Formulary Forum

Aggrenox: A Fixed-Dose Combination of Aspirin and Dipyridamole

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OBJECTIVE: To describe the pharmacology, pharmacokinetics, efficacy, and safety of a fixed-dose combination of aspirin and extended-release (ER) dipyridamole indicated for the secondary prevention of stroke.

DATA SOURCES: Published articles and abstracts were identified from a MEDLINE search (1966–December 1999) using the search terms dipyridamole, aspirin, antiplatelet, antiaggregation, and stroke prevention. Pertinent articles written in English were considered for review. Additional articles were identified from the references of retrieved literature.

STUDY SELECTION AND DATA EXTRACTION: Studies including a combination of aspirin/dipyridamole in human subjects were evaluated. Emphasis was placed on randomized, controlled trials.

DATA SYNTHESIS: Aspirin is a platelet inhibitor that works by inhibiting platelet cyclooxygenase, which reduces the production of thromboxane A_2. Dipyridamole is a platelet inhibitor that is thought to work in part by inhibiting platelet cyclic-3′,5′-adenosine monophosphate and cyclic-3′,5′-guanosine monophosphate phosphodiesterase. The active metabolite of aspirin, salicylic acid, is highly bound to plasma protein and has a plasma half-life of two to three hours. Dipyridamole is also highly bound to plasma proteins, and the ER formulation has a plasma half-life of 13 hours. The first European Stroke Prevention Study (ESPS-1) found the combination of aspirin/dipyridamole to be superior to placebo in the prevention of stroke and transient ischemic attack (TIA). The ESPS-1, however, did not include an aspirin-only treatment arm. Therefore, it was unclear whether the combination of aspirin/dipyridamole was superior to aspirin alone. As a result, a second trial was conducted that included treatment arms of aspirin alone, ER dipyridamole alone, combination therapy, and placebo. The combination of aspirin 25 mg plus ER dipyridamole 200 mg twice daily was shown in the ESPS-2 to be significantly better than either agent given individually in preventing stroke and TIAs ($p < 0.001$).

CONCLUSIONS: The American College of Chest Physicians (ACCP) recommends aspirin 50–325 mg/d to be the initial antiplatelet of choice for the prevention of atherothrombotic cerebral ischemic events. However, with the favorable results of the ESPS-2, it may be appropriate to substitute aspirin/ER dipyridamole for aspirin alone as the drug of choice. This combination appears to have a favorable adverse effect profile. The relative effectiveness of aspirin/ER dipyridamole compared with clopidogrel and ticlopidine has yet to be determined. If alternative antiplatelet therapy is needed, the ACCP recommends clopidogrel rather than ticlopidine because of its lower incidence of adverse effects. The ACCP further states that the combination of aspirin plus dipyridamole may be more effective than clopidogrel; these agents have a similarly favorable adverse effect profile.

KEY WORDS: aspirin, dipyridamole, antiplatelet, stroke prevention.

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In the US, stroke is the third leading cause of death. Approximately 730 000 people experience stroke annually, with an estimated 4 million survivors alive today.[1-3] The economic burden that results from stroke is enormous, estimated to be as much $43.3 billion in 1998.[2,4] Twenty percent of stroke survivors will experience another stroke.[1] Therefore, secondary prevention of cerebrovascular disease leading to stroke is the primary objective in reducing the disability and mortality associated with this disease.[5,6]

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Aspirin/dipyridamole (Aggrenox, Boehringer Ingelheim, Ridgefield, CT)

Stroke results from different pathophysiologic mechanisms.[2] While 15% of strokes can be categorized as hemorrhagic, the remaining 85% are thromboembolic (ischemic), caused largely by atherosclerosis. Atherosclerosis at the bifurcation of the carotid artery can cause stroke through embolization or decreased perfusion secondary to acute thrombosis. Thrombus formation can eventually lead to vessel occlusion, which in turn results in stroke.

