Can This Patient Take A Triptan?: Review Of The Cardiovascular Safety Of The Triptans And Recommendations For Patient Selection And Evaluation

E Loder, D Biondi

Citation

Abstract

Background: Treatment guidelines issued in 2001 by the United States Headache Consortium emphasize the use of 5-HT1B/1D agonists (triptans) as preferred agents for abortive treatment of moderate to severe migraine. Despite this, triptans are used by only a minority of patients whose attacks are severe enough to require prescription medication, primarily because of persistent concern about their cardiovascular safety.

Discussion: Serious triptan-related cardiac events have occurred, primarily in patients with known cardiac risk factors, but the efficacy and safety of triptans favor their use for the acute treatment of migraine in patients at low risk for cardiovascular disease. The use of simple, validated risk stratification systems such as the Framingham Risk Score, is one method of evaluating cardiovascular risk status in a clinical setting.

Summary: Triptans are safe for the majority of patients with migraine, but clinical assessment of the underlying probability of cardiovascular disease is important prior to triptan prescription.

Background

Migraine is a primary headache disorder that affects 17% of women and 6% of men in the United States. It is an important cause of chronic pain, disability and work absenteeism among otherwise healthy adults, especially women during their reproductive years. The World Health Organization considers that a day with severe migraine imposes disability comparable to that of a day with active psychosis, dementia or quadriplegia, and places migraine among the top 20 causes of disability worldwide.

Mild, transient “triptan sensations,” including chest pain that can resemble angina, occur in 3% to 8% of patients receiving a triptan in clinical practice. It can be difficult to distinguish these noncardiac symptoms from chest pain induced by coronary artery constriction. Furthermore, a small number of serious cardiac adverse effects, some fatal, have been associated with triptan use. Physicians have thus been understandably reluctant to prescribe triptans in the...
absence of reassuring long-term data about their cardiovascular safety.

The manufacturers’ package inserts for all available triptans state that the drugs are contraindicated in patients with confirmed or suspected coronary artery disease (CAD) and in patients with risk factors for coronary artery disease unless they have undergone a thorough cardiovascular evaluation providing “satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease.” However, they do not elaborate on what that evaluation should be, and point out that “the sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best.” They recommend that patients with risk factors predictive of CAD who have a satisfactory cardiovascular evaluation receive the first dose of sumatriptan in a medical setting and that consideration be given to obtaining an electrocardiogram immediately following use.

There is also little evidence about how patients who experience chest pain with triptan use should be evaluated. A postmarketing cohort study of sumatriptan-associated chest pain found that chest pain disappeared within 2 hours in 96% of patients. Based on this finding, the investigators recommended that patients who experience chest pain for more than 2 hours undergo electrocardiography to rule out myocardial infarction.

Thus, existing recommendations are vague and incomplete. They do little to resolve physician uncertainty about which patients are candidates for triptans, what sort of pre-prescription evaluation is necessary, or how to evaluate chest symptoms occurring after triptan use.

After over a decade of experience with the triptans, it seems appropriate to review the accumulated evidence regarding their cardiovascular safety, with a goal of putting this issue into perspective for physicians who treat migraine patients, and providing practical recommendations for pre-prescription evaluation and screening of patients with triptan-associated chest pain. Accurate understanding of the cardiovascular risks of triptans will deter use in patients who are not appropriate candidates for the drugs, or unnecessary withholding of the drugs from patients who might benefit.
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Figure 1
Table 1: Treatment-emergent adverse events reported by at least 2% of patients in controlled clinical trials of the tablet formulations of sumatriptan, zolmitriptan, rizatriptan, and naratriptan (6,7,8,9).

Figure 2
Within this category, pain and pressure sensations localized in the chest were reported by 1% to 2% of patients receiving oral sumatriptan, 2% to 4% of those receiving zolmitriptan, less than 2% to 3% of those receiving rizatriptan, and 1% to 2% of those receiving naratriptan. Reports of serious adverse cardiac events were rare (Table 2).

Figure 3
Table 2: Serious cardiac events associated with triptans in premarketing controlled and uncontrolled clinical trials (6,7,8,9).

