patients with comorbid conditions such as cardiovascular diseases including hypertension and neurological disease including depression, selection of medications that are both therapeutic for the comorbid conditions and preventive for migraine is recommended.

If superior acute medications are developed, the scope of indication for prophylactic therapy would decrease. If superior prophylactic therapies with little adverse effects are developed, the scope of indication for prophylactic therapy would expand. Therefore, with future advances in the development of both acute and prophylactic medications, the criteria for indication of prophylactic therapy are likely to change. At this time, the indications arrived by consensus of the guideline committee are recommended.

• References

1) Guidelines and recommendations for the treatment of migraine. Italian Society for the Study of Headache (SISC). Funct Neurol 1993; 8(6): 441-446.
2) Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, Robinson G, Stirling D, Worthington I: Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. CMAJ 1997; 156(9): 1273-1287.
3) Guidelines for the management of headache. Danish Neurological Society and the Danish Headache Society. Cephalalgia 1998; 18(1): 9-22.
4) 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.
5) Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM: Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine. the American Academy of Neurology, 2000. http://www.aan.com/professionals/practice/pdfs/gl0090.pdf
6) Sakai F, Araki N, Igarashi H, Hamada J, Sakuta M, Hirata K, Suzuki N, Takeshima T, Yamane K, Wakata N, Iwata M, Nakashima K; Chronic Headache Treatment Guideline Subcommittee: Japanese Society of Neurology Treatment Guideline- Chronic Headache Treatment Guideline 2002. Rinsho Shinkei 2002; 42(4): 330-362. (In Japanese)
7) Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicicans; American Collage of Physicians-American Society of Internal Medicine: Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med 2002; 137(10): 840-849.
8) Graud G, Lantri-Minet M, Lucas C, Valade D; French Society for the Study of Migraine Headache (SFEMC): French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther 2004; 26(8): 1305-1318.
9) Treatment Guideline Subcommittee of the Taiwan Headache Society: Treatment guidelines for preventive treatment of migraine. Acta Neurol Taiwan 2008; 17(2): 132-148.
10) 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.
11) Silberstein SD, Winner PK, Chmiel JJ: Migraine preventive medication reduces resource utilization. Headache 2003; 43(3): 171-178.

• Search terms and secondary sources

- Benefit of prophylactic therapy for migraine patient (2012/5/30)
  migraine
  & prophylaxis 2631
  & benefit 154
  & QOL 9
  & guideline 71
  & efficacy 622
  & preventive 756
  & benefit 55
  & QOL 8
  & guideline 27
  & efficacy 195

CQ II-3-2

What kinds of drugs are available for prophylactic therapy?

Recommendation

The drugs used in prophylactic therapy for migraine are shown in **Table 1**.

Furthermore, the prophylactic drugs for migraine can be classified into five efficacy groups as shown in **Table 2**, taking into consideration various factors including the strength of evidence, the effects, and risk of adverse events.

Grade B

Background and Objective

In many guidelines, various medications have been evaluated based on evidence and consensus. These medications have also been classified into efficacy groups based on evidence and consensus concerning their effectiveness and safety.

Comments and Evidence

Table 1 (list of prophylactic medications for migraine) and **Table 2** (efficacy groups) were constructed by reviewing the guidelines published to date[1)-13)] and adding the consensus of our study group.

The prophylactic medications for migraine covered by health insurance in Japan are lomerizine, valproic acid, propranolol, and dihydroergotamine. As of March 2013, verapamil and amitriptyline are approved for off-label use.

• References

1) Guidelines and recommendations for the treatment of migraine. Italian Society for the Study of Headache (SISC). Funct Neurol 1993; 8(6): 441-446.
2) Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, Robinson G, Stirling D, Worthington I: Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. CMAJ 1997; 156(9): 1273-1287.
3) Guidelines for the management of headache. Danish Neurological Society and the Danish Headache Society. Cephalalgia 1998; 18(1): 9-22.
4) 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.
5) Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM: Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine. the American Academy of Neurolgy, 2000. http://www.aan.com/professionals/practice/pdfs/gl0090.pdf
6) Sakai F, Araki N, Igarashi H, Hamada J, Sakuta M, Hirata K, Suzuki N, Takeshima T, Yamane K, Wakata N, Iwata M, Nakashima K; Chronic Headache Treatment Guideline Subcommittee: Japanese Society of Neurology Treatment Guideline- Chronic Headache Treatment Guideline 2002. Rinsho Shinkei 2002; 42(4): 330-362. (In Japanese)
7) Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians; American Society of Internal Medicine: Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med 2002; 137(10): 840-849.
8) Graud G, Lantri-Minet M, Lucas C, Valade D; French Society for the Study of Migraine Headache (SFEMC): French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther 2004; 26(8): 1305-1318.
9) Treatment Guideline Subcommittee of the Taiwan Headache Society: Treatment guidelines for preventive treatment of migraine. Acta Neurol Taiwan 2008; 17(2): 132-148.
10) 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.
11) Gallai V, Sarchielli P: Diagnostic and therapeutic guidelines for migraine. Italian Society for the Study of Headaches (SISC). J Headache Pain 2001; 2(1): S125-129.
12) Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society: Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78(17): 1346-1353.
13) Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standaeds Subcommittee of the American Academy of Neurology and the American Headache Headance Society: Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78(17): 1337-1345.

Table 1. Summary of evidence for prophylactic therapies

Drug	Quality of evidence[1)]	Scientific evidence	Clinical impression[2)]	Adverse effect	Recommendation grade[3)]	Efficacy group[4)]	Recommended dose
Antiepileptic drugs							
valproic acid	A	+++	+++	occasional-frequent	A	1	400–600 mg/day
topiramate	A	+++	+++	occasional-frequent	A**	1	50–200 mg/day
gabapentin	B	++	++	occasional-frequent		2	
levetiracetam	B	?	?	occasional-frequent		2	
Antidepressants							
amitriptyline	A	+++	+++	frequent	A*	1	10–60 mg/day
nortriptyline	C	?	+++	frequent		3	
imipramine	C	?	+	frequent		3	
clomipramine	C	?	+	frequent		3	
trazodone	C	?	+	occasional-frequent		3	
mianserin	C	?	+	occasional-frequent		3	
fluvoxamine	C	?	+	occasional		3	
paroxetine	C	?	+	occasional		3	
sulpiride	C	?	+	rare		3	
duloxetine	C	?	?	occasional		3	
fluoxetine	B	+	+	occasional		2	
Beta-blockers							
propranolol	A	++	+++	rare-occasional	A	1	20–60 mg/day
metoprolol	A	++	+++	rare-occasional	A**	2	40–120 mg/day
atenolol	B	++	++	rare-occasional		2	
nadolol	B	+	+++	rare-occasional		2	
timolol	A	+++	+	rare-occasional		1	
Calcium channel blockers							
lomerizine	B	+	++	rare	B	2	10–20 mg/day
verapamil	B	+	++	rare-occasional	B*	2	80–240 mg/day
diltiazem	C	?	++	rare-occasional		3	
nicardipine	C	+	++	rare-occasional		3	
flunarizine	A	++	+++	frequent		4	
ARB/ACE inhibitors							
candesartan	B	+	+	rare	B**	2	8–12 mg/day
lisinopril	B	+	+	occasional	B**	2	5–20 mg/day
enalapril	C	?	?	occasional		3	
olmesartan	C	?	?	occasional		3	
Others							
dihydroergotamine	A	++	++	occasional	B	4	2–3 mg/day
methysergide	A	+++	+++	frequent		4	
botulinum toxin type A (acute/chronic)	B/A	++	?	rare	C**/A**	2	
feverfew	B	++	+	rare	B	2	
magnesium preparation	B	+	+	rare	B**	2	
vitamin B2		B	+++	++	rare	B**	2
tizanidine	B	+	+	rare		2	
melatonin	C	?	?	rare	C	4	
olanzapine	C	?	?	frequent	C**	4	

[1)] Quality of evidence
A. Consistent results obtained from multiple RCT
B. Evidence from RCT exists but not complete
C. No evidence from RCT, but consensus obtained from the US MCH Consortium or Guideline Study Group of Japanese Ministry of Health, Labour and Welfare
RCT: randomized controlled trials
[2)] Clinical impression
0 ineffective, no improvement in most patients
+ somewhat effective: significant clinical improvement in a few patients
++ effective: significant clinical improvement in some patients
+++ markedly effective: significant clinical improvement in most patients
[3)] Recommendation grade: according to the descriptions in the main text of this guideline. Drugs approved for health insurance in Japan and drugs with high quality evidence are described. Quality of evidence is not necessarily equal.
[4)] See Table 2.
[5)] Recommended dose: according to the evidence and consensus obtained in Japan.
*Covered by health insurance as off-label use for migraine in Japan
**Not covered by health insurance in Japan
Drugs not currently available in Japan are written in italics

Table 2. Prophylactic medications categorized by efficacy

Group 1 (effective)	Group 2 (somewhat effective)	Group 3 (empirically effective)	Group 4 (effective, beware of adverse effects)	Group 5 (not effective)
Antiepileptic drugs valproic acid topiramate**	**Antiepileptic drugs** levetiracetam** gabapentin*	**Antidepressants** fluvoxamine** imipramine** nortriptyline** paroxetine** sulpiride** trazodone** mianserin** duloxetine** clomipramine**	**Calcium channel blockers** *Flunarizine***	**Antiepileptic drugs** chlonazepam** lamotrigine** carbamazepine
Beta-blockers propranolol *timolol***	**Beta-blockers** metoprolol** atenolol** nadolol**	**Calcium channel blockers** diltiazem** nicardipine**	**Others** *Methysergide*** dihydroergotamine *Melatonin*** Olanzapine**	**Calcium channel blockers** nifedipine**
Antidepressants amitriptyline*	**Antidepressants** *fluoxetine***	**ARB/ACE inhibitors** enalapril** olmesartan**		**Beta-blockers** acebutolol** pindolol** alprenolol** oxprenolol**
	Calcium channel blockers lomerizine verapamil*			**Others** clonidine**
	ARB/ACE inhibitors candesartan* lisinopril**			
	Others *feverfew*** magnesium preparation** vitamin B2** tizanidine** botulinum toxin type A**			

*Covered by health insurance as off-label use for migraine in Japan
**Not covered by health insurance in Japan
Drugs not currently available in Japan are written in italics

• Search terms and secondary sources

- Benefit of prophylactic therapy for migraine patient (2012/5/30)
  migraine
  & prophylaxis 2631
  & benefit 154
  & QOL 9
  & guideline 71
  & efficacy 622
  & preventive 756
  & benefit 55
  & QOL 8
  & guideline 27
  & efficacy 195

CQ II-3-3

How should multiple prophylactic therapies be used differentially?

Recommendation

For prophylactic therapy, select a drug with scientific evidence-based efficacy and few adverse effects, and start from a low dose. In the absence of adverse events, increase the dose gradually until a dose that yields adequate clinical efficacy, and evaluate the effectiveness for a period of two to three months. If no adequate response is obtained even after increasing to an adequate dose and after a sufficiently long observation period, then change to another drug. Select drugs taking into account comorbid conditions other than migraine as well as the physical condition.

Grade B

Background and Objective

Prophylactic therapy is selected when acute treatment alone is not adequate. The goals of prophylactic therapy are to (1) reduce headache frequency, severity and duration, (2) improve the response to treatment of acute attacks, and (3) improve function and reduce disability. To achieve these goals, it is necessary to choose the optimal prophylactic medication according to scientific evidence as well as the physical condition and needs of individual patients.

Comments and Evidence

Although various guidelines published to date[1)-13)] recommend to choose prophylactic drugs with high safety profile and start from a low dose, there is a lack of clear evidence regarding the criteria of selection, as is also the case for the indication criteria of prophylactic drugs.[14)]

The US Headache Consortium Guideline[4)5)] provides the following recommendations for selecting and using prophylactic drugs. A. Initiate prophylactic therapy with a drug that has the highest level of evidence-based efficacy. B. Initiate therapy with the lowest dose and increase dose slowly until adequate clinical efficacy is achieved in the absence of adverse events. C. Give each drug an adequate evaluation, which may take 2 to 3 months to reach clinical efficacy. D. Avoid using interfering medications (for example, overuse of acute medications). E. Use of a long-acting formulation may improve compliance.

