Use of the triptans

Marek J Gawel MD FRCPC

In the past 10 years, there have been great advances in the understanding of the pathophysiology of the migraine. This has been due in part to the realization that the migraine attack can be blocked by activating the serotonin receptor, namely the 5-hydroxytryptamine/1D receptor. This switches off the inflammatory process around the blood vessel, which is the cause of the migraine pain, and constricts the blood vessel involved, thus relieving pressure on it. The first drug that was developed to activate this system was sumatriptan, followed by zomirtriptan, naratriptan and rizatriptan. These drugs are, as a group, called the ‘triptans’.

This review summarizes the pathophysiology of migraine, examines the guidelines for the diagnosis of migraine, which is important because the drugs are relatively specific for migraine itself, and discusses the differences among the components in this class.

Key Words: Migraine; Neurogenic inflammation; Triptan; Serotonin

In the past 10 years, a new class of compounds has evolved for the treatment of migraine. This class is known as the triptans. These compounds have the property of activating the 1B and the 1d serotonin receptors. Their use is based on the theory that migraine is caused by the release of vasoactive peptides from the trigeminal nerves innervating the perivascular space around the intracranial extracerebral blood vessels. The release is thought to be triggered by antidromic discharges from the trigeminal nucleus caudalis, in turn activated by the recently described migraine centre in the brainstem. This centre is in the region of the periaqueductal grey matter and has been shown, by using a combined magnetic resonance imaging and positron emission tomographic technique, to increase in activity during a migraine attack. That it is a primary centre is to some extent supported by the fact that abolition of the pain peripherally has no effect on its activity and that, if it is still active when the effects of the medication wear off, the pain comes back. The inside of the skull is innervated by the first division of the fifth nerve as well as C1 and C2. Thus, pain arising from the process above is felt in the distribution of these nerves but is poorly localized, being visceral rather than somatic in nature. The triptans act on the 5-hydroxytryptamine receptors present on the blood vessels and the nerves as well as in the brainstem. They block the re-
leakage of vasoactive peptides, cause arterial vasoconstriction and, if they penetrate the blood brain barrier, inhibit neuronal discharges in the trigeminal nucleus (1).

Although the triptans have a very specific action in migraine response, response to them is not a diagnostic test. As outlined in the specific discussion of each triptan, even the best triptan does not work in 20% to 30% of attacks. Furthermore, pathways other than the trigeminovascular pathway described above are involved in the generation of the attack. It would be simplistic to assume that affecting one receptor family would stop every attack. At the same time, headaches other than pure migraine may be alleviated if at least part of the pathophysiology were common to that of migraine. The concept of neurogenic inflammation, discussed above, is involved in other pains, such as toothache. Admittedly, there is no toothache generator – the inflammatory loop being at the periphery. One may ask whether the triptans work in that situation. The answer is that a study to confirm this has not yet been done.

The definition of migraine is based on a clinical description of the attack. The International Headache Society (IHS), in a 1988 publication (2), defined migraine as follows. These criteria have been modified and used by the Canadian Headache Society.

**CRITERIA FOR DIAGNOSING MIGRAINE WITHOUT AURA**

A. At least five attacks fulfilling criteria B to D.

B. Each attack, untreated or unsuccessfully treated, lasts 2 to 72 h.

C. The attack has at least two of the following characteristics:

- **Unilateral location:** Migraines are most commonly unilateral; however, they can be bilateral in 30% to 40% of cases, and sometimes the pain begins on one side and later spreads to the other. Location should, therefore, be characterized by different phases of the attack, and early or mild attacks should be differentiated from full-blown attacks. Useful questions to ask the patient include the following. Do you feel the pain on one or both sides? If one sided, is it always on the same side? If present on both sides, did the pain start on one side? Is it usually maximal on one side?

- **Pulsating quality:** Over 50% of people who suffer from migraines report nonthrobbing pain during some attacks, and 30% of patients with tension-type headache may report pulsating pain. Headache quality may also vary over the duration of the attack. If the pain is throbbing at any phase of the attack, it is recommended that, for consistency, the quality be regarded as throbbing overall. Useful questions include the following. What kind of pain is it – tightening, pressing, throbbing, pounding, pulsating, burning or other? Do different types of pain occur at different time in any one attack? If so, which types?

- **Moderate or severe intensity:** The severity of the migraine inhibits or prohibits daily activity.

