The Significance of Optimized Formulation for Dipyridamole in Stroke Risk Reduction

a report by

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Stroke is a serious, common, age-related health problem that ranks as the third highest cause of mortality in the US, behind heart disease and cancer. Convincing evidence from numerous clinical investigations has been available for more than a decade showing that antiplatelet agents can be effective in preventing recurrent stroke.[1–3] It is now widely accepted that treatment for patients who survive ischemic stroke as well as for patients with history of transient ischemic attack (TIA) should usually include antiplatelet therapy to prevent recurrent episodes. However, the selection of any one antiplatelet agent from among those commonly available, including aspirin, dipyridamole, and the thienopyridine agents ticlopidine and clopidogrel, is a topic of considerable discussion. Indeed, a literature search for journal articles published during the last three years using the key words 'stroke prevention' and 'antiplatelet' returned 280 publications on this important topic. Integrating the available information to identify the most appropriate antiplatelet agent for an individual patient is not a trivial task for the prescribing clinician, who must factor not only efficacy and safety, but also compliance and often cost, into the decision-making process. The following article considers the advantages of the most common antiplatelet agents and discusses factors that should be considered when selecting a dipyridamole formulation.

Aspirin has been recognized for several decades as effective in preventing recurrent stroke;[4,5] however, the optimized dosing regimen remains a topic for debate.[6] Aspirin acts as an irreversible inhibitor of cyclo-oxygenases (COX-1, present in platelets) by irreversibly acetylating a serine residue near the COX-1 catalytic site to block arachidonic acid access to the catalytic site. This mechanism blocks the formation of thromboxane A_2, which usually causes platelets to change shape, release granules, and aggregate to maintain hemostasis. The prolonged seven- to 10-day effect of aspirin on platelet function corresponds to the average lifespan of platelets that lack the ability to replace inactivated COX-1 due to the absence of a nucleus and *de novo* protein synthesis capacity.[7] Low-dose aspirin effectively decreases serum thromboxane concentrations, and as little as 40mg administered every third day was shown to result in a 50% decrease in thromboxane.[8]

The thienopyridines ticlopidine and clopidogrel exert antiplatelet activity after bioactivation to active agents that irreversibly bind to the platelet membrane adenosine diphosphate (ADP) receptor $P2Y_{12}$. Selective $P2Y_{12}$ antagonists inhibit platelet aggregation that is induced through the ADP-mediated activation of the glycoprotein IIb/IIIa pathway. As ticlopidine was associated with severe hematological adverse events, including thrombotic thrombocytopenic purpura and neutropenia, it is rarely prescribed. Clopidofrel was associated with a much lower rate of adverse events. Different mechanisms of action of clopidogrel and aspirin prompted studies to investigate potential advantages of combining the agents. The effect of combined clopidogrel and aspirin on reducing risk of vascular events in patients after a stroke or TIA demonstrated no benefit of dual therapy over monotherapy.[9] A recent analysis of the Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) studies concluded that combination therapy with aspirin and clopidogrel offered no advantage compared with aspirin alone.[10]

The MATCH study demonstrated no significant difference between clopidogrel alone (16%) and clopidogrel plus aspirin (17%) in relative risk reduction after 18 months of treatment for the primary end-point of a composite of ischemic stroke, myocardial infarction (MI), death from vascular causes, or repeat hospitalization for an acute ischemic event. However, there was a highly significant increase in the number of life-threatening bleeding episodes with added aspirin compared with those taking clopidogrel alone (3 versus 1%; $p<0.0001$).[9] Similarly, in the CHARISMA study clopidogrel plus aspirin was not statistically different from placebo plus aspirin in reducing incidence of MI, stroke, or death from cardiovascular causes in patients with stable atherothrombotic disease.[10]

Dipyrimadole appears to act through a number of antithrombotic systems such as cyclic guanyl-dependent monophosphate (cGMP) phosphodiesterase (PDE) inhibition to increase platelet cGMP, scavenging of oxy- as well as peroxy-radicals, and blocking uptake of adenosine.[11,12] Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells, and erythrocytes *in vitro* and *in vivo*. The inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5–1.9mg/ml). This

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inhibition results in an increase in local concentrations of adenosine that act on the platelet A_2-receptor, thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels (Aggrenox prescribing information). This mechanism is thought to inhibit platelet aggregation in response to various stimuli such as platelet-activating factor (PAF), collagen, and ADP. Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cGMP-PDE, thereby augmenting the increase in cGMP produced by endothelium-derived relaxing factor (EDRF), now identified as nitric oxide (NO). Under therapeutically relevant conditions shown from both *in vitro* experiments and using platelets obtained after clinical administration of dipyridamole, studies showed that dipyridamole enhances platelet inhibition by amplifying the signaling of the NO donor sodium nitroprusside. The data support the concept that enhancement of endothelium-dependent NO/cGMP-mediated signaling is likely a component of dipyridamole action.[13] Additional studies indicate that dipyridamole affects soluble modulators of thrombosis, inflammation, and endothelial function such as von Willebrand factor and serum C-reactive protein in patients, and may help in preventing atherothrombogenesis.[14]

