

What are the acute treatments for migraine and how are they used?

Recommendation

The mainstay of acute treatment for migraine is pharmacotherapy. The drugs used include (1) acetaminophen, (2) non-steroidal anti-inflammatory drugs (NSAIDs), (3) ergotamines, (4) triptans and (5) antiemetics. Stratified treatment according to the severity of migraine is recommended: use NSAIDs such as aspirin and naproxen for mild to moderate headache, and use triptans for moderate to severe headache, or even mild to moderate headache when NSAIDs were ineffective in the past. It is necessary to give guidance and cautions to patients having acute attacks, and explain the methods of using medications (timing, dose, frequency of use) and medication use during pregnancy and breast-feeding.

Grade A

Background and Objective

The objective of acute treatment is to resolve the migraine attack completely and rapidly and restore the patient's normal functions. An ideal treatment should have the following characteristics: (1) resolves pain and associated symptoms rapidly; (2) is consistently effective; (3) no recurrence; (4) no need for additional use of medication; (5) no adverse effects; (6) can be administered by the patients themselves; and (7) low cost. Literature was searched to identify acute treatments that satisfy the above conditions.

Comments and Evidence

The acute treatment drugs for migraine generally include (1) acetaminophens, (2) non-steroidal anti-inflammatory drugs (NSAIDs), (3) ergotamines, (4) triptans, and (5) antiemetics. For severe migraines including status migrainosus and migraine attacks refractory to treatment, (6) anesthetics, and (7) corticosteroids (dexamethasone) are used (Tables 1 and 2).¹⁾⁻⁹⁾ There are two approaches to the selection and sequencing of these medications: "step care" and "stratified care". In step care, safe and low-cost drugs are initially selected, and if treatment fails, then more expensive and specific drugs such as triptans are used. In stratified care, drugs are selected according to the degree of disability caused by migraine. A randomized trial has proven the effectiveness of stratified care, and recommended stratified treatment according to the severity of migraine.¹⁰⁾ The recommended treatment is to use NSAIDs or NSAIDs + antiemetic for mild to moderate headache; and use triptans for moderate to severe headache, or even mild to moderate headache if NSAIDs were ineffective in the past. In any case, combined use with antiemetic is useful. In Japan, triptan tablet, nasal spray and subcutaneous injection are available. From these various formulations, the appropriate drug is selected taking into consideration the attack frequency, intensity, degree of disability, associated symptoms, patient's preference, past treatment history and medical history. When prescribing acute treatment, physicians has to explain to and caution the patients that regardless of the medication, regular overuse for more than three months may cause medication-overuse headache. Moreover, while prescribing medications, it is necessary to confirm whether the patients have conditions for which certain drugs are contraindicated, or whether they are pregnancy or breast-feeding. Finally, as counseling for patients having acute attacks, physicians have to provide tailor-made lifestyle guidance appropriate for individual patients, such as to rest in a quiet and dark place, to cool the painful site, and to avoid taking a bath (for details usage of different drugs, see the corresponding sections in this guideline).

References

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• Search terms and secondary sources

- Search database: PubMed (2012/2/10)
- migraine & management 2260
- migraine & management & acute 423
- migraine & management & acute & treatment 335
- migraine & management & acute & treatment & review 201
- migraine & management & acute & treatment & guideline 37
- migraine & management & acute & treatment & RCT 15

Table 1. Summary of evidence for acute treatment

Drug	Quality of evidence	Scientific evidence	Clinical impression	Adverse effect	Recommendation grade	Efficacy group	Recommended dose
Triptans							
sumatriptan	I	+++	+++	occasional	A	1	50 mg/dose, 200 mg/day
sumatriptan (nasal spray)	I	+++	+++	occasional-frequent	A	1	20 mg/dose, 40 mg/day
sumatriptan (injection ampoule)	I	+++	+++	frequent	A	1	3 mg/dose, 6 mg/day
sumatriptan (self-injection)	I	+++	+++	frequent	A	1	3 mg/dose, 6 mg/day
sumatriptan (suppository)	I	+++	-	-	A**	1	-
sumatriptan (subcutaneous)	II	++	-	-	A**	1	-
zolmitriptan	I	+++	+++	occasional	A	1	2.5 mg/dose, 10 mg/day
zolmitriptan (nasal spray)	I	+++	-	-	A**	1	-
eletriptan	I	+++	+++	occasional	A	1	20 mg/dose, 40 mg/day
rizatriptan	I	+++	+++	occasional	A	1	10 mg/dose, 20 mg/day
naratriptan	I	+++	+++	occasional	A	1	2.5 mg/dose, 5 mg/day
naratriptan (injection)	I	+++	-	-	A**	1	-
almotriptan	I	+++	-	-	A**	1	-
frovatriptan	I	+++	-	-	A**	1	-
Anxiolytics, antipsychotics, anesthetics, antiemetics							
metoclopramide	I	+++	++	occasional	A**	2	5 mg/dose, 30 mg/day
metoclopramide (intramuscular/intravenous)	I	+++	++	occasional	A**	2	10 mg/dose, 20 mg/day
domperidone	II	++	++	occasional	A**	2	5 mg/dose, 30 mg/day
domperidone (suppository)	II	++	-	occasional	B**	4	60 mg/dose
prochlorperazine	I	+++	-	occasional-frequent	B**	4	5 mg/dose
prochlorperazine (intramuscular)	I	+++	-	occasional-frequent	B**	4	5 mg/dose
chlorpromazine	I	+++	-	occasional-frequent	B**	4	30 mg/dose
chlorpromazine (intramuscular)	I	+++	-	occasional-frequent	B**	4	10 mg/dose
droperidol (intramuscular)	II	++	-	occasional-frequent	C**	4	-
propofol (intravenous)	III	+	-	frequent	C**	4	-
diazepam (intramuscular/ intravenous)	III	+	-	frequent	C**	4	-
Acetaminophen/NSAIDs							
acetaminophen	I	+++	++	occasional	A	2	0.5 (-10) g/dose, 1.5 (-4) g/day
aspirin	I	+++	++	occasional	A	2	330 mg/dose, 990 mg/day
ibuprofen	I	+++	++	occasional	A**	2	100-200 mg/dose, 600 mg/day
diclofenac	I	+++	++	occasional	A*	2	25-50 mg/dose, 75-100 mg/day
naproxen	I	+++	++	occasional	A**	2	100-300 mg/dose, 300-600 mg/day
etodolac	II	++	++	occasional	A**	2	100-200 mg/dose, 400 mg/day
celecoxib	II	++	++	rare-occasional	A**	2	100-200 mg/dose, 400 mg/day
mefenamic acid	II	++	++	occasional	A	2	250-500 mg/dose, 1,500 mg/day
zaltoprofen	III	+	++	occasional	A**	2	80-160 mg/dose, 240 mg/day
pranoprofen	III	+	++	occasional	A**	2	75-150 mg/dose, 225 mg/day
loxoprofen	III	+	++	occasional	A*	2	60-120 mg/dose, 240 mg/day
lornoxicam	III	+	++	occasional	A**	2	4-8 mg/dose, 24 mg/day