There are three options available for ischemic stroke prevention following a transient ischemic attack (TIA) or stroke. These options include revascularization (carotid endarterectomy or angioplasty), anticoagulation (warfarin), and antiplatelet therapy.[7,8] Aspirin is certainly the most widely studied antiplatelet agent and, until recently, was the only antiplatelet drug widely used to prevent stroke.[7] In the last few years, however, other antiplatelet drugs have been made available. Ticlopidine and clopidogrel have been shown to prevent stroke more effectively than aspirin.[7,9,10] A third antiplatelet alternative, dipyridamole, has been shown to be more effective than placebo in reducing the risk of stroke.[7] However, when dipyridamole is administered in combination with aspirin, the additive result is significantly more effective at reducing the risk of stroke than either agent administered alone.[11]

Aggrenox is a combination of aspirin and dipyridamole.[12] It is available as a hard gelatin capsule that contains dipyridamole 200 mg in an extended-release (ER) form and aspirin 25 mg in an immediate-release form. Aggrenox is indicated to reduce the risk of stroke in patients who have had TIA or a completed ischemic stroke due to thrombosis.

Pharmacology

Medical management of patients with TIA has traditionally included antiplatelet therapy. Antiplatelet agents prevent the formation of thrombi and emboli by interfering with platelet aggregation. Different antiplatelet agents interfere with platelet aggregation at different steps in the pathway.[13] Aspirin, the most widely used platelet inhibitor to prevent recurrent TIAs and stroke, works by irreversibly inhibiting platelet cyclooxygenase, which then inhibits the formation of thromboxane A_2 (TXA_2).[14] TXA_2 is a prostaglandin derivative that has been shown to be a potent vasoconstrictor and inducer of platelet aggregation and the platelet-release reaction.[13,15]

Dipyridamole's mechanism of action as a platelet inhibitor is not fully understood. A number of possibilities, however, have been suggested. Dipyridamole may work by increasing platelet cyclic-3′,5′-adenosine monophosphate (cAMP) concentrations through inhibition of adenosine uptake into platelets.[12] Increasing concentrations of cAMP affect platelet-activating factor, collagen, and adenosine diphosphate to inhibit platelet aggregation.[12,16,17] Dipyridamole also inhibits platelet cyclic-3′,5′-guanosine monophosphate (cGMP) phosphodiesterase, which, in turn, inhibits platelet activation and aggregation.[12] Dipyridamole also stimulates prostacyclin synthesis and potentiates the antiplatelet effects of prostacyclin.[16,18]

Pharmacokinetics

The pharmacokinetic data of aspirin and dipyridamole are addressed separately in this section. It should be noted, however, that coadministration of aspirin and dipyridamole does not affect the kinetics of either drug.

ASPIRIN

Aspirin is completely absorbed following oral administration. Absorption is rapid in the absence of food (0.8 h), but is slowed when administered with food (5.6 h).[19] During the absorption process, aspirin is partially hydrolyzed to salicylic acid and distributed to all body tissues and fluids, including breast milk and the central nervous system. After the administration of a 50-mg daily dose (given as 2 doses of 25 mg) of aspirin, the peak plasma concentration occurs at 0.63 hours (0.5–1).[12] Peak plasma concentrations at steady-state average 320 ng/mL (range 175–463).

Although aspirin is poorly bound to plasma protein, its metabolite (salicylic acid) has a high affinity for plasma proteins. This affinity is concentration-dependent, resulting in 90% binding at low concentrations (<100 µg/mL) and 76% binding at higher concentrations (400 µg/mL). Aspirin has a volume of distribution of 0.15 L/kg.[20]

Aspirin is hydrolyzed to salicylic acid in the plasma. The plasma half-life of aspirin is approximately 15–20 minutes and the plasma half-life of salicylic acid is approximately two to three hours at low dosages. Following very high dosages (10–20 g), the plasma half-life of salicylic acid can increase to >20 hours.[12,20] Aspirin is primarily conjugated in the liver and eliminated through first-order kinetics by the kidney.[12] Renal excretion of aspirin depends on urinary pH. As the urinary pH increases to >6.5, the renal clearance of unbound ionized salicylate increases from 2% to >80%.[12,20] Approximately 75% of aspirin is excreted in the urine as salicyluric acid, with 10% excreted as salicylic acid. The remaining is excreted in the urine as phenolic and acyl glucuronides.[12]

DIPYRIDAMOLE

Peak plasma concentrations are achieved in approximately two hours (range 1–6) following oral administration of dipyridamole at a daily dose of 400 mg (200 mg twice daily).[12,21-24] Oral bioavailability is 37–66%, with a steady-state volume of distribution of 2.4–3.4 L/kg.[21,23,25] Although dipyridamole is very lipophylic, it does not cross the blood–brain barrier to any significant degree and it is highly bound to plasma proteins (~99%).[12]

Following intravenous administration, the plasma concentration of dipyridamole is considered to be triphasic. The α half-life (the initial decline in plasma concentration following peak concentration) is approximately 3.5 min-

utes. The β phase has a half-life of around 40 minutes, which requires the immediate-release formulation to be dosed four times a day.[12,20,23,26] Dipyridamole has also been reported to have a prolonged elimination phase, with a half-life of 15.5 hours. Due to the ER component of dipyridamole in the Aggrenox formulation, only the terminal phase is apparent, which is reported[12] to have a half-life of approximately 13.6 hours.

Dipyridamole is metabolized in the liver; it is conjugated with glucuronic acid to form monoglucuronide, the primary metabolite. Partial enterohepatic circulation occurs with monoglucuronide, but most of the glucuronide metabolite (95%) is excreted through the bile into the feces.[12] Five percent of the glucuronide metabolite is eliminated through the kidneys.

Clinical Studies

Dipyridamole has been studied as an antiplatelet agent since the mid-1960s.[27] Early trials to prove its efficacy as a single agent compared with aspirin were not favorable and patients taking dipyridamole often experienced more adverse effects.[28,29] Dipyridamole as an immediate-release formulation requires four-times daily dosing to maintain adequate blood concentrations. As a result, researchers began administering dipyridamole with aspirin to see whether the combination would have a synergistic effect. An ER formulation of dipyridamole was then developed to maintain appropriate blood concentrations with twice-daily dosing.

Very few trials have evaluated the efficacy of aspirin plus dipyridamole as combined therapy for the prevention of stroke in patients with cerebrovascular disease. Until 1996, no studies were published that compared the aspirin/dipyridamole combination with aspirin alone, the standard therapy. All other trials of combination therapy either did not show efficacy or were compared only against placebo.

The AICLA (Accidents Ischemiques Cerebraux Lies a l'Atherosclerose) trial[30] was designed to determine whether aspirin 1 g/d or aspirin 1 g/d plus dipyridamole 225 mg/d would produce a significant reduction in fatal and nonfatal cerebral infarction compared with placebo. This study was double-blind, randomized, and placebo-controlled. Six hundred four patients who had experienced at least one atherothrombotic ischemic event in the preceding year were entered. Sixteen percent of the patients qualified for the study with a TIA and 84% qualified following a completed stroke. The subjects were followed for one year.

The results of the AICLA trial, with respect to recurrence of ischemic stroke, showed aspirin (15%, 31/204 pts.) to work significantly better than placebo (8.5%, 17/198 pts.) ($p < 0.05$). The aspirin/dipyridamole group (9%, 18/202) did not show a significant difference when compared with placebo in the prevention of recurring stroke, but did have a strong trend favoring the combination ($p < 0.06$). Likewise, no significant difference was reported when comparing the aspirin group with the aspirin/dipyridamole group (significance not reported) in the secondary prevention of stroke.[30]

Forty-one patients (7%) were withdrawn from the study as a result of adverse effects of the drugs; six (15%) of these patients were in the placebo group, 17 (41%) in the aspirin group, and 18 (44%) in the aspirin/dipyridamole group ($p < 0.03$). Peptic ulcers, gastrointestinal bleeding, and other hemorrhages were the major complications, which occurred predominately in the two treatment groups ($p < 0.01$); none of the complications were fatal. There were no differences in mortality between the three groups. The authors of the AICLA trial concluded that 1 g/d of aspirin could provide significant prevention against recurrent stroke and TIA.[30]

The American–Canadian Co-Operative Study Group (ACCSG)[31] designed a trial to determine whether persons with a history of TIA would have a lower risk of stroke, retinal infarction, or death if they took a combination of aspirin 325 mg plus dipyridamole 75 mg four times daily in comparison with aspirin 325 mg four times daily. This double-blind, randomized trial enrolled 890 patients; 90% of the subjects were followed for at least one year.

