VOLUME 4, ISSUE 1
JANUARY/FEBRUARY 2004

The journal with the practitioner in mind.

Improving Postoperative Pain Outcomes

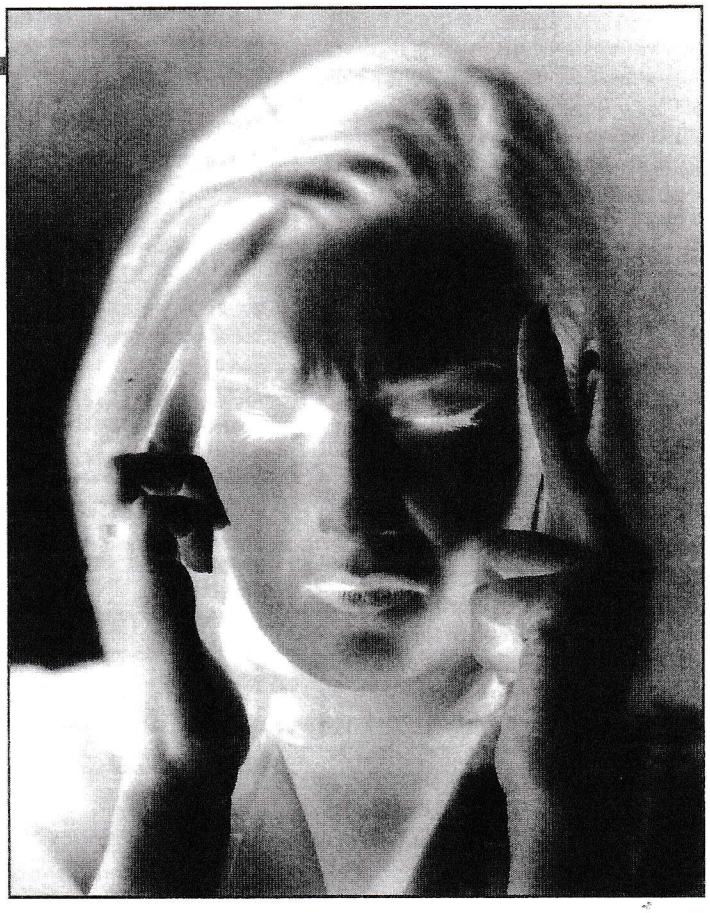
Peripheral Nerve Catheters for Acute Pain Control

The ABCs of Pain Clinic Referrals

Complications of Uncontrolled, Persistent Pain

Comm... publication
...magazine.com

TREATMENT-RESISTANT MIGRAINES



Alternate strategies may be required for overcoming the treatment resistance of certain types of migraines.

By Randall L. Oliver, MD and April Taylor, RN, BSN

Triptans have been available since 1992 and are now generally accepted to be the most predictable of treatments for migraines. However, triptans do not work for everyone. The fast acting oral triptan preparations (Imitrex, Maxalt, Zomig, Axert, Relpax) all work in approximately the same percentage of patients varying from 60 to 70% in different studies. The 30 or 40 % of patients that do not respond to one triptan may well respond to one of the other triptans.[1] Eletriptan has been found in one study to be effective in patients who found oral sumatriptan to be poorly effective or to cause side effects.[1] In another study, the 30% of the participants who failed with oral sumatriptan for migraine treatment responded to Zomig 71% of the time and to Maxalt 81% of the time.[2] Use of other formulations, such as Imitrex or Zomig nasal spray or the Imitrex injection, also increases the percentage of patients that may respond.

There is still a percentage of migraine patients that are triptan non-responsive. This article will deal with possible reasons for treatment-resistant migraines. (See table 1.)

Transformed Migraine

Transformed migraine initially has a typical migraine presentation. The migraines have an obvious start and finish with discrete headache-free periods between attacks. Gradually the headaches increase in duration with fewer and fewer pain-free days. The use of analgesics may increase over time with less and less response. The etiology of transformation may be time, under-treatment, or a comorbid condition. Transformed migraine can be subclassified as pseudo-transformed, rebound, or psychological and are discussed in the following sections.

Since the offending agent may be causing the patient's headache pattern to worsen, it may not be advisable to continue to prescribe such a medication since it may be causing more harm than good.

