CHAPTER 5

THE WOMAN WHO COULD NOT DECIDE WHICH MEDICATION TO TAKE

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Case History

This 35-year-old female patient presented with a long history of headache, which had begun since childhood. Since the age of 22 she had had attacks about eight to twelve times a year. In the past year she has had attacks three or more times a month, and the headache would last 4 to 6 hours.

The headaches were located on the side of her head, usually on the left but occasionally on the right, and were throbbing in nature. Frequently, just prior to each headache she would have visual symptoms consisting of "zigzag lines" in her right visual field, which would slowly move across her vision from right to left, and be followed by a black blank area in her vision. On other occasions she noticed that her headaches were preceded by numbness in her right tongue, then in her face and arm. She has noted trouble with her speech on occasion, in that she would have difficulty finding the right word. These headaches were usually associated with nausea and, if severe, with vomiting. She found that her headaches were worse if she moved her head or if she was exposed to bright lights, sounds, or perfumes.

Interestingly, but not surprisingly, she has occasional tension-type headaches, which can occur after a "migraine" or are independent of her "migraine headaches." There is a family history of migraine in her mother and sister, and a maternal uncle died of a "brain tumor."

The patient is an accountant who finds that her migraine headaches are interfering with her work and her family activities. She finds it hard to care for her two children, work, and carry on with her personal life. She wants to find a way to reduce the number of headaches she is having and is very interested in all forms of therapy for migraine. She was worried about a "tumor" originally, but recognizes that such a concern is "irrational." She does not like taking too many medications and wants to avoid side effects. Her expectation is that the "doctor" will manage her headaches. She has had and continues to have great difficulty deciding which treatment or medication she should take for her headaches. She had tried various medications without success.

Her neurologic and general examinations were completely within normal limits.

Questions about This Case

- What are your initial impressions of this case?
- What would you recommend in terms of investigations and why?
- What would you recommend in terms of treatment and management of her case?
- If she decides to take a triptan medication, then which one should she take and why?

Case Discussion

This is a case of migraine with aura, fitting the usual International Headache Society (IHS) criteria. The aura consists of the usual visual symptoms, but on some occa-

sions she has more speech and sensory symptoms, suggesting a more anterior localization of her neurologic dysfunction during some of her auras, which in her case precede her headaches. She has a typical "sensory march", which is analogous to the classical jacksonian motor and sensory marches seen in epilepsy but is much slower in onset and increased in duration.

This case does indicate that migraine has variability in each patient. It is not unusual for migraine patients to have different auras on occasion, and many have different intensities of headache as well. She also has some of her migraine headaches without aura.

This patient had a normal examination, which is what one would expect in a patient not having a migraine attack during an office visit, unlike someone in severe pain in the emergency room. It is important that the patient is between migraine attacks, since if she was in the ER having an attack she would look ill, and usually in such situations it is dificult to get a precise history. Thus the ER is not the place to start a therapeutic relationship with a migraine patient in severe pain. Treat the pain and have the patient return to your office to get a more detailed account of the headache, its triggers, and other medical information pertinent to the case.

It is interesting in this case to consider the mechanisms of migraine headache, the difference between various subtypes of migraine headache, the idea of aura, trigger factors, and prodromal symptoms. The patient did have some migraine headaches in childhood, and her migraine headaches were worse when she used oral contraceptives.

She has occasional "tension-type headaches" that can occur after a migraine or independent of her migraine headaches. This is not at all uncommon in migraine patients.

It is now accepted that neither computed tomography (CT) nor magnetic resonance imaging (MRI) are necessary in adult patients whose headaches fit a broad definition of recurrent migraine and who do not demonstrate any change in headache pattern, a history of seizures, or the presence of focal neurologic signs. In this case, one would be justified in not doing a neuroimaging procedure. However, all good clinicians would temper this decision based on the patient's concerns and family history, which in this case did not appear relevant. Sometimes a CT or MR can be "therapeutic" or help the patient and their physician get "beyond" the worry about an organic etiology.