Ergotamines							
ergotamine-caffeine combination	II	++	++	frequent	B	4	withdrawn from market in Japan
ergotamine-caffeine-pyrine combination	II	++	++	frequent	B	4	1 tablet/dose, 3 tablets/day, up to 10 tablets/week, combined use with triptans contraindicated
dihydroergotamine	II	++	++	frequent	B	4	1 mg/dose, 3 mg/day, combined use with triptans contraindicated
Steroids							
dexamethasone (intravenous)	III	+	++	occasional	C**	3	2–8 mg/dose
hydrocortisone	III	+	++	occasional	C**	3	200–500 mg/dose
Others							
tramadol	III	+	-	occasional-frequent	C**	4	100 mg/dose, 300 mg/day
tramadol-acetaminophen combination	III	+	-	occasional-frequent	C**	4	1 tablet/dose, 4 tablets/day
tramadol (intramuscular)	III	+	-	occasional-frequent	C**	4	
magnesium preparation	III	+	-	rare	C**	2	

Quality of evidence

I. Evidence from systematic review or meta-analysis, or from at least one randomized controlled trial

II. Evidence from non-randomized controlled trials or analytical epidemiological studies (cohort studies or case-control studies)

III. Evidence from descriptive studies (case reports or case series)

IV. Evidence from opinions of expert committees or individual experts, not based on patient data

Clinical impression

- little experience of use, currently difficult to evaluate
- + somewhat effective: significant clinical improvement in few patients
- ++ effective: significant clinical improvement in some patients
- +++ markedly effective: significant clinical improvement in most patients

Recommendation grade: according to the descriptions in the main text of this guideline. Drugs covered by health insurance in Japan and drugs with high level of evidence are described.

Recommended dose: according to the evidence and consensus obtained in Japan. All doses are for adults.

In recommended dose, “-” denotes difficult to assess currently regarding evaluation and doses.

*Covered by health insurance as off-label use for migraine

**Not covered by health insurance.

Drugs not currently available in Japan are written in italics

Table 2. Acute 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)
Triptans	Antiemetics	Steroids (intravenous infusion)	Anxiolytics, antipsychotics, anesthetics, antiemetics	
sumatriptan	metoclopramide**	dexamethasone**	domperidone (suppository)**	
sumatriptan (nasal spray)	metoclopramide (intramuscular) **	hydrocortisone**	prochlorperazine**	
sumatriptan (injection ampoule)	metoclopramide (intravenous) **		prochlorperazine (intramuscular) **	
sumatriptan (self-injection)	domperidone**		chlorpromazine**	
<i>sumatriptan (suppository)**</i>	Acetaminophen/NSAIDs		chlorpromazine (intramuscular) **	
<i>sumatriptan (subcutaneous)**</i>	acetaminophen		droperidol (intramuscular) **	
zolmitriptan	aspirin		propofol (intravenous) **	
<i>zolmitriptan (nasal spray)</i>	ibuprofen**		diazepam (intramuscular/ intravenous) **	
eletriptan	diclofenac*		Ergotamines	
rizatriptan	naproxen**		ergotamine-caffeine combination	
naratriptan	etodolac**		ergotamine-caffeine-pyrine combination	
<i>naratriptan (injection)**</i>	celecoxib**		dihydroergotamine	
<i>almotriptan**</i>	mefenamic acid		Others	
<i>frovatriptan**</i>	zaltoprofen**		tramadol**	
	pranoprofen**		tramadol-acetaminophen combination**	
	loxoprofen*		tramadol (intramuscular) **	
	lornoxicam**			
	Others			
	magnesium preparation**			

*Covered by health insurance as off-label use for migraine

**Not covered by health insurance.

Drugs not currently available in Japan are written in italics

What is the timing of taking triptans?

Recommendation

Triptans are effective if taken when headache is mild or in the early stage of headache attack (up to around one hour after onset). When taken during the aura phase or the premonitory phase of migraine, triptans have no negative effect but may not be effective.

Grade A

Background and Objective

Regarding the timing of using triptan uses, previous reports and use experience have demonstrate that the maximum effect is obtained generally when taken in the early stage of migraine attack. This section verifies the evidence for this observation. In addition, the effects of triptans when taken during the premonitory phase and aura phase before headache attack occurs are also verified.

Comments and Evidence

Various studies that examined the use of triptans during migraine attack have reported that triptans are effective when taken as early as possible after the onset of attack.¹⁾⁻⁹⁾ Among them, the Act when Mild (AwM) study was a randomized controlled trial (RCT) with 491 migraine patients taking almotriptan 12.5 mg when pain intensity was mild and in early headache onset or when pain had become moderate or severe. The results indicate that triptan is most effective if taken when migraine pain is still mild or within one hour of onset. Further analyses indicate that when the timing of taking triptan is missed, allodynia may occur concomitantly, which greatly worsens the effect.¹⁰⁾⁻¹²⁾

There are few reports on the effectiveness of oral triptan taken in the premonitory phase or aura phase, and therefore a clear conclusion is yet to be arrived. There are reports showing that use of sumatriptan subcutaneous injection, zolmitriptan tablet, and eletriptan tablet in the aura phase is not effective. While it is generally accepted that triptans should be taken when headache is still mild, the relationship with aura remains clear, and they are anticipated to be ineffective when taken in the aura or premonitory phase.¹³⁾¹⁴⁾

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- **Search terms and secondary sources**

- Search database: PubMed (2011/11/19)
 - migraine & {triptan} & {early} 74
 - migraine & {timing} & {trial} 11 or {randomized} 0
 - migraine & {treatment} & {triptan} 515
 - migraine & {treatment} & {triptan} & {preference} 22 or {comparison} 27
 - migraine & {treatment} & {triptan} & {aura} 52

How should patient preference for multiple triptans be determined?