A common physician complaint is not knowing "how to get the patient off the drug." While the process itself may be complicated, it starts by simply telling the patient that this pattern is harmful and should no longer continue. Then inform him or her that the analgesic will no longer continue to be prescribed. The patient's only choice will then be to either follow the weaning protocol or obtain a new physician. Allowing the patient to leave the practice and obtain a new physician is much preferable to allowing the patient to continue using a medication that is known to make the problem worse.

Transformed with Psychological Overlay

Migraines can become transformed and difficult to treat if a person has a history of treatment-responsive migraines but then experiences a psychological problem. The transformer, for example, could be a divorce, death of a loved one or anxiety. See the next category for further discussion of treatment-resistant psychological migraines.

Psychological Overlay

The difference between a transformed psychological migraine and a migraine caused by psychological issues is the timing of the migraines and the psychological issue. In transformed migraines, treatment-responsive migraines were present prior to a new psychological issue. The migraine then becomes transformed and no longer responds to a previously successful migraine treatment. However, many times the psychological problem is the trigger to migraines that previously did not occur. When the psychological problems are present and left untreated migraines develop. Certainly if the patient has a psychological problem contributing to his or her headache, the triptans will be less responsive as the baseline problem is not being addressed. Bipolar is a very common problem in migraines with some studies suggesting that as many as 10% of all migraineurs have a bipolar tendency. Depression and insomnia also co-exist with many migraines. It is important that when a physician treats someone with migraines that he or she also checks for concomitant depression, anxiety and insomnia.[7] Certainly if the patient has concomitant unaddressed depression, any treatment of the migraine will not be complete. Lack of restful sleep is a common migraine trigger. Not addressing the patient's insomnia will cause the migraines to be less responsive to treatment. If the patient has an ongoing stressful situation such as a divorce or work situation, the triptans or other treatment of migraines will be less effective.

Hormonal Imbalances

Three-fourths of migraineurs are female, and this is most likely due to estrogen and other hormonal manifestations.[9,10] Changes in hormonal levels are known to precipitate migraines. The usual times for hormonal changes are puberty, childbirth, menses and menopause. For example, many women start with migraines at puberty.

Three-fourths of migraineurs are female, and this is most likely due to estrogen and other hormonal manifestations.[9,10] Changes in hormonal levels are known to precipitate migraines.

Women who experience migraines may have an increased sensitivity to changes in hormone levels. There is no difference in menstrual cycles in women who do experience migraines from those who do not.[11] Approximately half of all female migraineurs relate that migraines occur around the menstrual cycle. The exact time around the cycle varies from woman to woman. It may be before, during or after menses. This is usually related to each particular woman's hormonal trigger (e.g. either estrogen level rising or dropping). Menstrual migraines are commonly thought to be less responsive to treatment, however two-thirds to three-fourths of menstrual migraines treated with a triptan report relief. Treatment can be both preventative and abortive. To prevent transformed migraine, it is important to treat early when the pain is mild.[11] Triptans, with different formulations, can be used for both. Triptans should be used for abortive therapy, but if the woman experiences more than three migraines per month, prevention needs to be considered.[12] Prevention is not recommended for less frequent migraines due to prolonged dosing and complex regimens compared to acute therapy. Prevention is also not recommended in unpredictable menses.[11]

Migraines are also very common during pregnancy. Women may relate that their migraines appeared with the first child, disappeared with the second and reappeared with the third child. The hormone changes in pregnancy may make the migraines disappear or they may make them worse and less responsive to treatment. Again, hormone changes affect migraines but the effect may be unpredictable in each individual.

Menopausal migraines are an interesting phenomenon. While it is known that many females with migraines will cease having migraines after menopause, many also experience worsening of migraines during the menopausal time itself. This is almost certainly due to the spiking of estrogen, the same effect that causes the hot flashes women encounter during menopause.[13] Migraine prevalence decreases with age and is believed to be caused from the decrease in estrogen after menopause.[13] It may be an assurance to the woman that while her migraines may worsen during menopause, migraines will generally improve after menopause. It is also important to administer a stable hormone level when using hormone replacement therapy after menopause for women with migraine tendencies. Treatment should incorporate a steady dose of hormones on a daily basis during the month. Cycling hormones, such as using an estrogen product for 25 days and cy-

