Migraine headaches affect approximately 12% of the adult population and are more prevalent in women (ranging from 15% to 18%) than men (6%). Their occurrence is dependent on age, sex, socioeconomic status, and race. Migraines are recurrent episodes of intense headache pain, often associated with nausea, vomiting, and sensitivity to light and sound. These episodes may last from a few hours to days. A migraine can be an extremely disabling event for its sufferer; the annual cost of labor lost to migraine disability is estimated at $5.6 to $17.2 billion. Every year, decreased productivity and absenteeism contribute to this economic impact.

Although the exact physiological mechanism of a migraine attack is not completely understood, the headache is thought to occur as a result of neuronal dysfunction. Within the trigeminovascular system, trigeminal nerves serve as important initiators and promoters of tissue inflammation. Vasoactive peptides such as calcitonin gene-related polypeptide, substance P, and neuropeptide A are released after neuronal activation. As a result, vasodilation and plasma protein extravasation occur. A neurogenic inflammatory response is initiated, sensitizing the surrounding tissues and producing a hyperalgesic state. Activity within this system is regulated primarily by serotonergic neurons and, to a lesser extent, by noradrenergic neurons.

Migraines are typically unilateral at onset, present with pulsating or throbbing pain, and are located in the frontotemporal region of the head or face. Other common characteristic features are nausea, vomiting, phonophobia, and photophobia. Peak headache pain intensity generally occurs within one hour of onset, and headache duration can last anywhere from four to 72 hours.

With the identification of patient-specific migraine triggers, alterations of neurotransmitter levels within the central nervous system can be avoided. For instance, loud noises, glare, caffeine, and certain food additives (e.g., sodium nitrate and monosodium glutamate) often provoke migraine attacks in susceptible individuals. In other patients, changes in temperature, humidity, or hormone levels can trigger a migraine attack.

There are two major pharmacological approaches to migraine treatment. Therapeutic management is targeted at either altering the attack once it is under way or at preventing the attack altogether. The daily administration of prophylactic agents is usually reserved for patients with more frequent and severe headaches.

Traditionally, migraine attacks had been treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, analgesics, narcotic analgesics, and ergot derivatives. The introduction of triptans to the pharmaceutical market revolutionized the treatment of migraine. All of the currently available triptan products are 5,5-substituted tryptamine derivatives. They are agonists at the 5-hydroxytryptamine (5-HT1D) receptor sites with varying affinity for the 5-HT1D, 5-HT1B, and 5-HT1D receptors. Headache pain is relieved as a result of cerebral vasoconstriction. These agents have been responsible for the most effective, complete relief of headache and associated symptoms, and they are regarded as a mainstay for abortive migraine therapy.

With the addition of each new drug to this class comes the burden of distinguishing it from other agents. Thus far, the similarities of these agents far outnumber the differences between them. However, the newest addition—frovatriptan succinate (Frova™, Elan)—has displayed remarkable characteristics that may set it apart. Frovatriptan is indicated for acute treatment of migraine attacks, with or without aura, in adults. It is not indicated as prophylactic treatment of migraine or for management of hemiplegic or basilar migraine.

Several in vitro and in vivo studies have shown that frovatriptan is a potent 5-HT1D receptor agonist, one with a long duration of action and good tolerability. Frovatriptan reverses cerebral vasodilation by activating 5-HT1D and it prevents neurogenic inflammation by activating 5-HT1D. In other words, frovatriptan and other 5-HT1D agonists constrict dilated cerebral vessels in such a way as to prevent the subsequent neurogenic inflammation.

When frovatriptan was compared with sumatriptan (Imitrex®, GlaxoSmithKline) and naratriptan (Amerge®, GlaxoSmithKline), all three drugs were shown to be full agonists on 5-HT1D/1B in the cerebral vasculature; however, frovatriptan was more potent, having a fourfold higher affinity to 5-HT1D. Frovatriptan not only is more potent in cerebral receptors but also, unlike sumatriptan, zolmitRIPTAN (Zomig®, AstraZeneca), and naratriptan, does not appear to constrict human coronary and peripheral arteries. Peripheral arterial constriction is the cause of decreased tolerability in patients. In addition to its favorable tolerability and potency, frovatriptan has the potential to be useful in patients with long-lasting or recurrent migraine.

Frovatriptan is eliminated by both the kidneys and the liver; unlike other triptans, however, the drug is not metabolized by monoamine oxidase (MAO) or the cytochrome P-450 (CYP-450) enzyme 3A4. In vitro, CYP-450 1A2 appears to be
the principal enzyme involved in the metabolism of frovatriptan. Frovatriptan is metabolized into hydroxylated frovatriptan, desmethyl frovatriptan, N-acetyl desmethyl frovatriptan, and hydroxylated N-acetyl desmethyl frovatriptan. Desmethyl frovatriptan is active but, compared with the parent compound, has a lower affinity for 5-HT1B/1D.

The elimination half-life of frovatriptan is approximately 26 hours, the longest of any agent in the triptan class (Table 1). Studies have shown no difference in mean terminal half-life between males and females.