Recommendation

Although all the triptans have proven efficacy, individual triptans differ slightly in characteristics. The efficacy and preference vary depending on patients, but adequate evidence is lacking.

Grade C

Background and Objective

When using triptans in the clinical setting, differences in efficacy among various triptans, and differences in effect among individual patients are often experienced. Given these differences and patients' preference, this section examines whether there are rational selection methods among multiple triptans.

Comments and Evidence

Triptans are a group of selective serotonin receptor agonists, but the pharmacological characteristics of individual triptans vary (Table 1) and the effects also differ depending on individual patients. Therefore, detailed comparison of various triptans is necessary, which would provide a basis for selecting the best triptan for individual patient. However, to date, few precise studies with adequate numbers of patients have been conducted. Moreover, there is no report comparing all the available triptans. Currently, seven types of triptan are being used in overseas countries, but only five types (only sumatriptan has oral, nasal spray, and subcutaneous injection formulations) are available in Japan. Regarding the pharmacokinetic characteristics of triptans as shown in Table 1, the time to reach maximum blood concentration (T_{max}) is approximately within 1 to 2 hours for all oral triptans, except zolmitriptan and naratriptan. Moreover, T_{max} is approximately 0.2 hour for sumatriptan injections (especially, 0.18 hour for self-injection). Sumatriptan injection is effective in patients with status migrainosus or in patients who have missed the timing of taking oral triptan, while sumatriptan nasal spray is useful in patients with nausea or vomiting, who have difficulties taking oral triptan. Most triptans have half-life of elimination ($T_{1/2}$) of 1.5-3 hours, and only naratriptan has a long $T_{1/2}$ of 5.05 hours. Therefore, this drug can be considered for recurrent migraine attacks and menstrual migraine. Patient preference for certain triptan is experienced clinically, but scientific evidence is limited to small-scale studies.¹⁾⁻⁸⁾

Table 1. Pharmacokinetics of triptans

Generic name	Formulations	Dose (mg)	T_{max} (hour)	$T_{1/2}$ (hour)
sumatriptan	tablet	50	1.8	2.2
	nasal spray	20	1.3	1.87
	injection (ampoule)	3	0.21	1.46
	self-injection	3	0.18	1.71
zolmitriptan	tablet	2.5	3.0*	2.4 [†]
	orally fast dissolving tablet	2.5	2.98*	2.9 [†]
eletriptan	tablet	20	1.0	3.2
rizatriptan	tablet	10	1.0	1.6
	orally fast dissolving tablet	10	1.3	1.7
naratriptan	tablet	2.5	2.68	5.05

T_{max} : time to reach maximum blood concentration; $T_{1/2}$: half-life of elimination; *: median; [†]: mean (Pharmacokinetics of the drugs are extracted from package inserts used in Japan)

• References

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• Search terms and secondary sources

- Search database: PubMed (2011/10/21)
migraine & {treatment} & {triptan} 515
& {preference} 22 OR {comparison} 27

When and how are non-oral formulations of triptans used for the treatment of migraine?

Recommendation

As acute treatment for migraine, non-oral formulations of triptan are effective for severe migraine attacks. Especially, use of injection and nasal spray formulations is indicated when severe migraine attacks cause serious disability in daily and social living, or when frequent vomiting impairs oral administration resulting in poor headache control. The time to response is the shortest for injection, followed by nasal spray. The appropriate formulation should be selected depending on the intended use in individual patients. **Grade A** (injection, nasal spray)

Background and Objective

Non-oral formulations of triptans (selective serotonin agonists) were developed as specific treatment for acute migraine attacks. Among the non-oral formulations of triptan, the effectiveness differs among injection, nasal spray, suppository and transdermal patch (suppository and transdermal formulation are not marketed in Japan as of March 2013). This section examines the evidence concerning the rational selection method and effects of the non-oral triptans.

Comments and Evidence

Currently, only two non-oral formulations of triptan are available in Japan: they are sumatriptan injection and sumatriptan nasal spray. In overseas countries, naratriptan injection, zolmitriptan nasal spray, sumatriptan transdermal patch, and sumatriptan suppository are being used.¹⁾⁻¹⁰⁾

Non-oral triptans are effective for severe migraine attacks, and are particularly useful when severe migraine attacks seriously impairs daily and social living, or when frequent vomiting and other symptoms impede oral administration resulting in poor headache control. Especially, injection, nasal spray, transdermal patch and suppository are indicated in patients with severe migraine attacks causing severe disability in daily and social living or patients with frequent vomiting and other gastrointestinal disturbances that render oral administration difficult resulting in poor headache control. Randomized controlled trials (RCT) have been conducted on individual formulations and effectiveness has been proven.¹⁾⁻¹⁰⁾ However, for the recently developed transdermal formulations, adequate evidence is not yet available.¹⁾ (See also CQ in Appendix “Guideline on self-injection of sumatriptan at home”)

Table 1. Pharmacokinetics of non-oral triptan formulations

	Dose	T _{max} (hour)	T _{1/2} (hour)
sumatriptan (nasal spray)	20 mg	1.3	1.87
sumatriptan (subcutaneous)	3 mg	0.21	1.46
sumatriptan (self-injection)	3 mg	0.18	1.71
sumatriptan (suppository)	25 mg	1.5	1.8
sumatriptan (transdermal)	120 mg	1.7	2.9
zolmitriptan (nasal spray)	2.5 mg	2.7–3	2.82–2.9

T_{max}: time to reach maximum blood concentration; T_{1/2}: half-life of elimination. Sumatriptan suppository and transdermal patch, and zolmitriptan nasal spray are currently not available in Japan. (Pharmacokinetics of the drugs are extracted and partially modified from package inserts and reference No. 5)

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• Search terms and secondary sources

- Search database: PubMed (2011/12/21)
 - {Migraine & randomized controlled trial 1669}
 - & sumatriptan 318
 - & injection or subcutaneous 61}
 - & nasal or spray 20
 - & rectal 17
 - & transdermal 4

How should the acute phase of migraine with brainstem aura and hemiplegic migraine be managed?

Recommendation

The acute phase of migraine with brainstem aura and hemiplegic migraine is managed in the same manner as acute treatment for migraine. However, the use of triptans and ergotamines is not actively recommended at present.