In addition, comorbid conditions should be considered in the choice of drugs. Some comorbid/coexisting conditions are commonly found in migraine patients. Some conditions such as stroke, myocardial infarction, Raynaud's phenomenon, epilepsy, affective disorders, and anxiety disorders are associated with both treatment opportunities and limitations. In such cases, it is important to: A. if possible, select a drug that can treat both the comorbid condition and migraine; B. select a migraine medication that is not contraindicated for the comorbid condition; C. select drugs for the treatment of comorbid condition which do not exacerbate migraine; and D. beware of all drug interactions.[4)5)]

As a special attention for women who are pregnant or who wish to become pregnant, prophylactic drugs may have teratogenic effects. If prophylactic therapy is absolutely necessary, drugs with the lowest risk to the fetus should be selected.[4)5)]

For the evaluation of prophylactic therapy, observing the properties and duration of headache as well as monitoring the amounts of acute drugs used are important, while the use of headache diary is very useful. Although detailed records would provide more information, simply recording the number of days with headache alone is useful.[1)10)] Switching of drug for prophylactic therapy is necessary for appropriate evaluation of the effectiveness of prophylactic therapy.

The latest guideline of the American Academy of Neurology (2012)[12)13)] lists the following drugs as having proven effectiveness for migraine prevention: *divalproex sodium*, sodium valproate, topiramate, metoprolol, propranolol, and *timolol*. In addition, the guideline recommends frovatriptan, a triptan currently not available in Japan, as short-term prophylactic therapy for menstrually related migraine. Moreover, butterbur (*Petasites hybridus*), a non-pharmaceutical product, has been regarded to be effective for migraine prevention, but due to possible association with hepatoxicity, the Ministry of Health, Labour and Welfare in Japan has issued a warning against its intake (February 2012).

The 2009 European Federation of Neurological Societies (EFNS) guideline[10)] recommends metoprolol (50 to 200 mg/day), propranolol (40 to 240 mg/day), *flunarizine* (5 to 10 mg/day), valproic acid (500 to 1,800 mg/day), and topiramate (25 to 100 mg/day) as drugs of first choice; and amitriptyline (50 to 150 mg/day), *venlafaxine* (75 to 150 mg/day), naproxen (2 × 250 to 500 mg/day), *petasites* (2 × 75 mg/day), and bisoprolol (5 to 10 mg/day) as drugs of second choice for prophylactic

therapy of migraine. Since continuous use of NSAIDs may induce medication-overuse headache, long-term use of naproxen as a prophylactic drug is still open to question.

In Taiwan[9], propranolol (20 to 160 mg/day) is recommended as the drug of first choice, and valproic acid (300 to 1,800 mg/day), topiramate (50 to 100 mg/day), *flunarizine* (5 to 10 mg/day), and amitriptyline (10 to 75 mg/day) as drugs of second choice for migraine prevention.

In clinical practice in Japan, it is also necessary to consider whether the drugs are covered by health insurance for use as migraine prophylactic therapy.

• References

1) Guidelines and recommendations for the treatment of migraine. Italian Society for the Study of Headache (SISC). Funct Neurol 1993; 8(6): 441-446.
2) Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, Robinson G, Stirling D, Worthington I: Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. CMAJ 1997; 156(9): 1273-1287.
3) Guidelines for the management of headache. Danish Neurological Society and the Danish Headache Society. Cephalalgia 1998; 18(1): 9-22.
4) 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.
5) Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM: Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine. the American Academy of Neurolgy, 2000. http://www.aan.com/professionals/practice/pdfs/gl0090.pdf
6) Sakai F, Araki N, Igarashi H, Hamada J, Sakuta M, Hirata K, Suzuki N, Takeshima T, Yamane K, Wakata N, Iwata M, Nakashima K; Chronic Headache Treatment Guideline Subcommittee: Japanese Society of Neurology Treatment Guideline- Chronic Headache Treatment Guideline 2002. Rinsho Shinkei 2002; 42(4): 330-362. (In Japanese)
7) Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family physicians; American Collage of Physicians; American Society of Internal Medicine: Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med 2002; 137(10): 840-849.
8) Graud G, Lantri-Minet M, Lucas C, Valade D; French Society for the Study of Migraine Headache (SFEMC): French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther 2004; 26(8): 1305-1318.
9) Treatment Guideline Subcommittee of the Taiwan Headache Society: Treatment guidelines for preventive treatment of migraine. Acta Neurol Taiwan 2008; 17(2): 132-148.
10) 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.
11) Gallai V, Sarchielli P: Diagnostic and therapeutic guidelines for migraine. Italian Society for the Study of Headaches (SISC). J Headache Pain 2001; 2(1): S125-129.
12) Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society: Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78(17): 1346-1353.
13) Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society: Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78(17): 1337-1345.
14) Ramadan NM, Schultz LL, Gilkey SJ: Migraine prophylactic drugs: proof of efficacy, utilization and cost. Cephalalgia 1997; 17(2): 73-80.

• Search terms and secondary sources

- Benefit of prophylactic therapy for migraine patient (2012/5/30)
  migraine
  & prophylaxis 2631
  & benefit 154
  & QOL 9
  & guideline 71
  & efficacy 622
  & preventive 756
  & benefit 55
  & QOL 8
  & guideline 27
  & efficacy 195

CQ II-3-4

How long should prophylactic therapy be continued?

Recommendation

It takes at least 2 months before the effectiveness of prophylactic therapy can be evaluated. Continue prophylactic therapy for 3 to 6 months if there is no adverse event. If good migraine control is achieved, taper the prophylactic drug slowly, and discontinue where possible. **Grade B**

Background and Objective

Prophylactic therapy is implemented when acute treatment alone does not adequately relieve disability in daily living. The goals of prophylactic therapy are to (1) reduce headache frequency, severity and duration, (2) improve the response to treatment of acute attacks, and (3) improve function and reduce disability. When these goals are achieved, tapering and discontinuation of the prophylactic drug should be considered.

Comments and Evidence

Consideration of the duration of prophylactic therapy as well as tapering and discontinuation of the therapy depends also on the severity of headache-induced disability before the prophylactic therapy, and no uniform criteria can be applied. The guidelines published to date recommend various regimens such as: to continue prophylactic therapy for at least 3 months, and taper and discontinue when a frequency of 1 to 2 headaches or less per month has continued for at least 2 months;[1] or to continue therapy for several months if the goal of 50% reduction of headache frequency and severity is achieved, followed by gradual tapering;[2] or to continue therapy for 6-12 months and then assess whether continuation is needed;[3] or to continue until treatment goal is achieved and stabilized, then taper and discontinue;[4)-6] or to continue for 6 months to 1 year if prophylactic therapy is effective, then taper over 3 to 6 months, and restart the same therapy if attack frequency increases again.[7]

Regarding prophylactic therapy for special migraine conditions with a risk of causing serious neurological damage, such as hemiplegic migraine, migraine with brainstem aura, migraine with prolonged aura, and migrainous infarction, evidence for the duration of therapy and the timing of discontinuation is insufficient. Discontinuation has to be conducted with extreme caution.

• References

1) Guidelines and recommendations for the treatment of migraine. Italian Society for the Study of Headache (SISC). Funct Neurol 1993; 8(6): 441-446.
2) Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, Robinson G, Striling D, Worthington I: Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. CMAJ 1997; 156(9): 1273-1287.
3) Guidelines for the management of headache. Danish Neurological Society and the Danish Headache Society. Cephalalgia 1998; 18(1): 9-22.
4) 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.
5) Sakai F, Araki N, Igarashi H, Hamada J, Sakuta M, Hirata K, Suzuki N, Takeshima T, Yamane K, Wakata N, Iwata M, Nakashima K; Chronic Headache Treatment Guideline Subcommittee: Japanese Society of Neurology Treatment Guideline- Chronic Headache Treatment Guideline 2002. Rinsho Shinkei 2002; 42(4): 330-362. (In Japanese)
6) Treatment guidelines for preventive treatment of migraine. Treatment Guideline Subcommittee of the Taiwan Headache Society. Acta Neurol Taiwan 2008; 17(2): 132-148.
7) Graud G, Lantri-Minet M, Lucas C, Valade D; French Society for the Study for the Study of Migraine Headache (SFEMC): French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther 2004; 26(8): 1305-1318.

• Search terms and secondary sources

- Benefit of prophylactic therapy for migraine patient (2012/5/30)
  migraine
  & prophylaxis 2631
  & benefit 154
  & QO L9
  & guideline 71
  & efficacy 622
  & preventive 756
  & benefit 55
  & QOL 8
  & guideline 27
  & efficacy 195

CQ II-3-5

Are beta-blockers (propranolol) effective for migraine prevention?

Recommendation

Beta-blockers (propranolol) are effective in preventing migraine attacks. Propranolol at an initial dose of 20 to 30 mg/day followed by 30 to 60 mg/day is recommended as one of the first-choice drugs for patients with migraine attacks that impair QOL. Beta-blockers have the additional merit that they can be used in patients with coexisting hypertension and coronary artery disease, and that they can be used to treat these comorbid conditions simultaneously.

Grade A

Background and Objective

Beta blockers are mainly used as therapeutic agents for hypertension, coronary artery disease and tachyarrhythmia, but these drugs have also been used for migraine prevention from the past.

Although the mechanisms of action and pharmacological evidence remain largely unclear, the effectiveness of beta blockers including propranolol, metoprolol, atenolol and nadolol has been proven. These agents can be used actively provided there are no comorbid conditions in which beta blockers are contraindicated, such as heart failure, asthma, and a depressive state. They are also prophylactic drugs that can be administered relatively safely in pregnant women. However, it should be noted that propranolol increases the blood concentration of rizatriptan, and co-administration of the two is contraindicated.

In Japan, propranolol as a prophylactic drug for migraine has been approved for health insurance coverage in March 2013.

Comments and Evidence

Over 46 clinical studies have been conducted on propranolol, the representative beta blocker. Placebo-controlled clinical trials have demonstrated the usefulness of propranolol as a migraine prophylactic drug. Moreover, meta-analysis has been conducted. According to a meta-analysis reviewing 53 studies (2,403 patients) conducted by Holroyd et al.,[1] the typical dose of propranolol was 160 mg/day and the mean response rate of propranolol in double-blind trials was 43.7% which was significantly ($p < 0.001$) higher than 14.3% for placebo. Propranolol reduced migraine attacks by 44% when headache diaries were used to assess treatment outcome. Propranolol achieved 65% improvement when subjective scales or clinical ratings of effectiveness were used. On the other hand, the improvement rate for placebo remained at around 14% for all the evaluation methods. Because of the variation in dose among studies, the dose-response relationship (dose versus migraine prophylactic effect) could not be established. Propranolol is well tolerated.

From the above results, the effectiveness of propranolol as a prophylactic drug for migraine is established. The usefulness of metoprolol has been demonstrated in more than four placebo-controlled clinical trials.[2][3] Although the quality of evidence is slightly inferior, metoprolol may be considered to have similar prophylactic effect as propranolol.

Three clinical trials of timolol have been reported, and the effectiveness has been demonstrated.[4] However, only timolol ophthalmic solution is available in Japan, and the oral formulation is currently not available.

Three placebo-controlled clinical studies have proven the effectiveness of atenolol.[5] The usefulness of nadolol has also been demonstrated in more than two placebo-controlled studies. In addition, a randomized control trial (RCT) comparing nadolol and propranolol was conducted in 48 migraine patients taking nadolol 80 mg/day or 160 mg/day or propranolol 160 mg/day for 12 weeks.[6] Headache frequency was reduced from 6.13 to 2.74 per month with nadolol 80 mg/day, from 5.56 to 2.93 per month with nadolol 160 mg/day, and from 7.42 to 4.54 per month with propranolol. While improvement was observed in all three groups, the improvement was the greatest with nadolol 80 mg/day. One RCT comparing nebivolol with metoprolol reported equivalent efficacy of the two drugs,[7] but nebivolol is currently not available in Japan.

Based on the above findings, beta blockers including propranolol, metoprolol, timolol, atenolol, and nadolol have proven prophylactic effect against migraine and few serious adverse reactions. Active use of these agents as prophylactic drugs for migraine is recommended.

Among beta blockers, those with intrinsic sympathomimetic activity (ISA) such as acebutolol,[8] pindolol, alprenolol,[9] and oxprenolol[10] have been investigated in clinical trials, but no prophylactic effect on migraine was observed. Therefore beta blockers with ISA cannot be expected to be effective in preventing migraine, but the reason is unknown.

Based on the sufficient evidence for propranolol, the US Headache Consortium Guideline[11)-13)] recommends propranolol at a dose of 120 to 240 mg/day for prophylactic therapy. In the Japanese chronic headache guidelines published in 2006, a dose range of 20 to 60 mg/day was recommended, which was based on the experience of use in Japan and lower than that based on overseas evidence. Following this recommendation, the experience of use in Japan has accumulated, and propranolol for migraine treatment was approved for health insurance coverage in March 2013.

In addition, the guidelines published to date state that when prophylactic therapy is necessary in pregnant women, beta blockers including propranolol are relatively safe.