The results of this study indicated that, one year after randomization and at the end of the study, the two groups were nearly identical with respect to the number of events that had occurred. Statistical analysis showed no significant difference, in all end points combined, between aspirin alone and aspirin plus dipyridamole ($p = 0.89$). Forty-three percent ($n = 382$) of the subjects stopped taking the study drug before completion of the study. The difference in adverse event rates between the two groups (43% aspirin vs. 44% aspirin/dipyridamole) was not statistically significant.[31]

These clinical trials[30,31] failed to demonstrate the benefit of using a combination of aspirin and dipyridamole over aspirin alone in the secondary prevention of TIA and stroke. Limitations included a small number of subjects and high dropout rates.

The first European Stroke Prevention Study (ESPS-1)[32] evaluated 2500 patients who previously had TIA, reversible ischemic neurologic deficits, or completed strokes. The objective of the ESPS-1 was to compare administration of dipyridamole 75 mg three times daily and aspirin 330 mg three times daily with placebo in the prevention of recurrent ischemic stroke. This randomized, double-blind study had a follow-up period of two years.

The combination of aspirin plus dipyridamole proved to be significantly more effective than placebo in preventing stroke (both fatal and nonfatal) ($p < 0.001$), death ($p < 0.01$), and all end points combined ($p < 0.01$). Thirteen percent ($n = 164$) of the aspirin/dipyridamole group versus 7% (84) of the placebo group dropped out of the study due to adverse drug effects ($p < 0.001$).[32]

The ESPS-1[32] showed that the combination of aspirin and dipyridamole was more effective than placebo in preventing stroke. This information, however, did not add new information regarding stroke prevention because it was already known that aspirin was superior to placebo in stroke prevention. As a result, the second European Stroke Prevention Study (ESPS-2)[33] was initiated in 1996 to as-

sess the effectiveness of ER dipyridamole plus low-dose aspirin in the prevention of stroke versus each drug given alone. A secondary objective was to determine whether low-dose aspirin was safe and effective.

The study randomized 6602 subjects equally into four treatment arms: placebo, aspirin 25 mg twice daily, ER dipyridamole 200 mg twice daily, and the combination of aspirin 25 mg plus ER dipyridamole 200 mg twice daily. Patients were eligible for entry if they had experienced a TIA or completed ischemic stroke within the previous three months. This study was multicentered, randomized, double-blind, and placebo-controlled, with a two-year follow-up period. The primary end points of the study were stroke, death from all causes, and stroke and/or death from all causes.[33]

Seventy-six percent (n = 5038) of the patients entering the study had experienced a previous ischemic stroke and 24% (1562) qualified for the study based on a prior TIA. The mean age was 67 years, with 58% (3828) of the subjects being male. Sixty-one percent (3997) of the patients had preexisting hypertension and 35% had ischemic heart disease.[33]

Consistent with the results of the ESPS-1, ESPS-2[33] showed a relative risk reduction of stroke of 37% ($p < 0.001$) with the aspirin/ER dipyridamole group compared with placebo. However, the ESPS-2 revealed an absolute risk reduction of stroke (fatal and nonfatal) of the combination group versus the aspirin group of 3%, with a relative risk reduction of 23% ($p = 0.006$). The absolute risk reduction of stroke (fatal and nonfatal) of the combination group compared with the dipyridamole group was also 3%, with a relative risk reduction of 24.7% ($p = 0.002$). It should be noted that although there was a decrease in the recurrence of stroke, there was no statistical significance between the four treatment groups regarding the effect of treatment on total mortality.[33,34]

The ESPS-2 was further evaluated[34] to look at new strokes that had occurred throughout the study. It was concluded that none of the antiplatelet drugs (aspirin, dipyridamole, combination therapy) decreased the severity of recurrent strokes. However, there was a trend that showed aspirin/ER dipyridamole therapy may lengthen the time the patient remains free from recurrent stroke. The mean time to the stroke end point occurred at 286 days for the placebo and dipyridamole groups and at 308 days for the aspirin group; this compares with 343 days for the combination group ($p = 0.057$).

The authors of the report on ESPS-2 reached the following conclusions.[35] First, aspirin alone and ER dipyridamole alone showed equal efficacy for the secondary prevention of stroke and TIA. When aspirin and ER dipyridamole are combined, the effects are additive and are more effective than either agent administered alone. The ESPS-2 was the first to show that the additive effect of aspirin and dipyridamole was superior to that of aspirin alone (Table 1).[30-33]

Prior to 1996, no study results had been published showing that combination aspirin/dipyridamole therapy was more effective than aspirin alone. The AICLA[30] and ACCSG[31] trials did compare the combination with aspirin alone, but at dosages of dipyridamole that were lower than those used in the ESPS-2.[33] The ESPS-2 is a landmark trial because it is the only one comparing the combination of aspirin and ER dipyridamole with aspirin alone and showing that the combination is more effective. This finding is important because ESPS-2 is the only trial showing that two antiplatelet agents given together can have an additive effect. It is therefore possible that other antiplatelet combinations may exist that will also prove to have better outcomes in secondary prevention of stroke than either agent given alone.