because it will generally work the fastest and most completely. It also has the widest range of usage, such as in the patient with nausea and vomiting. Patients generally prefer oral preparations.[3] If one oral preparation fails, remember that other oral preparations may still have utility.[16] Failure of one triptan does not mean failure of all oral triptans. When trying one triptan or another it is important to give each triptan a sufficient trial of a minimum of three different migraine events before determining that it is a failure. Even injectable triptan can have a first, second or even third-pass failure before it becomes effective. Stratified care will result in the greatest number of migraines resolved. Classification as triptan resistance may be premature if only one or two triptans have been tried when maybe the person will find relief with a different oral triptan, nasal spray or injection formulation.

When triptans, including the injectable version, are found ineffective, one should first look to the reasons why. First, one should reconsider the diagnosis. If it is confident, one should consider transformed migraine, such as rebound or incomplete migraine treatments, or comorbid conditions such as a psychological problem, hormonal problems or head injury.

When dealing with headaches, whether triptan-responsive or not, it is always appropriate to investigate and modify any medication that appears to possibly worsen headaches.Even nonprescriptive over-the-counter medications may be an offending agent. ■

Randall L. Oliver MD is Medical Director of the Oliver Headache & Pain Clinic, a regional pain center in Evansville, IN, and President of the Indiana Pain Academy. He regularly lectures, writes, and conducts research and seminars on multidisciplinary pain management. Dr. Oliver can be contacted at OliverClinic@cs.com.

April Taylor RN, BSN, is a research writer on multiple projects for Dr. Oliver. She is also a diabetes nurse educator for critical cardiac care patients at Methodist Hospital, Indianapolis, Indiana.

References

1. Farkkila M, Olesen J, Stovner LJ, Bruggen JP, Rasmussen S, Muirhead N, and Sikes C. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to oral sumatriptan. *Cephalalgia*. 2003. 23:463-471.

2. Jhee SS, Shiovitz T, Crawford AW, and Cutler NR. Pharmacokinetics and pharmacodynamics of the triptan antimigraine agents. *Clinical Pharmacokinetics*. 2001. 40:189-205.

3. Lipton RB and Stewart WF. Acute migraine therapy: Do doctors understand what patients with migraine want from therapy? *Headache*. 1999. 39(suppl 2):S20-S26.

4. Burstein R, Collins B, Bajwa Z, and Jakubowski M. Triptan therapy can abort migraine attacks if given before the establishment or in the absence of cutaneous allodynia and central sensitization: clinical and preclinical evidence. *Headache*. 2002. 42:390-391.

5. Kaniecki RG. Mixing sumatriptan: a prospective study of stratified care using multiple formulations. *Headache*. 2001. 41:862-866.

6. Rapoport A. Analgesic rebound headache in clinical practice: Data from a physician survey. *Headache*. 1996. 36:14-19.

7. Mathew NT. Transformed migraine, analgesic rebound, and other chronic daily headaches. *Neurologic Clinics*. 1997. 15:167-186.

8. Mathew NT. Drug induced refractory headaches-clinical features and management. *Headache*. 1990. 30:634-38.

9. Lipton RB, Stewart WF, Diamond S, Diamond ML, and Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001. 41:638-45.

10.Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF. Migraine diagnosis and treatment: results from the American Migraine Study II. *Headache*. 2001. 40:513-20.

11. Sosnowski C. Perimenstrual migraine: definition, pathophysiology, and treatment strategies. *Migraine Newsletter*. September 2003. pp11-13.

12. Silberstein SD. Menstrual-related migraine treatments. *Practical Pain Management*. 2002 2:16-22.

13. Mathew NT. Pathophysiology, epidemiology, and impact of migraine. *Clinical Cornerstone*. 2001. 4:1-17.

14. Packard RC. Post-traumatic headache: Introduction, definitions, and epidemiology. *Seminars in Headache Management*. 1997. 2:1-7.

15. Marcus DA. Central sensitization: An important factor in the pathogenesis of chronic headache. *Headache & Pain*. 2003. 14:19-23.

16. Kaniecki RG. Migraine and tension-type headache: an assessment of challenges in diagnosis. *Neurology*. 2002. 58(9) Supplement 6:S15-S20.