Triptans & Cardiovascular Risk: How to Assess Safety

Triptans are widely used in clinical practice for the acute treatment of migraine. Among diagnosed migraine patients in the United States, 51% of prescriptions for acute treatment are for triptans [1]. However, concern about cardiovascular safety continues to limit the use of triptans [2]. A careful look at the evidence may help to alleviate this concern and to more appropriately screen and select migraine patients for whom the benefit of a triptan outweighs potential side-effects.

All triptans are selective serotonin 5-HT1B/1D agonists. Their mechanism of action includes vasoconstriction of the cerebral vessels via the 5-HT1B receptor activity and neuronal inhibition (decreased release of neuroinflammatory peptides from nerve endings) via the 5-HT1D receptor activity. The vasoconstrictive activity of triptans affects coronary and peripheral arteries as well but to a lesser extent than the cerebral arteries [3]. All triptans are contraindicated in patients with known cardiovascular, cerebrovascular, or peripheral vascular disease.

What is the estimated rate of cardiovascular contraindications to triptan usage in the United States? Lipton, et al [4] evaluated respondents to the 2009 American Migraine Prevalence and Prevention (AMPP) study and identified 6,723 (1,496 males, 5,227 females) with episodic migraine (EM). Cardiovascular (CV) events or procedures were reported in 11.1% of those 40 or younger (n=1,457), 18.7% of those 40-59 (n=3,716) and 33.6% of those 60 or greater (n=1,550). Males had slightly higher rates than women for both events and procedures in all age groups. Census-based projections of net CV events and procedures yields 4.71 million persons with EM in the US (1.17 million males and 3.54 million females) where triptan use may be contraindicated. An additional 1.5 million (.38 million males and 1.12 million females) are at high risk for silent myocardial ischemia based on Framingham scores. This is a population who may have unmet treatment needs based in part on reluctance to prescribe triptans. Is this reluctance well-founded?
In a separate study published by Bigal, et al [5], triptan use as function of cardiovascular risk was examined. This was a population-based study and looked at 6102 individuals with migraine in the AMPP. Individuals with CV disease (CVD) and those with CV risk factors were identified. In addition, the level of migraine-related disability was correlated with triptan usage including in those with CVD or those with CV risk factors. Compared to migraineurs without risk factors for CVD, triptans were less likely to be used in individuals with diabetes (11.5% vs 18.3%), hypertension (14.8%), and by smokers (12.9%). In individuals with CVD, similar findings were seen including those with MI (8.5% vs 18.3%), stroke (7%), and heart surgery (9.3%). Significantly, use of triptans increased as a function of disability even in those with CV risk factors and with known CVD [5]. This study suggests that although there is concern about using triptans in patients with CVD or with CV risk factors, the potential benefit of using a triptan in these patients may have been felt to outweigh the safety concerns by the prescribing health care providers.

How much vasoconstriction occurs as a result of the 5-HT1B receptor activity of the triptans? In a review of in vitro pharmacologic date looking at coronary vasoconstrictor potential of triptans in human isolated coronary arteries, Maassen Van Den Brink et al, concluded that at therapeutically relevant concentrations, triptans have little potential to cause clinically significant constriction of nondiseased coronary arteries [6]. The triptans are craniovascular selective and as such, have greater vasoconstrictive activity on cerebral arteries than coronary or peripheral arteries. In a study published in Cephalalgia in 2015, DHE and sumatriptan were evaluated for vasoconstrictive activity in the isolated human proximal and distal coronary artery, the middle meningeal artery, and the saphenous vein [7]. Blood vessel segments were mounted in organ baths and concentration response curves were constructed. Maximal contractions to DHE were 84% proximal coronary artery, 32+/-7% meningeal, and saphenous 52+/-11%. Sumatriptan maximal contraction was 17+/-7% in proximal coronary artery, 61+/-18% meningeal, and 37+/-8% in saphenous. In the distal coronary artery, contractions to DHE (5+/-2%) were smaller than those to sumatriptan (17+/-9%). At clinically relevant concentrations, mean contractions to DHE and sumatriptan
were below 3% in proximal coronary arteries and below 6% in distal coronary arteries. Contractions in the meningeal artery and saphenous vein were higher (7%-38%). The higher contraction to DHE and sumatriptan in the meningeal arteries shows their cranioselectivity. Contractions to DHE in the saphenous vein are higher than with sumatriptan and would support venous contractile properties of DHE.