Since the major metabolic pathway for both propranolol and rizatriptan is oxidative deamination catalyzed by monoamine oxidase type A, there is a possibility that propranolol use may increase the blood level of rizatriptan and augment the effects. Therefore combined use of the two is contraindicated.[14)]

• References

1) Holroyd KA, Penzien DB, Cordingley GE: Propranolol in the management of recurrent migraine: a meta-analytic review. Headache 1991; 31(5): 333-340.
2) Kangasniemi P, Andersen AR, Andersson PG, Gilhus NE, Hedman C, Hultgren M, Vilming S, Olesen J: Classic migraine: effective prophylaxis with metoprolol. Cephalalgia 1987; 7(4): 231-238.
3) Steiner TJ, Joseph R, Hedman C, Rose FC: Metoprolol in the prophylaxis of migraine: parallel-groups comparison with placebo and dose-ranging follow-up. Headache 1988; 28(1): 15-23.
4) Stellar S, Ahrens SP, Meibohm AR, Reines SA: Migraine prevention with timolol. A double-blind crossover study. JAMA 1984; 252(18): 2576-2580.
5) Johannsson V, Nilsson LR, Widelius T, Jverfalk T, Hellman P, Akesson JA, Olerud B, Gustafsson CL, Raak A, Sandahl G, et al: Atenolol in migraine prophylaxis a double-blind cross-over multicentre study. Headache 1987; 27(7): 372-374.
6) Ryan RE Sr: Comparative study of nadolol and propranolol in prophylactic treatment of migraine. Am Heart J 1984; 108(4 Pt 2): 1156-1159.
7) Schellenberg R, Lichtenthal A, Whling H, Graf C, Brixius K: Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache 2008; 48(1): 118-125.
8) Nanda RN, Johnson RH, Gray J, Keogh HJ, Melville ID: A double blind trial of acebutolol for migraine prophylaxis. Headache 1978; 18(1): 20-22.
9) Ekbom K: Alprenolol for migraine prophylaxis. Headache 1975; 15(2): 129-132.
10) Ekbom K, Zetterman M: Oxprenolol in the treatment of migraine. Acta Neurol Scand 1977; 56(2): 181-184.
11) 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.
12) Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM: Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine. the American Academy of Neurolgy, 2000. http://www.aan.com/professionals/practice/pdfs/gl0090.pdf
13) Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E; Qualty Standards Subcommittee of the American Academy of Neurology and the American Headache Society: Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78(17): 1337-1345.
14) Kyorin Pharmaceutical Co. Ltd., Eisai Co. Ltd.: Package insert for Maxalt tablet 10 mg and Maxalt ROD tablet 10 mg, 7th edition, revised in June 2009. http: //www.eisai.jp/medical/products/di/PI/PDF/MAX_T-DT_PI.pdf (In Japanese)

• Search terms and secondary sources

- Search database: PubMed (2011/12/13)
  {migraine} OR {vascular headache} OR {hemicrania} 68566
  & propranolol 614
  & metoprolol 146
  & timolol 58
  & pindolol 32
  & nadolol 39
  & nebivolol 17
  & atenolol 101
  & acebutolol 11
  & alprenolol 7
  & acebutolol 11
  & bisoprolol 16
  & practolol 7
  & labetalol 33
  & carteolol 4
  & oxprenolol 10
  & prindolol 32

→ 447 articles excluded due to duplication or out of scope
10 articles adopted upon perusing abstract and text

- Secondary source, 4 references added by manual search (Nos. 11-14)

CQ II-3-6

Are calcium channel blockers (lomerizine) effective for migraine prevention?

Recommendation

When migraine patients who have two or more attacks per month are given the oral calcium channel blocker lomerizine 10 mg/day, reduction in frequency and severity of migraine attacks can be expected after 8 weeks in 64% of the patients. Adverse events are similar to placebo, indicating safety of the drug. Lomerizine is recommended as one of the first choice drugs for migraine prevention. **Grade B**

Background and Objective

Calcium channel blockers are a class of drugs widely used as antihypertensive agents. They have also been used as prophylactic drug for migraine from the past. Flunarizine is being used overseas as a migraine prophylactic drug, but is currently not available in Japan. As a similar diphenylpiperazine calcium channel blocker, lomerizine was developed in Japan and approved for health insurance coverage as migraine prophylaxis, and has been used since 1999. Literature was searched for evidence concerning the prophylactic effect of various calcium channel blockers for migraine.

Comments and Evidence

Over 45 clinical trials of calcium channel blockers for migraine prevention have been reported.

Among the calcium channel blockers, the quality of evidence for flunarizine is the highest, with effectiveness reported by more than 6 randomized placebo-controlled double-blind trials (RCT).[1)-7)] Furthermore, a meta-analysis using four of these reports also demonstrated its effectiveness, but sale of this drug was discontinued in Japan. For a similar compound lomerizine, one open-label study reported effectivess[8)] and one randomized placebo-controlled double-blind trial demonstrated effectiveness and usefulness.[9)] In an RCT of lomerizine compared with dimetotiazine, while the two drugs showed similar prophylactic effect for migraine, lomerizine was superior in safety. Although attention has to be given to adverse events such as Parkinsonism and depression (which are issues associated with flunarizine) when using lomerizine, clinical trials have found that adverse events of lomerizine are comparable to placebo. Despite being an open-label study, one trial has reported a 55.2% reduction in migraine attacks and absence of flunarizine-associated adverse effects even after prolonged use of flunarizine for 6 months, indicating the safety of this agent.[10)] For the phenylakylamine calcium channel blocker verapamil, two randomized placebo-controlled double-blind trials[11)12)] have demonstrated its usefulness. After migraine patients were treated with verapamil 320 mg (divided into 4 doses) for three months, migraine frequency decreased from 6.7 to 3.8 per month.[11)] In a cross-over study of verapamil 240 mg administered for 8 weeks, headache frequency was reduced significantly from 3.4 per month during placebo administration to 2.8 per month during verapamil administration, and the use of acute medications was also significantly reduced.[12)] According to the Notification from the Director of Medical Economics Division, Health Insurance Bureau, Ministry of Health, Labour and Welfare (Ho-I-Hatsu 0928 No. 1) "Health Insurance Handling Related to Off-Label Use of Pharmaceuticals" dated September 28, 2011, off-label use of verapamil for migraine and cluster headache was approved for health insurance coverage. For diltiazem, a benzothiazepine compound, one open-label study has shown its usefulness.[13)] For the dihydropyridine calcium channel blocker nimodipine, randomized placebo-controlled double-blind studies reported both effective[14)-16)] and ineffective[17)-19)] findings. This drug is currently not available in Japan. Another dihydropyridine compound nifedipine was considered to have no or very weak prophylactic effect,[20)21)] but one randomized placebo-controlled double-blind study on nicardipine has shown its usefulness.[22)]

Based on the above findings, lomerizine is recommended as the first choice calcium channel blocker that can be expected to exhibit prophylactic effect for migraine; although the number of clinical trials is small and evidence is slightly weak, this drug has been used for approximately 10 years in Japan and is covered by health insurance. Verapamil is recommended as the second choice, because there is evidence and the drug is covered by health insurance for off-label use.

• References

1) Louis P: A double-blind placebo-controlled prophylactic study of flunarizine (Sibelium) in migraine. Headache 1981; 21(6): 235-239.
2) al Deeb SM, Biary N, Bahou Y, al Jaberi M, Khoja W: Flunarizine in migraine:a double-blind placebo-controlled study (in a Saudi population). Headache 1992; 32(9): 461-462.
3) Pini LA, Ferrari A, Guidetti G, Galetti G, Sternieri E: Influence of flunarizine on the altered electronystagmographic (ENG) recordings in migraine. Cephalalgia 1985; 5(Suppl 2): 173-175.
4) Srensen PS, Hansen K, Olesen J: A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. Cephalalgia 1986; 6(1): 7-14.
5) Thomas M, Behari M, Ahuja GK: Flunarizine in migraine prophylaxis: an Indian trial. Headache 1991; 31(9): 613-615.
6) Mendenopoulos G, Manafi T, Logothetis I, Bostantjopoulou S: Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation. Cephalalgia 1985; 5(1): 31-37.
7) Frenken CW, Nuijten ST: Flunarizine, a new preventive approach to migraine. A double-blind comparison with placebo. Clin Neurol Neurosurg 1984; 86(1): 17-20.
8) Goto F, Tashiro K, Kutsuzawa N, et al. Early phase II clinical trial on the clinical effect of KB-2796 for migraine. Japanese Pharmacology & Therapeutics 1994; 22(12): 5031-5047. (In Japanese)
9) Goto F, Tashiro K, Kutsuzawa N, et al. Late phase II clinical trial on the clinical evaluation of KB-2796 (lomerizine hydrochloride) for migraine. Clinical Evaluation 1995; 23(1): 13-37. (In Japanese)
10) Imai N, Konishi T, Serizawa M, Okabe T: Do the effects of long-term lomerizine administration differ with age? Intern Med 2007; 46(10): 683-684.
11) Solomon GD, Steel JG, Spaccavento LJ: Verapamil prophylaxis of migraine. A double-blind, placebo-controlled study. JAMA 1983; 250(18): 2500-2502.
12) Markley HG, Cheronis JC, Piepho RW: Verapamil in prophylactic therapy of migraine. Neurology 1984; 34(7): 973-976.
13) Smith R, Schwartz A: Diltiazem prophylaxis in refractory migraine. N Engl J Med 1984; 310(20): 1327-1328.
14) Stewart DJ, Gelston A, Hakim A: Effect of prophylactic administration of nimodipine in patients with migraine. Headache 1988; 28(4): 260-262.
15) Havanka-Kanniainen H, Hokkanen E, Myllyl VV: Efficacy of nimodipine in the prophylaxis of migraine. Cephalalgia 1985; 5(1): 39-43.
16) Gelmers HJ: Nimodipine, a new calcium antagonist, in the prophylactic treatment of migraine. Headache 1983; 23(3): 106-109.
17) Migraine-Nimodipine European Study Group (MINES): European multicenter trial of nimodipine in the prophylaxis of classic migraine (migraine with aura). Migraine-Nimodipine European Study Group (MINES). Headache 1989; 29(10): 639-642.
18) Migraine-Nimodipine European Study Group (MINES): European multicenter trial of nimodipine in the prophylaxis of common migraine (migraine without aura). Migraine-Nimodipine European Study Group (MINES). Headache 1989; 29(10): 633-638.
19) Ansell E, Fazzone T, Festenstein R, Johnson ES, Thavapalan M, Wilkinson M, Wozniak I: Nimodipine in migraine prophylaxis. Cephalalgia 1988; 8(4): 269-272.
20) Shukla R, Garg RK, Nag D, Ahuja RC: Nifedipine in migraine and tension headache: a randomised double blind crossover study. J Assoc Physicians India 1995; 43(11): 770-772.
21) McArthur JC, Marek K, Pestronk A, McArthur J, Peroutka SJ: Nifedipine in the prophylaxis of classic migraine: a crossover, double-masked, placebo-controlled study of headache frequency and side effects. Neurology 1989; 39(2 Pt 1): 284-286.
22) Leandri M, Rigardo S, Schizzi R, Parodi CI: Migraine treatment with nicardipine. Cephalalgia 1990; 10(3): 111-116.

• Search terms and secondary sources

- Search database: PubMed (2011/12/13)
  {migraine} or {vascular headache} or {hemicrania} 68566
  & {calcium antagonists} or {Ca antagonists} 7587
  & flunarizine 337
  & diltiazem 103
  & nifedipine 293
  & verapamil 305
  & nimodipine 120
  & nicardipine 60
  & lomerizine 23
  & cinnarizine 66
  & dotarizine 7
  & amlodipine 115
  & azelnidipine 3
  & aranidipine 1
  & efonidipine 0
  & cilnidipine 1
  & nisoldipine 16
  & nitrendipine 53
  & barnidipine 4
  & felodipine 65
  & benidipine 1
  & manidipine 7
  & nilvadipine 6
  & cyclandelate 14

→ For 403 articles excluded due to duplication or out of scope, the abstracts were perused.
Although important articles focusing on placebo-controlled RCT and meta-analysis were adopted, some open studies and comparative studies with other drug groups were also adopted (22 references).

CQ II-3-7

Are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II blockers (ARB) effective for migraine prevention?

Recommendation

Lisinopril and candesartan are effective for the prevention of migraine. They are recommended for patients with migraine and coexisting hypertension. Start lisinopril at around 5 mg/day, and increase up to 20 mg/day where necessary. Candesartan at a dose of 8 mg/day is recommended for migraine prevention. **Grade B**

Background and Objective

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II blockers (ARB) are widely used as antihypertensive agents with few adverse effects. Accumulated experience that patients taking ACE inhibitors for hypertension tended to show reduced migraine frequency and severity had led to the report of several small-scale case series, which was followed by a randomized placebo-controlled cross-over trial on the ACE inhibitor lisinopril, demonstrating its prophylactic effect against migraine. Randomized studies have also been conducted on ARB (candesartan), and demonstrated its usefulness. Both migraine and hypertension are diseases with high prevalence, and the two coexist in many patients. ACE inhibitors and ARB are a group of drugs with few adverse effects and good tolerability, and the possibility of these drugs to become one of the prophylactic agents to improve the QOL of migraine patients is anticipated.

