SEROTONIN 5-HT\sub{1} RECEPTOR AGONISTS (TRIPTANS)

Migraine is an episodic headache disorder of moderate to severe intensity that is experienced by an estimated 24 million people in the United States.\textsuperscript{1} The 5-HT\sub{1} receptor agonists (triptans) are a novel class of agents now available for the treatment of migraine. The biological mechanism responsible for the onset of migraine headaches is poorly understood; however, several theories have been postulated to explain the underlying etiology of the disorder. One widely accepted hypothesis involves neuronal dysfunction within the trigeminovascular system.\textsuperscript{12} Potential changes in intracranial circulation and vasculature promote vessel dilation during a migraine attack. Vessel dilation triggers release of vasoactive peptides which subsequently induce a localized inflammatory response and produce migraine symptoms. Serotonin (5-hydroxytryptamine or 5-HT) and its receptors are thought to be important mediators of migraine and are routinely implicated in the pathophysiology of the disorder. Of the many serotonin receptors identified, 5-HT\sub{1a} and 5-HT\sub{1b} receptors are believed to be involved in migraine and are therefore the focus of research efforts.

The first generation triptan, sumatriptan, has well-established clinical efficacy in the treatment of acute migraine, however limitations in its pharmacokinetic profile prompted the development of newer, so-called second generation, formulations with improved pharmacokinetics.\textsuperscript{13} The first of the class, sumatriptan (Imitrex\textsuperscript{®}), and the newer second generation triptans, zolmitriptan (Zomig\textsuperscript{®}), naratriptan (Amerge\textsuperscript{®}), and rizatriptan (Maxalt\textsuperscript{®}), display high affinity and selectivity for 5-HT\sub{1b} receptor subtypes.

The triptans are indicated for the acute treatment of migraine attacks with or without aura in adults. These agents are not intended for the prophylactic treatment of migraine and should not be used in the management of patients with hemiplegic or basilar migraine.

Clinical Pharmacology and Kinetics

The triptans bind selectively and agonistically to 5-HT\sub{1b} receptors located on smooth muscle cells of intracranial blood vessels and 5-HT\sub{1d} receptors found on trigeminal nerve endings.\textsuperscript{10} The therapeutic activity of the triptans in migraine is attributed to their ability to activate the 5-HT\sub{1b} receptors. Stimulation of 5-HT\sub{1d} receptors results in selective vasoconstriction of cranial vessels, whereas activation of 5-HT\sub{1b} receptors directly inhibits the release of pro-inflammatory neuropeptides.\textsuperscript{11} The pharmacokinetic characteristics of the triptans have been evaluated extensively and minor differences in bioavailability, rate of absorption, half-life, and metabolism exist between the formulations. Subcutaneous (sc) sumatriptan (6 mg) is quickly absorbed, and reaches peak plasma drug concentration (C\textsubscript{max}) within 10 minutes.\textsuperscript{5} The average bioavailability of the sc formulation is 96%. After oral administration of therapeutic doses (100 mg) of sumatriptan, however, the time to reach peak plasma concentration (t\textsubscript{max}) is substantially longer (2.5 hours), and the bioavailability is low (14%). Sumatriptan exhibits low (14% to 21%) protein binding and has a mean volume of distribution of 2.7 L/kg. The elimination half-life of sumatriptan is approximately 2 hours regardless of oral, sc, or intranasal administration. Metabolism of sumatriptan occurs primarily in the liver via monoamine oxidase type A (MAO-A) and no active metabolites are produced.

The first of the second-generation triptans to be approved after sumatriptan was zolmitriptan.\textsuperscript{14} Zolmitriptan offers some advantages over its predecessor, including the ability to cross the blood-brain barrier and act directly on the CNS. It is also rapidly and extensively absorbed after oral administration with a bioavailability of 40% and a t\textsubscript{max} of 1-2 hours. Zolmitriptan is approximately 25% plasma protein bound and has a mean volume of distribution of 7 L/kg. Elimination occurs primarily through hepatic metabolism and urinary excretion. The CYP450 isozyme 1A2 is the major hepatic enzyme involved in the metabolism of zolmitriptan, whereas MAO plays a smaller role. Zolmitriptan yields 3 distinct metabolites, one of which (the N-desmethyl metabolite) is therapeutically active and at least twice as potent as the parent molecule. The elimination half-life of the parent compound and all metabolites is approximately 3 hours.

Naratriptan has both the highest bioavailability (63-74%) and the longest half-life (5-6 hours) of any orally administered triptan currently available on the market.\textsuperscript{6} Naratriptan is more lipophilic than sumatriptan and can more readily penetrate the CNS, however, the t\textsubscript{max} is prolonged in a migraine state from 2.5 hours to 3.5 hours. Plasma protein binding of naratriptan is 28% to 31% and the mean volume of distribution is 2.6 L/kg. Naratriptan is metabolized by a wide range of CYP450 isoenzymes into inactive metabolites, however 50% of the drug is eliminated unchanged in the urine. Both renal and hepatic impairment can therefore alter the pharmacokinetics of naratriptan.

Rizatriptan is well absorbed after oral administration and demonstrates bioavailability of approximately 45%, about 3 times greater than that of sumatriptan.\textsuperscript{7} The peak plasma concentration is achieved within 1 hour of oral administration. Rizatriptan exhibits low protein binding, approximately 14%, and has a mean volume of distribution of 2 L/kg. Rizatriptan is metabolized in the liver via oxidative deamination by MAO-A and gives rise to an active metabolite, N-monodesmethyl-rizatriptan. The elimination half-life for both the parent compound and metabolites is about 2 hours.