Grade B

Background and Objective

Migraine with brainstem aura and hemiplegic migraine are associated with intracranial vasoconstriction, which is assumed to cause aura and the associated symptoms. Literature was searched for the management of the acute phase of these types of migraine.

Comments and Evidence

There are no specific acute-phase treatments for migraine with brainstem aura and hemiplegic migraine. The main approach is symptomatic treatment, in the same manner as acute treatment for migraine.¹⁾²⁾

However, triptans and ergotamines are considered contraindicated, and their use cannot be supported actively. This is because pathophysiological hypothesis and pharmacological mechanism as well as experimental results suggest that vasoconstriction caused by triptans may exacerbate the clinical symptoms.

A case series reported that episodic use of triptans for migraine with brainstem aura was useful.³⁾ In addition, a retrospective study in patients with hemiplegic migraine reported that triptans were a safe and effective treatment.⁴⁾ There are no reports of clinically serious adverse events following actual use of triptans. Further accumulation of evidence is necessary.

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• Search terms and secondary sources

- Search database: PubMed (2011/8/27)
 - Basilar migraine 3732
 - & treatment 1430
 - acute 286
 - Hemiplegic migraine
 - & Management 21
 - Hemiplegic migraine 655
 - & treatment 153
 - acute 26

How are ergotamines used?

Recommendation

Ergotamine-caffeine combination has little effect when headache has already become moderate to severe, but there is value to use in patients with frequently relapsing headache while on triptans. Its use is limited because early treatment is as effective as or inferior to NSAIDs and adverse effects including vomiting are present. In addition, its use during pregnancy and breast-feeding is contraindicated.

Grade B

Background and Objective

Oral ergotamine-caffeine combination (Cafergot) had long been used as a specific treatment for migraine, but nausea occurs commonly and warning has been raised on the adverse events from long-term overuse. Since the advent of triptans, comparative studies consistently showed inferior effectiveness of Cafergot compared with triptans, and the role of this medication as a specific treatment becomes limited. Currently, the manufacturing and marketing of Cafergot have been discontinued in Japan, and ergotamine-caffeine-isopropylantipyrene combination (Clearmine) and dihydroergotamine are the only ergotamine preparations available in Japan.

Comments and Evidence

Oral ergotamine and ergotamine-caffeine combination (Cafergot) had been used as an acute treatment for migraine attacks for over thirty years. However, there are few placebo-controlled clinical studies, and the results of effectiveness have been inconsistent.¹⁾ Randomized controlled trials (excluding injection) comparing with other drugs include 6 studies with triptans,²⁻⁵⁾ 6 studies with NSAIDs,⁶⁻⁹⁾ and 2 studies with aspirin.¹⁰⁾ Compared with ergotamine, triptans improve symptoms more rapidly and are superior in improving associated symptoms. However, relapse within 48 hours was fewer with Cafergot treatment when compared with sumatriptan.²⁾ When compared with NSAIDs, Cafergot is equivalent in effectiveness as tolfenamic acid⁶⁾ but is inferior to naproxen,⁷⁾ diclofenac, ketoprofen,⁸⁾ piroprofen,⁹⁾ and aspirin,¹⁰⁾ while adverse effects were equivalent or more frequent in vomiting. By the time when headache becomes moderate to severe, oral administration of ergotamine combination is no longer effective. Some patients may respond to early treatment; but when treatment fails, triptan cannot be used within 24 hours as a rescue drug. Hence, use of ergotamines is very limited. Since ergotamine has oxytocic and vasoconstriction effects, continued use during pregnancy carries high risk. In the package insert and according to the US FDA, ergotamine is contraindicated during pregnancy. Furthermore, ergotamine-caffeine-isopropylantipyrene combination (Clearmine) is rated a score of 2 or 3 (score 3 for continued use) according to the Toranomon Hospital Drug Teratogenicity Risk Evaluation Criteria (6-point scale from scores 0 to 5).¹¹⁾ Ergotamine is contraindicated also during breast-feeding.

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- **Search terms and secondary sources**

- Search database: PubMed (2011/11/4)
migraine and ergotamine and randomized and controlled 63

Are acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) effective acute treatments for migraine?

Recommendation

Acetaminophen monotherapy and NSAIDs monotherapy are safe and low-cost treatments, and are recommended as first-choice drugs for mild to moderate migraine attacks. However, their effectiveness is limited compared with triptans. For migraine patients not responding to acetaminophen or NSAIDs, early use of triptan should be considered.

Grade A

Background and Objective

Acetaminophen is one of the frequently used over-the-counter (OTC) medications. Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin are also commonly used both prescription and OTC medications. This section verifies whether acetaminophen and NSAIDs are effective acute treatments for migraine.

Comments and Evidence

Acetaminophen and NSAIDs monotherapies are safe and inexpensive, and have been found to be effective for mild to moderate migraine attacks not requiring consultation of a medical facility. However, since migraine patients consult medical facilities when response to OTC drugs is diminished or when headache is severe, early treatment with triptans should be considered for these patients. Many randomized controlled trials (RCTs) and Cochrane reviews on acetaminophen and NSAIDs have been reported, and their effectiveness has been proven (grade A recommendation).

The grade of recommendation for each medication does not indicate the strength of effectiveness. The “quality of evidence” differs depending on the number of RCT reports (see Table 1, page 90).

I: acetaminophen,^{1,2)} aspirin,³⁾ ibuprofen,⁴⁾ diclofenac,⁵⁾ and naproxen⁶⁾

II: etodolac,⁷⁾ ketoprofen,⁸⁾ celecoxib,⁹⁾ and mefenamic acid¹⁰⁾

III: loxoprofen, zaltoprofen, pranoprofen, lornoxicam, others

Concerning the doses, acetaminophen 600 mg and 1,000 mg, which are the usual doses used overseas,^{1,2)} are increasingly being used also in Japan in recent years. On the other hand, since acetaminophen may cause hepatopathy, NSAIDs may cause gastrointestinal bleeding, and overuse of acetaminophen or NSAIDs may induce headache and other effects, it is essential to consider carefully the dosage, use frequency and method of drug taking, and to provide patient guidance.