Comments and Evidence

A report published in 1995 demonstrated the prophylactic effect of ACE inhibitors for migraine in 17 patients with migraine diagnosed according to the criteria of the International Headache Society.[1] The subjects aged 18 to 59 years had moderate to severe migraine with at least two migraine attacks per month, and were treated with ACE inhibitors for a duration ranging from 3 months to 3 years. Most were given enalapril, and some used lisinopril. The mean dose was 16.4 mg (10 to 25 mg)/day. Ten patients showed marked response, 6 achieved moderate improvement, and 1 slight improvement. The major adverse event was cough; 3 patients discontinued treatment because of coughing and 1 continued treatment despite coughing. A RCT has proven the prophylactic effect of lisinopril 20 mg/day for migraine.[2] Lisinopril 20 mg/day reduced the hours with headache, days with headache, and days with migraine by 20% (95% confidence interval: 5 to 36%), 17% (5 to 30%) and 21% (9 to 34%), respectively, compared with placebo. Moreover, lisinopril reduced the days with migraine by at least 50% compared with placebo in 14 participants (14/60, 23.3%). Other studies on lisinopril include a relatively well designed case series,[1] research using patient database,[3][4] and an open-label study suggested the effectiveness of lisinopril 5 mg/day.[5] For enalapril also, evidence exists even though it is inadequate.[1][6] There is no evidence for migraine for the other ACE inhibitors. For ARB, the prophylactic effect of candesartan for migraine has been examined.[7] In an intention-to-treat (ITT) analysis of 57 patients, the mean number of days with headache for 12 weeks (primary end point) was 18.5 for placebo versus 13.6 for candesartan, showing a significant (P = .001) decrease with candesartan. Furthermore, when candesartan responder was defined as at least 50% improvement compared with placebo, the responder rate was 18/57 (31.6%) when assessed by days with headache, and 23/57 (40.4%) when assessed by days with migraine. For other ARB, the prophylactic effect of olmesartan 10 to 40 mg/day in patients with coexisting migraine and hypertension was investigated in an open-label study, which showed usefulness and good tolerability of olmesartan.[8] The migraine prophylactic effect of telmisartan 80 mg/day was evaluated in a RCT, which suggested the usefulness of the drug, but with no significant difference.[9]

In Japan, one case in which ACE inhibitor enalapril was effective was reported,[10] and several cases in which ARB (candesartan and telmisartan) were effective[11]-[13] were also reported.

From the above findings, the ACE inhibitor lisinopril and the ARB candesartan are recommended as prophylactic drugs for migraine. Start lisinopril from 5 mg/day, and if reduction in migraine attacks is inadequate, increase stepwise up to 20 mg/day. For candesartan, overseas evidence indicates a dose of 16 mg/day, and the European Federation of Neurological Societies migraine treatment guideline [14] lists candesartan 16 mg/day as the drug of third choice. In Japan, the dosing regimen of candesartan for hypertension is "4 to 8 mg/day orally, and increase up to 12 mg as necessary". In Japan, an open-

label study using 8 mg/day has been reported. Considering the use experience in Japan and safety, candesartan 8 mg/day is recommended for migraine prevention. For enalapril and olmesartan, while the evidence is not strong, their usefulness has been suggested, and these agents may be options. ACE inhibitors and ARB are a group of anti-hypertensive drugs with high quality evidence. Active use of these agents is recommended in patients with migraine and coexisting hypertension, and dosing should take into account the dose for hypertension treatment. Although the usefulness of ARB in patients with migraine but no hypertension has been reported, further accumulation of evidence is necessary.

• References

1) Bender WI: ACE inhibitors for prophylaxis of migraine headaches. Headache 1995; 35(8): 470-471.
2) Schrader H, Stovner LJ, Helde G, Sand T, Bovim G: Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ 2001; 322(7277): 19-22.
3) Onder G, Pahor M, Gambassi G, Federici A, Savo A, Carbonin P, Bemabei R; GIFA study: Association between ACE inhibitors use and headache caused by nitrates among hypertensive patients: results from the Italian group of pharmacoepidemiology in the elderly (GIFA). Cephalalgia 2003; 23(9): 901-906.
4) Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC: Reduction in the therapeutic intensity of abortive migraine drug use during ACE inhibition therapy: a pilot study. Pharmacoepidemiol Drug Saf 2004; 13(1): 41-47.
5) Schuh-Hofer S, Flach U, Meisel A, Israel H, Reuter U, Arnold G: Efficacy of lisinopril in migraine prophylaxis-an open label study. Eur J Neurol 2007; 14(6): 701-703.
6) Camarda R, Monastero R, Mannino M, Camarda C: Enalapril prophylaxis for migraine with aura. Headache 2003; 43(2): 170.
7) Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G: Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA 2003; 289(1): 65-69.
8) Charles MD, Jotkowitz S, Byrd LH: Prevention of Migraine With Olmesartan in Patients With hypertension/prehypertension. Headache 2006; 46(3): 503-507.
9) Diener HC, Gendolla A, Feuersenger A, Evers S, Straube A, Schumacher H, Davidai G: Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia 2009; 29(9): 921-927.
10) Kowa H, Takeshima T, Fukuhara Y, Ijiri T, Araki H, Nakajima K: A case of ACE inhibitor effective to prevent migraine-like attack. Japanese Journal of Headache 2003; 30(1): 37-38. (In Japanese)
11) Owada K: Efficacy of candesartan in the treatment of migraine in hypertensive patients. Hypertens Res 2004; 27(6): 441-446.
12) Iwasaki Y, Ikeda K, Iguchi H, Ichikawa Y, Igarashi O: Effectiveness of candesartan for migraine. Neurological Medicine 2004; 60(2): 218. (In Japanese)
13) Iwasaki Y, Iguchi H, Ikeda K: Usefulness of telmisartan for migraine – study of five cases. Neurological Medicine 2006; 64(2): 186-188. (In Japanese)
14) Members of the task force; Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sndor PS: EFNS guideline on the drug treatment of migraine-report of an EFNS task force. Eur J Neurol 2006; 13(6): 560-572.

• Search terms and secondary sources

- Search database: PubMed (2012/1/9)
  Migraine & prophylaxis 2568
  Migraine & (angiotensin-converting enzyme inhibitors) 41
  Migraine & (angiotensin receptor blockers) 37
  Migraine & losartan 2
  Migraine & Valsartan 2
  Migraine & candesartan 19
  Migraine & telmisartan 2
  Migraine & Irbesartan 1
  Migraine & olmesartan 2
  11 articles adopted
- Search database: Ichushi (2012/1/9)
  (Migraine/TH or Migraine/AL) and prophylaxis/AL 451
  (Migraine/TH or Migraine/AL) and ("Peptidyl-Dipeptidase A"/TH or ACE/AL) 154
  (Migraine/TH or Migraine/AL) and ("Angiotensin II Type 1 Receptor Blockers"/TH or ARB/AL) 97
  3 articles adopted

CQ II-3-8

Are antiepileptic drugs (valproic acid) effective for migraine prevention?

Recommendation

When migraine patients with 2 or more headache attacks per month are treated with oral valproic acid, reduction in the number of attacks per month can be expected (grade A recommendation). In adults, oral sodium valproate 400 to 600 mg/day is recommended (grade A recommendation). 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 (grade A recommendation). Valproic acid is contraindicated in women who are pregnant or has a possibility of being pregnant. **Grade A**

Background and Objective

Valproic acid increases the 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. As a migraine treatment, some 20 years of use experience 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. In Japan also, valproic acid has been covered by health insurance since 2010. Topiramate is evaluated favorably overseas as a prophylactic drug for migraine, but is not covered by health insurance in Japan.

Comments and Evidence

Prospective studies of valproic acid for migraine prevention consist of two studies on sodium valproate and four on divalproex sodium (compound of valproic acid and valproate in 1:1 ratio). From these results, a Cochrane review concludes that valproic acid reduces the frequency of headache attacks and increases the number of patients for whom migraine frequency is reduced by 50% or more.[1] In addition, some reports indicate that valproic acid reduces headache frequency as well as decreases headache intensity and shortens headache duration.[2][3] On the contrary, other report shows that valproic acid reduces headache frequency but does not improve headache intensity or headache duration.[4] When compared with other drugs, valproic acid shows similar effectiveness as flunarizine,[5] propranolol,[6] and topiramate.

In overseas countries, the European Federation of Neurological Science (EFNS) migraine treatment guideline recommends valproic acid at level A.[7] The American Academy of Neurology migraine guideline recommends valproic acid at grade A,[8] and describes its indication under the following conditions: (1) two or more disabling attacks (6 or more days) per month, (2) contraindication or no response to acute treatments, (3) use of abortive medication two or more times per week, and (4) uncommon migraine conditions including hemiplegic migraine.

The dose range showing effectiveness in overseas studies was 400 to 2,000 mg/day.[9] In the US, use of divalproex sodium 500 to 1,000 mg/day is approved for migraine prevention. The EFNS guideline recommends 500 to 1,800 mg/day.[7] In Japan, a dose of 800 mg/day was used in a trial (open-label study) of valproic acid for migraine prevention,[10] and doses ranging from 200 to 1,000 mg/day have been reported when case reports are included. In one study, the group with blood level lower than 50 μg/mL had less adverse effects than the group with 50 μg/mL or higher, while showing 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.[11] Furthermore, another report indicated that in migraine patients who did not respond to low-dose valproic acid, dose increase did not improve response.[12] From the above findings, the recommended dose of sodium valproate is 400 to 600 mg/day. Reports that measured blood levels[13][14] also recommended a target blood level less than 50 μg/mL.

According to a survey on the use of valproic acid in Japanese, adverse effects include somnolence, hyperamonemia, dizziness, hepatic function impairment, elevated creatine phosphokinase, and anemia.[15]

Special attention has to be given when administering valproic acid to women of child-bearing potential. Regarding malformations associated with valproic acid, combined data of eight cohort studies showed 118 malformations among a total

of 1,565 pregnancies in which women took valproic acid, and the incidence was significantly higher compared to controls not exposed to valproic acid or with chromosomal malformations.[16] The rate of teratogenicity increases when the dose of valproic acid exceeds 1,000 to 1,500 mg/day,[17)-20)] suggesting a dose- and blood level-dependent increase in teratogenicity rate. In a prospective study of pregnant women with epilepsy receiving monotherapy of antiepileptic drug (carbamazepine, lamotrigine, 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.[21] 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 unlike epilepsy treatment, use of valproic acid for the prevention of migraine 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 when using multidrug antiepileptic therapy,[17)18)] combined use with other antiepileptic drugs should be avoided. Patients should be advised 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 supplement 0.4 mg/day.[22]

Use of other antiepileptic drugs for migraine prevention is currently not covered by health insurance.

The usefulness of topiramate in migraine prevention has been confirmed by RCT.[23)24)] In a relatively large-scale placebo-controlled study, the monthly headache frequency was reduced by 1.1 days with placebo versus 2.1 days with topiramate 100 mg/day ($p = .008$), and 2.4 days with 200 mg/day ($p < .001$).[24] The American Academy of Neurology guideline published in 2012[25] gives grade A recommendation for topiramate, as for valproic acid.

For gabapentin, a study comparing gabapentin 2,400 mg/day with placebo reported a significant decrease in monthly frequency of attack, and the presence of adverse effects of moderate somnolence and dizziness.[26]

On the other hand, there are few reports indicating the effectiveness of lamotrigine for migraine. A study comparing lamotrigine 50 mg/day with placebo failed to demonstrate the effectiveness for the primary end point.[27] For carbamazepine and chlonazepam, there is a lack of evidence and effectiveness has not been demonstrated.

