

Triptans for Migraine Prodrome

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Key words: migraine, prodrome, triptans

(*Headache*. 2002;42:83-84)

Treatment of migraine with oral triptans when the headache is mild is more effective than later treatment, when the headache is moderate or severe. Would even earlier treatment be yet more effective?

CLINICAL HISTORY

A 43-year-old woman has a history of recurrent migrainous headaches since aged 7 years. She develops blurred vision, goose bumps on her arms, slight nausea, clear nasal drainage, and a “tight” feeling in the right superior trapezius area, followed the next day by severe, incapacitating, right-sided headache with associated nausea and light sensitivity, lasting 3 days. These episodes have been occurring once monthly for the last 4 years, at varying points throughout her menstrual cycle. She is not aware of any triggers. She does not have neck pain at other times. Acute treatment with ibuprofen, acetaminophen, Excedrin, or Midrin has not helped. Neurologic examination is normal.

Questions.—How common is migrainous prodrome, and what clinical features may be present? What is the pathophysiology of prodrome? Would triptan therapy during the prodrome be likely to be beneficial?

EXPERT COMMENTARY

This patient suffers from migraine without aura. The International Headache Society uses the term *premonitory* to describe symptoms that may precede headache by up to 48 hours, but some authors prefer the term *prodrome*. Prodrome should be distinguished from migraine aura, with the latter involving focal neurologic symptoms which typically develop gradually over 5 to 20 minutes, last less than 60 minutes, and are followed by headache within an hour.¹

Clinical manifestation of prodrome include, but are not limited to, changes in mood (irritability, depression); changes in energy level (hyperactivity, hypoactivity); repetitive yawning; gastrointestinal symptoms (food cravings, nausea, constipation/diarrhea); fatigue/tiredness/sleepiness; fluid retention/swelling; and muscle tenderness/stiffness.¹⁻⁵ Patients may not spontaneously report prodromal symptoms but typically are able to distinguish those symptoms from similar nonmigrainous symptoms or the symptoms of aura.³⁻⁵ Prodrome has been reported in anywhere from less than 10% to more than 80% of migraineurs, the differences reflecting inconsistencies of definitions and reporting methods.^{4,6}

Prodrome is considered the first phase of a “complete” migraine attack.² Although the pathophysiology of migraine is not completely understood, evidence is accumulating that central factors are involved, and possible sources for the symptoms of prodrome include hypothalamic dysfunction and hyperexcitability of central pain signal processing.^{2,7} Certain of the symptoms experienced by the patient described here,

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may represent cutaneous allodynia resulting from the transient increase in the responsiveness of central pain neurons.⁷ Other prodromal symptoms may reflect changes in dopaminergic activity. Peroutka has suggested that increased dopaminergic activity in migraine may account for the yawning, nausea and vomiting, mood changes, gastrokinetic changes, and hypotension so often reported by migraineurs or observed during attacks.⁸

Accurate and timely identification of prodrome symptoms may provide us with a unique treatment opportunity, the ultimate "early intervention." By treating during prodrome, patients may be able to forestall progression to headache. Successful prevention of the headache via treatment administered during prodrome has been reported. In an open-label study, domperidone taken during prodrome prevented up to 63% of headaches. (The best results were obtained when medication was taken 6 or more hours before anticipated headaches. Headaches that did occur were of lower severity.⁶) In a placebo-controlled trial, domperidone 30 mg administered during prodrome prevented migraine in 66% of patients, compared with a 5% prevention rate in patients receiving placebo.⁹ There was no difference between the two treatment groups in the severity of the headaches that did occur, and the optimal time for treatment was not determined. In a more recent study, 20 patients with predictable prodrome followed by headache took oral naratriptan 2.5 mg at the point they felt headache was inevitable.³ Of 63 treated prodromes, 38 (60%) were not followed by headache. In the headache that did occur despite treatment during prodrome, severity was less than that typically experienced in the past. Headache occurred more often when naratriptan was administered within 2 hours of anticipated onset of headache.

How these medications may act during prodrome to prevent or modify subsequent headache is not fully understood. For domperidone, an effect on dopaminergic activity has been postulated, but other central

mechanisms also are likely to be involved.^{5,6,9} Regardless, the timing of prodromal treatment appears to be critical and seemingly must occur at least several hours prior to anticipated headache onset. There may exist a "point of no return" in the progression of prodromal symptoms to headache.⁵

Clinicians can assist their patients in identifying prodromal symptoms, and treatment during early prodrome may enable patients to circumvent the headache phase. Specifically, this may represent another early intervention opportunity for the triptans.

REFERENCES

1. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*. 1988;8(suppl 7):19-21.
2. Blau JN. Migraine prodromes separated from the aura: complete migraine. *BMJ*. 1980;281:658-660.
3. Luciani R, Carter D, Mannix L, Hemphill M, Diamond M, Cady R. Prevention of migraine during prodrome with naratriptan. *Cephalalgia*. 2000;20:122-126.
4. Russell MB, Rasmussen BK, Fenger K, Olesen J. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. *Cephalalgia*. 1996;16:239-245.
5. Waelkens J. Warning symptoms in migraine: characteristics and therapeutic implications. *Cephalalgia*. 1985;5:223-228.
6. Waelkens J. Dopamine blockade with domperidone: bridge between prophylactic and abortive treatment of migraine? A dose-finding study. *Cephalalgia*. 1984;4:85-90.
7. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. *Ann Neurol*. 2000;47:614-624.
8. Peroutka SJ. Dopamine and migraine. *Neurology*. 1997;49:650-656.
9. Amery WK, Waelkens J. Prevention of the last chance: an alternative pharmacologic treatment of migraine. *Headache*. 1983;23:37-38.