Aspirin 1,000 mg is an effective acute treatment for migraine, and adding metoclopramide 10 mg attenuates nausea and vomiting.³⁾

Ibuprofen at both doses of 200 mg and 400 mg significantly reduces the severity of headache after 2 hours. Moreover, the 400 mg dose was effective against scintillating scotoma and tinnitus.⁴⁾

Diclofenac 50 mg was demonstrated to mitigate acute migraine attacks and also the associated symptoms, and the adverse effects were mild or treatable.⁵⁾

Naproxen 750 mg significantly increased the headache improvement rate after 2 hours compared with placebo, but because various adverse events may occur when used to treat moderate to severe migraine, caution has to be exercised during use.⁶⁾ A comparison of paracetamol (acetaminophen) 1,000 mg, etodolac 400 mg and etodolac 800 mg for the treatment of acute migraine attacks revealed comparable efficacy in the three groups.⁷⁾ A comparison of ketoprofen (75 mg and 150 mg) with placebo and zolmitriptan 2.5 mg reported similar efficacy of ketoprofen and zolmitriptan.⁸⁾ Gastrointestinal symptoms are class adverse effects of NSAIDs, but use of cyclooxygenase-2 inhibitor (celecoxib) is expected to reduce gastrointestinal symptoms.⁹⁾ Mefenamic acid 500 mg monotherapy was reported to be effective against menstrually related migraine, compared to placebo.¹⁰⁾

Empirically, the propionic acid derivatives (including loxoprofen, zaltoprofen, and pranoprofen) and oxicam derivatives (including lornoxicam and meloxicam) of NSAIDs are sometimes effective for migraine attacks, but there is no report at RCT level.

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• Search terms and secondary sources

- Search database: PubMed (2013/1/25)
 - Migraine & randomized controlled trial 1714
 - Migraine & randomized controlled trial & NSAIDs 211
 - Migraine & randomized controlled trial & aspirin 70
 - Migraine & randomized controlled trial & acetaminophen 55
 - Migraine & randomized controlled trial & ibuprofen 34
 - Migraine & randomized controlled trial & naproxen 29
 - Migraine & randomized controlled trial & indomethacin 20
 - Migraine & randomized controlled trial & diclofenac 18
 - Migraine & randomized controlled trial & ketoprofen 6
 - Migraine & randomized controlled trial & mefenamic acid 3
 - Migraine & randomized controlled trial & celecoxib 1
 - Migraine & randomized controlled trial & etodolac 1

Are antiemetics useful acute treatment for migraine?

Recommendation

Antiemetics are effective against nausea and vomiting which are associated symptoms of migraine. Various options of administration routes are available, including oral, intravenous, intramuscular, and suppository. Adverse effects are few. Hence, active combined use is recommended. Especially, combined use with triptans, ergotamines, and nonsteroidal anti-inflammatory drugs (NSAIDs) is useful.

Grade B

Background and Objective

Nausea, vomiting and delayed gastrointestinal absorption occur in the acute phase of migraine. These associated symptoms, together with headache, are factors that worsen the patients' QOL. In addition, these symptoms also affect the taking and absorption of acute treatment drugs. Treatment of migraine with antiemetics alone has also been attempted. This section reviews the evidence of antiemetics as an acute treatment for migraine.

Comments and Evidence

Placebo-controlled studies of metoclopramide administered intravenously,¹⁾ and of prochlorperazine administered intravenously, intramuscularly and transrectally (by suppository)²⁾ have demonstrated that these formulations are efficacious. In another study, intramuscular metoclopramide did not differ from placebo in improving migraine, but significantly improved nausea.³⁾ Domperidone 30 mg taken orally during the aura phase before migraine attack was significantly superior to placebo in controlling the attack.⁴⁾ In comparative studies between intravenously administered antiemetics, prochlorperazine 10 mg was more effective than metoclopramide 10 mg,⁵⁾ while prochlorperazine 10 mg and metoclopramide 20 mg,⁶⁾ as well as chlorpromazine (0.1 mg/kg) and metoclopramide (0.1 mg/kg) were equivalent in efficacy.⁷⁾ In a comparative study of intramuscular metoclopramide 10 mg versus prochlorperazine 10 mg for acute migraine, prochlorperazine was more effective but the results showed that antiemetics when used as alone are not adequate for pain relief.⁸⁾ When compared with subcutaneous injection of sumatriptan 6 mg, intravenous prochlorperazine 10 mg + diphenhydramine 12.5 mg was more effective,⁹⁾ whereas intravenous metoclopramide 20 mg was similarly effective.¹⁰⁾ Intramuscular sumatriptan 6 mg and intravenous chlorpromazine 12.5 to 37.5 mg were equally efficacious.¹¹⁾ However, intravenous injections of prochlorperazine and chlorpromazine are currently not available in Japan.

In a study of antiemetic combination therapy in migraine patients who failed to achieve adequate relief from sumatriptan 50 mg alone, each patient took additional metoclopramide 10 mg or placebo during two consecutive moderate to severe migraine attacks, and the intensity of headache was compared before and after the oral treatment. Headache was improved in 10 of 16 migraine patients (63%) treated with sumatriptan plus metoclopramide combination compared with 5 (31%) patients treated with sumatriptan plus placebo. There was no difference in adverse effects compared with placebo. Hence, combining metoclopramide with triptan was useful in migraine patients who failed to achieve adequate pain relief from triptan alone.¹²⁾ In addition, combining antiemetic with ergotamine¹³⁾ or with acetaminophen¹⁴⁾ also improves headache intensity and gastrointestinal symptoms during the acute phase of migraine.

From the above findings, intravenous metoclopramide, which is a central and peripheral antiemetic widely used in Japan, is recommended as the first-choice antiemetic (grade A recommendation). As the second choice, intramuscular prochlorperazine is recommended considering the antiemetics available in Japan (grade B recommendation). All antiemetics have limited efficacy when used alone, and therefore combined use with other acute treatment drugs is recommended.

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• Search terms and secondary sources

- Search database: PubMed (2012/1/27)
 {migraine} OR {vascular headache} OR {hemicrania} 69051
 & metoclopramide 289
 & prochlorperazine 101
 & domperidone 46
 & chlorpromazine 71

What other acute treatment drugs for migraine are available?

Recommendation

As acute treatments for migraine, intravenous corticosteroids (dexamethasone), intravenous magnesium, intramuscular tramadol, and oral tramadol-acetaminophen combination may be considered. However, because of a lack of adequate evidence, they are not the first-choice drugs. Intravenous, intramuscular, suppository, and combination formulations of prochlorperazine are recommended in the literature, but their use for migraine treatment is not covered by health insurance in Japan.