**RESULTS**

Frovatriptan has been studied in healthy male and female subjects, in subjects with renal or hepatic impairment, in elderly subjects, and in individuals with migraine headache during and between attacks.

**Healthy Subjects**

Following oral administration of frovatriptan, 2.5-mg mean maximum blood concentrations in patients are achieved in approximately 2 to 4 hours. With regard to age, the area under the curve (AUC) in healthy subjects aged 65 to 77, compared with subjects aged 21 to 37, was 1.5-fold to twofold higher in the older individuals. Blood concentrations and the AUC were greater in healthy women (7.0 ng/ml, 94 ng/ml per hour) than in healthy men (4.25 ng/ml, 42.9 ng/ml per hour). The absolute bioavailability in healthy subjects is about 20% in males and 30% in females. Protein binding of frovatriptan is low (approximately 15%).

**Elderly Populations**

Blood concentrations were higher in older women than in older men and higher in both older men and women than in younger subjects. Mean values of maximum concentration (Cmax) and the AUC were ranked in the following order: (1) elderly women, (2) young women, (3) elderly men, and (4) young men.

**Subjects with Renal Impairment**

No significant difference was noted in subjects with renal impairment compared to healthy subjects. Less than 10% of frovatriptan is excreted renally after an oral dose, thus making it unlikely that the kinetics of frovatriptan would be affected by renal impairment.

**Subjects with Hepatic Impairment**

Four men and four women were given a single oral dose, or 2.5 mg of frovatriptan. Of these four subjects, two men and two women had mild impairment (Child-Pugh score A) and two men and two women had moderate impairment (Child-Pugh score B). The AUC in women with moderate impairment appeared higher than that in women with mild impairment. No relationship was seen in the men, and there appeared to be no correlation between the degree of hepatic impairment and the kinetics of frovatriptan. In addition, these values were consistent with studies comparing the young and elderly, with mean concentrations in both young and elderly women being higher than those in the men. Furthermore, the mean AUC and Cmax were nearly twice as high in heptically impaired subjects, when compared with the data in young subjects (aged 21 to 37). However, the mean AUC and Cmax were just as high in heptically impaired women as in women taking combined oral contraceptives (COCs). In short, decreased hepatic function affects the kinetics of frovatriptan in a similar manner as concurrent administration of COCs.

**Subjects with Migraine**

Twelve patients (six of both sexes) were given frovatriptan 2.5 mg as a single oral dose and were examined during a migraine attack and during a migraine-free period. Blood concentrations were twofold higher in women than men, with no significant differences apparent in either sex. In addition, there appeared to be little difference in blood concentrations or kinetics during a migraine or during a migraine-free period.

In sum, as a result of increased bioavailability, blood concentrations of frovatriptan were higher in women than in men during migraine attacks. Further, the presence of migraine headache does not seem to affect the kinetics of frovatriptan.

**COMPARATIVE EFFICACY**

**Headache Relief**

The efficacy of frovatriptan was assessed in men and women aged 18 to 55 at 2, 4, and 6 hours after administration of the dose using the International Headache Society’s four-point scale of 0 to 3 (0 indicating no headache and 3 indicating severe headache). At two hours, the lowest effective dose, 2.5 mg, was observed to provide an effect of 40%, compared to an effect of 23% with placebo. The effect was defined as a change from severe or moderate (3 or 2 on the four-point scale) to mild or no headache (1 or 0).

Doses ranging from 5 to 40 mg were also given but were no more effective than the dose of 2.5 mg; similarly, 0.5 mg and 1-mg doses proved no more effective than placebo.

### Table 1 Pharmacokinetic Properties of FDA-Approved Oral Triptan Products

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sumatriptan (Imitrex®)</th>
<th>Naratriptan (Amerge®)</th>
<th>Rizatriptan (Maxalt®)</th>
<th>Zolmitriptan (Zomig®)</th>
<th>Almotriptan (Axert®)</th>
<th>Frovatriptan (Frova®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (%)</td>
<td>14%–15%</td>
<td>~ 63%–75%</td>
<td>~ 45%</td>
<td>~ 49%</td>
<td>~ 70%–80%</td>
<td>24%–30%</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>~ 2 hr</td>
<td>~ 6 hr</td>
<td>~ 2 hr</td>
<td>~ 3 hr</td>
<td>3–3.7 hr</td>
<td>25 hr</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2–2.5 hr</td>
<td>2–3 hr</td>
<td>0.5–2.5 hr</td>
<td>2–4 hr</td>
<td>1–4 hr</td>
<td>2–4 hr</td>
</tr>
<tr>
<td>Onset</td>
<td>1–2 hr</td>
<td>1 hr</td>
<td>&lt; 30 min</td>
<td>&lt; 2 hr</td>
<td>1–2 hr</td>
<td>2 hr</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>~ 50%</td>
<td>~ 70%</td>
<td>~ 65%</td>
<td>~ 65%</td>
<td>≤ 75%</td>
<td>10%–32%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
<td>Liver, MAO-A</td>
<td>Liver</td>
<td>MAO-A, Liver</td>
<td>Cyt. P-450</td>
<td>Cyt. P1A2</td>
</tr>
</tbody>
</table>