• 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 valporate 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.
9) Vikelis M, Rapoport AM: Role of antiepileptic drugs as preventive agents for migraine. CNS Drugs 2010; 24(1): 21-33.
10) Oana K, Takemae N: Effectives of valproic acid for migraine and its evaluation. Japanese Journal of Headache 2007; 34(2): 179-184. (In Japanese)
11) 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.
12) Ghose K, Niven B: Prophylactic sodium valproate therapy in patients with drug-resistant migraine. Methods Find Exp Clin Pharmacol 1998; 20(4): 353-359.
13) 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.
14) 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.
15) Tezuka S, Nakame N, Sato F, Sasamoto T, Mikura M, Goto T: Special Investigation of sodium valproate for patients with manic-depressive state due to mania or depression and mania. Japanese Journal of Clinical Psychopharmacology 2008; 11(10): 1909-1920. (In Japanese)
16) Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, de Jong-van den Berg LT; EUROCAT Antiepileptic Study Working Group: Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med 2010; 362(23): 2185-2193.
17) 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.
18) 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.
19) 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.
20) Vajda FJ, Hitchcock A, Graham J, Solinas C, OBrien 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.
21) 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.
22) Yerby MA: Management issues for women with epilepsy: neural tube defects and folic acid supplementation. Neurology 2003; 61(6 Suppl 2): S23-26.
23) Storey JR, Calder CS, Hart DE, Potter DL: Topiramate in migraine prevention: a double-blind, placebo-controlled study. Headache 2001; 41(10): 968-975.
24) Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, Neto W, Schwabe S, Jacobs D; MIGR-002 Study Group: Topiramate for migraine prevention: a randomized controlled trial. JAMA 2004; 291(8): 965-973.
25) Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society: Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78(17): 1337-1345.
26) Mathew NT, Rapoport A, Saper J, Magnus L, Klapper J, Ramadan N, Stacey B,Tepper S: Efficacy of gabapentin in migraine prophylaxis. Headache 2001; 41(2): 119-128.
27) Gupta P, Singh S, Goyal V, Shukla G, Behari M: Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). Headache 2007; 47(3): 402-412.

• Search terms and secondary sources

- Search database: PubMed (2010/12/30)
  (migraine) and ((preventive) or (prophylactic) or (prophylaxis)) and ((valproate) or (valproic acid))225
- 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)
  Valproic acid and migraine 68

CQ II-3-9-1

Are antidepressants effective for migraine prevention?

Recommendation

Amitriptyline is effective for migraine prevention. In September 2012, amitriptyline was approved for off-label use for migraine and tension-type headache in Japan. Start from a low dose (5 to 10 mg/day before bedtime), and titrate upward while confirming the effect. A dose of 10 to 60 mg/day is recommended. **Grade A**

Background and Objective

Chronic headache may coexist with a depressive state. Use of antidepressants is known not only to improve the depression state but also to reduce headache. Antidepressants are also considered to be useful in patients with migraine not accompanied by a depressive state. The pathophysiology of migraine has been associated with neurotransmitters such as serotonin. Many antidepressants are considered to exhibit anti-depressive effect by increasing the extraneuronal serotonin and norepinephrine concentrations in the central nervous system. Although the mechanisms of action by which antidepressants prevent migraine remain unknown, these drugs have long been used in various countries.

Comments and Evidence

Amitriptyline, a tricyclic antidepressant, is the most studied and clinically the most widely used drug in this class. Three randomized placebo-controlled trials on amitriptyline have been conducted.[1)-4)] Using headache index and frequency of migraine attacks as outcome measures, the doses and treatment durations of 50 to 150 mg/day for 8 weeks,[4)] 50 to 100 mg/day for 4 weeks,[2)] and 30 to 60 mg/day for 27 weeks[3)] have consistently showed effectiveness, and a metaanalysis[5)] has also demonstrated its usefulness.

Two studies compared amitriptyline and propranolol. The evaluations of amitriptyline 50 to 150 mg/day and propranolol 80 to 240 mg/day for a treatment period of 8 weeks yielded almost equivalent prophylactic effect for migraine.[4)] In a report comparing amitriptyline 25 to 75 mg/day and propranolol 60 to 160 mg/day for 6 months or longer,[6)] both agents were effective, but the efficacy of amitriptyline was higher than that of propranolol in patients with migraine and coexisting tension-type headache. Regarding the dose of amitriptyline used in Japan, the starting dose is recommended to be 5 to 10 mg/day based on experience.

Whether the anti-migraine effect of amitriptyline and other antidepressants is mediated via the antidepressant effect or is an independent action remains inconclusive. However, clinically the prophylactic effect of amitriptyline for chronic headache is definitive irrespective of whether or not a depressive state exists.[5)]

Two placebo-controlled studies of clomipramine have been reported, but its usefulness is not yet proven. Although combined use of nortriptyline and topiramate[7)] or propranolol[8)] has been reported to be effective, the prophylactic effect of nortriptyline alone has not been proven. No placebo-controlled clinical study on imipramine has been conducted.

For tetracyclic antidepressants, mianserin has been studied in one RCT.[9)] Treatment with mianserin 60 mg/day significantly reduced the intensity and frequency of headache compared to the observation period but the effect was not significant compared with placebo. Trazodone has been shown to be useful in children with migraine.[10)] There is no evidence for maprotiline and setiptiline.

Among the selective serotonin reuptake inhibitors (SSRI), fluoxetine was studied in three RCT,[11)] two of which showed usefulness. Fluvoxamine which is available in Japan has been suggested to have the same effectiveness as amitriptyline,[12)] but no placebo-controlled study has been conducted. Although cases responsive to paroxetine have been reported, evidence is insufficient. The effectiveness of sertraline has not been reported.

For serotonin norepinephrine reuptake inhibitors (SNRI), reports have suggested the effectiveness of venlafaxine[13)] (currently not available in Japan) and duloxetine[14)-16)] (available in Japan), but no placebo-controlled clinical trials have been reported. There is no report on the migraine prophylactic effect for milnacipran. Further studies on SSRI and SNRI are required in the future.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), has been suggested to be effective for migraine prevention in some case reports,[17)18)] but large-scale clinical trials have not been reported.

As for other antidepressants, some reports have suggested the usefulness of sulpiride, but evidence is unclear.

Tricyclic antidepressants have well known adverse effects (such as somnolence and thirst) due to the anticholinergic action. Although these adverse events occur at high frequencies, they can be reduced by starting from low doses.[3)]

• References

1) Couch JR, Hassanein RS: Amitriptyline in migraine prophylaxis. Arch Neurol 1979; 36(11): 695-699.
2) Couch JR, Ziegler DK, Hassanein R: Amitriptyline in the prophylaxis of migraine. Effectiveness and relationship of antimigraine and antidepressant effects. Neurology 1976; 26(2): 121-127.
3) Gomersall JD, Stuart A: Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. J Neurol Neurosurg Psychiatry 1973; 36(4): 684-690.
4) Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J: Migraine prophylaxis. A comparison of propranolol and amitriptyline. Arch Neurol 1987; 44(5): 486-489.
5) Tomkins GE, Jackson JL, OMalley PG, Balden E, Santoro JE: Treatment of chronic headache with antidepressants: a meta-analysis. Am J Med 2001; 111(1): 54-63.
6) Mathew NT: Prophylaxis of migraine and mixed headache. A randomized controlled study. Headache 1981; 21(3): 105-109.
7) Krymchantowski AV, da Cunha Jevoux C, Bigal ME: Topiramate plus nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders. J Headache Pain 2012; 13(1): 53-59.
8) Dominques RB, Silva AL, Domingues SA, Aquino CC, Kuster GW: A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for preventive treatment of migraine. Arq Neuropsiquiatr 2009; 67(4): 973-977.
9) Monro P, Swade C, Coppen A: Mianserin in the prophylaxis of migraine: a double-blind study. Acta Psychiatr Scand Suppl 1985; 320: 98-103.
10) Battistella PA, Ruffilli R, Cernetti R, Pettenazzo A, Baldin L, Bertoli S, Zacchello F: A placebo-controlled crossover trial using trazodone in pediatric migraine. Headache 1993; 33(1): 36-39.
11) dAmato CC, Pizza V, Marmolo T, Giordano E, Alfano V, Nasta A: Fluoxetine for migraine prophylaxis: a double-blind trial. Headache 1999; 39(10): 716-719.
12) Bnk J: A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. Headache 1994; 34(8): 476-478.
13) Tarlaci S: Escitalopram and venlafaxine for the prophylaxis of migraine headache without mood disorders. Clin Neuropharmacol 2009; 32(5): 254-258.
14) Taylor AP, Adelman JU, Freeman MC: Efficacy of duloxetine as a migraine preventive medication: possible predictors of response in a retrospective chart review. Headache 2007; 47(8): 1200-1203.
15) Volpe FM: An 8-week, open-label trial of duloxetine for comorbid major depressive disorder and chronic headache. J Clin Psychiatry 2008; 69(9); 1449-1454.
16) Artemenko AR, Kurenkov AL, Nikitin SS, Filatova EG: Duloxetine in the treatment of chronic migraine. Zh Nevrol Psikhiatr Im S S Korsakova 2010; 110(1): 49-54.
17) Brannon GE, Rolland PD, Gary JM: Use of mirtazapine as prophylactic treatment for migraine headache. Psychosomatics 2000; 41(2): 153-154.
18) Lvy E, Margolese HC: Migraine headache prophylaxis and treatment with low-dose mirtazapine. Int Clin Psychopharmacol 2003; 18(5): 301-303.

• Search terms and secondary sources

- Search database: PubMed (2012/1/16)

migraine and antidepressant 723
migraine and antidepressant and {(randomized and controlled) or double-blind} 122
migraine and amitriptyline and {(randomized and controlled) or double-blind} 44
migraine and imipramine and {(randomized and controlled) or double-blind} 0
migraine and clomipramine and {(randomized and controlled) or double-blind} 3
migraine and nortriptyline and {(randomized and controlled) or double-blind} 3
migraine and trimipramine and {(randomized and controlled) or double-blind} 0
migraine and lofepramine and {(randomized and controlled) or double-blind} 0
migraine and amoxapine and {(randomized and controlled) or double-blind} 0
migraine and dosulepin and {(randomized and controlled) or double-blind} 0
migraine and mianserin and {(randomized and controlled) or double-blind} 3
migraine and maprotiline and {(randomized and controlled) or double-blind} 0
migraine and setiptiline and {(randomized and controlled) or double-blind} 0
migraine and trazodone and {(randomized and controlled) or double-blind} 5
migraine and SSRI and {(randomized and controlled) or double-blind} 34
migraine and paroxetine and {(randomized and controlled) or double-blind} 3
migraine and fluvoxamine and {(randomized and controlled) or double-blind} 3
migraine and sertraline and {(randomized and controlled) or double-blind} 1
migraine and SNRI and {(randomized and controlled) or double-blind} 0
migraine and milnacipran and {(randomized and controlled) or double-blind} 0
migraine and sulpiride and {(randomized and controlled) or double-blind} 1
migraine and duloxetine 8
migraine and mirtazapine 5

CQ II-3-9-2

Is combined use of antidepressants (SSRI/SNRI) and triptan safe?

Recommendation

Combined use of triptans and antidepressants (SSRI/SNRI) is possible. However, attention must be paid to serotonin syndrome. **Grade B**

Background and Objective

Migraine occurs coincidentally with depressive disorder/depressive state at high frequency. In migraine patients, serotonergic drugs such as serotonin selective reuptake inhibitors (SSRI) and serotonin noradrenalin reuptake inhibitors (SNRI) are used frequently as prophylaxis for migraine or treatment for depressive disorder/depressive state. The potential risk of developing serotonin syndrome by combined use of triptans (serotonin receptor agonist) and SSRI/SNRI is a concern. The evidence concerning safety of their use is commented below.

Comments and Evidence

Serotonin syndrome is caused by excessive serotonergic activities, and manifests nervous and muscular symptoms (such as increased tendon reflex, myoclonus, and muscle rigidity), autonomic symptoms (such as fever, tachycardia, sweating, tremor, diarrhea, and rubeosis), and psychiatric symptoms (such as anxiety, agitation, confusion, and hypomania). The SSRI/SNRI, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, lithium carbonate, analgesics, antitussives, and supplements (St. John's wort) are known to be associated with serotonin syndrome.[1] Hunter Serotonin Toxicity Criteria[2] and Sternbach criteria[3] are used as diagnostic criteria.

In 2006, the US Food and Drug Administration (FDA) issued an alert to the effect that the risk of serotonin syndrome may increase by combined use of triptan and SSRI/SNRI, based on a report of 29 cases of serotonin syndrome occurring in patients treated with triptans and SSRIs/SNRIs.[4] In 2008, Soldin and Tonning[5] reported that of over 100 million persons worldwide using triptans since 1991, there were 11 cases of serotonin syndrome associated with the use of triptan alone. Additionally, a one-year prospective study showed that of 12,339 persons using subcutaneous sumatriptan, 1,784 also used SSRI in combination and there was no report of serotonin syndrome.[5]

In 2010, the American Headache Society re-evaluated the 29 cases that formed the basis of the FDA alert and the 11 cases reported by Soldin and Tonning.[5] Among the 29 cases, 10 cases fulfilled the Sternbach criteria but none of the cases satisfied the Hunter Serotonin Toxicity Criteria. Regarding the 11 cases reported by Soldin and Tonning,[5] detailed evidence for a diagnosis of serotonin syndrome was not provided. From the above findings, the American Headache Society currently concludes that there is inadequate evidence to support an increase in risk of serotonin syndrome with triptan monotherapy or combined triptan and SSRI/SNRI therapy. Moreover, triptan has high affinity for 5-HT1B/1D/1F but low affinity for 5-HT1A receptors. On the other hand, serotonin syndrome is associated with 5-HT2A receptor stimulation in animals models; therefore the skepticism about the speculated association with 5-HT1A stimulation is also supported from the pharmacological viewpoint.

