Triptans & Cardiovascular Safety: How to Assess the Risk?

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Disclosures

- Advisory Panel: Alder, Allergan, Avanir, Pernix, Teva
- Speakers Bureau: Allergan, Avanir. Pernix, Teva

Learning Objectives

- Define the effects of the triptans on the cardiovascular system
- Examine published data on triptan cardiovascular adverse events
- Discuss screening of patients for cardiovascular risk & appropriateness for triptan usage

Case Study

- 67 year old pediatrician with chronic migraine on Topiramate 200 mg qhs & receives Botox every 12 weeks takes Sumatriptan 50 mg every evening as a preventive
- “I need at least 30 tablets a month of Sumatriptan in order for me to function in my life as a physician”

Triptans

- Widely used for acute treatment of migraine (over 50% of acute treatment prescriptions are triptans)
- Concern over cardiovascular safety continues to limit their usage
- Is this concern valid?

Triptans & Mechanism of Action

- All triptans are 5-HT1B/1D receptor agonists.
- Vasoconstriction of cerebral, coronary, and peripheral arteries occurs via the 5-HT1B receptor activity
- Neuronal inhibition (decreased release of neuroinflammatory peptides) occurs via the 5-HT1D receptor activity

Contraindications to triptans include:

Ischemic coronary artery disease (CAD) or coronary artery vasospasm, including Prinzmetal's angina

WPW syndrome or other arrhythmias associated with other cardiac accessory conduction pathway disorders

History of stroke, TIA, or hemiplegic or basilar migraine

Peripheral vascular disease

Uncontrolled hypertension

Side-Effects Triptans

- Chest pain, pressure, tightness
- Neck, throat, jaw pain
- Shortness of breath
- Dizziness
- Flushing
- Palpitations
- Elevated blood pressure

Estimated Rate of CV Contraindications

- AMPP Study identified 6723 (1496 males, 5227 females) with Episodic Migraine (EM). CV events reported in 11.1% of 40 or younger, 18.7% in 40-59 age group, 33.6% 60+ age group. Males slightly higher rates than women
- Census-based projections 4.71 million individuals with EM in US where triptan use may be contraindicated. Additional 1.5 million at high risk silent MI based on Framingham scores.

Lipton RB, Buse D, Fanning DM, et al. Cardiovascular contraindications to triptans in the migraine population. Results from the American Migraine Prevalence and Prevention (AMPP) study. Cephalalgia, suppl. 1 33 June 2013:17-18.

Triptan Use & CV Profile

- 6102 Individuals with migraine in AMPP Study
- Triptans less likely to be used in diabetes (11.5% vs 18.3%), hypertension (14.8%), and smokers (12.9%), myocardial infarction (8.5%), stroke (7%), and heart surgery (9.3%).
- Use of triptans increased as a function of disability regardless of CVD status or presence of CVD risk factors.

Bigal M, Golden W, Buse D, et al. Triptan Use as a Function of Cardiovascular Risk. A Population-Based Study. Headache. Feb 2010:256-263.

Vasoconstriction & 5-HT1B Receptor Activity of Triptans

- Review of in vitro pharmacologic data looking at coronary vasoconstriction potential of triptans in human isolated coronary arteries concluded “at therapeutically relevant concentrations, triptans have little potential to cause significant constriction of nondiseased coronary arteries”.

Maassen VanDenBrink A, Saxena PR. Coronary vasoconstrictor potential of triptans: a review of in vitro pharmacologic data. Headache. May 2004:S13-9.

Craniovascular Selectivity

- Triptans-greater vasoconstrictive activity on cerebral arteries than coronary or peripheral arteries
- DHE & Sumatriptan vasoconstrictive activity measured in isolated human proximal and distal coronary artery, the middle meningeal artery, and the saphenous vein. Mean contractions to DHE & Sumatriptan were below 3% in proximal coronary arteries and below 6% in distal coronary arteries at clinically relevant concentrations.
- Contractions in meningeal arteries higher (61+/-18% Suma, 32+/-7% DHE) and in saphenous vein (37+/-8% Suma, 52+/-11% DHE). Higher contractions in saphenous vein to DHE supports venous contractile properties of DHE.

Labruijere S, Chan K, de Vries R, et al. Dihydroergotamine and sumatriptan in isolated human coronary artery, middle meningeal artery and saphenous vein. Cephalalgia 35.2, Sp. Iss. SI (Feb 2015):182-189.

Coronary Side-Effect Potential Triptans vs DHE/Ergotamine

- All current triptans & DHE/ergotamines contract the human coronary artery in vitro but at therapeutic plasma concentrations do not reach levels likely to cause myocardial ischemia in those individuals with normal coronary circulation
- Disadvantage of DHE/ergotamines is the sustained coronary artery contraction

Maassen VanDenBrink A, Reekers M, Bax WA, et al. Coronary Side-Effect Potential of Current and Prospective Antimigraine Drugs. Circulation. 1998;98:25-30.

Triptan Use in CAD

- Patients undergoing coronary angioplasty (symptomatic single-vessel disease) randomized to 6 mg IV eletriptan/SC saline, IV Saline/6 mg SC sumatriptan, or IV placebo/SC placebo. Fifteen minutes, changes in coronary artery diameter at the focal point of the stenosed segment measured: dilation 2.6% eletriptan group (n=18), constriction 6.8% sumatriptan group (n=17), constriction 4.5% placebo group (n=10).
- No correlation between effects on coronary artery diameter and triptan concentration or between hemodynamic or EKG changes and presence (n=13) or absence (n=33) of chest pain.