The patient had tried simple analgesics, ergotamine, NSAIDs, as well as a dihydroergotamine (DHE) nasal spray. She did not feel the analgesics helped at all, and the NSAIDs only helped if her migraine was mild. She did not prefer nasal DHE because of nasal congestion and the device needed to administer the spray, although it did seem to help, but took a long time. She had tried oral sumatriptan at a dose of 100 mg, but had experienced chest symptoms that she did not like, but did feel that it helped her more moderate and severe headaches within a couple of hours. She also noted that several times after oral sumatriptan she would get a recurrence of her headaches or that it did not work for every migraine, and she did not wish to take any more.

In terms of future management, her case represents the tyical dilemma faced by clinicians and patients. Although guidelines are available for acute and prophylactic treatment of migraine, they do not specify which agent to use, but suggest that treatment be based on severity. This makes sense to the physician as well as the patient, but with the development in recent years of more migraine-specific medications for abortive therapy, it could become increasingly more difficult to give advice on which medication to use and when.

She should certainly explore all the nonpharmacologic therapies and look at the management of migraine triggers, all of which have been dealt with in other cases in this book. However, when it comes to managing her severe migraine headaches, she will have to decide which of the new triptans to use, as they appear to have the greatest efficacy, best side-effect profile, and safety. The discussion of all of the current triptans available will follow, but for now her therapeutic options include the following management strategies.

Management Strategies

- Consider using an ergot preparation including a suppository.
- Use oral sumatriptan at a dose of 50 mg or fewer, which could help many of her moderate and some of her severe headaches, with fewer side effects than with an ergot.
- Use nasal sumatriptan, 20 mg, which could reduce her chest symptoms and give fast onset of relief as well as if not better than oral sumatriptan.
- Use naratriptan in a dose of 2.5 mg for her moderate migraines and recognize that the onset may be slower, up to 4 hours, but recurrence is less frequent and side effects are negligible in most patients.
- Use oral zolmitriptan, which may work slightly faster than and is likely to give similar side effects as oral sumatriptan, but possibly the lower dosage of 2.5 mg will help and will be just as efficacious for her moderate to severe migraines. She may expect a more consistent response with this triptan.
- Consider in the near future, when released in North America, whether to try rizatriptan at a dose of 5 mg for her moderate migraine headaches or 10 mg for

more severe headaches. She could expect relief as fast as with or faster than sumatriptan, but will have similar side effects, although nausea may be less.

She decided, after discussion, to try a dose of sumatriptan that was lower than 50 mg and found it helpful, with few problems, but not as good as the higher dosage. She did have a very good response to nasal sumatriptan and was very thankful that she had no chest symptoms, so she decided to stay with that medication for now. With one headache per month she was not a candidate for prophylaxis. As you can see from the above and the following discussion she has many, options for the future management of her migraine headaches.

Case Summary

- This patient has migraine with aura and without aura, which is variable in severity.
- She has both visual and sensory auras.
- She does not require investigation based on current knowledge, but this is always a matter of clinical judgement in an individual patient.
- She represents what will become an increasing problem for patients and physicians managing migraine in the future, with respect to what medication to use for acute treatment. Her case also raises the question of what prophylactic treatment actually means, when there are so many new effective abortive agents available.

How to Pick a Triptan or Ergot for your Patient—an Overview

The patient in this case has a varying, but rather typical, migraine picture. She has migraine with aura and migraine without aura. She has moderate migraine and she has severe migraine. When she has severe attacks, she is disabled from work and she is unable to take oral medication. The frequency of migraine is low enough to suggest that daily preventive therapy may not be necessary, if acute treatment is available to reliably restore her to normal function. So the question for the treating physician is how to craft an acute migraine strategy given all of her clinical variables?

Two concepts may prove helpful, **stratifying** her care and **staging** her attacks. Stratifying her care means figuring out how high the treatment needs are for the patient.