Adverse Effects

The results of the ESPS-2[33] may be the best indicator of the frequency and type of adverse events associated with Aggrenox, since this is the only published trial using the same dosing regimen as that of the Aggrenox product. Table 2[33,36] summarizes the adverse events that occurred in the ESPS-2. Common adverse events ranged from headache, dizziness, and gastrointestinal disturbances (dyspepsia, diarrhea, nausea) to serious bleeding events.[12,33,35] The addition of dipyridamole to aspirin results in a bleeding risk similar to that of aspirin alone. The overall incidence of dose-limiting adverse effects with aspirin/dipyridamole is very similar compared with dipyridamole alone (Table 2).

Drug Interactions

Currently, no drug–drug interaction studies have been conducted with Aggrenox. The potential interactions that

Table 1. Summary of Clinical Trials for Aspirin/Dipyridamole Combination

Reference	Pts. (n)	Dose (mg/d)		Significant Difference		Length of Study (mo)
		Aspirin	Dipyridamole	vs. Placebo	vs. Aspirin	
AICLA[30]	604	990	225	no ($p < 0.06$)	no	12
ACCSG[31]	890	1300	300	NA[a]	no ($p = 0.89$)	12
ESPS-1[32]	2500	990	225	yes ($p < 0.01$)	NA[b]	24
ESPS-2[33]	6602	50	400	yes ($p < 0.001$)	yes ($p = 0.006$)	24

ACCSG = American–Canadian Co-Operative Study Group; AICLA = Accidents Ischemiques Cerebraux Lies a l'Atherosclerose; ESPS-1 = European Stroke Prevention Study — One; ESPS-2 = European Stroke Prevention Study — Two; NA = not applicable.
[a]No placebo group involved.
[b]Combination of aspirin/dipyridamole was only compared against placebo.

exist with Aggrenox are the same as those previously reported for aspirin and dipyridamole as separate drugs. Drug–drug interactions with dipyridamole include adenosine and cholinesterase inhibitors (tacrine, donepezil). Drug–drug interactions with aspirin include angiotensin-converting enzyme inhibitors, acetazolamide, anticoagulants (warfarin, heparin), anticonvulsants (phenytoin, valproic acid), β-blocking agents, diuretics, methotrexate, nonsteroidal antiinflammatory drugs, oral hypoglycemics, and uricosuric agents (probenecid, sulfinpyrazone).[12,20,21]

Contraindications

Aggrenox is contraindicated in patients with hypersensitivity to dipyridamole or aspirin. Aspirin hypersensitivity generally presents with the triad of symptoms that includes asthma, rhinitis, and nasal polyps. Therefore, aspirin has a relative contraindication in patients with these symptoms. Aspirin is also contraindicated in patients with a known allergy to nonsteroidal antiinflammatory drugs.[12] Aspirin should not be given to children or teenagers with viral infections because of the risk of Reye's syndrome. Aspirin should also be avoided in patients with a history of gastrointestinal disturbances such as bleeding or peptic ulcer disease, as it may worsen their condition. No other contraindications currently exist for dipyridamole.

Special Populations

Caution should be used when administering Aggrenox to pregnant or nursing women since there have been no adequate studies with Aggrenox in this population. Aspirin and dipyridamole are classified as pregnancy category D and B agents, respectively. Aggrenox should only be used in pregnant women if the benefits outweigh the risks. Both dipyridamole and aspirin are excreted in breast milk; therefore, caution should be used when administering Aggrenox to nursing mothers.[12]

Aggrenox is not recommended for children and teenagers, since its efficacy and safety have not been studied in this population. As stated above, Aggrenox should not be administered in the pediatric population during viral infections because of the risk of Reye's syndrome.

