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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Migraine Headache Agents. [Updated 2018 Dec 10].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Migraine Headache Agents

Updated: December 10, 2018.

OVERVIEW

Migraine headaches are marked by repeated, paroxysmal attacks of moderate-to-severe throbbing, one-sided headaches which (without treatment) last 4 to 72 hours and are usually associated with symptoms of nausea and vomiting. Migraine headaches are typically exacerbated by motion, bright lights and loud noises. Migraines may be associated with focal neurological symptoms referred to as "aura" which are typically visual, but may be sensory or motor. Migraine headaches are common, affecting at least 18% of women and 6.5% of men in the United States. The pattern of paroxysmal headaches typically arises in adolescence or young adulthood and may be life-long. The headaches often interfere with daily activities and can be incapacitating, result in major time loss from work and precipitate multiple physician and emergency room visits. Patients with migraine may also be at increased risk for other vascular complications such as stroke and eclampsia.

The cause of migraine headaches is not fully understood, but appears to be related to arteriolar vasodilation and inflammation of the trigeminal nerve endings, perhaps caused by local release of vasoactive peptides. The most convincing candidate mediator of migraines is the calcitonin gene related protein (CGRP), a neuropeptide found throughout the central and peripheral nervous systems which has potent vasodilator and pain-signaling activities. Circulating levels of CGRP are elevated in pateints with migraines, and the efficacy of migraine therapies such as serotonin receptor agonists and ergot alkaloids is associated with lowering of circulating CGRP levels. Antagonists of CGRP have become a focus of migraine headache prevention and therapy.

Therapy of migraine headache usually combines preventive treatments with early intervention for acute attacks. Early treatment approaches to migraine have included a number of different classes of medications including nonsteroidal antiinflammatory agents, opiate and nonopiate analgesics, barbiturates, antiemetics, ergot alkaloids, and serotonin receptor agonists. Medications used specifically to treat migraine headaches and discussed here are the ergot alkaloids and the more recently developed serotonin receptor agonists (triptans). The ergot alkaloids have been in use for many years, and currently available forms include ergotamine (Cafergot: year of approval, 1948) and dihydroergotamine (Migranal: 1946). The triptans include sumatriptan (Imitrex: 1997), zolmitriptan (Zomig: 1997), naratriptan (Amerge: 1998), rizatriptan (Maxalt: 1998), almotriptan (Almogran, Axert: 2001), frovatriptan (Frova: 2001), and eletriptan (Relpax: 2002).

The identification of CGRP as an important mediator of vasodilation and pain in patients with migraine led to development of potent and well tolerated CGRP antagonists to prevent episodic and chronic migraine. Both small molecule and monoclonal antagonists of CGRP signaling have been developed, but only the monoclonal antibodies have been approved for use in prevention of migraine headaches in the United States. These antagonists include monoclonal antibodies to CGRP such as fremanezumab (Ajovy: 2018) and galcanezumab (Emgality: 2018]) and to the CGRP receptor such as erenumab (Aimovig: 2018). These agents are given

subcutaneously once monthly or every three months and have been found to reduce the frequency of migraines but rarely to eliminate them completely. They are not effective in treatment of ongoing, acute migraine.

The ergot alkaloids and triptans rarely cause liver injury, perhaps because they are used for a short time only and in low doses. Rare instances of clinically apparent liver injury have been described in patients taking zolmitripan and rizatriptan. The monoclonal antibody antagonists to CGRP have had limited general use, but appear to be free of significant hepatotoxicity.

General references on the safety and hepatotoxicity of the drugs used specifically for migraine are provided with this introductory section. The specific agents are discussed after each overview section (ergot alkaloids and triptans) or as separate drug records (the monoclonal antibodies) with a more complete set of references regarding their safety and postential for hepatotoxicity.

The following links are to individual drug records.

- Ergot Alkaloids: Ergotamine, Dihydroergotamine
- Monoclonal Antibodies: Erenumab, Fremanezumab, Galcanezumab
- Triptans: Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan

ANNOTATED BIBLIOGRAPHY

References updated: 10 December 2018

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Expert review of hepatotoxicity published in 1999; ergotamine and triptans are not discussed).