Nevertheless, given the seriousness of the condition, clinicians should pay attention when using these drugs and ensure appropriate treatment in the remote event that serotonin syndrome occurs.[6]

• References

1) The Manual Committee of Japanese Society of Clinical Neuropsychopharmacology, Japanese Society of Hospital Pharmacist, and Commission of Comprehensive Measures for Serious Adverse Reactions: Manual of serious adverse effects according to disease: serotonin syndrome. Ministry of Health, Labour and Welfare, 2010. (In Japanese)
http://www.info.pmda.go.jp/juutoku/file/jfm1003003.pdf
2) Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM: The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003; 96(9): 635-642.
3) Sternbach H: The serotonin syndrome. Am J Psychiatry 1991; 148(6): 705-713.
4) Food and Drug Administration (FDA): Public Health Advisory - Combined Use of 5-Hydroxytryptamine Receptor Agonists (Triptans), Selective Serotonin Reuptake Inhibitors (SSRIs) or Selective Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) May Result in Life-threatening

Serotonin Syndrome. 2006.
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm124349.htm
5) Soldin OP, Tonning JM; Obstetric-Fetal Pharmacology Research Unit Network: Serotonin syndrome associated with triptan monotherapy. N Engl J Med 2008; 358(20): 2185-2186.
6) Evans RW, Tepper SJ, Shapiro RE, Sun-Edelstein C, Tietjen GE: The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. Headache 2010; 50(6): 1089-1099.

• Search terms and secondary sources

- Search database: PubMed (2011/12/21)
  {triptans} and {(SSRI) or (SNRI)} 397
  {triptans} and {(SSRI) or (SNRI)} and {serotonin syndrome} 40
  {triptans} and {serotonin syndrome} 2661
  {triptans} and {serotonin syndrome} and {migraine} 86

CQ II-3-10

Are magnesium, vitamin B12, feverfew, and analgesics effective for migraine prevention?

Recommendation

Magnesium, vitamin B2, and feverfew can be expected to prevent migraine to some extent. Because of the absence of serious adverse reactions and the low cost, these medications may be considered as an option for migraine prophylaxis. NSAIDs and naproxen have significant migraine prophylactic effect compared with placebo, but medication-overuse headache and drug dependence are issues, and therefore should be used only for short-term prophylactic therapy.

Grades B and C (magnesium, vitamin B2 and feverfew: B; NSAID short-term prophylaxis: C)

Background and Objective

Some organic foods and ingredients used in supplements, represented by magnesium, vitamin B2 (riboflavin) and feverfew, have been suggested to have prophylactic effect for migraine. Some migraine patients who do not favor prophylactic therapy with prescription drugs prefer to take these supplements. In addition, NSAIDs that are used as acute treatment are commonly used as short-term prophylactic therapy for menstrual migraine and menstrually related migraine. A literature search was conducted to examine the migraine prophylactic effects of these compounds.

Comments and Evidence

The blood magnesium level and intrathecal magnesium level have been reported to be lowered in migraine patients, and magnesium supplementation has been attempted for migraine prevention. There are five reports of randomized control trial (RCT) on migraine prophylaxis with oral magnesium, four of which reported effectiveness[1)-4)] and one study reported no efficacy.[5)] Therefore, magnesium is considered to be effective for the prevention of migraine (grade B recommendation). There are three reports of RCT on acute treatment of migraine with intravenous magnesium. One study using 2 g reported no effect.[6)] Another study using 1 g reported that the treatment was effective and safe.[7)] The third study found that while 2 g was useful in alleviating headache, there was no significant difference compared with metoclopramide or placebo.[8)]

From the hypothesis of an association between mitochondrial dysfunction and migraine, RCT have been conducted on its migraine prophylactic effect. In a study of 55 migraine patients treated with oral vitamin B2 400 mg/day or placebo for three months, vitamin B2 significantly decreased headache frequency and shortened the number of days with headache in migraine patients.[9)] Two RCT on children have been reported. Studies using 200 mg/day and using 50 mg/day both demonstrated no effectiveness.[10)11)] Because of its high efficacy, good tolerability, and low cost, vitamin B2 is a promising option for migraine prophylaxis in adults (grade B recommendation). One RCT using coenzyme Q10, another useful agent that improves mitochondrial function, also reported its effectivenss.[12)]

Feverfew is a herb and has been considered to be effective in preventing migraine from the past. There are three reports of RCT on feverfew, two of which indicated its effectiveness[13)14)] while one observed effectiveness only in intention-to-treat (ITT) analysis. Adverse effects were similar to placebo, with no dose-dependent difference (grade B recommendation).[15)] An RCT using the feverfew CO_2-extract (MIG-99) also reported its effectiveness.[16)]

In 2004, a study investigating the effectiveness of a compound containing the three above-mentioned agents was reported.[17)] Forty-nine migraine patients were treated with a combination of magnesium 300 mg, vitamin B2 400 mg and feverfew 100 mg, or placebo containing vitamin B2 25 mg for three months. There were no significant differences in the frequency and intensity of headache between two groups, but significant headache improvement compared to before treatment was observed in both groups, which may suggest that the effect observed with the combination could reflect the migraine prevention effect of vitamin B2 25 mg alone. Although the number of clinical trials for magnesium, vitamin B2 and feverfew remains small, their effectives for migraine prevention is being proven gradually.

Among analgesics such as NSAIDs, naproxen has been shown in at least five RCT to have significant prophylactic effect for migraine compared with placebo, and although gastrointestinal events are thought to be common, adverse effects did not

differ compared to placebo.[18)19)] Aspirin taken orally at a dose of 1,300 mg/day is known to be effective for migraine prevention.[20)21)] Among the selective cyclooxygenase (COX)-2 inhibitors, rofecoxib has been reported to be an effective short-term prophylactic therapy for menstrually related migraine, but evidence remains insufficient.[22)] There is no evidence for migraine prevention with loxoprofen, diclofenac, selective COX-2 inhibitors, meloxicam, etodolac and nabumetone, which are currently available in Japan. Since some analgesics including NSAIDs exhibit prophylactic effect for migraine, they may be considered as options not only as acute treatment but also as prophylactic drugs. However, due to the issue of medication-overuse headache, these agents are not suitable for long-term prophylactic therapy. There is one report on RCT of short-term prophylactic therapy for menstrual migraine. In this study, subjects took naproxen 500 mg twice daily for 13 days during each menstrual cycle, for three cycles, and naproxen significantly reduced headache frequency and intensity compared to placebo.[23)] Evidence for menstrually related migraine is insufficient,[24)] and generally 5 to 7-day treatment is considered. Although there is no report of RCT for status migrainosus, drugs are administered empirically for 3 to 7 days. From the above findings, their use should be limited to short-term prophylactic therapy for menstrual migraine, menstrually related migraine, and status migrainosus (grade C recommendation).

• References

1) Facchinetti F, Sances G, Borella P, Genazzani AR, Nappi G: Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. Headache 1991; 31(5): 298-301.
2) Peikert A, Wilimzig C, Khne-Volland R: Prophylaxis of migraine with oral magnesium: results from a prospective, multicenter, placebo-controlled and double-blind randomized study. Cephalalgia 1996; 16(4): 257-63.
3) Wang F, Van Den Eeden SK, Ackerson LM, Salk SE, Reince RH, Elin RJ: Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial. Headache 2003; 43(6): 601-610.
4) Kseoglu E, Talaslioglu A, Gnl AS, Kula M: The effects of magnesium prophylaxis in migraine without aura. Magnes Res 2008; 21(2): 101-108.
5) Pfaffenrath V, Wessely P, Meyer C, Isler HR, Evers S, Grotemeyer KH, Taneri Z, Soyka D, Gbel H, Fischer M: Magnesium in the prophylaxis of migraine: a double-blind, placebo-controlled study. Cephalalgia 1996; 16(6): 436-440.
6) Corbo J, Esses D, Bijur PE, Iannaccone R, Gallagher EJ: Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency department treatment of migraine headache. Ann Emerg Med 2001; 38(6): 621-627.
7) Demirkaya S, Vural O, Dora B, Topuolu MA: Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. Headache 2001; 41(2): 171-177.
8) Cete Y, Dora B, Ertan C, Ozdemir C, Oktay C: A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the Emergency Department. Cephalalgia 2005; 25(3): 199-204.
9) Schoenen J, Jacquy J, Lenaerts M: Effectiveness of high-dose riboflavin in migraine prophylaxis: A randomized controlled trial. Neurology 1998; 50(2): 466-470.
10) Bruijn J, Duivenvoorden H, Passchier J, Locher H, Dijkstra N, Arts WF: Medium-dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomized, double-blind, cross-over trial. Cephalalgia 2010; 30(12): 1426-1434.
11) MacLennan SC, Wade FM, Forrest KML, Ratanayake PD, Fagan E, Antony J: High-dose riboflavin for migraine prophylaxis in children: A double-blind, randomized, placebo-controlled trial. J Child Neurol 2008; 23(11): 1300-1304.
12) Sndor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, Seidel L, Agosti RM, Schoenen J: Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology 2005; 64(4): 713-715.
13) Johnson ES, Kadam NP, Hylands DM, Hylands PJ: Efficacy of feverfew as prophylactic treatment of migraine. Br Med J (ClinResEd) 1985; 291(6495): 569-573.
14) Murphy JJ, Heptinstall S, Mitchell JR: Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. Lancet 1988; 2(8604): 189-192.
15) Pfaffenrath V, Diener HC, Fischer M, Friede M, Henneicke-von Zepelin HH; Investigators. The efficacy and safety of Tanacetum parthenium (feverfew) in migraine prophylaxis: a double-blind, multicentre, randomized placebo-controlled dose-response study. Cephalalgia 2002; 22(7): 523-532.
16) Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH: Efficacy and safety of 6.25 mg t.i.d. feverfew CO2-extract(MIG-99) in migraine prevention: a randomized, double-blind, multicentre, placebo-controlled study. Cephalalgia 2005; 25(11): 1031-1041.
17) Maizels M, Blumenfeld A, Burchette R: A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. Headache 2004; 44(9): 885-890.
18) Welch KM, Ellis DJ, Keenan PA: Successful migraine prophylaxis with naproxen sodium. Neurology 1985; 35(9): 1304-1310.
19) Bellavance AJ, Meloche JP: A comparative study of naproxen sodium, pizotyline and placebo in migraine prophylaxis. Headache 1990; 30(11): 710-715.
20) Ryan RE Sr, Ryan RE Jr: Migraine prophylaxis: a new approach. Laryngoscope 1981; 91(9 Pt 1): 1501-1506.
21) ONeill BP, Mann JD: Aspirin prophylaxis in migraine. Lancet 1978; 2(8101): 1179-1181.
22) Von Seggern RL, Mannix LK, Adelman JU: Rofecoxib in the prevention of perimenstrual migraine: an open-label pilot trial. Headache 2004; 44(2): 160-165.
23) Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G: Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. Headache 1990; 30(11): 705-709.
24) Pringsheim T, Davenport WJ, Dodick D: Acute treatment and prevention of menstrually related migraine headache: evidence-based review. Neurology 2008; 70(17): 1555-1563.