The elderly population should be dosed the same as younger patients. The age distribution in the ESPS-2 showed that 60% of the participants were ≥65 years old. Aggrenox was shown to be safe and effective in older as well as younger patients.[12]

Therapeutic Issues

Until recently, the number of antiplatelet agents available has been limited. Aspirin is the most widely used and studied of the antiplatelet agents. The Antiplatelet Trialist meta-analysis[36] showed that aspirin reduced the odds of the composite outcome of stroke, myocardial infarction (MI), or vascular death in all high-risk patients with symptomatic atherosclerosis by 25%. Aspirin has also been shown to reduce the odds of stroke by 30%. The Food and Drug Administration and the American College of Chest Physicians (ACCP) recommend the use of aspirin for secondary stroke prevention. The dosage of aspirin that each agency recommends is between 50 and 325 mg/d. Aspirin is inexpensive, but is associated with some risk of bleeding; lower dosages, however, have been associated with a decreased risk of bleeding.

Other oral antiplatelet agents include ticlopidine and clopidogrel. Ticlopidine is a thienopyridine agent that inhibits adenosine diphosphate. Adenosine diphosphate induces fibrinogen binding to platelets, which is a necessary step in the platelet aggregation process.[7,20,21] The Ticlopidine Aspirin Stroke Study (TASS)[9] demonstrated that ticlopidine 250 mg twice daily was associated with a 21% greater relative risk reduction for stroke than aspirin 650 mg twice daily. Ticlopidine appeared to be approximately 10% better than aspirin in reducing the composite outcome of stroke, MI, or vascular death. The Canadian American Ticlopidine Study (CATS)[37] concluded that ticlopidine 250 mg twice daily reduced the relative risk of stroke, MI, or vascular death by 30% compared with placebo. Ticlopidine, however, is associated with a clinically important incidence of neutropenia, dermatologic reactions, and thrombotic thrombocytopenia purpura.[7]

Clopidogrel is a thienopyridine derivative similar to ticlopidine. Clopidogrel also inhibits platelet aggregation by inhibiting adenosine diphosphate. The antithrombotic effect of clopidogrel was evaluated in the CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) study.[10] Patients receiving clopidogrel 75 mg/d showed a relative risk reduction of ischemic stroke, MI, or vascular death of 9.4% compared with aspirin 325 mg/d. This is similar to the results seen with ticlopidine in

Table 2. Percentage of Patients Experiencing Adverse Events[33,36]

Adverse Event	Treatment Groups: Dipyridamole plus Aspirin (n = 1650)	Aspirin (n = 1649)	Dipyridamole (n = 1654)	Placebo (n = 1649)
Headache	38	33	37	32
Bleeding				
overall	9	8	5	5
leading to drug discontinuation	1.3	1.2	0.2	0.3
Gastrointestinal disturbances	33	30	31	28
Dizziness	30	29	30	31
Any adverse events leading to drug discontinuation	16	8.5	15	7.7
Any adverse event	64	60	63	57

the TASS. Clopidogrel, however, does have a better safety profile than ticlopidine, especially related to hematologic toxicity. The CAPRIE study showed no major differences between clopidogrel and aspirin in terms of safety and adverse events.

Ticlopidine, clopidogrel, and the combination of aspirin/dipyridamole have all been directly compared with aspirin in clinical trials. There have not, however, been any studies that directly compare these agents with each other. Because of this, therapeutic decisions as to which of these antiplatelet agents is most appropriate for use should be based on contraindications, drug–drug interactions, adverse effect profile, cost of therapy, and the data that are available comparing each agent with aspirin. A summary of the trials that compare the relative risk reduction of these antiplatelet agents with aspirin is shown in Table 3.[9,10,33] The cost of these drugs is shown in Table 4.[38]

The 1998 Fifth ACCP Consensus Conference on Antithrombotic Therapy[7] guidelines recommend that every patient who has experienced a stroke or TIA receive an antiplatelet agent as secondary stroke prevention unless there are contraindications. Aspirin 50–325 mg/d should be the initial treatment of choice. If aspirin is contraindicated, an alternative agent should be used. The ACCP recommends using clopidogrel over ticlopidine because of its more favorable adverse effect profile. It also states that the combination of aspirin plus ER dipyridamole may be more effective than clopidogrel and has a similarly favorable adverse effect profile.