- **Pain is aggravated by walking up and down stairs or similar routine physical activity.** Patients who prefer not to move around should be considered as experiencing aggravation of pain by physical activity. Possibly useful questions about other, less equivocal aggravating factors include the following. Do you avoid movement of even a minor nature (head movement or bending down) during an attack?

D. During an attack, at least one of the following symptoms should be present.

- **Nausea or vomiting:** it is important that nausea be differentiated from anorexia, which is common among patients with anxiety or tension-type headaches.

- **Photophobia, phonophobia and osmophobia:** Although the IHS criteria mention only photophobia and phonophobia, the panel for the Canadian Headache Society Guidelines recommends the presence of osmophobia (aversion to odours) also be determined, because this is a highly sensitive and specific feature of migraine. Useful questions to ask the patient include the following. During a headache, are you unusually sensitive to light, noises or odours? Do you take steps to avoid them? Because there is some degree of overlap of symptoms between migraine and tension-type headache, the severity of such symptoms should be graded as mild, moderate or severe as with pain severity.

E. There is no evidence from the patient’s history or physical examination of any other disease that might cause headaches.

**CRITERIA FOR DIAGNOSING MIGRAINE WITH AURA**

The criteria for diagnosing migraine with aura are the same as those for migraine without aura, but they include symptoms of neurological dysfunction (including visual disturbance) occurring before or during the attack (3).

This definition is seen by some to be too restrictive, and it certainly excludes some patients who are known to suffer from migrainous headaches but who lack the full complement of diagnostic criteria. Why such patients are classified as migraine sufferers is, of course, part of a circular argument, but it may affect the way that they are treated. Thus, vascular headaches lacking the nausea, photophobia and phonophobia may still respond to triptans.

The diagnosis of migraine is missed by family doctors in about 25% of contacts. This figure is not too bad when the problems in communication are considered. Remember that to make the diagnosis, the patient has to have had at least five attacks. The other confounding factor is that people often confuse migraine with headache severity. Thus, headaches that have all the necessary criteria but are mild may not be classified as migraine.

What is the significance of the aura? The migraine aura precedes the headache in about 15% of individuals but not necessarily before every attack. The most common form of aura is visual. There is most often a spread of bright zigzag...
TABLE 1
Efficacy – Pain relief

<table>
<thead>
<tr>
<th>Product/dosage</th>
<th>Pain relief at 2 h, % (range)</th>
<th>Pain-free at 2 h, % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naratriptan 2.5 mg</td>
<td>21 (18-24)</td>
<td>15 (12-18)</td>
</tr>
<tr>
<td>Rizatriptan 5 mg</td>
<td>29 (20-40)</td>
<td>21 (16-24)</td>
</tr>
<tr>
<td>Rizatriptan 10 mg</td>
<td>36 (21-52)</td>
<td>32 (24-38)</td>
</tr>
<tr>
<td>Rizatriptan wafer 10 mg</td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td>Sumatriptan 50 mg</td>
<td>33 (25-40)</td>
<td>22 (14-30)</td>
</tr>
<tr>
<td>Sumatriptan 100 mg</td>
<td>34 (29-36)</td>
<td>26 (18-32)</td>
</tr>
<tr>
<td>Sumatriptan nasal 20 mg</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>Zolmitriptan 2.5 mg</td>
<td>34 (27-41)</td>
<td>19 (14-24)</td>
</tr>
</tbody>
</table>

Reproduced with permission from reference 15

Gawel

lines, starting in the centre or one corner of the visual field and spreading to cover the rest of the vision. In the centre of the area bounded by the bright margins is an area of loss of vision. The spread, as seen during cerebral blood flow studies, starts in the occipital cortex and moves forward. It is thought that the aura is caused by a wave of excitation, followed by a wave of depression of the electrical activity of the cortex. One form of aura is a combination of tingling and numbness in the face and tongue, associated with the same in the hand. This phenomenon is called Cheiro oral paresthesia. It can be very disturbing and reminiscent of a stroke. The distinguishing feature is that the sensations are positive (ie, tingling as opposed to just numbness). Sometimes the aura can be prolonged and result in numbness or weakness, which lasts several days.

This complex of symptoms differentiates migraine from other pain situations and adds a further dimension to treatment and diagnosis.

The attack itself varies in length, and its pattern may be different within the same subject or among different subjects. This variability makes assessment of a treatment modality difficult because the response of an attack starting rapidly and lasting 5 h is different from the response of an attack building slowly and lasting two days. The pharmacokinetics of the drug in question remain the same irrespective of the attack type.

