Expert Opinion

Are Triptans Effective and Safe When Taken During the Aura Phase of Migraine?

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Triptans are much more effective when taken when the migraine is of mild rather than of moderate-to-severe intensity. For those with aura, would not earlier treatment during the aura be even more effective?

CLINICAL HISTORY

A 28-year-old woman has migraine with visual aura about two times per month. The visual aura lasts about 30 minutes and is followed by a hemicranial throbbing headache, which becomes severe associated with nausea, light, and noise sensitivity with a duration of up to 24 hours.

Questions.—Would an oral triptan or sumatriptan administered subcutaneously be more effective if given during the aura than if given when the headache was mild or moderate to severe? Is there any risk of prolongation of the aura or neurologic deficit if a triptan is given during the migraine aura?

EXPERT COMMENTARY

The patient suffers from typical migraine with aura. The International Headache Society defines migraine aura as a fully reversible visual, sensory, or speech symptom occurring prior to headache.[1] Up to 18% of migraineurs experience aura, although not consistently with each attack.[2] While described most commonly with migraine, auras are also known to occur with cluster headaches and hemicrania continua.

The visual aura is the most common occurring in 99% of cases and may consist of photopsias, scotomas, fortification spectrums, phosphenes, or other rare distortions of vision. In about 30% of cases, auras can involve the spreading sensation of tingling or numbness involving the limbs or facial region. Speech and language disturbances may occur in up to 20% of cases. A true motor aura is rare; often sensory ataxia or a heavy feeling is misinterpreted as "weakness."

The warning sign of migraine aura is readily recognized by patients. The time of duration from onset of aura to the headache phase usually occurs over 30 to 60 minutes. Triptan therapy is known to be more effective when given during the mild or moderate phase of migraine. Triptans have also been shown to prevent migraine when given during the prodrome phase.[3] The presence of aura offers the potential to treat an attack prior to development of the headache phase, therefore completely preventing the occurrence of pain. There exists however, a paucity of clinical data showing their efficacy during migraine aura.

In a previous double-blind, placebo-controlled study in which sumatriptan was administered subcutaneously during the aura phase, there was no statistically significant difference in headache occurrence between the two groups—68% among those receiving sumatriptan and 75% among those receiving placebo.[4] Sumatriptan though ineffective, did not prolong or alter the nature of the migraine aura.

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A similar crossover trial of 16 patients studied the use of zolmitriptan 20-mg oral formulation when given during the migraine aura.[5] This particularly high dosage was given to guarantee therapeutic plasma levels early during aura, with the subsequent hope of achieving headache prevention. This trial was similarly ineffective, with only 3 of 16 patients responding with headache prevention. There were no adverse events reported when taken during the aura phase.

A more recent multicenter, double-blind, parallel group, placebo-controlled trial examined the safety and efficacy of eletriptan 80 mg when taken during the aura phase for the prevention of migraine.[6] The primary outcome measure was the proportion of patients not developing moderate to severe headache within 6 hours of dosing. There was no significant difference in the proportion of patients developing moderate-to-severe headaches on eletriptan (61%) versus placebo (46%). Typical transient triptan adverse events were observed, however, eletriptan was well tolerated and did not prolong the aura phase.

The lack of efficacy of sumatriptan, zolmitriptan, and eletriptan suggests these shortcomings are applicable to the entire triptan class. Questions and theories abound regarding the timing of treatment and the lack of patient response when given during aura. A pharmacokinetic explanation is unlikely when each study is examined in detail. Subcutaneous sumatriptan's rapid onset of action and absorption ensure therapeutic plasma levels. The zolmitriptan 20-mg dose also provided adequate plasma levels early that were also maintained well into the headache phase. Inadequate plasma levels were also an unlikely culprit in the eletriptan study, given the administration of the 80-mg dose and its T_{max} of 1.5 hours.

Another alternative explanation is that a blood-brain barrier defect must be present for triptans to reach central receptors.[7] Animal data has suggested sumatriptan does not cross the normal blood-brain barrier.[8] This implies only after the blood-brain barrier is disrupted would the drug be able to reach its site of action. This theory is dismissed when applied to other triptans (eletriptan and zolmitriptan in the previously cited studies), as the half-life of both is at least 3 hours. This ensures adequate plasma levels when blood-brain barrier disruption occurs.

A final explanation is a triptan lack of efficacy in migraine with aura. This is also invalid, given the wealth of conclusive evidence of triptan efficacy in both subtypes of migraine. In each of the three studies discussed above, patients who violated protocol and treated the headache after the development of pain reported positive treatment responses.

It has been suggested that early administration of triptans result in an acute tolerance at the $5HT_{1B/1D}$ receptor.[9] This theory is intriguing and warrants further study. Multiple sites of migraine therapy continue to be identified as we develop a better understanding of migraine pathophysiology.

In conclusion, the administration of various triptans during the migraine aura phase does not adversely affect the duration of or characteristic of that aura. However, this early treatment is not significantly effective in preventing progression of a migraine headache. Therefore, there is no benefit in treatment with triptan therapy prior to the development of a mild or moderate headache.

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