The Age of the Triptans (1999)

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The choices available for relief of the acute migraine are increasing, thanks to a number of new members of the "triptan" family. The flood started, of course, with sumatriptan (Imitrex) in injectable form, which met with impressive success, despite some drawbacks. Now, available agents also include oral and nasal forms of sumatriptan, oral zolmitriptan (Zomig), oral naratriptan (Amerge), and oral and lingual tablet forms of rizatriptan (Maxalt, and Maxalt MLT). More are on the way, with varying properties, strengths, and weaknesses. Dihydroergotamine is of course now available in nasal form, which offers a powerful alternative as well.

Theories about the etiology of migraine have been numerous. There is mounting evidence for a unified theory involving one or more trigger factors activating a midline brainstem "migraine generator", which, in turn, leads to painful vasodilation and inflammation of vascular and muscular tissue intra- and extracranially. The migraine generator almost certainly includes raphe nuclei and the locus ceruleus, but limbic and other structures may be involved as well. Migraine generator regions have a high density of serotonin and norepinephrine neurons, and serotonin activity in particular seems to be crucial in at least two of the steps in the above cascade.

Clearly, drugs which have serotonin type 1 receptor agonist properties are helpful in aborting the migraine process. The mechanism of action of these 5-HT1 agonists seems to be an inhibition of the release of various peptide neurotransmitters like Substance P and CGRP which promote pain transmission. In some fascinating PET studies both zolmitriptan and DHE seem to actually turn off the migraine generator areas during a migraine attack.

While sharing many properties, the newer migraine abortives differ in some key areas, including absorption, onset of action, half-life, recurrence rate, and side effect profile. The typical "triptan" reaction of paresthesias, often in the upper torso and neck, a sensation of warmth in the same areas, dizziness, palpitations, and chest pain, is common to all agents in the family. It is more pronounced, of course, with the parenteral, and to a lesser extent, nasal forms, as compared to oral preparations. Ventricular fibrillation and MI have been reported with sumatriptan, and thus all triptan family members are considered to be contraindicated in patients with known cardiac disease. Patients with a family history of cardiac disease or other risk factors for cardiac disease are at some risk, although the degree is uncertain. DHE also carries cardiovascular risk, but this seems to be relatively minor. Ergotamine and DHE can induce nausea which may be prohibitory, although pretreatment with an antinauseant such as metoclopromide, orally or parenterally, can prevent this.

Table 1 summarizes some important pharmacokinetic data concerning ergotamine, DHE and members of the triptan family.

Rizatriptan displays the shortest time to onset, thus may be one of the best choices for migraines which produce symptoms quickly. Naratriptan, with its long system life might be best in patients troubled by migraine recurrence. While not yet available, frovatriptan and almotriptan promise to have low recurrence rates as a result of long half-lives, and will perhaps even lend themselves to prophylactic use. Sumatriptan seems to be more poorly absorbed from the GI tract than others, but is available in multiple forms to counteract this. Naratriptan seems to have the highest absorption rate, which would be a plus in patients who seem to have poor GI absorption during migraine attacks.

Virtually all migraine sufferers ask for a "rescue" medication for use at the time of particularly severe headaches. Simple analgesics and even compound analgesics such as butalbital (Fioricet, Fiorinal, Phrenilin) and isometheptine (Midrin) have often proven to be only partially effective in these situations. Opioid analgesics are helpful in some situations but analgesic rebound limits their use for patient s experiencing frequent migraines. The newer "migraine-specific" triptan family is filling this need for symptomatic relief for many thousands of patients. Each member of this family has unique pharmacokinetics and a unique side-effect profile, though all have similar properties. Rebound seems not to occur with these compounds, although this has not yet been proven. In patients without contraindications, this group of medications should be considered for treatment of acute severe migraine, and while not panaceas, they are likely to bring relief to numerous individuals in years to come.

Table 1 - Properties of agents used for migraine relief

Drug	Onset	Tmax	Recurrence (% when available)
Ergotamine po	1-2h	3h	low
Ergotamine pr	30-60 min	3h	low
DHE IV	30 min	10 h	low
DHE NS	1-2 h	10 h	low
Sumatrip SC	15-30 min	12 min	mod 32-38%
Sumatrip NS	30-60 min	1 h	mod 32%
Sumatrip po	1-2 h	2-2.5 h	mod 34%
Zolmitrip po	1 h	2 h	mod 30%
Naratriptan po	2-3 h	3-4 h	low 19-28%
Rizatriptan po	30-80 min	1.3 h	mod 35%
Eletriptan		1-2 h	mod 32-33%
Frovatriptan		2-4 h	low 13%
Almotriptan		1.4-3.8 h	low 18%