Data from drug product information. Cyt. = cytochrome; F = bioavailability; FDA = Food and Drug Administration; MAO = monoamine oxidase; T1/2 = elimination half-life; Tmax = time of maximum plasma concentration.
Headache Recurrence

Headache recurrence was defined as taking place in patients who had a 1 or 0 response and whose headache recurred to grade 2 or 3 in a 24-hour period after administration of 2.5 mg of frovatriptan. The rate of recurrence was significantly less with frovatriptan than with placebo—9% to 16% in contrast to 27%. The smaller recurrence rate may be due to the long duration of action of frovatriptan as a result of its 26-hour half-life.5,6

SAFETY AND TOLERABILITY

All doses of frovatriptan given in the studies, from 0.5 mg to 40 mg, were well tolerated.7,9 The most common adverse events reported were dizziness, nausea, and fatigue. It should be noted that these effects are commonly experienced during migraine attacks and are also dose-related effects of sumatriptan, zolmitriptan, naratriptan, and rizatriptan (Maxalt®, Merck). These effects are also dose-related in frovatriptan, with the highest incidence seen at doses of 10 mg and above. Most of the adverse events were of mild to moderate intensity and of short duration. Other adverse events with low incidence (at least 1%) were paresthesia, flushing, chest pain, dyspepsia, and skeletal pain.9

All doses of frovatriptan, except for 0.5 mg and 1 mg, were more efficacious than placebo at relieving nausea, photophobia, and phonophobia associated with migraines, but 2.5 mg was shown to be the lowest effective dose.7,9 In a single study (VML 251/96/09, study 4) frovatriptan 2.5 mg was better tolerated than sumatriptan 100 mg. Patients experienced adverse events at a rate of 36% with frovatriptan and at 43% with sumatriptan. The total number of adverse events reported was 50% higher for sumatriptan.9

DRUG INTERACTIONS

In vitro, frovatriptan is not an inhibitor of human MAO enzymes or cytochrome P-450 (isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). No induction of drug metabolizing enzymes was observed.4

- Ergotamine. When ergotamine was administered concurrently with frovatriptan, both the AUC and the Cmax of frovatriptan were decreased by 25%.8,10
- Propranolol. When propranolol was taken with frovatriptan, the AUC of frovatriptan was increased by 60% in males and the Cmax of frovatriptan was increased by 23% in males and by 16% in females.5,10
- Combined oral contraceptives. Both the Cmax and the AUC of frovatriptan were 30% higher in patients taking COCs in contrast to patients who were not taking COCs.5,10
- Fluvoxamine. The half-life of frovatriptan was decreased from 26 hours to 17 hours. The AUC of frovatriptan was increased by 39% in men, by 41% in women taking COCs, and by 28% in women not taking COCs. Frovatriptan appears to be metabolized by CYP-450 1A2, as is fluvoxamine.10

DOsing

The recommended dosage is one 2.5-mg tablet, up to three tablets a day, at no less than two-hour intervals.5

Overdosage: The maximum single dose given to men and women was 40 mg (16 times the recommended dose), and the maximum single dose given to men was 100 mg, without significant effect.5 Therefore, the possibility of overdose is very slim, because several times the recommended dosage was consumed without adverse effects. In addition, patients receive only nine tablets per carton of frovatriptan.

availability

Frovatriptan is available as a round, white, film-coated 2.5-mg tablet. Tablet markings show a “77” on one side and an “e” logo on the other. The drug is available in a card of nine tablets with one blister pack per carton.4

conclusion

In general, it is clear that the triptans are an effective means of providing abortive migraine therapy. From a pharmacoeconomic standpoint, the higher cost of the triptans can be offset by the overall reduction in cost of medical care. Arguably, sumatriptan has been the standard of care since its approval. Its limitations—its high incidence of adverse effects, its short duration of action, its short half-life, and the high recurrence rates of migraine—has led to the need for more well tolerated and efficacious agents. The addition of frovatriptan to the market significantly increases the choices for the effective treatment of a disabling health condition that affects many people in the U.S.

Frovatriptan’s potency as a cerebral vasoconstrictor, its dual elimination by the kidneys and liver, and its selectivity make frovatriptan a unique agent for the treatment of acute migraines. Its selectivity for cerebral vessels lessens the potential for undesirable peripheral effects. In addition, frovatriptan’s 26-hour half-life provides the possibility of reducing migraine recurrence and decreasing the need for repeated dosing.

Frovatriptan may be taken without regard to meals.6 There appears to be no need to adjust the dose in patients with renal or hepatic impairment, in older adults, or in women taking COCs, because frovatriptan is well tolerated in these individuals. Frovatriptan provides an option for migraine sufferers with long-lasting or frequently recurring headaches.

REFERENCES