In a study looking at coronary side-effect potential of current and prospective antimigraine drugs, the conclusion was that all such drugs contract the human coronary artery in vitro. However, with the exception of avitriptan, therapeutic plasma concentrations of the drugs did not reach levels likely to cause myocardial ischemia in individuals with normal coronary circulation. The sustained coronary artery contraction induced by ergotamine and dihydroergotamine was felt to be an important disadvantage to the triptan drugs [8].

What do we know about triptan usage in patients with established CVD? Only a few studies have evaluated triptans in patients with obstructive CAD to quantify the vasoconstrictive effect on diseased coronary vessels. In a published study [9], patients who were to undergo coronary angioplasty for symptomatic single-vessel CAD were randomized to one of 3 groups: (1) 6 mg IV eletriptan plus subcutaneous (SC) placebo, (2) IV infused placebo plus 6 mg SC sumatriptan, (3) IV infused placebo plus SC placebo as simultaneous administrations in a double-blind fashion. Serial arteriograms, hemodynamic indices, electrocardiography and triptan plasma concentrations were obtained. Fifteen minutes after triptan challenge, changes in coronary artery diameter at the focal point of the stenosed segment were: dilation of 2.6% in the eletriptan group (n=18); constriction of 6.8% in the sumatriptan group (n=17); and constriction of 4.5 % in the placebo group (n=10). There was no correlation between effects on coronary artery diameter (CADM) and triptan concentration, or between hemodynamic or electrocardiograph changes and the presence (n=13) or absence (n=33) of chest pain. The conclusion of this study was that triptans had little effect on diseased epicardial coronary arteries in a small group of angina sufferers with established CAD.
So, what guidelines may be helpful to headache clinicians trying to decide if a triptan is a safe treatment option for a particular patient? In 2002, the American Headache Society (AHS) convened the Triptan Cardiovascular Safety Expert Panel to evaluate the evidence on triptan-associated cardiovascular risk and to formulate consensus recommendations for making informed decisions for their use in migraine [10]. This consensus statement is available on the AHS Website. This panel was composed of a multidisciplinary group of experts. An exhaustive search of the relevant published literature was done by panel members in preparation of the meeting. The conclusions are: (1) Most of the data on triptans are derived from patients without known coronary artery disease. (2) Chest symptoms occurring during use of triptans are general nonserious and are not explained by ischemia. (3) The incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice appears to be extremely low. (4) The cardiovascular risk-benefit profile of triptans favors their use in the absence of contraindications.

In 2013, American College of Cardiology and the American Heart Association published what are known as the 2013 ACC/AHS Guideline on the Assessment of Cardiovascular Risk [11]. In conjunction with this guideline and other related guidelines, an atherosclerotic cardiovascular disease (ASCVD) Risk Estimator was developed to help health care providers and patients estimate 10-year and life time risk for ASCVD. This Risk Estimator is available as an app on most electronic devices. Age, gender, race, total cholesterol, HDL, Systolic blood pressure, Hypertension, Diabetes, and Smoking status are all part of this calculation. Utilizing this app could be a practical way of assessing appropriateness of triptan therapy in our migraine patients. In addition, many of us as headache clinicians are not our patient’s primary care provider. Collaboration with other health care providers taking care of our patients including cardiologists, internal medicine, and primary care is critical to assess our patients’ cardiovascular risk and appropriateness for triptan therapy. As we age, so do our patients so periodic reassessment of our patient’s cardiovascular risk is prudent on follow-up visits.
Fortunately, the data supports the safety of triptans for the majority of our migraine patients.

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References: