Almotriptan: a balanced approach to migraine

Roger Cull

Effective acute treatment of migraine is possible with the $5HT_{1B/1D}$ agonists (triptans), but their use has been limited in the UK because of concerns about limited efficacy, recurrence of attacks, adverse events, and cost. Almotriptan (Almogran, Lundbeck Ltd, Milton Keynes), the most recently available member of the class, offers some advantages over previously available agents.

Migraine is extremely common, affecting at least 10% of the population (Ferrari, 1998) in a ratio of approximately 3:1 female to male (Stewart et al, 1995) and occurring in all ethnic groups.

Typical symptoms include unilateral, pulsating pain of moderate or severe intensity that is aggravated by routine physical activity and often associated with nausea and photophobia and/or phonophobia (International Headache Society (IHS), 1988). Attacks typically last between 1 and 3 days, and patients are often disabled by their symptoms. In its diagnostic criteria, the Headache Classification Committee of the IHS distinguishes between migraine with aura ('common migraine') and without aura ('classic migraine'). The IHS defines true migraineurs as patients who have had at least two attacks with aura or at least five attacks without aura (IHS, 1988). Migraine without aura is the more common condition, with approximately twice the lifetime prevalence of migraine with aura (Russell et al, 1995).

While the pathophysiology of migraine is not completely understood, it is thought that excess neuronal activity in the occipital cortex and brainstem activates the trigeminal nerve causing dilation of blood vessels in the brain, meningeal membranes, face and spinal cord, leading to plasma leakage, swelling, inflammation and pain. Serotonin (5-hydroxytriptamine; 5-HT) has been implicated in this process, and it is believed that $5\text{-HT}_{1B/1D}$ receptors are particularly important (Martin, 1997) (*Table 1*).

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BURDEN OF ILLNESS

Effective acute treatment is available for migraine. However, it is an episodic condition, i.e. patients are free from symptoms between attacks. Although it rarely leads to hospitalization, migraine seriously affects the quality of life of both patient and family, and has serious economic implications. Prevalence varies by age, increasing until about the age of 40 years and declining thereafter in both men and women (Stewart et al, 1994), and it has been estimated that every day 90 000 people in the UK may be absent from work or school because of migraine (British Association for the Study of Headache (BASH), 2000a). Unsurprisingly, the economic costs are high: estimates of the annual financial burden of migraine are reported to be in the region of £741 million (Cull et al, 1992), although some estimate the financial burden may be as high as £1.5 billion per year (BASH, 2000b) — the majority of costs resulting from lost productivity. In 1999, the NHS spent in excess of £42 million on oral triptans alone (Department of Health, 1999).

Despite these costs, two-thirds of patients with migraine self-medicate with over-the-counter treatments, with one-third using prescription-only medications, although it has been estimated that 75% of migraine sufferers will consult their doctor at one time (Dowson and Jagger, 1999). According to the BASH guidelines, the management of migraine should comprise (BASH, 2000b):

- Correct and timely diagnosis
- Explanation and reassurance
- Identification and avoidance of predisposing factors or triggers
- Intervention (non-drug and drug)
- Careful follow-up.

DIAGNOSIS

Although the numbers of migraine sufferers seen in secondary care remains low, many patients

that are referred for specialist neurological investigation are done so unnecessarily — impacting on both waiting lists and hospital resources (Laughey et al, 1999). It is, therefore, essential that the secondary care community support and encourage primary care clinicians regarding the recommended treatment options for migraine and the use of available resources such as the IHS guidelines.

When a patient presents with headache, it is of course essential to exclude conditions that require urgent intervention, but the history and examination usually indicate intracranial lesions. There are currently no diagnostic tests that distinguish migraine from, for example, chronic tension-type headache. A careful history is therefore essential in order to avoid misdiagnosis and inappropriate investigation and treatment. This takes time that may not be available in primary care consultation, and it can be useful to ask the patient to keep a diary of the frequency and nature of the headaches that can then be discussed at a subsequent, longer appointment and used to confirm the diagnosis.

MANAGEMENT

The aim of treatment is to control symptoms in order to minimize as far as possible the effects of migraine on the patient's life. While this may be a rather simplified description of the aims of secondary care, it is important to reassure the patient and to appreciate that many may be extremely anxious upon referral to hospital — fearing the diagnosis of a more serious condition. Patients may also have had previous disappointing encounters with health professionals and their expectations of treatment may be low. Therefore, together with reassurance and careful follow-up, patients need clear explanation of the aims of treatment and encouragement to persevere with alternative treatments until their migraine is controlled.

Many sufferers have learnt to abstain from particular foods that often seem to precede a migraine attack. These 'trigger factors' may also include relaxation after stress, changes in habit, bright lights and/or loud noise and unaccustomed exercise (BASH, 2000b). It is important to distinguish these precipitating or trigger factors from predisposing factors which, in some people, may include stress, depression, menstruation, menopause, head or neck trauma (BASH, 2000b). In some circumstances lifestyle changes or other types of non-pharmacological therapy (such as biofeedback and relaxation techniques) may supplement

TABLE 1.
International Headache Society diagnostic criteria for migraine

Migraine headache without aura	An idiopathic recurring headache disorder with	At least 5 attacks fulfilling the second to fourth criteria below	
		Headache lasting 4–72 hours	
		Headache having at least two of the following:	Unilateral location
			Pulsating quality
			Moderate or severe intensity
			Aggravation by routine physical activity
		During headache at least one of the following:	Nausea and/or vomiting
			Photophobia
		At least one of the following:	History and examination do not suggest any condition to which headache may be secondary
			History and/or examination do suggest such a condition, but this has been excluded by examination
			Such a condition exists, but migraine did not begin in temporal relation to it
Migraine headache with aura	At least two attacks fulfilling second criterion		
	At least three of the following:	One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brainstem dysfunction	
		At least one aura symptom develops gradually over more than four minutes, or two or more symptoms occur in succession	
		No aura symptoms last for more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased	
		Headache follows aura with a free interval of less than 60 minutes (it may also begin before or simultaneously with the aura	

From Headache Classification Committee of the International Headache Society (1988)

migraine-specific treatment. Dealing with these predisposing and/or trigger factors may also help some patients to feel that they are 'in control' of their migraine.

The IHS suggests that if a person with migraine suffers four or more attacks per month, he or she may need daily prophylactic treatment with, for example, beta blockers, sodium valproate, pizotifen or amitriptyline (BASH, 2000b). If attacks total less than four per month, then a migraine-specific treatment (triptan) should be the treatment of choice. According to the BASH guidelines, the evidence base for all current prophylactic anti-migraine drugs is poor, and they should be used in addition to, and not instead of, acute treatment.

The BASH guidelines outline a treatment 'ladder' for acute migraine, with failure on at least three occasions indicating progression to the next step (some patients may need encouragement to persevere). Step 1 is simple, preferably soluble, oral analgesia — already used by most patients seeking medical help — followed by prescription-only analgesia (step 2) and specific antimigraine treatment with the 5-$HT_{1B/1D}$ agonists or triptans (step 3).

If treatment with a triptan is ineffective, BASH recommends reconsideration of the diagnosis and a review of compliance, and suggests that it is 'worth trying' dihydroergotamine nasal spray or ergotamine suppository (step 4), or a combination of acute treatments (step 5). However, response to the triptans can be idiosyncratic and unpredictable and, before embarking upon steps 4 and 5, patients should be encouraged to try the various formulations of each triptan until they find a drug that suits them and successfully manages their symptoms (BASH, 2000b).

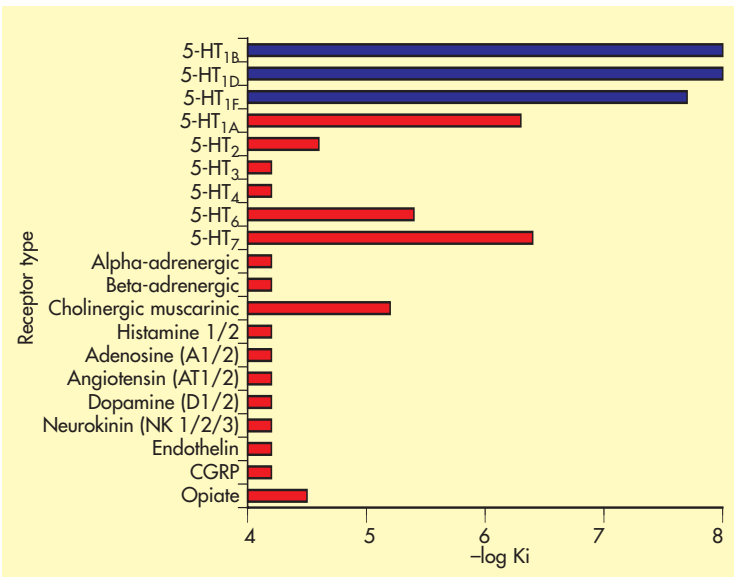

Figure 1. Pharmacodynamics of almotriptan. Unpublished data, Lundbeck Ltd, 2000. CGRP = calcitonin gene-related peptide.