Newman C, Starkey I, Buller N, et al. Effects of sumatriptan and eletriptan on diseased epicardial coronary arteries. European Journal of Clinical Pharmacology 61.10 Nov 2005:733-742.

Chest Symptoms with Triptans: Clinically Relevant?

Chest Symptoms & Triptans

- Chest tightness, pressure and pain 24% of patients receiving oral sumatriptan and 41% receiving subcutaneous sumatriptan in a post marketing study
- No EKG or angiographic changes shown in patients with chest symptoms

Visser WH, Jaspers NM, de Vriend RH, et al. Chest symptoms after sumatriptan: a two-year clinical practice review in 735 consecutive migraine patients. Cephalalgia. 1996;16:162-164.

Welch KM, Mathew NT, Stone P, et al. Tolerability of sumatriptan: clinical trials and post-marketing experience. Cephalalgia. 2000;20:687-695.

Possible Explanation of Chest Symptoms

- Triptans (eletriptan, naratriptan, rizatriptan, sumatriptan, and almotriptan) induced vasoconstriction in thoracic blood vessels (arteries & veins) in 38-57% of patients in a published study of 29 patients during coronary artery bypass graft surgery. The vessels obtained from original site in thoracic wall.
- Vasoconstriction induced in small thoracic arteries 39-50% of patients, small thoracic veins 40-57% of patients. Amount of vasoconstriction similar for triptans used.
- Not all patients had blood vessels that responded to triptans. Blood vessels in 43-62% of patients no vasoconstrictive response that differed from baseline.

Wackenfors A, Jarvius, Ingemansson et al. Triptans Induce Vasoconstriction of Human Arteries and Veins from the Thoracic Wall. J Cardiovasc Pharmacol 2005;45:476-484.

Consensus Statement AHS-Cardiovascular Safety of Triptans

- Triptan Cardiovascular Safety Expert Panel convened in 2002 (multidisciplinary group) by AHS
- Extensive search of relevant published literature was reviewed
- Conclusions: Most of data on triptans is derived from patients without known coronary artery disease (CAD). Chest symptoms occurring during use of triptans are generally nonserious and are not explained by ischemia. Incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice appears to be extremely low. The cardiovascular risk-benefit profile of triptans favors their use in the absence of contraindications.

Dodick D, Lipton RB, Martin V, et al. Consensus Statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. Headache. May 2004:414-25.

From Consensus Statement to Patient Decision Making: Assessing Cardiovascular Safety of using a triptan in an individual with migraine

ACC-AHA 2013 Guidelines

- Developed jointly by the NHLBI, ACC, and AHA to provide clinical practice guidelines for:

1. Assessment of cardiovascular risk
2. Lifestyle modifications to reduce risk
3. Management of blood cholesterol
4. Management of overweight & obesity

- circ.ahajournal.org/content/129/25_suppl_2/S49 accessed 10/19/14
- ACC=American College of Cardiology
- AHS=American Heart Association
- NHLBI=National Heart, Lung, & Blood Institute

ASCVD Risk Estimator

- Developed by ACC/AHA for providers and patients to estimate 10-year and lifetime risk for Atherosclerotic Cardiovascular Disease (ASCVD)

- Free download: ASCVD Risk Estimator

ASCVD Risk Estimator: What Does it Include?

- Gender, Age, Race
- Total Cholesterol; HDL
- Systolic Blood Pressure
- Treatment for HTN, Diabetes
- Smoker

Other CVD Risk Factors

1. hsCRP
2. Apolipoprotein B (ApoB)
3. Glomerular Filtration Rate (GFR)
4. Microalbuminuria
5. FH
6. Cardiorespiratory fitness
7. Ankle-brachial index (ABI)
8. Carotid intima-media thickness (CIMT)
9. Coronary artery calcium (CAC) score

Summary of Systematic Reviews and Meta-Analyses

- None of these markers (shown on previous slide) have been evaluated as a screening test in RCT's with clinical events as outcomes
- The work group (ACC/AHA) felt the most promising for clinical utility: FH premature CVD, hs-CRP, CAC, & ABI

- http://circ.ahajournals.org/content/129/25_suppl_2/S49.full accessed 10/26/14

Back to Case Study

- 67 year old pediatrician taking 50 mg sumatriptan every evening
- Stress Echo 2015 normal
- Coronary artery calcium score 2015 “zero”
- Accepts risks of daily sumatriptan and feels for her, the benefits outweigh the risks

Suggested Documentation in Office Setting

- Any new/existing cardiovascular condition; if yes, list condition and status (stable?)
- Additional CVD Info: EKG, Cholesterol/HDL, Glucose, Stress Echo, Smoking, HTN or Diabetes Treatment, FH premature heart disease, consider ASCVD Risk Calculation
- List other treating providers (PCP, cardiologist)
- Consider verbal/written consent form for triptans if significant risk factors are present

Summary

- All triptans exhibit vasoconstriction of the cerebral, coronary, and peripheral arteries.
- For the majority of migraineurs, the amount of vasoconstriction is not clinically significant and is unlikely to cause myocardial ischemia.
- Screening of patients for cardiovascular risk can help identify those who can be safely prescribed triptans. Fortunately, the majority of our patients can take triptans for acute migraine management.