

Do triptans increase the risk of thromboembolic stroke?

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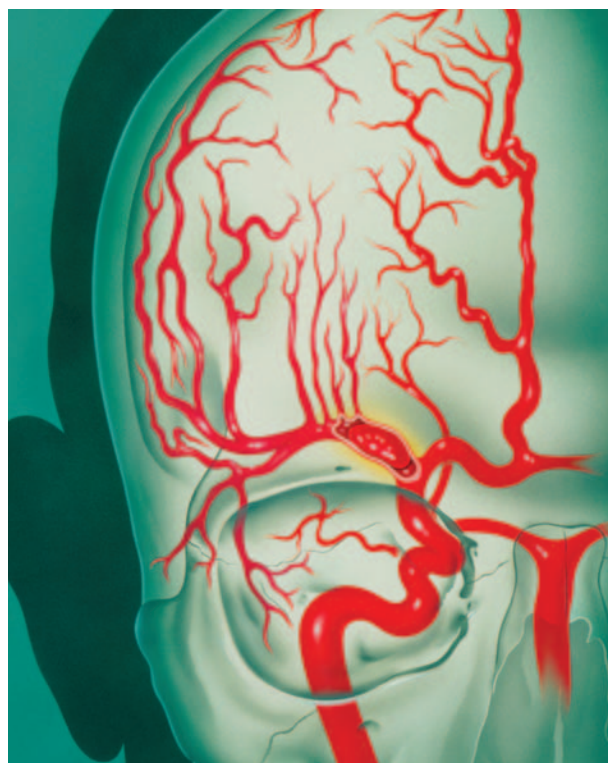
A 32-year-old nonsmoking female migraineur presents to your primary care office seeking more effective abortive treatment for her migraines. She is having one to two headaches per month that are only partially relieved by NSAIDs. Each headache lasts 2 to 3 days and negatively impacts her ability to work and to care for her two children. She is currently asymptomatic. Her medical history is negative for diabetes mellitus, hypertension, and dyslipidemia. Her family history is positive for migraine headaches and negative for cerebrovascular and coronary artery disease. Medications include NSAIDs as needed and amitriptyline, which has been an effective prophylactic agent for her. She does not take oral contraceptives. At this time, results of a physical examination are normal.

Chart review reveals that this patient's typical migraine manifests with a visual aura followed by left arm paresthesias. The aura resolves in less than an hour and is followed by the onset of unilateral throbbing pain, photophobia, phonophobia, nausea, and vomiting. There is hyperesthesia in the left hand, but the findings on physical examination are otherwise normal. The patient has undergone multiple cranial imaging studies that have all been without significant findings. Based on the above symptomatology, typical aura-type migraine headache is diagnosed using the second edition of *The International Classification of Headache Disorders*.¹ You consider initiating therapy with a triptan for abortive treatment, but you are hesitant because of concern that triptan therapy may predispose a patient with prominent aura symptoms to having a stroke.

Clinical question

Do triptans increase the risk of thromboembolic stroke in female, nonsmoking patients with migraine who do not have other risk factors for stroke?

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An embolus, shown in section, is lodged in a branch of the carotid artery. The resulting neurologic damage can vary from muscle weakness to complete hemiplegia.

Search criteria and results

The data sources searched for this article include MEDLINE (1966 to January 2005), EMBASE (1980 to 2005), and Cochrane Collection's CENTRAL. The search is considered up-to-date through January 2005. Inclusion criteria were randomized controlled trials, prospective comparative studies, retrospective case-control studies, and retrospective cohort studies that directly studied the rate of stroke associated with triptan use. Each data source was searched using the search terms *cerebrovascular accident AND triptan*.

A total of eight unique articles were identified using this search strategy. To ensure articles were not being omitted, a secondary search strategy utilizing the

search terms *migraine* with the therapy subheading *AND cerebrovascular accident* was conducted. The secondary search strategy did not identify any new articles that addressed the question. Further searching of Cochrane Collection Reviews and *Bandolier* yielded no secondary review articles pertinent to the question. Of the eight unique articles identified, only two articles—those by Hall and colleagues² and by Velentgas and colleagues³—were deemed to meet the initial inclusion criteria. Both articles are retrospective cohort studies written by coauthors who have received support from Pfizer Inc. without restriction on publication or currently are employed by Pfizer.^{2,3}

Evaluating the evidence

Hall and colleagues published a retrospective cohort study that analyzed epidemiologic data from the United Kingdom's General Practice Research Database.² The analysis of 63,575 patients with migraine and 77,239 control subjects found that migraine sufferers in general had a higher incidence of stroke in both males and females in all age groups except females aged 45 to 59 years. Stroke risk was determined by calculating an adjusted hazard ratio (HR). An HR is the "weighted relative risk over the entire study."⁴ In the Hall study, the HR was adjusted for vascular risk factors including hypertension, diabetes, cardiac disease, obesity, hypercholesterolemia, oral contraceptive use, and smoking status.² The increased incidence of stroke was noted in patients not treated with a triptan (HR 1.51 with a 95% confidence interval [CI] 1.26-1.82). Interestingly, migraine patients treated with a triptan did not have an increased risk of stroke (HR 1.13 with a 95% CI 0.78-1.65). The authors attribute these findings to differences in prescribing practices because the study also found triptans were less likely to be prescribed to patients with vascular risk factors.²

Velentgas and colleagues' article is a retrospective cohort study that analyzes epidemiologic data.³ The database for this study was "Ingenix's research database containing pharmacy and medical claims for United Healthcare members, and the National Death Index."³ The study included 130,411 migraineurs and 130,411 controls. The authors found that when relative risk (RR) was adjusted for the presence of comorbid conditions (including ischemic heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, hypertension, and hyperlipidemia in the past 12 months) as well as for use of oral contraceptives and estrogen replacement therapy, the migraine patients were found to have an increased risk of stroke (adjusted RR 1.67 with a 95% CI 1.31-2.13), compared to patients without migraine. However, those treated with triptans currently (RR 0.90 with a CI 0.64-1.26) or recently (RR

0.84 with a CI 0.46-1.55) were not found to have this associated increased risk of stroke compared to migraine patients who reported no triptan use in the past 6 and 12 months, respectively.³

To date, the best available medical literature supports the conclusion that when triptan medication is prescribed to migraine sufferers who lack vascular risk factors, the risk of stroke does not increase. The data are subject to two possible biases. First, these studies were directly funded by a pharmaceutical company. Second, selection bias in how clinicians approach prescribing triptans to migraine sufferers may account for the lower associated stroke risk in patients treated with triptans than in those treated with other antimigraine medications.

The two studies described provide further evidence that stroke is more common in migraineurs than in the general population.

Theoretically, the level of evidence regarding this topic could be improved if studies that prospectively compared two cohorts or, ideally, randomized controlled trials were undertaken. Another option would be a meta-analysis of all triptan therapeutic trials. However, it may not be possible to accurately identify all participants who withdrew from therapeutic trials secondary to cerebrovascular hemorrhage.

Clinical bottom line

The amount of evidence that directly addressed the concern about triptan-induced stroke available in the medical literature before 2004 was of little value. The two studies described in this article provide further evidence that stroke is more common in migraineurs than in the general population. However, when triptans are prescribed to migraineurs who lack vascular risk factors, the risk of stroke does not appear to increase. Caution should be used when evaluating and treating patients with atypical migraine symptoms, but patients who prove to truly have migraine headaches may be considered candidates for treatment with triptans. □

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