Figure 4
Table 3: Non-triptans commonly used for acute treatment of migraine (3,4,17).

Three obstacles prevent a completely accurate characterization of the upper body discomfort reported by patients treated with triptans. First, estimates of the

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incidence of these sensations vary widely, because some investigations have focused narrowly on chest pain, whereas others have examined different types of abnormal sensations in variously defined parts of the upper body. Second, most of this research has been conducted in patients taking sumatriptan, making it impossible to distinguish between effects specific to sumatriptan and those pertaining to all triptans. Third, the incidence of symptoms depends to some extent on the method of drug administration. Patients receiving subcutaneous sumatriptan tend to have a quicker onset and faster resolution of chest pain than do those receiving sumatriptan tablets, perhaps because of a more rapid rise in plasma concentration. (23) For other types of upper body sensations in patients taking sumatriptan, 10% to 20% of those receiving tablets and 30% to 40% of those receiving subcutaneous injections experienced tightness, heaviness, or pressure in the chest, neck, or throat. (24,25)

Triptan-induced chest pain and other types of upper body discomfort are not reliably correlated with electrocardiographic changes or angiographically demonstrated vasoconstriction. It has been suggested that these sensations might result from peripheral serotoninergic action leading to altered esophageal motor dysfunction. (26) Mitochondrial dysfunction in skeletal muscle, (27) anxiety reactions due to activation of 5-HT1A receptors, (28) intercostal muscle spasm, bronchospasm, pulmonary arteriovenous shunting, pulmonary vasoconstriction, or facilitation of nociceptive neurotransmission (29). Because patients with migraine may have a lower pain threshold or experience pain in a different way than do those without migraine, the discomfort associated with these sensations might be intensified in these patients. (30) Most instances of triptan-induced upper body discomfort are believed to be caused by mechanisms other than coronary vasoconstriction, with a much smaller number of cases attributable to cardiac effects, which are most likely to occur in patients with coronary artery disease. (31,32)

Although the low incidence of serious triptan-associated cardiovascular adverse events in Phase III trials is encouraging, such trials cannot adequately detect rare but serious adverse events because of their limited size. (33) Furthermore, the findings of many phase III trials are limited by the demographics of the study populations. Controlled clinical trials frequently enroll patients who are not entirely representative of those who will ultimately receive the drug. Elderly patients, patients with serious comorbidities, and those taking other medications often are excluded. Although a patient population without complex medical histories is needed to assess the efficacy of a drug for treating a specific disorder, a relatively pristine population is less useful in characterizing that drug’s safety profile. In the case of pre-marketing triptan trials, patients with known coronary artery disease or judged to be at increased risk for coronary artery disease were excluded from participation. This limits the ability to extrapolate or generalize safety data from these trials to a broader population.

POSTMARKETING TRIALS AND SURVEILLANCE

Extensive postmarketing data are available only for sumatriptan. Serious cardiovascular events, including some resulting in death, have been reported in patients receiving subcutaneous and oral sumatriptan. Cardiovascular events that began within 1 hour of sumatriptan administration, which are most likely to have a causative association with sumatriptan, have included coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation, cardiac arrest, and death. Some of these events occurred in patients without coronary artery disease and appeared to result from coronary artery vasospasm. However, among U.S. reports of serious cardiac events occurring within 1 hour of sumatriptan treatment, almost all patients had risk factors for and were later found to have coronary artery disease. (33)

A review of post-marketing spontaneous reports of adverse events reported for sumatriptan found that, between 1991 and December 1998, 92 deaths from cardiovascular causes occurring at any time after sumatriptan administration were reported. In many of these cases, the association between sumatriptan and death is unclear. Over this period, it was estimated that more than 9 million patients had used sumatriptan to treat more than 236 million migraine attacks. Thus, the reported occurrence of serious cardiovascular adverse events was less than 1 per 4 million uses. (33) It is widely recognized, though, that postmarketing adverse event reporting is subject to considerable bias, especially underreporting; organized post-marketing surveillance efforts in well-defined populations provide more reliable estimates of risk. (34)