• Search terms and secondary sources

- Search database: PubMed (2012/6/4)
  migraine OR vascular headache OR hemicranias 68389
  & magnesium 271
  & vitamin B 271
  & riboflavin 78
  & feverfew 75
  & naproxen1 95
  & flurbiprofen 22
  & ketoprofen 41
  & tolfenamic acid 34
  & aspirin 735
  & fenoprofen 8
  & ibuprofen 228
  & indomethacin 575
  & lornoxicam 6
  & rofecoxib 30
  & meloxicam 3
  & etodolac 8
  & nabumetone 4
  & loxoprofen 7
  & diclofenac 102
  & mefenamic acid 31
  & tramado l17
- Search database: Ichushi Web for articles published in Japan (2011/11/21)
  (migraine/TH or migraine/AL) and (magnesium/TH or magnesium/AL) 21
  (migraine/TH or migraine/AL) and ("magnesium sulfate"/TH or sulfate magnesium/AL) 4
  (migraine/TH or migraine/AL) and (riboflavin/TH or vitamin B2/AL) 11
  (migraine/TH or migraine/AL) and feverfew/AL 4
  (migraine/TH or migraine/AL) and (aspirin/TH or aspirin/AL) 61
  (migraine/TH or migraine/AL) and (indomethacin/TH or indomethacin/AL) 20
  (migraine/TH or migraine/AL) and (ibuprofen/TH or ibuprofen/AL) 43
  (migraine/TH or migraine/AL) and (rofecoxib/TH or rofecoxib/AL) 3
  (migraine/TH or migraine/AL) and (meloxicam/TH or meloxicam/AL) 1
  (migraine/TH or migraine/AL) and (naproxen/TH or naproxen/AL) 12
  (migraine/TH or migraine/AL) and (ketoprofen/TH or ketoprofen/AL) 1
  (migraine/TH or migraine/AL) and (loxoprofen/TH or loxoprofen/AL) 18
  (migraine/TH or migraine/AL) and (diclofenac/TH or diclofenac/AL) 11
  (migraine/TH or migraine/AL) and ("mefenamic acid"/TH or mefenamic acid/AL) 5
  flurbiprofen, tolfenamic acid, fenoprofen, lornoxicam, Etodolac Nabumetone, tramadol, tramadol-acetaminophen 0

CQ II-3-11

Are other prophylactic therapies effective for migraine prevention?

Recommendation

Since dihydroergotamine has long been used as a migraine prophylactic drug, and large-scale trials have proven its effectiveness, this drug can be considered appropriate as a prophylactic agent. In actual fact, however, dihydroergotamine is not used as the first choice drug for prophylaxis because combined use with triptan is contraindicated. For melatonin, although occasional reports have indicated its prophylactic effect for migraine, RCT has not demonstrated its usefulness. However, since serious adverse reactions are not observed, this drug may be considered for migraine prophylaxis in cases not responding to other prophylactic therapies. Regarding olanzapine, there are occasional reports of effectiveness, but evidence is insufficient. Paying close attention to adverse effects, this drug may be considered in cases not responding to other prophylactic therapies.

Grades B and C (dihydroergotamine: B, melatonin and olanzapine: C)

Background and Objective

A literature search was conducted on the prophylactic effect of dihydroergotamine for migraine attacks, focusing on large-scale trials. Regarding melatonin, since control of migraine attacks has been reported occasionally, a search for evidence of its usefulness was conducted. The antipsychotic olanzapine has been used empirically for refractory headache. Accordingly, literature was searched for evidence of the prophylactic effect of olanzapine. In addition, evidence for the migraine prophylactic effect of butterbur (*Petasites hybridus*) was also searched.

Comments and Evidence

Several randomized controlled trials (RCT) on dihydroergotamine have been reported. The PROMISE study [PROphylaxis of Migraine with SEglor (dihydroergotamine mesilate)] conducted in France included 363 migraine patients treated with dihydroergotamine or placebo for 5 months after a 1-month placebo run-in period.[1] In this study, oral dihydroergotamine was effective in preventing migraine attacks and in improving quality of life. The administration method is 1 mg three times daily. Several other clinical studies have been conducted, and reports that dihydroergotamine is generally effective in preventing migraine attacks are encountered. However, in Japan, while dihydroergotamine is sometimes used also in children, it is not frequently used as the first-choice drug in adult patients.

Melatonin secreted from the pineal gland affects hypothalamic function and is known to be closely associated with the pathophysiology of migraine. In migraine patients, impaired melatonin secretion has been reported to cause abnormal release of calcitonin gene-related peptide (CGPR). Therefore, from the mechanism of action, melatonin has strong potential as one of the migraine prophylactic drugs. While melatonin 3 mg/day was reported to be effective in preventing migraine attacks, an RCT of 48 migraine patients found no significant difference between patients taking melatonin 2 mg orally one hour before bedtime and patients taking placebo.[2][3] In any case, both studies included small numbers of subjects, and further large-scale RCT is needed.

In the clinical setting, olanzapine has been used in cases of refractory headache, but the number of reports on olanzapine remains small. The report of Silberstein et al.[4] showed effectiveness in a small series. In this study, 50 patients with refractory migraine were treated with olanzapine for at least 3 months, and oral olanzapine 5 mg/day or 10 mg/day was markedly effective in improving headache attacks. The report concluded that olanzapine is very effective for patients with headache not responding to other available prophylactic drugs, or patients who have coexisting psychiatric diseases such as depressive disorder and bipolar disorder. However, it should be noted that weight gain as an adverse event is observed in 38% of the patients, and olanzapine is therefore contraindicated in patients with impaired consciousness and diabetes.

There are two RCT on butterbur (*Petasites hybridus*). A total of 293 migraine patients were randomized to butterbur (Petadolex) 150 mg/day, Petadolex 100 mg/day or placebo, and the three groups were compared. After treatment for 3 to 4 months with butterbur, the frequency of attacks was reduced significantly and over 50% of the patients showed symptomatic

improvement. Furthermore, adverse reactions are primarily gastrointestinal symptoms (such as burping), and few serious reactions are observed. Impaired liver function and malignant tumor have been reported.[5)-8)]

In January 27, 2012, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued an alert that butterbur is associated with liver toxicity and advised consumers not to use products containing butterbur (*Petasites hybridus*). Accompanying this move, the Japanese Ministry of Health, Labour and Welfare also issued a warning advising not to take these products (February 8, 2012).

• References

1) Pradalier A, Lantri-Minet M, Graud G, Allain H, Lucas C, Delgado A: The PROMISE study: PROphylaxis of migraine with SEglor (dihydroergotamine mesilate) in French primary care. CNS Drug 2004; 18(15): 1149-1163.
2) Alstadhaug KB, Odeh F, Salvesen R, Bekkelund SI: Prophylaxis of migraine with melatonin: A randomized controlled trial. Neurology 2010; 75(17): 1527-1532.
3) Peres MF, Zukerman E, da Cunha Tanuri F, Moreira FR, Cipolla-Neto J: Melatonin, 3mg, is effective for migraine prevention. Neurology 2004; 63(4): 757.
4) Silberstein SD, Peres MF, Hopkins MM, Shechter AL, Young WB, Rozen TD: Olanzapine in the treatment of refractory migraine and chronic daily headache. Headache 2002; 42(6): 515-518.
5) Agosti R, Duke RK, Chrubasik JE, Chrubasik S: Effectiveness of Petasites hybridus preparation in the prophylaxis of migraine: a systematic review. Phytomedicine 2006; 13(9-10): 743-746.
6) Lipton RB, Gbel H, Einhupl KM, Wilks K, Mauskop A: Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. Neurology 2004; 63(12): 2240-2244.
7) Pothmann R, Danesch U: Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. Headache 2005; 45(3): 196-203.
8) Diener HC, Rahlfs VW, Danesch U: The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. Eur Neurol 2004; 51(2): 89-97.

• Search terms and secondary sources

- Search database: PubMed (2011/11/18)
  migraine & {melatonin} 61
  & {olanzapine} 5
  & {butterbur} 35
  & {dihydroergotamine} 391& {prevention} 76
  & {prophylaxis} 88

CQ II-3-12

Is botulinum neurotoxin (BoNT) effective for migraine prevention?

Recommendation

Multiple randomized placebo-controlled trials have proven that botulinum neurotoxin type A is effective in reducing symptoms of chronic migraine. Moreover, several studies have verified that its symptom-reducing effect for chronic migraine is equivalent to that of topiramate. On the other hand, the effect on episodic migraine is not clear. Therefore, botulinum neurotoxin type A may be considered for chronic migraine when other treatments have failed. In Japan, this treatment is not covered by health insurance. **Grade A**

Background

Botulinum neurotoxin (BoNT) is a zinc metalloprotease produced by *Clostridium botulinum*. In nerve endings, BoNT binds receptors and are taken up into the nerve cells, where it cleaves the SNARE (soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor) protein and blocks exocytosis. As a result, secretion of neurotransmitters and expression of cell membrane receptors are affected. BoNT is classified into types A to G. Type A (BoNT-A) is used clinically for the treatment of migraine. BoNT-A has proven efficacy not only for dystonia but also for pain disorders and autonomic dysfunctions. Although the mechanism by which BoNT-A exhibits therapeutic effect against migraine remains unclear, inhibition of calcitonin gene-related protein (CGRP) release and inhibition of muscle contraction may be involved.[1)]

Comments and Evidence

Botulinum neurotoxin type A (BoNT) is marketed worldwide as products brand named Botox or Dysport. The former is used clinically in Japan mainly for the treatment of dystonia. From around 2000, the prophylactic effect of BoNT-A for paroxysmal migraine began to be investigated by randomized placebo-controlled double-blind trials. Using the change from baseline in number of headache attacks as the primary end point, no significant difference was observed compared to placebo.[2)] Due to the difficulties in interpreting some results such as that the effect of BoNT-A 25 U is superior to that of 75 U,[3)] Evers et al.[4)] concluded that the prophylactic effect of BoNT-A for paroxysmal migraine is not certain. However, a recent double-blind randomized placebo-controlled trial of Dysport showed superiority of Dysport compared to placebo at some secondary end points.[5)] In addition, since some open-label studies have reported the effectiveness of BoNT-A, the prophylactic effect of BoNT-A for paroxysmal migraine cannot be totally excluded.

On the other hand, the effect of BoNT-A on chronic daily headache (CDH) and chronic migraine has attraction attention in North America. Mathew et al.[6)] randomized CDH patients to placebo- and BoNT-A-treated groups, and examined the therapeutic effect during treatment for 180 days. During this period, the majority of the CDH patients had chronic migraine. For the primary end point, which was the change from baseline in frequency of headache-free days in a 30-day period, there was no difference between BoNT-A- and placebo-treated groups. However, significant differences were observed in secondary end points including the percentage of patients with a decrease in headache frequency of 50% or greater. Furthermore, a subanalysis of patients not receiving other prophylactic medications revealed significant improvement in headache symptoms for many outcome measures in BoNT-A-treated group compared to placebo-treated group.[7)] With this background, multiple centers in North America and Europe jointly planned a phase III clinical trial called PREEMPT (the Phase III Research Evaluating Migraine Prophylaxis Therapy) to investigate the efficacy of BoNT-A for chronic migraine. Eventfully PREEMPT 1 was conducted in North America and PREEMPT 2 in Europe in parallel. In this trial, a total of 1,384 patients with chronic migraine participated and the BoNT-A-treated group was administered doses of 155 to 195 U. The double-blind trial period was planned for a relatively long period of 24 weeks. In PREEMPT 1, no significant difference was observed between BoNT-A- and placebo-treated groups with respect to the primary end point, which was mean change from baseline in number of headaches per 28 days.[8)] However, in PREEMPT 2, a significant difference was detected between two groups for the primary end point of change from baseline in number of days with headache per 28 days.[9)] An analysis of the pooled data of PREEMPT 1 and 2 concluded that BoNT-A significantly improves headache symptom compared with placebo in chronic

migraine patients.[10] Regarding the symptom reduction effect for chronic migraine, BoNT-A demonstrated equivalent efficacy as topiramate in comparative studies.[11][12] Many clinical studies have evaluated BoNT-A as having few serious adverse reactions and high tolerability. Based on the results of PREEMPT, BoNT-A is approved for the treatment of chronic migraine in American and European countries.

• References

1) Durham PL, Cady R: Insights into the mechanism of onabotulinumtoxinA in chronic migraine. Headache 2011; 51(10): 1573-1577.
2) Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A: Botulinum toxin A in the prophylactic treatment of migraine –a randomized, double-blind, placebo-controlled study. Cephalalgia 2004; 24(10): 838-843.
3) Silberstein S, Mathew N, Saper J, Jenkins S: Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. Headache 2000; 40(6): 445-450.
4) Evers S, Rahmann A, Haase J, Husted IW: Treatment of headache with botulinum toxin A-a review according to evidence-based medicine criteria. Cephalalagia 2002; 22(9): 699-710.
5) Chankrachang S, Arayawichanont A, Poungvarin N, Nidhinandana S, Boonkongchuen P, Towanabut S, Sithinamsuwan P, Kongsaengdao S: Prophylactic botulinum type A toxin complex (Dysport) for migraine without aura. Headache 2011; 51(1): 52-63
6) Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C; BOTOX CDH Study Group: Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache 2005; 45(4): 293-307.
7) Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD; BOTOX CDH Study Group: Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. Headache 2005; 45(4): 315-324.
8) Aurora SK, Dodick DW, Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, Diener HC, Brin MF; PREEMPT 1 Chronic Migraine Study Group: OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 2010; 30(7): 793-803.
9) Diener HC, Dodick DW, Aurora SK, Turkel CC, DeGryse RE, Lipton RB, Silberstein SD, Brin MF; PREEMPT 2 Chronic Migraine Study Group: OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 2010; 30(7): 804-814.
10) Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB, Diener HC, Brin MF; PREEMPT Chronic Migraine Study Group: OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010; 50(6): 921-936
11) Mathew NT, Jaffri SF: A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache 2009; 49(10): 1466-1478.
12) Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU: A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache 2011; 51(1): 21-32.