Summary

The prevention of cerebrovascular disease leading to recurring stroke is the primary objective in reducing the number of strokes that occur each year. The standard dosage of aspirin used in the US is 81 mg or 325 mg/d. No studies have compared Aggrenox with these dosages of aspirin; therefore, we cannot say for certain that Aggrenox is more effective than the standard dose of aspirin. However, the combination of aspirin 25 mg plus ER dipyridamole 200 mg given twice daily has been shown to be more effective at preventing stroke than either agent given alone at these same dosages. The dosage of aspirin that the ACCP recommends (50–325 mg/d) as the initial treatment of choice for secondary stroke prevention encases the amount of aspirin in the Aggrenox formulation, as well as standard dosage of aspirin used in the US. In light of this information, there is still a question as to which therapy is most effective for the secondary prevention of stroke. Aspirin 81 or 325 mg/d is certainly effective at reducing the risk of recurring stroke and is, by far, the least-expensive antiplatelet agent available. The ESPS-2, however, does offer some hope that other antiplatelet combinations may exist and prove to be synergistic and provide superior protection against recurring stroke. Further research may answer this question. For now, aspirin alone appears to still be the initial agent of choice for the secondary prevention of stroke if the patient has no contraindications to aspirin.

Table 4. Cost Comparison of Antiplatelet Agents[38]

Drug	Approximate AWP/30 Days ($)
Aggrenox (aspirin 25 mg/ dipyridamole 200 mg bid)	88.50
Aspirin (81–325 mg/d)	0.80
Dipyridamole (75 mg tid)	28.00
Ticlid (ticlopidine 250 mg bid)	120.00
Plavix (clopidogrel 75 mg/d)	90.00

AWP = average wholesale price.

Table 3. Relative Risk Reduction of Antiplatelet Agents Compared with Aspirin

Relative Risk Reduction	TASS[9] (ticlopidine) (n = 3069)	CAPRIE[10] (clopidogrel) (n = 6431)	ESPS-2[33] (aspirin/dipyridamole) (n = 3299)
Stroke	21%	7.3%	23.1%
(95% CI)	(4% to 38%)	(–5.7% to 18.7%)	(NA)
p value	0.024	0.26	0.006
All events (stroke/MI/ vascular death)	12.0%	8.7%	12.9%
(95% CI)	(–2% to 26%)	(0.3% to 16.5%)	(NA)
p value	0.048	0.043	0.056

CAPRIE = Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; ESPS-2 = European Stroke Prevention Study — Two; MI = myocardial infarction; NA = not applicable; TASS = Ticlopidine Aspirin Stroke Study.

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EXTRACTO

OBJETIVO: Describir la farmacología, farmacocinética, eficacia, y seguridad de una combinación de dosis fija de aspirina con dipiridamole de liberación extendida (LE), indicada para la prevención de apoplegía.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda computadorizada con MEDLINE de la literatura (1966–1999) utilizando los términos dipiridamole, aspirina, antiplaquetarios, antiagregación, y prevención de apoplegía. Se consideraron para la revisión los artículos pertinentes escritos en inglés. Se identificaron otros artículos de las referencias de la literatura seleccionada. Se evaluaron los estudios que incluyeron la combinación de aspirina/dipiridamole en humanos.

SÍNTESIS: Aspirina es un inhibidor de plaquetas que trabaja inhibiendo la cyclooxigenasa de plaquetas que reduce la producción de tromboxano A_2. Dipiridamole es un inhibidor de plaquetas que se cree trabaja inhibiendo las fosfodiesterasas cAMP y cGMP de las plaquetas. El metabolito activo de aspirina, ácido salicílico, está altamente enlazado a las proteínas del plasma y tiene una vida media plasmática de dos a tres horas. Dipiridamole está también altamente enlazado a las proteínas del plasma y la formulación LE tiene una vida media plasmática de 13 horas. El Estudio Europeo para la Prevención de Apoplegía (ESPS-1) encontró que la combinación de aspirina/dipiridamole fue superior a placebo en la prevención de apoplegía y ataques isquémicos transitorios (TIA). Este estudio, sin embargo, no incluyó un brazo de tratamiento con aspirina solamente. Por lo tanto, no estaba claro si la combinación de aspirina/dipiridamole era superior a aspirina sola. Como resultado, se realizó un segundo estudio que incluyó tratamiento con aspirina solamente, dipiridamole-LE solamente, terapia de combinación, y placebo. El ESPS-2 demostró que la combinación de aspirina 25 mg/dipiridamole-LE 200 mg BID fue significativamente mejor que los agentes individuales en prevenir apoplegías y TIAs ($p < 0.001$).