In the largest such postmarketing triptan safety study conducted to date, 12,339 patients self-administered subcutaneous sumatriptan over 1 year. (35) These patients
treated a total of 185,579 migraine attacks, for an average of 15.4 attacks per patient. There were 25 deaths, most of which were clearly unrelated to sumatriptan use (e.g., death from acquired immunodeficiency syndrome or cancer). Cardiovascular events were reported in 4 patients—unspecified cardiac arrest (2 patients), cardiac dysrhythmia (1 patient), and unknown, sudden (1 patient). These events occurred 5 to 329 days after sumatriptan administration and were therefore judged to be unrelated to the drug, which has a half-life of only 2 hours. Of the 36 fatal and nonfatal cardiac events reported, only 2 occurred within 24 hours of sumatriptan treatment. One patient, who had successfully used sumatriptan in the past, experienced angina 1 day after administration. Another patient experienced mild tachycardia after administering 3 injections in a 24-hour period, exceeding package insert instructions to limit use to 2 injections within 24 hours. The other events were temporally remote from sumatriptan use. The incidence of sumatriptan-related adverse events was not increased in patients who had risk factors for cardiovascular disease but who did not have signs of cardiovascular disease on screening. This long-term study provides strong evidence of the cardiovascular safety of the triptans in a naturalistic setting.

Another large study involved a cohort of patients with migraine identified from 321 general practices in the United Kingdom. Migraine sufferers who had been treated with a triptan were then compared with migraine sufferers who had not received triptan treatment as well as age, sex and practice-matched controls. Database records were searched to identify any record of myocardial infarction, stroke, transient ischemic attack, ischemic heart disease, ventricular arrhythmias, death and death with an underlying cardiac cause. Incidence rates per 1000 person-year of observation were calculated and compared. 13,664 of 63,575 migraine patients had received a triptan prescription. No association was observed between triptan prescription and any outcome, including coronary events. In fact, the group of migraine patients not prescribed a triptan had an increased risk of stroke and ischemic heart disease compared to the other two groups of patients. This led the authors of the paper to suggest that this group of patients might have had a higher baseline risk of CAD, leading physicians to avoid prescribing triptans for them. The authors concluded that in general practice, triptan treatment of migraine did not increase the risk of cardiovascular or cerebrovascular events or mortality. The results of this study provide more evidence of the long-term safety of triptan use in a clinical setting.

Two retrospective studies were conducted to learn more about sumatriptan-related chest pain. In a postmarketing cohort study comparing 137 patients with chest pain and 229 patients without chest pain, Ottervanger et al found that hypertension was a major risk factor for sumatriptan-induced chest pain in men but not in women. The investigators concluded that, at least in some patients, sumatriptan-related chest pain may have a vascular mechanism and may involve the coronary arteries.

A clinical practice review of the experience of 453 patients who had used at least 1 dose of sumatriptan over a 2-year period concluded that patients with chest pain or other upper body symptoms do not have an increased incidence of cardiovascular disease or cardiovascular risk factors, and that these symptoms are not caused by coronary artery vasoconstriction. (9)

Serious cardiovascular events have been reported, both in clinical trials and in postmarketing experience, for other triptans. (13, 15, 16, 17) It is important to put the lower number of reported cardiovascular events for the newer triptans in perspective. Because these drugs have been in clinical use for shorter periods of time than sumatriptan, the number of reported adverse cardiovascular events is proportionately lower than for sumatriptan. It is inappropriate to conclude, based on this, that these newer drugs are somehow “safer” than earlier drugs. At clinically relevant doses, the cardiovascular effects of all of the triptans are indistinguishable, (13) and any cardiovascular side effects are likely to be a class effect.

SPECIAL STUDIES
Specialized pharmacology and clinical studies have increased our knowledge of the cardiac effects of the triptans, particularly the relationship between triptan administration and coronary artery vasoconstriction.

