Chapter 53

Prioritizing Acute Pharmacotherapy of Migraines

Peer Tfelt-Hansen

Treatment should be prioritized as a joint venture between doctor and patient. The vast majority of migraine attacks are and should be treated by the patients at home or at work. The following discussion focuses on information necessary to the physician in helping patients choose the best treatment for their migraine attacks (for treatment in a surgery setting or in an emergency department, see Chapter 140).

As mentioned in the discussion of general and pharmacologic migraine management (see Chapter 47), acute treatment should be tailored to the individual patient, taking into account available drugs, efficacy versus side effects, contraindications, suitability, convenience, acceptability of route of administration, and costs. An overview of some of these factors is given in Table 53-1. In addition, treatment should be selected based on the overall severity of the patient's disease. The patient with occasional mild migraine has different treatment needs than the patient with frequent and disabling migraine. Finally, treatment also should be tailored to the individual attack, taking into account severity, duration, and whether treatment is taken at the beginning of an attack or whether a full-blown attack is to be treated as when an attack is fully developed on awakening.

As shown in Table 53-1, the availability of drugs differs considerably. Whereas aspirin is available worldwide, this is not the case for the triptans. The authors' opinions on efficacy and occurrence of side effects for the current drugs for treatment of migraine attacks are indicated in Table 53-1. The variability of reporting results in different controlled clinical trials for older drugs such as ergotamine and nonsteroidal anti-inflammatory drugs (NSAIDs; see Chapters 49 and 50) makes it impossible to compare these results with the results reported for the triptans in recent years in controlled clinical trials (see Chapter 51). Relatively few controlled clinical trials, eight with sumatriptan, two with zolmitriptan, one with rizatriptan, and one with eletriptan (see Chapter 51), have compared standard treatment with a triptan, and we will probably never have a definite scientific foundation for the rating of efficacy and side effects as given in Table 1.

Sumatriptan given as a subcutaneous injection has therapeutic gain (proportion of patients responding to active drug minus proportion of patients responding to placebo) of 50% after 1 hour in controlled clinical trials (for results with the triptans, see Chapter 51) and is rated as the most efficacious. Oral, intranasal, and rectal sumatriptan are less effective than subcutaneous sumatriptan, with therapeutic gains of approximately 30% after 2 hours, and similar results are reported for oral zolmitriptan, oral rizatriptan, oral almotriptan, and oral eletriptan. Oral naratriptan in the low dose chosen for clinical use has a therapeutic gain of approximately 20% after 2 hours. Frovatriptan has a therapeutic gain of 20%. Oral sumatriptan, oral rizatriptan, and oral eletriptan was found to be superior to oral ergotamine. Oral sumatriptan was somewhat more effective than aspirin plus metoclopramide in one trial and comparable with this combination in another trial. Intranasal and subcutaneous sumatriptan were both superior to intranasal dihydroergotamine, whereas rectal sumatriptan was inferior to rectal ergotamine plus caffeine in one trial. Subcutaneous sumatriptan was superior to subcutaneous dihydroergotamine for the first 2 hours, but the two drugs were comparable at later time points.

Speed of onset is highly valued by patients (2,5), and subcutaneous sumatriptan has an onset of action after 10 minutes, intranasal sumatriptan and zolmitriptan after 15 minutes, and 50 to 100 mg sumatriptan, 10 mg rizatriptan, 12.5 mg almotriptan, and 40 mg eletriptan after 30 minutes. It should be noted that, apart from subcutaneous sumatriptan, this early effect of the triptans is of relatively small magnitude. Thus, if a quick and clinically significant effect is needed, subcutaneous sumatriptan is

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TABLE 53-1 Availability, Efficacy, Side Effects, Convenience/Acceptability of Route of Administrations, and Costs for Currently Used Medication for Migraine Attacks Rated From + to ++++

Drug	*Availability Worldwide*	*Efficacy*	*Side Effects*	*Convenient/ Acceptable*[a]	*Costs*
Aspirin	+++	+ to ++	+	++++	+
Paracetamol	++++	+	+	++++	+
Triptans					
Sumatriptan					
Tablets	++	+++	+ to ++	++++	++++
Intranasal	++	+++	+ to ++	+++	++++
Suppositories	++	+++	+ to ++	++	++++
Subcutaneous injection[b]	++	++++	+++?	+ to ++	++++
Zolmitriptan					
Tablets	++	+++	+ to ++	++++	++++
Orally disintegrating tablets	++	+++	+ to +	++++	++++
Intranasal	++	+++	+ to ++	+++	++++
Naratriptan tablets[d]	++	++	+[c]	++++	++++
Rizatriptan tablets	++	+++	+ to ++	++++	++++
Rizatriptan wafer[d]	++	+++	+ to ++	++++	++++
Almotriptan tablets	++	+++	+[c]	++++	++++
Eletriptan tablets	++	+++	+ to ++	++++	++++
Frovatriptan tablets	++	++	+ to ++	++++	++++
Ergot alkaloids					
Ergotamine tablets	+++	+ to ++	+	++++	++
Ergotamine suppositories	++	+++	+++	++	++
Dihydroergotamine injections	++	+++[e]	++?	+ to ++	++
Dihyergotamine intranasal	+	++	+ to ++	+++	++
NSAIDs	+++	++	+	++++	++
NSAIDs + metoclopramide	++	++ to +++	+	++++	++