Grade B and C (prochlorperazine: B; dexamethasone, magnesium, tramadol, and tramadol-acetaminophen combination: C)

Background and Objective

Many drugs have been used empirically with the expectation to abort an acute migraine attack. However, the mechanisms of action remain unknown for many of these drugs. On the other hand, clarification of the therapeutic effects of novel agents may contribute to further elucidation of the pathophysiology of migraine. From this field in which establishment of new EBM may be expected, this section focuses on those drugs that can be used by clinical doctors, such as dexamethasone, magnesium, and tramadol.

Comments and Evidence

Intravenous corticosteroid (dexamethasone)¹¹⁻⁵⁾ is not likely to become the first-choice acute treatment drug for migraine, because there is no adequate evidence at randomized controlled trial (RCT) level and some RCT conducted in recent years reported no significant difference when used as acute treatment for migraine. On the other hand, there are also studies showing a significant difference in preventing recurrence of migraine attack within several days compared to standard treatment,²⁾ and a reduction in the rate of recurrence.⁵⁾ Moreover, intravenous magnesium may be considered for use as an acute treatment,^{6,7)} but there is no adequate scientific evidence and its use is not covered by health insurance in Japan.

Intramuscular tramadol (Tramal Injection), tramadol capsule (Tramal Capsule), and oral tramadol-acetaminophen combination (Tramcet Combination Tablet) are useful. However, due to adverse effects of nausea and vertigo (especially for injection) and the issue of medication-overuse headache induced by analgesic combinations, tramadol is not the first-choice drug at the present time. Use of tramadol, a weak opioid, as acute treatment has been reported. To date, a randomized blinded study comparing intramuscular tramadol and intramuscular diclofenac,⁸⁾ a randomized placebo-controlled study of intravenous tramadol,⁹⁾ and a randomized double-blind study of tramadol-acetaminophen combination¹⁰⁾ have been conducted, and the effectiveness of tramadol has been reported. However, due to adverse reactions such as nausea and vertigo as well as the issue of medication-overuse headache induced by weak opioid and analgesic combinations, there is an opinion that their use for migraine should be limited to patients who cannot use triptans due to ischemic heart diseases or other reasons.¹¹⁾ Furthermore, the risk of inducing serotonin syndrome or seizures by combined use with tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) has been reported. Caution has to be exercised when used as prophylactic treatment for migraine.¹²⁾

Evidence (evidence level: I) has been accumulated for intravenous, intramuscular, suppository, and combination formulations of prochlorperazine (a phenothiazine antipsychotic) based on the experience of use in emergency rooms (ER) overseas.¹³⁻¹⁵⁾ In Japan, prochlorperazine is indicated for nausea and vomiting before and after surgery, and its use in severe vomiting associated with headache may be considered. Similarly, occasional reports have indicated the effectiveness of the anesthetic propofol,¹⁶⁾ but propofol for migraine is currently not approved for health insurance coverage in Japan.

Research is on-going to study novel acute treatment drugs currently being developed, including calcitonin gene-related peptide receptor (CGRP) antagonists, transient receptor potential cation channel subfamily V member 1 (TRPV1) antagonists, and serotonin receptor agonists.¹⁷⁾

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- Search database: PubMed (2011/12/26)
 - Migraine & randomized controlled trial 1668
 - Migraine & randomized controlled trial & steroid 43
 - Migraine & randomized controlled trial & dexamethasone 9
 - Migraine & randomized controlled trial & magnesium 19
 - Migraine & randomized controlled trial & prochlorperazine 24
 - Migraine & randomized controlled trial & tramadol 17

What are the acute treatments for severe migraine attacks and status migrainosus?

Recommendation

1. Rule out secondary headaches.
2. Fluid replacement (secure intravenous route): improvement of dehydration due to vomiting and be prepared for hypotension and other drug-related adverse effects
3. Subcutaneous injection of sumatriptan 3 mg: pay attention to the total dose within 24 hours and headache recurrence
4. Intravenous or intramuscular injection of antiemetic: intravenous metoclopramide 10 mg or intramuscular prochlorperazine 5 mg
5. Intravenous dexamethasone

Grade B

Background and Objective

Status migrainosus is a severe migraine attack lasting for more than 72 hours, occurring in a patient who has “migraine without aura” (International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta): 1.4.1 *Status migrainosus*). Even when the severity does not reach status migrainosus, many patients with severe migraine attacks present at the emergency outpatient department. Due to the strong headache and vomiting, history taking is often difficult. At presentation, first of all investigations for dangerous secondary headaches such as subarachnoid hemorrhage should be carried out. Treatment can be started after confirming the general condition.

Comments and Evidence

Although there are no large-scale or double-blind studies on status migrainosus, various drugs such as dihydroergotamine,¹⁾ droperidol,²⁾ corticosteroids,³⁾ lidocaine,¹⁾ and intravenous valproic acid⁴⁾ have been used as empirical treatments. There are several randomized controlled trials (RCTs) on acute treatment for migraine in the emergency outpatient setting. Placebo-controlled studies of intravenous metoclopramide,⁵⁾ as well as intravenous, intramuscular and transrectal (by suppository)⁶⁾ prochlorperazine have demonstrated that these drugs are efficacious. When compared with subcutaneous injection of sumatriptan 6 mg, intravenous prochlorperazine 10 mg + diphenhydramine 12.5 mg was more effective,⁷⁾ while intravenous metoclopramide 20 mg⁸⁾ was equally effective. Intramuscular sumatriptan 6 mg and intravenous chlorpromazine 12.5 to 37.5 mg were almost equivalent in efficacy.⁹⁾ However, prochlorperazine and chlorpromazine for intravenous injection are currently not available in Japan. When intramuscular droperidol 0.1 mg, 2.75 mg, 5.5 mg and 8.25 mg was compared with placebo, the headache improvement rates after 2 hours were significantly higher with droperidol 2.75 mg, 5.5 mg and 8.25 mg.¹⁰⁾ Intramuscular droperidol 2.5 mg had the same efficacy as intramuscular pethidine (1.5 mg/kg).¹¹⁾ Regarding adverse effects, droperidol does not cause hypotension, but may induce akathisia or sedation, which requires attention. Although rare, droperidol is associated with the risk of dose-dependent QTc prolongation and torsades de pointes, which prompted the US FDA to issue a black-box warning to the label of droperidol.¹²⁾ Use of droperidol should be limited to cases where other drugs are not effective. In European and American countries, dihydroergotamine injection has been evaluated as a highly effective acute treatment for severe migraine. One RCT¹³⁾ showed that dihydroergotamine 1 mg and subcutaneous sumatriptan 6 mg were similarly effective for moderate to severe headache, but the recurrence rate was higher with sumatriptan and the dose may increase in patients with recurring headache. Intravenous valproic acid 500 mg (currently not approved in Japan) was equally effective as intravenous dihydroergotamine 1 mg + intravenous metoclopramide 10 mg,¹⁴⁾ and was inferior to intravenous prochlorperazine 10 mg.¹⁵⁾ However, dihydroergotamine and valproic acid for intravenous injection are currently not available in Japan. Pethidine was reported to be effective in a placebo-controlled study,¹⁶⁾ but in a meta-analysis using 11 studies conducted by Friedman et al.,¹⁷⁾ pethidine was less effective than dihydroergotamine, tended to be less effective than antiemetics, and was similar to the NSAID ketorolac. When weighing effectiveness against adverse effects such as sedation and vertigo, carefully consideration has to be given when prescribing pethidine. Intravenous dexamethasone