PHARMACOLOGY STUDIES
The coronary vasoconstrictive properties of many antimigraine drugs, including sumatriptan, zolmitriptan, rizatriptan, and naratriptan, were recently evaluated by examining coronary vessel segments from 14 donors who died of noncardiac causes. (14) These segments were exposed to triptans and ergot derivatives, and the contractile responses they provoked before and after repeated vessel washings were recorded. The investigators concluded that
therapeutic doses of sumatriptan, zolmitriptan, rizatriptan, and naratriptan cause little coronary artery constriction in otherwise healthy patients with migraine. However, even small changes in vessel diameter could produce clinical consequences, including myocardial ischemia, in patients with preexisting coronary arterial lesions and those with increased coronary artery sensitivity to serotonin. The authors also observed that the contractile effects of the triptans quickly disappeared with vessel washing, while those of ergotamine and dihydroergotamine persisted even after repeated washings. This finding may help explain the prolonged substernal chest pain and discomfort that have repeatedly been described with ergot alkaloids, particularly ergotamine.

A related study involved a post-hoc analysis of sumatriptan concentration-response curves in 62 isolated human coronary arteries. The objective was to determine whether donor-related characteristics, such as age, sex, cause of death, and the functional endothelial integrity and muscle mass of the coronary artery were related to the efficacy of sumatriptan in inducing arterial contraction. Surprisingly, the study found an inverse relationship between the efficacy of sumatriptan and the functional integrity of the vessel endothelium. This suggests that sumatriptan-induced coronary artery constriction is more pronounced in patients with nondiseased coronary arteries with an intact endothelium. Nevertheless, sumatriptan-induced myocardial ischemia is unlikely in patients with healthy coronary arteries because of the high coronary reserve in these patients. In contrast, even a small contraction can be harmful in patients with coronary artery disease.

**ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY STUDY**

The investigational triptan avitriptan was used to determine whether upper body discomfort is associated with objective impairment of myocardial function as revealed by a 12-lead electrocardiogram (ECG), continuous ECG monitoring, and echocardiography in patients with migraine. The study included 51 migraineurs who had no clinically significant cardiovascular abnormality at baseline but who had a history of at least one experience of upper body discomfort after taking sumatriptan. When a high dose of oral avitriptan (150 mg) was administered outside of a migraine attack, no clinically significant cardiovascular abnormalities occurred in any of the 23 patients who reported abnormal sensations in the chest, neck, or throat. The investigators concluded that triptan-induced chest, neck, and throat symptoms are unlikely to be of cardiovascular origin.

Another study examined the use of frovatriptan 2.5 mg or placebo in 75 subjects determined to be at risk of coronary artery disease, which they defined as a score of greater than or equal to 14 using the Framingham Coronary Heart Disease Risk Prediction model. The mean age of the study population was 55.5 years. No electrocardiographic differences were noted between the two treatment groups in the mean PR, QTc or QRS intervals post-dose. Subjects in the placebo-treated group were more likely to have significant ECG changes compared with baseline than those in the frovatriptan group. Subjects in both groups had ST-segment changes suggestive of myocardial ischemia on 24 hour continuous electrocardiographic monitoring (4/37 patients in the frovatriptan group and 5/38 patients in the placebo group), but these changes were not statistically different between the two groups. All episodes of ischemia were clinically silent. The authors concluded that frovatriptan treatment was well-tolerated and not associated with an increase in cardiovascular monitoring abnormalities. Although these results are interesting, the number of subjects in this study is far too small to allow any conclusions to be drawn about triptan safety in patients with CAD or CAD risk factors. Given the size of this study, the true risk of clinically serious events could still be as high as 3/75.

**POSITRON EMISSION TOMOGRAPHY STUDY**

Nineteen adult women with migraine but at low risk of ischemic heart disease participated in a NH3 positron emission tomography study to test the hypothesis that sumatriptan produces coronary artery vasoconstriction. Patients participated in 2 scanning sessions during which a baseline dynamic NH3 positron emission tomography scan was acquired, followed by a second scan 10 minutes after subcutaneous injection of placebo or sumatriptan 6 mg. 6 patients developed symptoms of chest pain. When regional myocardial perfusion was measured in 5 myocardial regions, no treatment-related differences were observed in any patient.