CONCLUSIONES: El Colegio Americano de Médicos Torácicos (CAMT) recomienda aspirina 50 mg a 325 mg diarios como antiplaquetario de primera selección en la prevención de eventos isquémicos aterotrombóticos cerebrales. Sin embargo, con los resultados favorables del ESPS-2, no sería inapropiado sustituir la combinación aspirina/dipiridamole-LE por aspirina solamente como el agente de elección. Esta combinación aparenta tener un perfil de efectos secundarios favorable. La efectividad relativa de aspirina/dipiridamole-LE comparada con ticlopidina y clopidogrel aún está por determinarse. Como terapia antiplaquetaria alterna, el CAMT recomienda clopidogrel sobre ticlopidina debido a una incidencia menor de efectos adversos. El CAMT establece que la combinación de aspirina con dipiridamole podría ser más efectiva que clopidogrel con un perfil similar de efectos secundarios.

Giselle C Rivera-Miranda

RÉSUMÉ

OBJECTIF: Décrire la pharmacologie, la pharmacocinétique, l'efficacité, et la sécurité d'emploi d'une association fixe d'aspirine et de dipyridamole à libération prolongée (LP), indiquée dans la prévention secondaire des accidents vasculaires cérébraux (AVC).

REVUE DE LITTÉRATURE: Les articles et résumés publiés ont été identifiés à partir d'une recherche MEDLINE (1966–1999) en utilisant les termes de recherche dipyridamole, aspirine, antiplaquettaire, antiagrégant, et prévention des AVC. Les articles pertinents écrits en anglais ont été retenus pour analyse. Des articles supplémentaires ont été identifiés à partir des références issues de la littérature obtenue.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Les études comprenant l'association aspirine/dipyridamole chez l'homme ont été évaluées.

RÉSUMÉ: L'aspirine est un inhibiteur plaquettaire qui agit en inhibant la cyclooxygénase plaquettaire, ce qui réduit la production de thromboxane

A_2. Le dipyridamole est un inhibiteur plaquettaire supposé agir en partie en inhibant la phosphodiestérase de l'AMPc et GMPc. Le métabolite actif de l'aspirine, l'acide salicylique, est fortement lié aux protéines plasmatiques et a une demi-vie plasmatique de deux à trois heures. Le dipyridamole est également fortement lié aux protéines plasmatiques et la formulation LP a une demi-vie plasmatique de 13 heures. L'Etude Européenne de Prévention des AVC (ESPS-1) a montré que l'association aspirine/dipyridamole était supérieure au placebo dans la prévention des AVC et des accidents ischémiques transitoires (AIT). Cependant, l'essai ESPS-1 ne comportait pas de bras de traitement par aspirine seule. De ce fait, on ne savait pas bien si l'association aspirine/dipyridamole était supérieure à l'aspirine seule, le dipyridamole LP seul, le traitement combiné, et le placebo. L'association de 25 mg d'aspirine avec 200 mg de dipyridamole LP deux fois par jour s'est révélée dans l'essai ESPS-2 significativement meilleure que chacune des molécules prises individuellement dans la prévention des AVC et des AIT ($p < 0.001$).

CONCLUSIONS: L'American College of Chest Physicians (ACCP) recommande l'aspirine à la dose de 50 à 325 mg par jour comme traitement antiagrégant de choix dans la prévention des accidents ischémiques cérébraux athérothrombotiques. Cependant, suite aux résultats favorables de l'essai ESPS-2, il peut ne pas être inapproprié de substituer l'association aspirine/dipyridamole LP à l'aspirine seule comme médicament de choix. Cette association se révèle avoir un profil d'effets indésirables favorables. Il reste encore à déterminer l'efficacité relative de l'association aspirine/dipyridamole LP par rapport au clopidrogel et à la ticlopidine. Si une alternative thérapeutique est nécessaire, l'ACCP recommande le clopidrogel de préférence à la ticlopidine en raison de sa plus faible incidence d'effets indésirables. De plus, l'ACCP considère que l'association aspirine/dipyridamole peut être plus efficace que le clopidrogel avec un profil favorable d'effets secondaires comparable.

Michel Le Duff