There are several ways to do this. One can take a history of peak intensity of the migraine, time to peak intensity, disability, and time to disability, e.g., nausea, vomiting, and those associated symptoms that would prevent the patient from functioning. Or one could use a validated, simple disability scale, such as the Migraine Disability Assessment Scale (MIDAS), which allows one to stratify the patient's disability in terms of work and social loss over the previous 3 months. Either way, this patient would stratify to a high level of disability with high treatment needs, because of the intensity of the pain and the time lost due to illness. High treatment needs dictate the use of migraine-specific medications, such as the triptans and to a lesser extent the ergots.

Clearly not every attack that this patient has requires injectable triptan or ergot use, so this is an opportunity for the doctor to allow the patient to stage her attacks, giving her several medication options to use depending on the severity and speed of development of the attack. Lower-level attacks might be treated with oral mixed analgesics such as aspirin/acetaminophen/caffeine combinations, antiheadache compounds, containing isometheptene or butalbital, and/or antinauseants such as metoclopramide. The concern in staging with low-level medicine is that overuse of these medications can lead to analgesic rebound or transformed migraine, with increased overall frequency of headache and decreasing response to all medications. And if the patient guesses wrong, and the attack becomes severe, she must have a higher-level medication to stage up to, to restore normal function.

For the more severe attacks, use of an ergot or triptan is indicated. Ergots are the old standby, but they are difficult to use and to a great extent have been superseded by the triptans. ***Ergotamine tartrate*** is available in the United States in oral-tablet, sublingual, and suppository forms. However, the oral form is poorly absorbed, and all forms usually produce nausea. Ergotamine is also habituating, with a low threshold for triggering rebound. Finally, peripheral vasoconstriction can be a problem with its use.

If the patient is distressed by the occasional aura, she might wish to use an ergotamine suppository at the beginning of the aura, since ergots, but not triptans, have been shown to shorten aura and the attack that follows. She would need to try out the suppository in advance and titrate her dose by cutting it with a razor blade to find the highest non-nauseating dose up to a full suppository to use at the onset of aura. The starting dose is no more than one-quarter of a suppository (0.5 mg).

Dihydroergotamine mesylate (DHE) is used both parenterally and intranasally. It is less nauseating and less habituating than ergotamine. The nasal spray is somewhat cumbersome to use, as it requires considerable patient preparation, but it achieves headache relief in about 60% of patients in 2 hours. It has a long duration of action, with a low recurrence rate, which makes it reasonable for longer menstrual migraines, especially if the patient wakes up too nauseated to take a tablet. Adverse effects of DHE are few, consisting primarily of nausea, leg cramps, gastrointestinal problems, and local intranasal problems with the spray.

Sumatriptan is available in the United States as a tablet, as a nasal spray, and as a subcutaneous 6-mg injection with autoinjector. Both the tablet and the spray yield a headache response of 60 to 65% in 2 hours, but the spray works faster for some patients. The optimal dose is 50 mg for the tablet and 20 mg for the spray. The injection gives 50% of patients pain relief in 30 minutes and 80 to 90% in 2 hours.

Sumatriptan offers this patient some unique advantages because the United States has contraindicated patients from switching between ergots and triptans or among different triptans in the same day. So if this patient takes one nonsumatriptan orally and it does not work, she cannot rescue herself with injectable DHE or sumatriptan in the same 24 hours. However, it is acceptable to switch forms of sumatriptan, so if she takes the pill and then the migraine worsens and she proceeds to prostration, she can use the shot. So providing her with multiple sumatriptan forms will allow her to stage her headache and virtually guarantee her ability to restore herself to normal function.

Maximum amounts per 24 hours are 200 mg of sumatriptan tablets, two injections, two sprays, or combinations of a 100-mg tablet plus one injection or spray, or one injection plus one spray. All doses should be separated by 2 hours.

Zolmitriptan has the best headache response at 2 hours for an oral triptan (67.1% for 2.5 mg versus 63.8% for 50-mg sumatriptan) and the highest consistency reported in open label studies over a year (95% of attacks aborted with one to two doses). The optimal dose is 2.5 mg, and the maximum is 10 mg per 24 hours. If a 2.5-mg dose is not effective, a 5-mg dose often is.

