

Appendix III

**Guideline for Migraine Treatment
by Propranolol (Provisional Edition)**

Introduction

The Japanese Headache Society together with the Japanese Society of Neurology requested the Ministry of Health, Labour and Welfare to approve health insurance coverage of propranolol for the treatment of migraine. This issue was considered to qualify as medical and pharmaceutical data in the public domain at the Meeting of the First Committee on Drugs of the Pharmaceutical Affairs and Food Sanitation Council held on August 31, 2012. As a result, treatment of migraine by propranolol (Inderal[®]) was approved for health insurance coverage from August 31, 2012.

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

Furthermore, instruction has been issued to publicize the following:

- (1) Be well aware of the precautions for use of this drug. Strive to give prior explanations to patients regarding the treatment contents and possible adverse reactions, and obtain their informed consent.
- (2) When a serious adverse effect becomes known, report to the relevant company or to the Ministry of Health, Labour and Welfare. Strive to obtain information of the cases in the case of off-label use

With this background, Board Director Sakai instructed the Treatment Promotion Committee to produce a guideline (provisional edition) urgently in order that “migraine treatment by propranolol” can be used effectively and safely.

Guideline Committee:

The Guideline Committee was inaugurated in September 2012. The Committee is composed of chairman: Kiyomi Yamane; vice-chairmen: Takao Takeshima, Nobuo Araki; members: Hisaka Igarashi, Shoji Kikui, Tomokazu Shimazu, Naoto Fujiki; assessor: Fumihiko Sakai

Production process and contents of guideline

The guideline was produced based on evidence and according to the “Diagnostic and Treatment Guidelines for Chronic Headache” compiled by the Japanese Headache Society.

The guideline contains the following clinical questions (CQ):

- CQ 1. Is propranolol effective for migraine prevention?
Is there international consensus for propranolol as prophylactic medication for migraine?
- CQ 2. What kinds of migraine patients are treated by propranolol?
- CQ 3. What doses of propranolol are used for the treatment of migraine?
- CQ 4. What precautions have to be taken during administration of propranolol (adverse reactions, interactions)?

Conclusion

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

On behalf of the authors, November 6, 2012

Fumihiko Sakai, Board Director of the Japanese Headache Society

Kiyomi Yamane, Chair of Guideline for Migraine Treatment by Propranolol (Provisional Edition)
Committee

*This guideline was first published in Japanese Journal of Headache 2013; 39(3): 297-302.

Is propranolol effective for migraine prevention?

Is there international consensus for propranolol as prophylactic medication for migraine?

Recommendation

Oral administration of propranolol to migraine patients with headache attacks two or more times a month can be expected to reduce the number of attacks per month. Guidelines in European and American countries also recommend propranolol as the first choice of prophylactic medication for migraine.

Grade A

Background and Objective

Propranolol is a beta-blocker used mainly for the treatment of hypertension, coronary arterial diseases and tachyarrhythmia, but it is also used as a prophylactic drug for migraine. Many good quality clinical trials with placebo control have demonstrated the effectiveness of propranolol, and meta-analysis has also been conducted. Although many aspects of the mechanism of action and pharmacological evidence remain unclear, studies suggest that the actions involve not only peripheral blood vessels and beta blockade of autonomic nerves but also central neurotransmission.¹⁾ In American and European countries, propranolol together with another beta blocker metoprolol, the antiepileptic drugs valproic acid and topiramate, as well as the antidepressant amitriptyline are listed as first-choice drugs for migraine prevention.

Comments and Evidence

At least 46 studies on propranolol have been conducted, and placebo-controlled clinical trials have proven the effectiveness of propranolol as a prophylactic drug for migraine. In addition, meta-analysis has been conducted. In a meta-analysis of 53 studies (2,403 subjects) reported by Holroyd et al.,²⁾ the modal dose of propranolol was 160 mg/day. Double-blind studies showed a mean effective rate of 43.7% for propranolol and was significantly ($p < 0.001$) higher than the rate of 14.3% for placebo. Propranolol yielded a 44% reduction in migraine attacks when headache diary was used to assess treatment outcome, and a 65% improvement when clinical or subjective ratings of improvement were used, whereas placebo gave approximately 14% improvement for both assessment methods. While the doses used varied among studies, the dose–response relationship for migraine prevention is not clear. Propranolol is well tolerated. Apart from propranolol, other drugs that exhibit migraine prophylactic effect include metoprolol,³⁾⁴⁾ timolol,⁵⁾ atenolol,⁶⁾ and nadolol.⁷⁾ In general, beta blockers that stimulate intrinsic sympathomimetic activity lack effectiveness in migraine prevention, although the reason is unknown.

When compared with other drugs, propranolol has almost equivalent effectiveness as flunarizine,⁸⁾ valproic acid,⁹⁾ topiramate,¹⁰⁾ and amitriptyline.¹¹⁾

In overseas countries, the European Federation of Neurological Science (EFNS) migraine treatment guideline recommends propranolol 40 to 240 mg/day for migraine prophylaxis at level A.¹²⁾ The American Academy of Neurology migraine guideline also recommends propranolol at grade A.¹³⁾¹⁴⁾ Therefore, international consensus has been obtained for propranolol as a prophylactic medication for migraine.