THE TRIPTANS

Sumatriptan was the first triptan to be marketed in the UK in 1991, followed by zolmitriptan, rizatriptan and naratriptan. It is difficult to compare triptans as each behaves differently in the human body and all trials use their own benchmarks to measure their efficacy parameters. Triptans can generally be differentiated from other migraine therapies and from each other by the following attributes:

- Speed of onset of action
- Consistent efficacy
- Recurrence of attacks
- Tolerability
- Cost.

ALMOTRIPTAN

Almotriptan is indicated for the acute treatment of migraine with or without aura and is available in 12.5 mg tablets. Almotriptan should be taken after the onset of a migraine attack, and may be taken with or without food. As an acute treatment, it should not be used as prophylaxis.

At the time of publication, almotriptan has been shown to have a selective affinity for 5-$HT_{1B/1D}$ receptors (unpublished data, Lundbeck Ltd, 2000) and acts very selectively at human cranial vessels with little activity at peripheral human arteries (unpublished data, Lundbeck Ltd, 2000). Furthermore, as shown in *Figure 1*, almotriptan has little affinity for other vascular and cerebral non-serotonin-specific receptors (unpublished data, Lundbeck Ltd, 2000). Almotriptan may also be more selective than sumatriptan for cranial blood vessels, as it is slightly more potent in constricting isolated human meningeal arteries but significantly less powerful in constricting isolated non-cranial human blood vessels (unpublished data, Lundbeck Ltd, 2000).

Onset of action

Almotriptan should be taken immediately upon the onset of a migraine attack. In clinical studies, significantly more patients ($P<0.05$) taking almotriptan were pain free within 30 minutes of treatment compared to placebo, and the percentage of patients obtaining pain relief continued to increase for the first 2 hours after active treatment (unpublished data, Lundbeck Ltd, 2000; Pascual et al, 2000). This rapid onset of action is

not surprising as almotriptan has one of the highest oral bioavailability measures of the triptans, with about 70% of the drug absorbed within the first hour after administration (Holm and Spencer, 1999).

Clinical efficacy

Almotriptan 12.5 mg is significantly ($P>0.05$) more effective than placebo in relieving pain, with a 2-hour response rate of 57–65% (unpublished data, Lundbeck Ltd, 2000; Pascual et al, 2000). These results are equivalent to published data on other triptans such as rizatriptan (Gijsman et al, 1997; Kramer et al, 1998), sumatriptan (Perry and Markham, 1998), and zolmitriptan (Rapoport et al, 1997). In a direct comparative trial there was no significant difference in response rates between almotriptan 12.5 mg and sumatriptan 100 mg (unpublished data, Lundbeck Ltd, 2000). Almotriptan was consistently more effective than placebo in relieving symptoms such as nausea and vomiting (unpublished data, Lundbeck Ltd, 2000) and was not significantly different from sumatriptan (unpublished data, Lundbeck Ltd, 2000).

In a randomized, double-blind, placebo-controlled study (Pascual et al, 2000), almotriptan was consistently effective in treating three consecutive migraine attacks, and remained effective at 1 year in a large, open study (Pascual et al, 2001). Almotriptan has also been found to be effective in those patients requiring relapse medication (Pascual et al, 2000).

Almotriptan is effective in men and women at all ages. In a large open study (Pascual et al, 2001), response to almotriptan was similar in both male and female patients (pain relief at 2 hours in 84.7% *vs* 84.1%).

Recurrent headache

Use of the triptans is associated with the return of symptoms within 24 hours in 20–40% of patients who initially respond to treatment (BASH, 2000b). In trials, the recurrence rate for almotriptan 12.5 mg was 18–30% (unpublished data, Lundbeck Ltd, 2000; Pascual et al, 2000), and was lower than that for sumatriptan 100 mg in a direct comparative study (18% for almotriptan 12.5 mg compared with 25% for sumatriptan 100 mg; unpublished data, Lundbeck Ltd, 2000).

Tolerability

Almotriptan's elimination half-life is approximately 3.5 hours (unpublished data, Lundbeck Ltd, 2000), with no clinically or statistically significant differences in pharmacokinetics between healthy controls and patients with mild or moderate renal dysfunction (Summary of Product Characteristics, Lundbeck Ltd, 2000).