Naratriptan is the most unusual of the available triptans in that it has a different profile for use. It is slow in its onset of activity with 48% of patients showing pain relief at 2 hours and 66% at 4 hours. However, it has a very gentle adverse-event profile, with side effects comparable to placebo. It has a long duration of action, with half the recurrence rate seen with sumatriptan or rizatriptan.

Naratriptan can thus be used in a number of specific situations. It can be used for moderate migraine, especially if the lower-level, nonspecific medications have failed. It can be used in a prolonged migraine, in place of DHE, if the patient can take an oral tablet. Recurrence is least likely if the naratriptan is taken in the first 90 minutes of the attack. It can also be used in depressed patients as a monoamine oxidase (MAO) inhibitor, as it is the only currently available triptan that is not metabolized by MAO. Finally, in patients who are sensitive to the adverse effects of these medications, naratriptan is the "gentle triptan."

Rizatriptan is an oral triptan available in both conventional oral-tablet and orally dissolvable-tablet or melt form. The optimal dose is 10 mg, but patients who are on propranolol need to be given the 5-mg dose. The 2-hour headache relief resulting from the 10-mg dose is indistinguishable from that obtained with the 50-mg sumatriptan dose.

The melt has a mint taste, dissolves rapidly in saliva, and is swallowed without water. It is not absorbed through the oral mucosa, but is absorbed like any other tablet in the gut. The rate of onset of effect and the overall headache response is identical for the tablet and melt forms.

This patient could use the melt in a number of circumstances. If getting to water was difficult (i.e., at a movie or while driving) or embarrassing (i.e., in a corporate board room making a presentation), dropping a mint-like tablet on the tongue could be both convenient and discreet.

So, to summarize, if a patient has migraine that varies widely in speed and intensity, the use of sumatriptan allows for switching forms in the same day. The injection sets the standard for speed of onset and overall efficacy. The nasal spray is usually faster than any tablet and bypasses the gut in a nauseated patient. The tablet has identical efficacy to rizatriptan.

If the patient desires the most effective tablet at 2 hours, with the highest consistency, and never needs a spray or shot, zolmitriptan is the correct choice. When the patient needs discretion, cannot get to water, or does not like to drink liquid when having a migraine, the rizatriptan melt can be used.

If the patient wants to shorten the aura and the migraine that follows, an ergot should be used. If a patient needs to bypass the gut in a long menstrual migraine, a DHE nasal spray can be used. Finally, for moderate migraine, for prolonged migraine, or in patients who are sensitive to side effects or on MAO inhibitors naratriptan is optimal.

Allowing the patient multiple options to stage her headache empowers the patient and furthers the therapeutic alliance. Stratifying the patient to low-, moderate-, or high-treatment needs matches the treatment to the patient to maximize the likelihood of success.

Selected Readings

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Editorial Comments

Undoubtedly one of the major problems for patients and their physicians in the foreseeable future will be in deciding which is the best abortive agent for their migraine attacks. It may be that with all of the new triptan medications available at present and in the future, the choice will be much easier, but one does not necessarily expect that that will be the case. Physicians make choices based on the best knowledge and experience, patients make choices for similar reasons, but on other occasions make entirely separate choices regarding therapies, some of which make no sense to clinicians at all.

This will then be the challenge, which we as editors offer to the reader in this case, with the excellent assistance of Dr. Tepper, and that is that patients and their doctors must sit down together, discuss what they know and do not know and agree on a mutually acceptable management strategy. Now that sounds like good medicine and must be seen as in the best interests of our patients.

The knowledge and science behind the triptans has markedly increased the awareness of migraine and its unique neurobiology. One of the outcomes, however, may never have been expected in the laboratories where these compounds are made, and that is that patients and doctors will have to start "talking" again, suggesting to us that the art of migraine management is still very much alive. Advanced headache therapy will require advanced communication skills!