10 to 24 mg has been reported to be effective in one¹⁸⁾ and ineffective in other studies¹⁹⁾⁻²²⁾ for preventing recurrence of migraine. Although the number of cases was small, a meta-analysis of 7 studies with a total of 742 subjects conducted by Singh et al.²³⁾ found dexamethasone to be effective in preventing recurrence of migraine, with a 9.7% reduction in relative risk after 24 to 72 hours.²³⁾ A RCT of dexamethasone as acute treatment for migraine in the emergency department suggested that dexamethasone was effective to a certain extent in patients with status migrainosus although there was no significant difference compared with placebo.²⁰⁾

Based on the above findings, in patients with status migrainosus, first rule out secondary headaches while securing the intravenous line and starting fluid replacement. Considering the agents available in Japan, administer subcutaneous injection of sumatriptan together with an antiemetic of intravenous metoclopramide or intramuscular prochlorperazine. When recurrence of migraine is a concern, consider using intravenous dexamethasone.

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- **Search terms and secondary sources**

- Search database: PubMed (2012/4/30)
 1. "status migrainosus" 57
 - & treatment 49
 - & management 7
 - & randomized control trial 0
 2. migraine & (refractory or intractable or "very severe") 496
 - & (treatment or management) 450
 - & (treatment or management) & randomized control trial 2
 3. migraine & emergency 559
 - & randomized control trial 17
- One reference added by manual search (No. 12)

How should migraine be treated (acute and prophylactic) during pregnancy and breast-feeding?

Recommendation

When attacks are severe and require treatment, acetaminophen is recommended as an acute treatment. The safety of using triptans during pregnancy has not been established, but there is no report that use during early pregnancy increases the rate of fetal teratogenicity. Since most migraine patients experience reduced frequency of migraine attacks during pregnancy, few patients require prophylactic drugs. Although administration of prophylactic drugs is not recommended, beta-blocker may be used where necessary. For breast-feeding women who are using triptans, it is recommended to avoid breast-feeding for 12 hours after taking sumatriptan and for 24 hours after taking other triptans.

Grade B

Background and Objective

Migraine is prevalent in women of reproductive age. “How should migraine be treated during pregnancy or breast-feeding?” is a frequently asked question from patients.

Literature was searched to identify the characteristics of migraine during pregnancy and breast-feeding, and the usefulness and safety when conducting pharmacotherapy.

Comments and Evidence

Migraine tends to improve from the first to third trimester of pregnancy. In the third trimester, migraine attacks are alleviated in 60-80% of the patients.¹⁾⁻³⁾ The degree of improvement is lower in patients who have migraine with aura than in those who have migraine without aura.⁴⁾⁻⁶⁾ In over one-half of the patients, migraine recurs within one month postpartum. Some studies indicated no difference in the frequency and severity of headache between breast-feeding and bottle-feeding,³⁾ while others suggested possible inhibition of migraine recurrence by breast-feeding.¹⁾ At least, breast-feeding presumably does not aggravate migraine. An increasing number of reports indicate a higher risk of stroke during pregnancy and pregnancy-related hypertension in migraine patients,⁷⁾⁻⁹⁾ but most are case-control studies and large-scale prospective studies are awaited.

In general, the risk associated with drug use during pregnancy depends on the risk of the drug per se and also the duration of use. Since there is no effect from the first day of the last menstruation to the 27th day, taking migraine medications several times during this period does not pose a concern. Because the first trimester, especially during the 4th to 11th week of pregnancy, is the organogenetic period, use of medications should be avoided if possible. After the 12th week, there is no teratogenic risk, but fetal functional disturbance and fetal toxicity are issues. Although the safety of medications for acute migraine attacks in pregnant women has not been established, acetaminophen is widely used empirically and is recommended in published guidelines.¹⁰⁾⁻¹¹⁾ Because bleeding tendency in mother and neonate associated with aspirin as well as Botallo ductal constriction or occlusion associated with NSAIDs have been reported, these drugs should be avoided especially during the third trimester.¹²⁾ Due to the oxytocic effect of ergotamine leading to a risk of preterm birth, this drug is contraindicated during pregnancy as stated in the package insert and the US FDA guidelines. Among the antiemetics, metoclopramide is rated as “benefits justify potential risks” and is relatively widely used for hyperemesis in Japan, and adverse effect on the fetus has been ruled out.¹³⁾ For domperidone, teratogenicity has been reported from animal experiments and this drug is described as contraindicated for pregnant women in the package insert. As for the safety of triptans, post-marketing surveys have reported no increase in risk of fetal teratogenicity associated with the use of sumatriptan, naratriptan and rizatriptan during the first trimester of pregnancy.¹⁴⁾⁻¹⁵⁾ Other than the post-marketing surveys, the largest number of reports was on the use of sumatriptan during pregnancy, and the conclusion is that use of sumatriptan during early-stage pregnancy does not increase the risk of fetal teratogenicity.¹⁶⁾ For other triptans also, larger cohort studies have indicated no greatly increased risk of fetal teratogenicity from use in early-stage pregnancy, and have reported no serious effect on the outcome of pregnancy.¹⁷⁾⁻¹⁸⁾

For prophylactic therapy during pregnancy, the antiepileptic drug valproic acid is the most high-risk drug for the fetus, and caution is always required when used in women of reproductive age. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) have been reported to cause fetal circulatory disturbance when used in the second and third trimesters of pregnancy.¹²⁾ Calcium channel blockers are also contraindicated in the first trimester of pregnancy. When prophylactic medication is necessary during pregnancy, beta-blocker, especially propranolol, is an option based on experience.¹⁰⁾