**CLINICAL ANGIOGRAPHIC STUDIES**

Two angiographic studies performed several years apart but with a similar design were undertaken to determine the effects of intravenous sumatriptan (a) and subcutaneous naratriptan (b) on central hemodynamics and coronary artery diameter. In the first study, 10 patients undergoing
diagnostic coronary arteriography but without coronary artery disease received a 10-minute infusion of sumatriptan to a total dose of 48 µg/kg. (a) After sumatriptan administration, systemic and pulmonary arterial pressures were significantly increased (P < .05) and coronary artery diameter was significantly decreased, from 4.3 ± 1.6 mm to 3.6 ± 1.6 mm (P < .001). In the second study, 10 patients with similar characteristics received naratriptan 1.5 mg administered subcutaneously. (c) Statistically significant increases occurred in systolic arterial pressure (P = .0015), total systemic vascular resistance (P = .003), pulmonary artery systolic pressure (P = .003), pulmonary vascular resistance (P = .025), and pulmonary artery wedge pressure (P = .009) but not in coronary artery vasoconstriction. Whether these different vasoconstrictive effects resulted from differences in the patients participating in the 2 studies or from minor differences in the 5-HT1B/1D receptor profiles of the 2 triptans is not known.

Significant coronary artery constriction has been observed in patients receiving the investigational triptan eletriptan. (c) In a study in which eletriptan was administered intravenously to 10 patients without coronary artery disease who were undergoing cardiac catheterization, 1 patient experienced marked segmental right coronary artery constriction during drug infusion. Although this episode was associated with chest pain, no electrocardiographic abnormalities were noted. The investigators speculated that the chest pain could have resulted from catheter irritation, but such a result occurring after infusion of a known coronary vasoconstrictor is a serious matter, especially because the patient did not experience similar constriction during earlier infusion of a placebo saline solution.

Based on pooled data from all 10 patients, the authors reported that the coronary arteries underwent no overall effect and that eletriptan caused no significant coronary arterial constriction in patients without significant obstructive coronary artery disease. However, these pooled data seem to obscure the significant individual response of a particular patient. The results could also be interpreted to show that coronary vessel constriction, although infrequent, does occur in response to triptans. In view of the serious potential consequences of such an effect, even if rare, the conclusions are open to question.

PATIENTS WITH HYPERTENSION

Because the triptans can increase blood pressure, they are contraindicated in patients with uncontrolled hypertension.
benefit from them. Similarly, a normal ECG or the absence of chest pain with triptan use does not rule out coronary disease in a patient with multiple risk factors since, as discussed earlier, angiographically documented coronary artery constriction with triptan administration has occurred in the absence of chest pain or ECG changes. A normal ECG or the lack of triptan-induced chest pain with an in-office dose might lead to an unwarranted sense of security about prescribing triptans in patients with multiple risk factors.

It thus seems most reasonable that the “thorough cardiac evaluation” recommended before prescription of triptans to patients with cardiac risk factors should take the form of a careful stratification of patients based on their risk of underlying coronary artery disease. A model for risk factor stratification has been developed based on results from the Framingham study and validated. Assessment of six variables (sex, age, cholesterol level, blood pressure, diabetes, and smoking status) has been shown to generate reliable estimates of a patient’s 10 year risk for coronary heart disease, based on longitudinal information obtained in the Framingham Heart Study. (44, 45) A calculator for determining the Framingham Risk Score is available on-line at the following URL:

http://www.nhlbi.nih.gov/about/framingham/riskabs.htm

Based on risk factor assessment, patients can be stratified into those at low, intermediate or high risk of cardiovascular disease. In low-risk patients (less than 10% risk of symptomatic coronary heart disease during the next 10 years), the use of triptans should be considered safe and further evaluation should not be pursued. High risk patients (those with 20% or greater risk of symptomatic coronary heart disease in the next 10 years) should generally not be prescribed triptans, although exceptional circumstances may occasionally lead physicians and patients to judge that they are necessary.