Clinical Toxicology

The triptans are generally well tolerated when given in therapeutic doses for acute migraine attacks. In clinical trials the most frequently (≥ 2%) reported adverse events were atypical sensations (parasthesias, warm/cold temperature sensations), nausea/vomiting, dizziness, drowsiness and fatigue.\textsuperscript{6,7} Also, approximately 3-5% of patients experienced sensations of heaviness, pressure, and tightness in the chest after administration of one of the triptans. Isolated cases of coronary vasospasm with ischemia, myocardial infarction, and ventricular dysrhythmia have been reported both with and without fatalities. Significant elevations in blood pressure, including hypertensive crisis, have also been reported in patients with and without a history of...
hypertension. The cardiac events have been observed to have an onset within 1 hour of administration of a triptan, most often within 1 hour of sumatriptan administration. Although the occurrence of these serious cardiac events have been rare, all triptans are labeled with a black box warning of this potential effect and all are contraindicated in patients with a history of ischemic heart disease, angina pectoris, Prinzmetal's angina, previous myocardial infarction, and uncontrolled hypertension. It is also recommended that 5-HT_1 agonists be avoided in patients at risk for unrecognized coronary artery disease (post-menopausal women, men > 40 years old, smokers, hypertension, hypercholesterolemia, obesity, diabetes, family history of CAD). 5-HT_1 agonists may also cause vasospastic reactions in areas other than the coronary artery; both peripheral vascular ischemia and colonic ischemia have been reported rarely with the triptans.

The mechanism of cardiac toxicity observed with administration of a 5-HT_1 agonist is thought to be due to the presence of 5-HT_1 receptors in vascular beds distinct from the cranial circulation, including the human coronary artery. Addition to their strong vasoconstrictor effects in cranial arteries, all 5-HT_1 agonists have demonstrated a small but significant constrictor response in human coronary arteries, both in vitro and in viva. In the coronary artery 5-HT_1 receptors predominately mediate vasoconstriction, with only a small percentage of constriction attributable to activation of the 5-HT_1 receptor. Therefore, at therapeutic doses the magnitude of 5-HT_1-mediated constriction is unlikely to cause ischemia in individuals with normal coronary circulation. However, in patients with pre-existing coronary artery lesions/stenosis even the minor contraction of coronary arteries that occurs with therapeutic doses may have deleterious effects.

Drug-Drug Interactions

Concomitant administration of selective serotonin reuptake inhibitors (SSRI) and triptans has been reported, rarely, to cause symptoms suggestive of serotonin syndrome including weakness, hyperreflexia, and incoordination. Clinical evidence supporting this potential drug interaction is lacking, however, combination therapy should be undertaken cautiously. Sumatriptan, zolmitriptan, and rizatriptan utilize the MAO-A enzyme for metabolism; therefore, concomitant therapy with MAO-A inhibitors is contraindicated. MAOIs enhance serotonergic activity as well as reduce the clearance of the specified triptans resulting in increased risk for the development of MAOI-related serotonin syndrome.

Management

Reports of overdose with triptans are scarce; therefore the mainstay of therapy is supportive care and observation. The monitoring period for overdose is dependent upon which triptan was ingested as each agent has an individual elimination half-life. The elimination half-life of sumatriptan is 2 hours. Therefore observation post-overdose should continue for approximately 10 hours or while symptomatic. There is no specific antidote available for a triptan overdose. Gastrointestinal decontamination (gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with a triptan alone or with co-ingestants. The effects of hemodialysis or peritoneal dialysis on serum concentrations of the available triptans are unknown.

Patients may present with chest pain and/or symptoms consistent with angina pectoris or with dysrhythmias. Those patients who present with cardiac symptoms of toxicity should undergo ECG monitoring. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Patients should be monitored regularly for development of hypertension and/or ventricular arrhythmias. For patients who develop mild/moderate asymptomatic hypertension pharmacological intervention is generally not necessary. However, the occurrence of a hypertensive emergency requires immediate therapy.

Nitroprusside is the preferred agent for hypertensive emergencies at a dose of 0.1mcg/kg/min IV infusion titrated to clinical effect. Other agents that can be employed for the management of hypertensive emergencies include nitroglycerin, beta-blockers, and calcium channel blockers.

Patients who present with suspected co-ingestion with a MAOI and/or SSRI and have symptoms consistent with a serotonin syndrome may require pharmacological intervention. Benzodiazepines (diazepam) or barbiturates (phenobarbital) can be initiated to control agitation, treat seizures, decrease muscle activity, and reduce the hyperthermia associated with serotonin syndrome. Cooling blankets and fans can help lower the patient's temperature. Cyproheptadine is a non-specific 5-HT antagonist that has been used experimentally in the treatment of serotonin syndrome. If clinically indicated cyproheptadine can be given at a dose of 4-8mg orally every one to four hours until a therapeutic response is observed.

Conclusion

The 5-HT_1 agonists have a relatively mild toxicity profile consisting primarily of transient cardiovascular sequelae. Neither a minimal lethal exposure nor a maximum tolerated exposure dose has been defined for the available triptans. In the event of intoxication with a triptan the cornerstone of management is observation of cardiovascular function and supportive measures with pharmacological intervention if clinically indicated. A potentially problematic presentation is one of co-ingestion with a MAOI. Although the literature is not abundant with respect to the severity and management of this type of intoxication, it is reasonable to assume that intervention may be required.

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References