In a large double-blind study (Pascual et al, 2000), there was no significant difference between almotriptan and placebo in the percentage of patients reporting adverse events. From a total of 408 patients taking almotriptan 12.5 mg, only three patients withdrew as a result of adverse events. The majority were mild and there were no serious drug-related events associated with almotriptan. Almotriptan 12.5 mg has also been shown to have a tolerability profile similar to that of placebo and significantly better ($P<0.05$) than sumatriptan 100 mg (unpublished data, Lundbeck Ltd, 2000). The tolerability of almotriptan compared with placebo in three controlled trials is summarized in *Table 2* (unpublished data, Lundbeck Ltd, 2000). In a long-term open study (Pascual et al, 2001), age or sex did not influence the incidence of adverse events, and tolerability was not reduced in patients taking more than two doses of almotriptan.

TABLE 2.
Adverse events with almotriptan 12.5 mg compared with placebo

Adverse events	Almotriptan 12.5 mg (*n*=722)	Placebo (*n*=386)
Asthenia	0.6% (4)	0.5% (2)
Chest pain	0.1% (1)	0.3% (1)
Fatigue	1.2% (9)	1% (4)
Headache	1.7% (12)	1.3% (5)
Temperature change sensation	0.6% (4)	0
Dizziness	2.2% (16)	2.6% (10)
Paraesthesia	2.2% (16)	0.8% (3)
Speech disorder	0	0
Tremor	0.1% (1)	0.3% (1)
Vertigo	0.1% (1)	0.5% (2)
Abdominal pain	1% (7)	0.3% (1)
Diarrhoea	0.6% (4)	1% (4)
Dyspepsia	0.4% (3)	0.3% (1)
Mouth dry	1.7% (12)	0.5% (2)
Nausea	2.1% (15)	0.8% (3)
Vomiting	1.2% (9)	1.8% (7)
Palpitation	0.1% (1)	0.5% (2)
Myalgia	0.6% (4)	0.8% (3)
Skeletal pain	1.2% (9)	0.5% (2)
Somnolence	1.7% (12)	1.3% (5)
Vision abnormality	0	0.5% (2)

Unpublished data, Lundbeck Ltd, 2000

No interactions have been observed between almotriptan and commonly prescribed co-medications, including beta-blockers, calcium channel-blockers, selective serotonin-reuptake inhibitors, monoamine oxidase A inhibitors, ergot derivatives or inhibitors of cytochrome P450 isoenzymes 3A4/2D6 (Summary of Product Characteristics, Lundbeck Ltd, 2000).

Cost

In the UK, the triptans are regarded as expensive. This is in spite of their acknowledged efficacy and may be in part the result of a failure to appreciate the suffering and disability caused by migraine. Almotriptan is the least expensive of the five triptans currently available in the UK and, given its favourable clinical profile described above, could potentially offer a cost-effective treatment for many patients with acute migraine with or without aura (*Table 3*).

TABLE 3.
Costs of various migraine prescription medicines currently available in the UK

Drug	Class	Cost per tablet
Tolfenamic acid	NSAID	£1.50
Domperidone	Analgesic/ antidopaminergic	£0.88
Buclizine hydrochloride	Analgesic/antiemetic	£0.23
Sumatriptan	5-$HT_{1B/1D}$ agonist	£4.90–8.00
Rizatriptan	5-$HT_{1B/1D}$ agonist	£4.46
Naratriptan	5-$HT_{1B/1D}$ agonist	£4.00
Zolmitriptan	5-$HT_{1B/1D}$ agonist	£4.00
Almotriptan	5-$HT_{1B/1D}$ agonist	£3.25

From Monthly Index of Medical Specialities (2001). NSAID = non-steroidal anti-inflammatory drug

KEY POINTS

- Migraine is a common and disabling problem, affecting women more than men.
- It is especially common in people of working age. The loss in productivity associated with migraine represents a significant economic burden.
- Failure to appreciate the morbidity associated with migraine has led to the condition being both under-recognized and under-treated.
- Effective acute treatment is possible with the triptans, but their use has been limited by a number of concerns, including their cost.
- A new triptan, almotriptan, offers the advantages of efficacy, tolerability and comparatively low cost.

CONCLUSIONS

Migraine is a common condition, with a serious impact on the quality of life of patients and their relatives, which represents a considerable financial burden to society. It is a condition that is not effectively managed at present and the launch of almotriptan is to be welcomed in increasing the choice of effective treatments. The availability of several triptans is an advantage and increases the number of people who will achieve optimum treatment of their illness (BASH, 2000a). **HM**

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