• References

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• Search terms

- Search database: PubMed (2012/8/31)
- 1. {migraine} OR {vascular headache} OR {hemicrania} 71380
 - & propranolol 633
 - & metoprolol 149
 - & timolol 62
 - & nadolol 41
 - & atenolol 102
- 2. {migraine} OR {vascular headache} OR {hemicrania} & {propranolol}
 - & flunarizine 72
 - & valproate 61
 - & topiramate 63
 - & amitriptyline 84
- Secondary source, 3 references added by manual search (Nos. 12-14)

What kinds of migraine patients are treated by propranolol?

Recommendation

Propranolol prophylactic therapy is recommended when migraine attacks occur two or more times a month and disability in daily living is not adequately resolved 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. In addition, propranolol is recommended as the first-choice prophylactic therapy when patients have comorbidities of hypertension, coronary artery diseases, or tachyarrhythmia.

Grade A

Background and Objective

Propranolol is one of the therapeutic agents for hypertension, coronary artery disease and tachyarrhythmia, but has also been shown to be useful for migraine prevention. Propranolol can be used as long as the patients have no comorbidities that are contraindications for propranolol, such as heart failure and asthma, and is a relatively safe prophylactic drug for pregnant women.

Comments and Evidence

Placebo-controlled clinical trial has shown that propranolol is useful as a prophylactic drug against migraine for patients who have migraine attacks two or more times a month and disability in daily living not resolved by acute treatment alone.¹⁾ In American and European countries, propranolol together with another beta blocker metoprolol, the antiepileptic drugs valproic acid and topiramate, as well as the antidepressants amitriptyline are listed as first-choice drugs for migraine prevention.²⁾⁻⁹⁾

The US Headache Consortium³⁾⁻⁵⁾ recommends that choice of prophylactic medication should consider the comorbidities. Several comorbid conditions are present in migraine patients, and are associated with both opportunity and limitation for treatment. Hence, it is important to choose medications that can treat both the comorbidities and migraine, and at the same time are not contraindications or do not aggravate the comorbid conditions. Therefore, in patients who have co-existing hypertension, coronary artery disease or tachyarrhythmia for which propranolol is a therapeutic agent, propranolol is recommended as the first choice in such patients. On the other hand, propranolol cannot be used in patients with heart failure, asthma or other comorbid conditions for which propranolol is contraindicated. In addition, since propranolol may increase the blood level of rizatriptan, co-administration of the two is contraindicated. Furthermore, attention has to be given to the possibility of occurrence of depressive state as an adverse reaction.

Guidelines published so far state that when prophylactic therapy is unavoidable in pregnant women, beta blockers including propranolol are relatively safe.²⁾⁻¹²⁾

Although study has indicated that valproic acid and propranolol have equivalent efficacy in children,¹³⁾ evidence is inadequate. Overseas guidelines do not recommend propranolol for use in pediatric cases.

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• Search terms

- Search database: PubMed (2012/9/10)
 - migraine & propranolol 521
 - & guideline 14
 - & benefit 25
 - & prophylaxis 258
 - & preventive 44

What doses of propranolol are used for the treatment of migraine?

Recommendation

For adults, start with propranolol 20 to 30 mg/day. If response is inadequate, titrate up to 60 mg/day, to be taken orally in 2 or 3 divided doses per day.

Grade A

Background and Objective

Since August 31, 2012, Inderal has been approved for health insurance coverage in Japan, through an application based on public domain data. The use of this drug is expected to increase in the future. The approved doses of propranolol as prophylactic therapy for migraine are 80 to 240 mg in the United States and 80 to 160 mg/day in the United Kingdom. In Japan, the approved doses for cardiovascular diseases such as hypertension are much lower, at 30 to 60 mg/day. There is a need to recommend the safe and effective doses of propranolol as prophylactic therapy for migraine.

Comments and Evidence

Propranolol is mainly used as therapeutic agents for hypertension, coronary artery disease and tachyarrhythmia, but this drug has also been used for migraine prevention from the past. According to a meta-analysis reviewing 53 studies (2,403 patients) conducted by Holroyd et al.,¹⁾ the modal 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, and achieved 65% improvement when subjective scales or clinical ratings of effectiveness were used. The improvement rate for placebo remained at around 14% for both evaluation methods. While the doses used vary among studies, the dose-response relationship for migraine prophylactic effect is unclear. Propranolol is well tolerated.

