

The DUR Discovery

Exploring ways to improve pharmacotherapy

Antidepressants and GI Hemorrhage

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Gastrointestinal (GI) hemorrhage is a well-recognized potential adverse effect associated with the use of several classes of medications including non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticoids, and anticoagulants. Much less appreciated, however, is the GI risk associated with serotonergic antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs), with some studies showing that this class may increase the

GI bleed in the general adult population is estimated at about 1 case per 1,000.⁵ With SSRI use alone, the adjusted relative risk (RR) of upper GI hemorrhage increased nearly three-fold (RR=2.6; 95% CI 1.7 to 3.8) and with NSAID use alone, the adjusted relative risk of upper GI hemorrhage was slightly higher at 3.7 (95% CI 3.2 to 4.4).¹

Most importantly, when concurrent use of an NSAID and an SSRI was considered, the

Table I: Comparison of SSRI- and NSAID-induced GI Bleeding

Study	Type	Pts (n)	Pt age (yrs)	RR NSAID (95% CI)	RR SSRI (95% CI)	RR SSRI + NSAID (95% CI)
de Abajo ¹	Case control	69,593	40-79	3.7 (3.2-4.4)	2.6 (1.7-3.8)	15.6 (6.6-36.6)
van Walraven ⁶	cohort	317,824	65+	2.8 (2.4-3.3)	3.1 (not avail)	6.2 (not avail)
Dalton ⁷	cohort	26,005	16-105	4.5 (3.9-5.2)	3.6 (2.7-4.7)	12.2 (7.1-19.5)

risk of gastric or duodenal hemorrhage to a similar degree as NSAIDs.¹ Although established sources of drug information describe these risks, many clinicians remain unaware of the link between SSRIs and upper GI bleeding, as well as the potential magnitude of this adverse effect.²

A proposed mechanism by which serotonergic antidepressants increase upper GI bleeding risk involves the role serotonin plays in platelet aggregation and vasoconstriction. Serotonergic antidepressants decrease the uptake of serotonin into platelets, thereby decreasing serotonin stores, diminishing serotonin's function in hemostasis, and increasing bleeding time.^{3,4}

Evidence of upper GI bleeding involving antidepressants comes from retrospective cohort studies, case-control studies, and case reports. No randomized clinical trials have been published on this subject. Table I summarizes data from retrospective studies of upper GI bleeding that required hospitalization. The annual incidence of

adjusted relative risk increased nearly sixteen-fold; reported as 15.6 (95% CI 6.6 to 36.6).¹

Generally accepted risk factors for upper GI hemorrhage include a history of prior hemorrhage (relative risk 5.0; 95% CI 4.1-6.1), age greater than 80 years (relative risk 3.0; 95% CI 2.6-3.6), smoking, alcohol consumption, and the use of certain classes of medications, especially NSAIDs, glucocorticoids, and anticoagulants.⁶ In addition, the risk of NSAID-induced GI bleed is likely dose and duration dependent. Some clinicians employ gastroprotectant agents in at-risk patients including proton-pump inhibitors (PPIs), misoprostol, histamine-2 receptor blockers, and bismuth compounds, but the full magnitude of such protection has yet to be fully elucidated.

Although currently available information regarding the risk of GI hemorrhage with SSRIs is not overwhelming, it may still be advisable to review any history of prior upper GI bleeding before initiating

(Antidepressants continued on page 4)

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Appropriate Use of Non-aspirin Antiplatelet Agents

By Eliza Borzadek, PharmD and Chris Owens, PharmD

Non-aspirin anti-platelet agents and most notably clopidogrel (Plavix®) are being used with increasing frequency in routine medical practice. The reasons most often cited for this increased utilization include ASA allergy, gastrointestinal (GI) intolerance to ASA, or insufficient clinical response with ASA alone. In 2004, Idaho Medicaid spent over \$1.2 million on these agents, representing a cost increase of approximately 45% over the previous year. In 2004, clopidogrel alone represented about 84% of the total cost of non-aspirin antiplatelet agents and was ranked number 32 in terms of cost according to Idaho Medicaid records.