In intermediate-risk patients (with a risk of symptomatic coronary heart disease in the next 10 years of 10% or greater, but less than 20%), the decision to use a triptan is more complex. Treatment of some sort is imperative, not optional, for most patients with severe migraine. The choice is thus not between using a triptan and using nothing but between using a triptan and using another form of treatment. Not all patients require the use of a triptan to treat migraine. However, other categories of drugs used for the acute treatment of migraine are associated with their own long-term safety or tolerability risks. Because migraine is a chronic, recurrent illness in which the selected treatment will be used repeatedly over many years, an understanding of the cumulative risks of a treatment is essential. Risks that seem acceptable in treating an individual attack may be unacceptable over a lifetime of cumulative use. The efficacy of treatment alternatives must also be assessed; few match that of the triptans for severe migraine attacks. Some patients, however, may choose to accept the generally lower efficacy of non-triptan drugs in preference to the small but real risk of cardiovascular events with triptans. As patients age, or if preventive migraine therapy is intensified, non-triptan treatment may become more effective. The categories of common non-triptan drugs for migraine, and their principal advantages and disadvantages, are summarized in Table 1.

In other cases, the patient and physician may choose to assume some degree of cardiovascular risk from triptan use in exchange for effective migraine treatment. This is especially understandable when headache-related disability is severe and responds poorly to non-triptan therapy. In this situation, further characterization of the degree of underlying cardiovascular risk may be reasonable, including the use of ECG and exercise stress testing. In the authors’ experience, many patients believe the advantages of using an effective medication for migraine attacks that cannot otherwise be satisfactorily treated through other means outweigh the risks involved.

**EVALUATION OF CHEST SYMPTOMS OCCURRING AFTER TRIPTRAN USE**

A considerable challenge for clinicians is that triptan-related chest symptoms are highly likely to be a minor adverse effect unrelated to coronary artery vasoconstriction; uncommonly, however, they may be a sign of underlying coronary ischemia or infarction. In patients with mild, transient triptan-related chest pain whose prior probability for underlying cardiovascular disease is low based on risk factor assessment mild, self-limited triptan-associated chest symptoms represent a tolerability, not a safety concern and further evaluation is not seem warranted.

The occurrence of triptan-associated chest symptoms in patients at intermediate risk of underlying cardiovascular disease represents a more difficult clinical situation, and one in which no evidence exists to guide decisions. Even in this group of patients, mild, transient pain is unlikely to be due to coronary artery constriction. However, prolonged or severe chest pain resembling angina requires further evaluation.
The use of ECG in this setting has important limitations. In a few patients, triptan-induced chest pain has been associated with angiographically demonstrated constriction but no ECG changes. Conversely, an abnormal ECG in a patient treated with a triptan does not necessarily mean the drug caused the problem. Thus, further evaluation may include stress testing, angiography or other clinical evaluations. As with the initial decision to prescribe triptans to a patient in this category, the decision about whether to continue use despite chest symptoms depends on a composite evaluation of the patient’s headache severity and disability and the efficacy of treatment alternatives.

SUMMARY

More than a decade of experience with the triptans provides evidence that these drugs are remarkably safe for the majority of patients with migraine. However, because rare cases of serious triptan-related cardiac events have occurred, primarily in patients with known cardiac risk factors, clinical assessment of risk factors and the underlying probability of cardiovascular disease is important prior to triptan prescription.

There is no evidence that ECG or other testing strategies are superior to clinical risk stratification in deciding whether patients are at low, intermediate or high risk from triptan use. Most patients requiring treatment for migraine are women of childbearing age who are at low risk for underlying coronary artery disease. For low-risk patients, triptans should be considered safe if guidelines and contraindications to their use are respected. In these patients, the occurrence of mild, transient chest symptoms is an issue of tolerability rather than safety, and does not require special investigation. Triptans should generally not be prescribed for high-risk patients. The decision to prescribe triptans to intermediate-risk patients should be individualized, taking into account patient preferences, the efficacy of treatment alternatives and the severity of migraine-associated pain and disability.

CORRESPONDENCE TO

Elizabeth Loder, MD, FACP 125 Nashua Street Boston, MA 02114 Telephone: 617-573-2493 Facsimile: 617-573-2489 Email: eloder@partners.org

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Author Information

Elizabeth Loder, MD, FACP
Director, Assistant Professor of Medicine, Headache and Pain Management Programs, The Spaulding Rehabilitation Hospital, Harvard Medical School

David Biondi, MD
Director, Instructor in Neurology, Outpatient Pain Program, The Spaulding Rehabilitation Hospital, Harvard Medical School