Larrey D, Ripault MP. Benzodiazepines. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 455. *(Review of hepatotoxicity of neuroleptic drugs does not mention*

ergotamine or the triptans).

Sanders-Bush E, Mayer SE. 5-Hydroxytryptamine (Serotonin): receptor agonists and antagonists. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 297-315.

(Textbook of pharmacology and therapeutics).

Geraud G, Compagnon A, Rossi A; COZAM Study Group. Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study. Eur Neurol 2002; 47: 88-98. PubMed PMID: 11844897.

(Among 666 patients with migraine treated with either zolmitriptan or aspirin/metoclopramide, side effects of paresthesias and dizziness were more common with zolmitriptan; no mention of any hepatic side effects).

Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ; Eletriptan and Cafergot Comparative Study Group. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. Eur Neurol 2002; 47: 99-107. PubMed PMID: 11844898.

(Among 733 patients with migraine treated with either eletriptan or ergotamine/caffeine, side effects were transient and predominately mild or moderate; "No clinically significant laboratory…abnormalities were recorded").

Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med 2002; 137: 840-9. PubMed PMID: 12435222.

(Guidelines for management of acute migraine and chronic prevention; recommends use of nasal dihydroergotamine or a triptan in patients whose migraines fail to respond to aspirin, acetaminophen or nonsteroidal antiinflammatory agents).

Jamieson DG. The safety of triptans in the treatment of patients with migraine. Am J Med 2002; 112: 135-40. PubMed PMID: 11835952.

(Review of the safety of triptans in migraine therapy focusing on vascular risk, stroke, myocardial infarction and ischemic bowel disease; no mention of hepatotoxicity).

Loj J, Solomon GD. Migraine prophylaxis: who, why, and how. Cleve Clin J Med 2006; 73: 793-4, 797, 800-1 passim. PubMed PMID: 16970133.

(Preventive therapy of migraine has limited efficacy and may take 2-3 months to have an effect; the most commonly used agents are beta-blockers, calcium channel blockers, anticonvulsants, tricyclic antidepressants and selective serotonin reuptake inhibitors [SSRIs]).

Whyte CA, Tepper SJ. Adverse effects of medications commonly used in the treatment of migraine. Expert Rev Neurother 2009; 9: 1379-91. PubMed PMID: 19769452.

(Extensive review of common side effects of medications used to treat migraine; nausea is the most common and dose limiting side effect of ergot alkaloids and can require antiemetics; 1-8% of patients who take triptans develop "triptan sensations with throat and chest tightness, numbness and tingling and hot/cold sensations which may vary with different forms").

Loder E. Triptan therapy in migraine. N Engl J Med 2010; 363: 63-70. PubMed PMID: 20592298.

(Review of the pathophysiology of migraine headache and the mechanism of action, efficacy, tolerance and safety of the serotonin receptor agonists [triptans]; no mention of ALT elevations of clinically apparent liver injury).

Taylor FR. Acute treatment of migraine headaches. Semin Neurol 2010; 30: 145-53. PubMed PMID: 20352584.

(Review of diagnosis and acute management of migraine headaches).

Drugs for migraine. Treat Guidel Med Lett 2011; 9: 7-12. PubMed PMID: 21304447.

(Concise review of current medications used for migraine; no discussion of hepatotoxicity).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to drugs for migraine headaches).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to the triptans or other drugs for migraine headaches).

Drugs for migraine. Med Lett Drugs Ther 2017; 59 (1514): 27-32. PubMed PMID: 28170366.

Corrected and republished in: JAMA 2017; 317 (21): 2230-1. PubMed Citation (Concise review of current medications used for migraine; no discussion of hepatotoxicity).

Edvinsson L. The CGRP pathway in migraine as a viable target for therapies. Headache 2018; 58 Suppl 1: 33-47. PubMed Citation

(Review of the calcitonin gene related peptide [CGRP] and its receptor including their relationship to migraine headaches and development of small molecular inhibitors and monoclonal antibody therapies based upon their inhibition).

Tepper SJ. History and review of anti-calcitonin gene-related peptide (CGRP) therapies: from translational research to treatment. Headache 2018; 58 Suppl 3: 238-75. PubMed Citation (Review of the role of CGRP in pathogenesis of migraine headaches and the development of small molecules and monoclonal antibody antagonists of CGRP actions).