The GI tolerability of these agents relative to ASA has recently been questioned. A study by Chan et al. demonstrated that the risk of rebleeding in patients with prior GI ulceration due to ASA was greatly reduced when a proton pump inhibitor (PPI) was added to ASA therapy versus switching patients to clopidogrel.¹

Clopidogrel is the most prescribed of all non-ASA antiplatelet agents. In addition to its labeled indications, it has demon-

strated benefit in other conditions; most notably, it has become the standard of care for use in combination with aspirin after coronary stent placement.^{2,3,4}

Table II: Comparison of Anti-Platelet Agents on FDA-Approved Indications

Antiplatelet Agents	ACS	Stroke/		Post-Stent	IC	Generic Cost*	Brand Cost*
		TIA	PVD				
Aspirin	X	X				\$0.6-1.7	N/A
Clopidogrel (Plavix®)	X	X	X			N/A	\$ 15
Ticlopidine (Ticlid®)		X		X		\$86	\$145
Aspirin/ER Dipyridamole (Aggrenox®)		X				N/A	\$122
Cilostazol (Pletal®)					X	\$27	\$112

* Monthly cost based on prices obtained from www.drugstore.com on August 25, 2005. Abbreviations: ACS=acute coronary syndrome, TIA=transient ischemic attack, PVD=peripheral vascular disease, IC=intermittent claudication.

strated benefit in other conditions; most notably, it has become the standard of care for use in combination with aspirin after coronary stent placement.^{2,3,4}

Ticlopidine has fallen out of favor with many prescribers due to reports of life-threatening hematological adverse reactions including agranulocytosis, neutropenia, and thrombotic thrombocytopenic purpura. In addition, according to Beers' criteria, ticlopidine is often misused in elderly and should be avoided when possible in that population.⁵

Current ACCP guidelines (2004) recommend that patients with noncardioembolic stroke (atherothrombotic, lacunar or cryptogenic) or transient ischemic attack (TIA) receive treatment with aspirin (50-325 mg) daily, the combination of ASA/ER dipyridamole (25/200 mg) twice daily or clopidogrel (75 mg)

daily.² ACCP suggests the use of ASA/ER dipyridamole (preferred) or clopidogrel over aspirin.² According to the PCI-CURE trial, combination therapy with aspirin (75-325 mg) and clopidogrel after percutaneous coronary intervention (PCI) significantly reduced the incidence of the composite endpoint of cardiovascular death and MI at one year (p=0.002).³ The composite primary endpoint (death, MI, stroke) in the CREDO trial was significantly reduced at one year in patients treated with clopidogrel 300 mg x 1 then 75 mg and aspirin 325 mg for coronary stent placement (RR 0.73, 95% CI 0.57-0.95).⁴ As a general rule, CHEST guidelines recommend use of clopidogrel 75 mg po daily as an adjunct to aspirin for at least 6-12 months after coronary stent implantation, the treatment duration is variable and depends on the type of stent used.²

Aspirin is the mainstay of treatment in patients with acute coronary syndrome (non-ST-segment elevation MI or unstable angina). Aspirin 160-325 mg should be administered upon presentation and continued indefinitely at 75-162 mg daily.²

In patients with aspirin allergy or GI intolerance to aspirin, a loading dose of clopidogrel 300 mg followed by 75 mg daily indefinitely is recommended.^{2,6} However as previously mentioned, a recent study by Chan et al. demonstrated that the risk of rebleeding in patients with GI ulceration due to aspirin was greatly reduced when the PPI was added to aspirin therapy as compared with switching to clopidogrel.¹

Patients with symptomatic peripheral vascular disease are at high risk for vascular death due to coronary or cerebrovascular causes. According to the

ACCP guidelines, these patients should receive daily aspirin (160-325 mg) instead of clopidogrel.² Initiation of cilostazol is suggested in patients with disabling intermittent claudication unresponsive to conservative measures who also are not surgical candidates.²

In conclusion, both aspirin and non-ASA antiplatelet agents are the therapeutic mainstays for secondary prophylaxis of vascular disease. Aspirin has been the gold standard of antiplatelet therapy for many years and it is still considered a cost-effective first line of therapy for most patients. While the use of non-ASA antiplatelet agents beyond their FDA-approved indications may be appropriate, it is important to base such utilization upon quality medical evidence, ideally-ran-

Cost Corner: Migraine Treatment and Prophylaxis

by Brock Crystal, PharmD Candidate and Chris Owens, PharmD

Although the pathogenesis of migraine headache (MH) is unclear, it has been postulated that local vasodilation of cranial blood vessels and the release of vasoactive and pro-inflammatory peptides via serotonin (5-HT) receptor blockade play a role. Activation or agonism of these receptors has been shown to be beneficial in mitigating MH symptoms and this observation has resulted in the development of several pharmacologic agents with significant clinical utility in the treatment of MH, the class of drugs known as 5-HT receptor agonists or more commonly, the 'triptans'.^{1,2}