In overseas countries, the European Federation of Neurological Science (EFNS) migraine treatment guideline recommends propranolol 40 to 240 mg/day for migraine prophylaxis at level A.²⁾ The American Academy of Neurology migraine guideline recommends propranolol 120 to 240 mg/day.³⁻⁵⁾ In Japan, the approved doses for cardiovascular diseases such as hypertension are much lower, at 30 to 60 mg/day. With this background, the doses used as prophylactic therapy for migraine in Japan are lower than those used overseas, and open studies have indicated that those doses are effective and safe.⁶⁻⁸⁾ In the chronic headache guidelines published in 2006, doses of 20 to 60 mg/day were recommended based on the experience of use in Japan although there was little evidence, and this dose range was lower than that based on overseas evidence. Following this recommendation, the experience of use in Japan has accumulated.⁹⁾¹⁰⁾ Kikui et al.¹⁰⁾ treated 16 Japanese patients requiring prophylactic therapy with propranolol 20 to 40 mg/day (mean 29.4 ± 4.4 mg/day), and reported a significant decrease in number of days with migraine from one month of treatment, with a reduction of 36.8% at two months compared to before treatment, and continuation of the effect even after six months. They concluded that low dose propranolol is an effective prophylactic therapy for migraine.

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• Search terms and secondary sources

- Search database: PubMed (2012/8/31)
{migraine} OR {vascular headache} OR {hemicrania} 71380
& propranolol 633
- Search database: Ichushi Web for articles published in Japan (2012/8/31)
(migraine) & (propranolol) 67
- Secondary source: 4 articles added by manual search (Nos. 3-5, 6)

What precautions have to be taken during administration of propranolol (adverse reactions, interactions)?

Recommendation

Propranolol has been used as a therapeutic agent for hypertension, angina pectoris, and arrhythmia since 1966, and data of adverse reactions have been accumulated adequately. As a prophylactic drug for migraine, adequate data including meta-analysis indicates good tolerability. The same applies to interactions. When used as a prophylactic drug for migraine, special attention has to be given to the contraindication for co-administration with rizatriptan.

Grade A

Background and Objective

In Japan, since the approval of the application based on public domain data for the use of propranolol as a prophylactic drug for migraine, this drug is expected to be increasingly prescribed in the future. This section examines the adverse reactions and drug interactions that require special attention when propranolol is administered.

Comments and Evidence

Propranolol has been used as a therapeutic agent for hypertension, angina pectoris, and tachyarrhythmia since 1966, and adequate data on adverse reactions and drug interactions has been accumulated.¹⁾ As a prophylactic drug for migraine, dozens of clinical trials have been conducted overseas,²⁾ and meta-analysis has also been conducted.³⁾ According to the meta-analysis conducted by Holroyd et al.³⁾ on 2,403 subjects, propranolol is well tolerated and no severe adverse effects have been reported. When propranolol is used as a prophylactic drug for migraine, the ages of the target patients in general are conceivably younger than those treated for hypertension and heart diseases, and the doses used would not exceed those for hypertension and heart disease patients (dose approved in Application Based on Public Domain Data: up to 60 mg/day). Therefore when prescribing for migraine patients in Japan, it is sufficient to pay attention to the adverse reactions accumulated so far for the indicated diseases.

The package insert of propranolol lists heart failure, bradycardia, orthostatic hypotension, and bronchial spasm as “serious adverse reactions”, and bronchial asthma, metabolic acidosis, severe bradycardia, atrioventricular or sinoatrial block, congestive heart failure, hypotension, severe periphery circulatory disturbance, and variant angina as “contraindications for propranolol administration”. Therefore, when prescribing migraine prophylactic drugs for patients with the above comorbid conditions, drugs other than propranolol should be chosen.

As for weight gain that often constitutes a problem in prescribing migraine prophylaxis, while this adverse effect also occurs with propranolol, the rate is extremely low compared to amitriptyline and valproic acid.⁴⁾ In the package insert of propranolol, weight gain is not listed as an adverse effect.

Propranolol has been reported to interact with many drugs. Among them, co-administration with thioridazine and with rizatriptan is contraindicated. Since rizatriptan is an acute medication for migraine, special attention has to be paid to ensure that this drug is not co-administered.¹⁾⁵⁾ When healthy adults taking repeated oral doses of propranolol were administered a single dose of rizatriptan benzoate, the area under the curve (AUC) was 1.67 times, and the maximum drug concentration (C_{max}) was 1.75 times higher compared to when propranolol was not taken in combination,⁶⁾ suggesting a possibility that the effect of rizatriptan may be augmented. Although the mechanism of this interaction has not been elucidated, propranolol is suspected to inhibit rizatriptan metabolism via monoamine oxidase A. The same phenomenon has been confirmed for propranolol and zolmitriptan,⁷⁾ but the changes in AUC and C_{max} are relatively small compared to rizatriptan and the effects on the cardiovascular system is not related to whether propranolol is taken. Therefore, co-administration of zolmitriptan and propranolol is not a contraindication and dose reduction is not required. The same interaction is not observed with sumatriptan.⁸⁾

Caution is needed when propranolol is co-administered with many other drugs.¹⁾ Most of these drugs are used for treating cardiovascular diseases and their actions are augmented by the interaction. Note that the list of drugs requiring caution for

co-administration also includes calcium channel blocker such as verapamil that may be used as migraine prophylactic medication, ergot alkaloids such as ergotamine that may be used as acute treatment for migraine, and nonsteroidal anti-inflammatory drugs such as indomethacin.

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• Search terms

- Search database: PubMed (2012/9/3)
Migraine & propranolol & side effect 26
Migraine & propranolol & interaction 19