As for the use of triptans during breast-feeding, after subcutaneous injection of sumatriptan 6 mg, approximately 3.5% of the maternal dose is passed into breast milk. Given that oral bioavailability is 14%, the dose transferred to breast milk is estimated to be around 0.5%.¹⁹⁾ In a statement of the American Academy of Pediatrics, sumatriptan is considered a drug that is compatible with breast-feeding.²⁰⁾ According to a report from the manufacturer, in 8 women given a single dose of eletriptan 80 mg, 0.02% of the mean total dose of eletriptan is transferred to breast milk 24 hours after administration.²¹⁾ According to the drug risk classification in “Medications and Mothers’ Milk 14th edition”,²²⁾ only eletriptan is classified as level 2 (relatively safe), while other triptans are classified as level 3 (moderately safe).²²⁾ The package inserts contain descriptions that breast-feeding should be avoided for 12 hours after taking sumatriptan and breast-feeding should be avoided after taking other triptans. For the other medications, their use should be considered on an individual basis, referring to specialized books and internet sites where necessary.¹²⁾²²⁾⁻²⁴⁾ In Japan, the “Japan Drug Information Institute in Pregnancy” website²⁵⁾ of the National Center for Child Health and Development as a project of the Ministry of Health, Labour and Welfare provides useful reference.

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• Search terms and secondary sources

- Search database: PubMed (2011/8/11)
 1. Migraine
 - 2.1 & {pregnancy} 626
 - 3.1 & {lactation} or {breast feeding} 52
 - 4.2 & treatment 352
 - 5.3 & treatment 40
 - 6.2 & prophylaxis 73
 - 7.3 & prophylaxis 13
- Search database: Ichushi Web for articles published in Japan
(migraine/TH or migraine/AL) and (pregnancy/TH) or pregnancy/AL) 45
(migraine/TH or migraine/AL) and (lactation/TH) or lactation/AL) 13

The diagnosis and treatment of menstrual migraine

Recommendation

Menstrual migraine is diagnosed according to the International Classification of Headache Disorders 3rd Edition beta version (ICHD-3beta). To establish the relationship between menstrual cycle and migraine attack, confirmation of the headache diaries is required (for three menstrual cycles). Since headache attacks tend to be severe in menstrually related migraine without aura, triptan is recommended for acute treatment when previous attacks did not respond to NSAIDs. Prophylactic treatment is conducted according to that used for general migraine, but when attacks occur mainly in association with menstruation, short-term prophylactic therapy may be one option.

Grade B

Background and Objective

Approximately one-half of the women with migraine are self-aware that migraine attacks occur in relation to the menstrual cycle. Even in surveys using headache diaries, migraine attacks occur frequently from several days before menstruation to during menstruation. The attacks occurring during this period are more severe and last longer than attacks occurring outside this period, and are often refractory to treatment.

Comments and Evidence

In the past, menstruation-related headache had various names such as menstrual migraine, premenstrual migraine, and perimenstrual migraine, with no common definition regarding the time of headache occurrence. In the Appendix of ICHD-3beta, migraine is classified into A1.1 *Migraine without aura*, A1.1.1 *Pure menstrual migraine without aura*, A1.1.2 *Menstrually related migraine without aura*, and A1.1.3 *Non-menstrual migraine without aura*.¹⁾²⁾

According to the criteria proposed by MacGregor et al.,³⁾ A1.1.1 *Pure menstrual migraine without aura* is defined as attacks occurring exclusively on day 1 ± 2 (*i.e.*, from 2 days before menstruation to day 3 of menstruation) in at least two out of three menstrual cycles and at no other times of the cycle, while A1.1.2. *Menstrually-related migraine without aura* as attacks occurring not only in the period specified in A1.1.1 but also in other times of the cycle. Menstrual migraine tends to be more severe and lasts longer than migraine occurring in other times.⁴⁾⁵⁾

With respect to pharmacotherapy for menstrual migraine, basically both acute treatment and prophylactic therapy are the same as those for general migraine. However, since the attacks are often severe, triptans have been reported to be effective as the acute treatment drug. Randomized controlled trials (RCT) have demonstrated the effectiveness of subcutaneous sumatriptan 6 mg⁶⁾ and oral sumatriptan (50 mg and 100 mg),⁷⁾ oral zolmitriptan (1.25 mg, 2.5 mg and 5 mg)⁸⁾⁹⁾ oral rizatriptan (10 mg),¹⁰⁾ and oral naratriptan (2.5 mg)¹¹⁾ for menstrually related migraine. One systematic review and meta-analysis concluded that grade B recommendation can be given for the use of oral sumatriptan (50 mg and 100 mg), mefenamic acid (500 mg every 8 hours from the initial menstrual migraine attack until during menstruation),¹²⁾ and rizatriptan (10 mg) as acute treatments for menstrually related migraine.¹³⁾ Although currently not approved in Japan, oral sumatriptan 85 mg + naproxen 500 mg combination tablet has been proven by RCT to be effective even in dysmenorrhea.¹⁴⁾ In cases of inadequate response to acute treatment or recurring attacks, prophylactic therapy can be considered for patients who use large quantities of acute medications. When the menstrual cycle is predictable and attacks are mainly associated with menstruation with few attacks in other times, the effectiveness of short-term prophylactic therapy with triptans¹⁵⁾ or NSAIDs¹⁶⁾ taken from before menstruation to end of menstruation was verified. Use of other short-term prophylactic therapies including vitamin E,¹⁷⁾ magnesium,¹⁸⁾ and phytoestrogen¹⁹⁾ has been reported. For hormonal therapy, the effectiveness of estradiol was examined in an RCT.²⁰⁾ The above-mentioned systematic review and meta-analysis also reported grade B recommendation for transdermal estradiol 1.5 mg/day, oral naratriptan 1 mg twice daily, and oral frovatriptan (currently not approved in Japan) 2.5 mg twice daily as short-term prophylactic therapies.

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- Search database: PubMed(2011/12/21)
 1. Menstrual migraine 629
 - 2.1 & treatment 396
 - 3.1 & prophylaxis 108
 - 4.1 & prevention 94
- Search database: Ichushi Web for articles published in Japan (menstruation/TL or menstruation/AL) and (migraine/TL) or migraine/AL) 63