• Search terms and secondary sources

- Search database: PubMed (2011/12/21)
  Botulinum neurotoxin and migraine 198

CQ II-3-13

How is typical aura without headache diagnosed and treated?

Recommendation

1. Diagnosis

Typical aura without headache is diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders 2nd Edition (ICHD-II). **Grade A**

2. Treatment

Although the absolute number of cases is small, the risk of cerebral infarction is increased in patients who have migraine with aura. On the other hand, there is no report that typical aura without headache increases the risk of cerebral infarction. Therefore, active treatment is currently considered unnecessary for typical aura without headache. However, in the case of frequent occurrence and long duration, and in the case of strong patient anxiety, use of prophylactic drugs such as valproic acid and lomerizine may be considered. **Grade C**

Background and Objective

The ICHD-II defined visual, sensory or speech symptoms as aura of migraine, and visual aura is the most frequently encountered. Visual aura without headache is observed especially in the elderly. In this section, literature was searched on the diagnosis and the relevance of treatment for typical aura without headache.

Comments and Evidence

1. Diagnosis

According to the International Classification of Headache Disorders 2nd Edition (ICHD-II),[1)2)] the diagnostic criteria for typical aura without headache are as follows.

A. At least 2 attacks fulfilling criteria B to D

B. Aura consisting of at least one of the following, with or without speech disturbance, but no motor weakness:

1. fully reversible visual symptoms including positive features (such as flickering lights, spots or lines) and/or negative features (loss of vision)
2. fully reversible sensory symptoms including positive features (pins and needles) and/or negative features (numbness)

C. At least two of the following:

1. homonymous visual symptoms or unilateral sensory symptoms (or both)
2. at least one aura symptom develops gradually over ≥5 minutes, and/or different aura symptoms occur in succession over ≥5 minutes
3. each symptom lasts ≥5 and ≤60 minutes
4. not aggravated by routine physical activity such as walking or climbing stairs

D. Headache does not occur during aura or within 60 minutes following aura

E. Not attributed to another disorder

In the Framingham study including 2,110 subjects, visual aura without headache was reported by 26 subjects (1.23%), 77% of whom started having the symptoms after age 50 years, 42% had no history of migraine, and 58% never had accompanying headache.[3)] In another study of 100 women with migraine and 245 healthy women, The prevalence of visual aura without headache was 37% in migraine patients and 13% in the general population.[4)] In a study that observed patients who had migraine with aura for 10 to 20 years, 11% of the patients evolved to visual aura without headache.[5)] Therefore, it may be concluded that typical aura without headache is relatively common in elderly persons, and patients who have migraine with aura tend to evolve to only visual aura with advancing age.

It is important to differentiate from other diseases such as transient ischemic attack, recurrent cerebral embolism, epileptic seizure, and retinal disease. Special attention has to be given to cases of elderly onset without a history of migraine. In these cases, head MRI, magnetic resonance angiography (MRA) and electroencephalography should be conducted actively.

2. Treatment

There is no clear evidence concerning the necessity of treatment for typical aura without headache. The Framingham study reported no relationship between visual aura per se and increased risk of stroke.[3] On the other hand, studies have demonstrated that cerebral infarction is more frequent in patients who have migraine with aura.[3] A meta-analysis of eight studies that stratified the risk of cerebral infarction by the presence or absence of aura in migraine patients reported that the risk was significantly higher in patients who had migraine with aura [2.16 (1.53 to 3.03)] compared to patients who had migraine without aura [1.23 (0.90 to 2.11)], but the absolute number was very small.[6] Furthermore, in a population-based cross-sectional study of 780 subjects, patients who had migraine with aura had significantly high odds ratio of 12.4 for deep white matter lesion and 3.4 for cerebral infarction, but there was no association with cognitive impairment.[7]

The above findings thus indicate that for typical aura without headache that is common seen in the elderly, active acute treatment or prophylactic therapy is not necessary. However, in the case that the symptoms occur frequently or last a long duration, or when they cause disability in daily living, use of prophylactic drugs for migraine may be considered. Although the evidence so far is limited to case reports, valproic acid, gabapentin, topiramate, propranolol, and lomerizine are being used for prophylactic therapy. Among them, valproic acid and lomerizine that are covered by health insurance in Japan are recommended.[8] In a randomized double-blind, placebo-controlled cross-over study of tonabersat, a gap junction inhibitor, although the frequency of headache per se did not decrease, aura was significantly reduced from a mean of 3.2 episodes to 1 episode per 12 weeks. This agent may become a new treatment option in the future.[9] Since triptans do not reduce aura, use of triptans for typical aura without headache has no clinical relevance.[10][11]

• References

1) Headache Classification Subcommittee of the International Headache Society: The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004; 24(Suppl 1): 9-160.
2) The Headache Classification Committee of International Headache Society: International Classification of Headache Disorders 2nd Edition (ICHD-II). Japanese Journal of Headache 2004; 31(1): 13-188. (In Japanese)
3) Wijman CA, Wolf PA, Kase CS, Kelly-Hayes M, Beiser AS: Migrainous visual accompaniments are not rare in late life: the Framingham Study. Stroke 1998; 29(8): 1539-1543.
4) Mattsson P, Lundberg PO: Characteristics and prevalence of transient visual disturbances indicative of migraine visual aura. Cephalalgia 1999; 19(5): 479-484.
5) Cologno D, Torelli P, Manzoni GC: Migraine with aura: a review of 81 patients at 10-20 years follow-up. Cephalalgia 1998; 18(10): 690-696.
6) Schrks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T: Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009; 339: b3914.
7) Kurth T, Mohamed S, Maillard P, Zhu YC, Chabriat H, Mazoyer B, Bousser MG, Dufouil C, Tzourio C: Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. BMJ 2011; 342: c7357.
8) Kunkel RS: Migraine aura without headache: benign, but a diagnosis of exclusion. Cleve Clin J Med 2005; 72(6): 529-534.
9) Hauge AW, Asghar MS, Schytz HW, Christensen K, Olesen J: Effects of tonabersat on migraine with aura: a randomised, double-blind, placebo-controlled crossover study. Lancet Neurol 2009; 8(8): 718-723.
10) Bates D, Ashford E, Dawson R, Ensink FB, Gilhus NE, Olesen J, Pilgrim AJ, Shevlin P: Subcutaneous sumatriptan during the migraine aura. Sumatriptan Aura Study Group. Neurology 1994; 44(9): 1587-1592.
11) Olesen J, Diener HC, Schoenen J, Hettiarachchi J: No effect of eletriptan administration during the aura phase of migraine. Eur J Neurol 2004; 11(10): 671-677.

• Search terms and secondary sources

- Search database: PubMed (2012/6/4)
  Typical migraine aura without headache 228
  Typical aura without headache 3665
  & stroke 442
  & brain infarction 114
- Search database: Ichushi Web for articles published in Japan (2012/6/4)
  Typical aura without headache 5
  Typical migraine aura without headache 0

CQ II-3-14

How should chronic migraine be treated?

Recommendation

When migraine becomes chronic, implement appropriate prophylactic therapy (initiate prophylactic drug for migraine, or increase the dose, or change prophylactic drug, or add prophylactic drug) as early as possible. Investigate the reason for chronification, and simultaneously treat comorbid conditions if present. **Grade B**

Background and Objective

The goals of treating chronic migraine are to reduce headache frequency and severity, and duration of chronic migraine, and at the same time to limit the use of acute treatment drugs, prevent transformation to medication-overuse headache, and improve the functions and activities of daily living.[1] In recent years, the pathophysiology of chronification and organic changes in the brain have been elucidated gradually [see CQ II-1-6-1 What is the prognosis of migraine (including chronification of migraine)? (page 77)]. Also, compared to episodic migraine, chronic migraine results in more severe functional impairment, lower quality of life, anxiety and depression, and higher rate of medical facility consultation.[2] Therefore treatment for chronic migraine is very important. Literature was searched focusing on double-blind placebo-controlled trials of pharmacotherapy (excluding botulinum neurotoxin type A) for chronic migraine, especially chronic daily headache.

Comments and Evidence

Literature in English language from 1993 to 2011 was searched. Double-blind randomized controlled trials (RCT) of prophylactic therapies for chronic migraine (CM) and chronic daily headache (CDH) with drugs currently used in Japan (including those not covered by health insurance) were identified. The drugs comprise antiepileptic drugs of gabapentin (GBP), valproic acid (VPA), topiramate (TPM) and levetiracetam (LEV); the antidepressant amitriptyline; and the central muscle relaxant tizanidine.

In a GBP–placebo cross-over study reported in 2003 in which GBP 2,400 mg/day was administered for 6 weeks, percent headache-free days was 9.1% more with GBP.[3] Adverse effects were observed in 31% of subjects taking GBP, mainly vertigo, somnolence, deconditioning and nausea.

In a study of VPA 1,000 mg/day given for 3 months compared with placebo, patients with CM showed significant decreases in scores for the maximum pain scale (visual analog scale: VAS) and the usual VAS, together with a significant decrease in headache frequency.[4] The adverse effects of VPA were rare.

A large volume of evidence is available for TPM.[5)-7)] Treatment with approximately 100 mg/day for 3 months significantly reduced the number of days with headache per month. However, regarding whether TPM prevents the progression of frequent episodic migraine to CDH, there was no significant difference compared with placebo. Major adverse effects were paresthesia, fatigue, dizziness, and nausea, but there were no serious adverse effects.

A placebo-controlled study of LEV 3 g/day reported that LEV did not significantly reduce the number of days with headache, but significantly improved VAS score.[8]

A study on amitriptyline conducted in 1976-79 was reported in 2011.[9] At 8 and 16 weeks after amitriptyline (25 to 100 mg/day) treatment was started, headache frequency in CDH patients was reduced significantly. The adverse effects of amitriptyline included thirst, constipation, urinary retention, and dizziness.

In a placebo-controlled study of tizanidine, an A2 adrenergic receptor agonist, tizanidine (mean 18 mg/day) was effective in reducing the number of days with headache, headache intensity and headache duration.[10] However, tizanidine and placebo did not differ in the MIDAS score.

According to the above findings, valproic acid, topiramate (currently not covered by health insurance), and amitriptyline (off-label use for migraine) may be recommended for the treatment of CM and CDH in Japan. Considering the experience gained until now, lomerizine may also be added to this list.

• References

1) DAmico D: Pharmacological prophylaxis of chronic migraine: a review of double-blind placebo-controlled trials. Neurol Sci 2010; 31(Suppl 1): S23-28.
2) Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, Manack A, Goadsby PJ, Lipton RB: Disability, HRQoL and resource use among chronic and episodic migraineurs:results from the International Burden of Migraine Study (IBMS). Cephalalgia 2011; 31(3): 301-315.
3) Spira PJ, Beran RG; Australian Gabapentin Chronic Daily Headache Group: Gabapentin in the prophylaxis of chronic daily headache: a randomized, placebo-controlled study. Neurology 2003; 61(12): 1753-1759.
4) Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F: The effect of sodium valproate on chronic daily headache and its subgroups. J Headache Pain 2008; 9(1): 37-41.
5) Lipton RB, Silberstein S, Dodick D, Cady R, Freitag F, Mathew N, Biondi DM, Ascher S, Olson WH, Hulihan J: Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia 2011; 31(1): 18-30.
6) Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, Brandes JL, Bigal M, Saper J, Ascher S, Jordan DM, Greenberg SJ, Hulihan J; Topiramate Chronic Migraine Study Group: Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. Headache 2007; 47(2): 170-180.
7) Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ; TOPMAT-MIG-201 (TOP-CHROME) Study Group: Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia 2007; 27(7):814-823.
8) Beran RG, Spira PJ: Levetiracetam in chronic daily headache: a double-blind, randomized placebo-controlled study. (The Australian KEPPRA Headache Trial [AUS-KHT]). Cephalalgia 2011; 31(5): 530-536.
9) Couch JR; Amitriptyline Versus Placebo Study Group: Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache 2011; 51(1): 33-51.
10) Saper JR, Lake AE 3rd, Cantrell DT, Winner PK, White JR: Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. Headache 2002; 42(6): 470-482.

• Search terms and secondary sources

- Search database: PubMed (2011/12/21)
  chronic daily headache treatment 17966
  & chronic migraine 1641
  & therapy 1468
  chronic daily headache double-blind placebo-controlled study 764
  chronic migraine & treatment 2029
  & therapy 1764
  & double-blind placebo-controlled study 47