Triptan drugs are classified as 'abortive agents' in that they provide relief during acute migraine attacks, but lack the ability to prevent future headaches. Currently there are seven triptans available in the US: almotriptan (Axert®), eletriptan (Relpax®), frovatriptan (Frova®), naratriptan (Amerge®), rizatriptan (Maxalt®), sumatriptan (Imitrex®), and zolmitriptan (Zomig®). Although triptans have an established benefit in periodic acute MH therapy, excessive use of these drugs has been associated with significant problems including rebound or medication overuse headache and important economic concerns.³ In 2004, Idaho Medicaid spent nearly \$1 million on triptan drugs.

Besides drug costs, important quality of life issues are a major concern in patients suffering from MH. Studies have shown that patients with inadequately treated MH have more bedridden days per year than the general population and must restrict normal daily activities more often.⁴

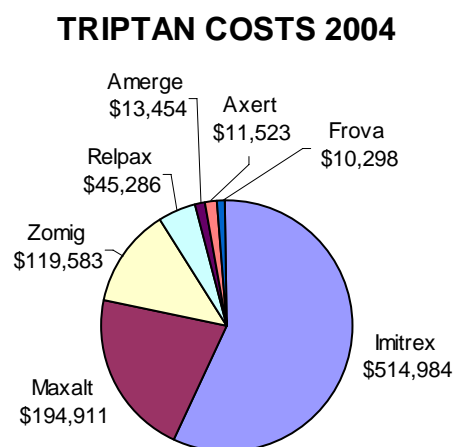
In addition to appropriate abortive therapy, another important issue for adequate treatment of MH involves prophylaxis of future headaches. Prevention is advocated by numerous headache organizations and guidelines regarding migraine prophylaxis have been published by the American Academy of Neurology.^{1,2} Established guidelines state that prophylactic treatment is warranted in the following circumstances:

- i) The frequency of migraines occurs two or more times per month
- ii) The patient experiences disabling headaches which occur less frequently but are unresponsive to usual abortive measures
- iii) Patients who have headaches that occur in a predictable pattern

To date, MH prophylactic agents found to be the most effective include amitriptyline, propranolol, divalproex sodium, verapamil, and topiramate.^{5,6} Although tolerability of many of these agents can often be problematic for patients, it is important to offer therapy for individuals meeting established criteria and counsel patients on the risk of adverse effects and ways to minimize them. Of note, a review of the Idaho Medicaid DUR database indicated that approximately 1,900 patients in the

state received a least one prescription for a triptan drug in 2003. Of these, about 280 patients were using a triptan on a regular basis. Interestingly, only about 11 percent of regular triptan users were also on prophylactic therapy.

In summary, migraine headache is a common, often incapacitating disorder associated with a variety of quality of life issues, personal and societal burdens, and significant economic concerns. Available abortive therapy is effective, but frequent use



can lead to adverse outcomes. Prophylactic therapy is indicated for frequent sufferers and can result in improved patient functioning and cost savings. The treatment of migraines is patient-specific and should be undertaken as a collaborative effort with frequent follow-up and patient input regarding therapy selection and evaluation.

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WHAT'S INSIDE!

Antidepressants and GI Hemorrhage
Cost Corner: Migraine Treatment and Prophylaxis
Appropriate Use of Non-aspirin Antiplatelet Agents

Antidepressants

(continued from page 1)

treatment with a serotonergic antidepressant. Also, it would be prudent to review any known or suspected GI risk factors including smoking, alcohol consumption, and use of other medications. Concurrent chronic use of an SSRI and an NSAID is best avoided when possible. For patients who must take serotonergic antidepressants chronically, alone or in combination with NSAIDs, increased monitoring for signs of upper GI hemorrhage is recommended, with consideration given to concurrent use of a PPI or other gastroprotective agent in high-risk patients.

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Anti-platelet Agents

(continued from page 2)

domized controlled trials. Based on the adverse event profile alone, clopidogrel is safer than ticlopidine. Safety profile of clopidogrel is similar to medium dose aspirin.⁷ When a combination of clopidogrel and aspirin is used, it may be prudent to use aspirin 75-100 mg to minimize the bleeding risk. In patients who suffer a GI bleed while on aspirin, the addition of a PPI is likely safer than switching to clopidogrel.¹

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