The measurement of response has also been a problem. Since the early 1980s, it has been customary to define headache as mild, moderate, severe or none. A responder is a patient whose headache goes from severe or moderate to mild or none. Defining headache in this manner tends to degrade the data; more recently, response has been defined as complete pain relief or no pain. There are also measures for the other aspects of migraine such as nausea and disability. The responses are usually quoted at the 2 h time point. Recurrence is defined as a headache that has gone to mild or none at 2 h and returns within 24 h.

Adverse events with use of the triptans tend to follow a very similar pattern within the class. The most worrying adverse events are chest tightness and pain, tightness and squeezing feelings in the neck and throat, and fatigue. The chest tightness and pain may be due to the effect of the triptans on the coronary circulation, but it is interesting that drugs with 5-hydroxytryptamine1F activity, which have no vasoactivity, also have the same adverse effect. Other adverse events are dizziness, fatigue, dry mouth and nausea. These are generally well tolerated and do not pose a problem in most people (4).

SUMATRIPTAN

Sumatriptan was the first triptan. It is available as a tablet (100 mg and 50 mg), a nasal spray (5 mg and 20 mg) and an injection (6 mg). The injection has a response rate of 70% to 77% at 1 h and 81% to 87% at 2 h (5).

The 100 mg tablet has a response rate of 55% to 67% at 2 h, and the 50 mg tablet has a similar efficacy. The recurrence rate is of the order of 30% (6). Nasal sumatriptan 20 mg has a comparable efficacy to the tablet, but the onset is somewhat faster (7).

ZOLMITRIPTAN

Zolmitriptan has better bioavailability than oral sumatriptan (8). A recent study showed that zolmitriptan 2.5 mg produced a significantly better response at 2 h than sumatriptan 50 mg (67.1% versus 63.8%). Pain relief over 24 h was better with zolmitriptan (9).

NARATRIPTAN

Naratriptan is prescribed at a dose of 2.5 mg, which ensures reasonable efficacy (60% at 4 h) with minimal side effects (equal to placebo in one study) (10). Headache recurrence is less of a problem, and the 24 h efficacy is similar to that of sumatriptan. Naratriptan is probably more suitable for patients with mild to moderate headache or those who have prolonged attacks.

RIZATRIPTAN

Rizatriptan is the latest triptan to be launched. It is available as a 5 mg and 10 mg tablet, and a rapidly dispersible wafer formulation. The wafer dissolves very rapidly on the tongue and is absorbed by the gastric mucosa after trickling down the esophagus. It is not absorbed sublingually. Efficacies of both the 10 mg tablet and the wafer are excellent (11,12). Studies have been performed comparing rizatriptan with sumatriptan (13), zolmitriptan (14) and naratriptan (15). Rizatriptan seems to have a slightly faster onset of efficacy than sumatriptan and zolmitriptan, and is much faster than naratriptan.

THERAPEUTIC GAIN

Therapeutic gain gives an idea of the efficacy of a drug when the placebo effect is subtracted. Care must be exercised in ascribing too much importance to a particular figure because study conditions and populations vary (Table 1).

CONCLUSIONS

The triptans are a class of compounds recently introduced for the acute treatment of migraine. Their mode of action focuses on the 5-hydroxytryptamine1B1D receptor. While this receptor obviously plays an important role in the migraine attack, it
is not the only system involved. It is thus reasonable that not all attacks are treated in responders, and that not all people respond. Choosing a particular triptan has been the subject of much debate. While using the data from studies as shown above may be useful, in the long term patient preference is the arbiter. Some physicians give the patient a selection of triptans to see which they prefer. This does not address the question of consistency of response. Others may start with naratriptan on the grounds that it has fewer adverse events, but then, if it is insufficiently efficacious, the patient may not wish to go to the next step. There are data, however, on the effect of using a second triptan when one has failed. (15). It does seem worth trying another drug in this situation. What the role of the triptans will be in other areas of pain is completely unknown. It of course have no role, but this has to be studied.

REFERENCES
6. Salonen R, on behalf of the study group, Glaxo Wellcome and Turku Headache Center, Turku, Finland. Patient preference among 25 mg, 50 mg, and 100 mg oral doses of sumatriptan. EFNS Symposium, Rome, October 28-30, 1996.
8. Martin GR. Pre-clinical pharmacology of zolmitriptan (Zomig; formerly 31 1C90), a centrally and peripherally acting 5HT-1D/1B agonist for migraine. Cephalalgia 1997;17(Suppl 18):4-12.