The ranking is based on a combination of my judgment of the literature and the author's personal experience and may be different in the experience of others.
[a] Convenience/acceptability depends heavily on cultural factors (see text).
[b] An auotoinjector is used.
[c] In controlled trials naratriptan and almotriptan resulted in no more side effects than placebo.
[d] A rapidly dissolving oral wafer; subcutaneous dihydroergotamine has a slower onset of action than subcutaneous sumatriptan (see text).

probably the best alternative. Because of to their pharmacodynamic properties, ergot alkaloids are generally more slowly acting drugs than the triptans (see Chapter 50).

The classic drug ergotamine, which has effects on many receptors (see Chapter 50), undoubtedly also has the most side effects, and increased nausea may limit oral and rectal use of the drug. NSAIDs have been comparable with oral ergotamine and generally have fewer side effects (see Chapter 49). Subcutaneous sumatriptan 6 mg causes more transient side effects than 100 mg oral sumatriptan, which causes generally the same side effects as oral zolmitriptan, oral rizatriptan, and oral eletriptan. The lower 25- and 50-mg doses of sumatriptan, the 2.5-mg dose of naratriptan, and 12.5 mg almotriptan cause in controlled clinical trials no more side effects than placebo. Sumatriptan 100 mg causes more side effects than the combination of aspirin plus metoclopramide, whereas rectal sumatriptan causes fewer side effects than rectal sumatriptan.

Contraindications can determine the choice of drugs. Whereas NSAIDs are contraindicated in patients with a peptic ulcer, they can be the drug of first choice for migraine patients with cardiovascular diseases, in whom ergot alkaloids and triptans are contraindicated.

The choice between routes of administration depends on convenience, suitability, and acceptability by patients. The most convenient way to administer drugs is normally by the oral route, but this may not be suitable in a migraine attack with severe nausea and vomiting. In this situation, one can either treat the nausea with an antiemetic and prokinetic drug such as metoclopramide (see Chapter 52) or try alternative routes of administration to circumvent the problems. The alternatives routes of administration are subcutaneous injection, rectal administration, and intranasal administration; but only a few of the drugs for acute migraine treatment—sumatriptan, zolmitriptan, and dihydroergotamine—are available in these forms. Even if a route of administration is

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convenient and suitable, it may not be acceptable for the patient; for example, some patients detest injecting themselves. Furthermore, there are considerable cultural differences in the acceptability of routes of administration, as exemplified by the following citation from a British textbook on clinical pharmacology (3) on the use of ergotamine: "Suppositories are more effective than oral administration, though less effective than injection, but they are unpopular with all except a perverse minority." This statement would, of course, be unlikely in a French textbook.

If a migraine patient has, for example, one attack per month, then the abuse potential is not important, but in patients with frequent migraine attacks or a mixture of migraine attacks and frequent or daily tension-type headaches, the abuse potential should be a primary factor in drug selection (see Chapter 118). Thus, any instant-relief drug for headache, when taken daily or almost daily, seems to induce more migraine or headache, leading to a vicious circle. The risk is greatest with opioids, which in our opinion are never indicated for migraine. Ergotamine is also easily abused and should not be taken more than twice a week (see Chapter 50). Abuse of triptans, most often in previous drug abusers, has also been reported (see Chapters 51 and 118).

The costs of migraine drugs should be taken into account. Depending on the country and the availability of health insurance, cost may be an issue for the healthcare system, the government, or the patient. In some countries, patients do not pay for their medication. The drugs used for treatment of migraine attacks vary, from inexpensive drugs such as aspirin and acetaminophen, the drugs used for most migraine attacks worldwide, to relatively inexpensive drugs such as ergotamine and NSAIDs, to expensive drugs such as the triptans. It can be argued that a very expensive but effective drug such as sumatriptan is not that expensive when the cost and benefits for the patients and the society are taken into account (see Chapter 5). In one placebo-controlled clinical trial, subcutaneous sumatriptan was found to reduce productivity loss during migraine attacks (1). Even if there is a general benefit to society, the price of triptans may still limit their use in many patients. Currently, many of our patients are aware of the price differences, especially between ergot alkaloids, NSAIDs combined with metoclopramide, and triptans, and ask advice on which of the these drugs to use, because they envisage the use of migraine drugs for years. We advise patients to treat three attacks with each of these alternatives. Patients can then decide whether there is a difference in effectiveness and side effects that justifies the price difference. Similar single-case experiments also can be undertaken for other drugs or forms of administration of a drug.

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