Pharmacological studies indicate that the protective effects of aspirin and dipyridamole should be complementary as they act through non-competing mechanisms. Pharmacokinetic studies in healthy volunteers found that plasma profiles for aspirin and dipyridamole did not change when the drugs were given together. This supports combination therapy.[15,16] However, results from several long-term clinical trials in patients with cardiovascular disease that examined the efficacy of dipyridamole used in combination with high-dose aspirin were equivocal compared with aspirin alone.[17] Pharmaceutical scientists suggested that one explanation for the lack of additive effect in large-scale and long-term clinical trials could be associated with limited dipyridamole absorption, as well as patient compliance with a thrice-daily dosing regimen.

Pharmaceutically, dipyridamole is a poorly water-soluble weak base that shows pH-dependent absorption. Studies in healthy elderly patients showed that the commonly used H2-receptor antagonist famotidine, which increases gastric pH, dramatically decreased dipyridamole absorption.[18] As proton pump inhibitors, H2-receptor antagonists and antacids are commonly used by the same patient population likely to require antiplatelet therapy, it was suggested that elevations in gastric pH could explain divergent results among efficacy trials evaluating dipyridamole plus aspirin dosing regimens. While elderly subjects are more likely to take drugs that increase gastric pH, there is some evidence that healthy elderly subjects have altered gastric pH. Examination of gastric pH in a sample of 79 healthy elderly subjects with a mean age of 71±5 years revealed that fasted gastric pH, fasted duodenal pH, and duodenal pH values during the meal were statistically increased compared with values observed in young subjects. In addition, the elevated duodenal pH during a meal took longer to return to fasting levels in the elderly. The authors found that 11% of healthy elderly subjects had fasting gastric pH values >5, a pH value that could compromise drug absorption.[19]

To mitigate the effects of gastric pH on absorption and develop a combination antiplatelet treatment, a composite formulation was developed that combined immediate-release low-dose aspirin (25mg) with buffered extended-release (ER) dipyridamole (200mg) encapsulating a tartaric acid core. Absorption needs to be assured in the high-pH environment of the intestine, as sustained-release or ER preparations depend on continued drug absorption for a prolonged time after gastric contents move into the intestine. Standard enteric coatings are not effective for compounds that are not absorbed at neutral or basic pH. Rather, an extended-release formulation of dipyridamole requires a sufficiently acidic local milieu within the basic pH environment of the intestine for prolonged absorption. The composite ER dipyridamole formulation was developed to facilitate drug absorption under pathological or pharmaceutically induced low-acidic conditions in the stomach, as well as to enhance drug absorption from the neutral or basic intestinal environment.

Table 1: Pharmacokinetic Parameters for Dipyridamole in Subjects with Low Gastric Acidity

Parameter	Composite Extended-release Dipyridamole Capsule with Aspirin	Immediate -release Dipyridamole plus Aspirin	Ratio Immediate-release versus Buffered Extended-release Composite (95% Confidence Interval)
$AUC_{0–12}$ (ng•h/ml)			
Mean	7,883	3,943	0.50*(0.41, 0.59)
Range	3,976–12,341	994–7,709	
$AUC_{0–48}$ (ng•h/ml)			
Mean	11,896	9,051	0.76*(0.65, 0.88)
Range	4,753–21,188	1,389–25,159	
C_{max} (ng/ml)			
Mean	1,842	848	0.46*(0.31, 0.61)
Range	1,000–3,302	202–1,643	
C_{12} (ng/ml)			
Mean	237	362	1.53*(1.19, 1.87)
Range	66–621	78–909	
t_{max} (h)			
Mean	2.2	2.8	1.28 (0.86, 1.69)
Range	1.5–3.0	0.75–8.0	

Pharmacokinetic parameters for dipyridamole in subjects with low gastric acidity (pH>4.0) after a single composite capsule containing 200mg extended release (ER) dipyridamole, tartaric acid, and 25mg aspirin or after two immediate-release dipyridamole 100mg tablets that were separated by six hours combined with an 81mg aspirin tablet given with the first tablet.
**immediate release significantly different than ER composite, p<0.01.*
Source: Derendorf et al., 2005.[28]

The European Stroke Prevention Study-2 (ESPS-2) included this composite ER formulation given twice daily in the prevention of stroke in over 6,600 patients with prior TIA or completed ischemic stroke. Results of ESPS-2 were the first definitively to show additive effects of dipyridamole and aspirin compared with the same daily dose of aspirin or ER dipyridamole alone in reducing the risk of stroke.[20] The more recent European–Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) confirmed and extended the results of ESPS-2. In the ESPRIT trial, 83% of patients in the dipyridamole and aspirin group used the composite ER dipyridamole formulation. At mean follow-up of three to five years in patients with a TIA or a minor ischemic stroke of presumed arterial origin, study results confirmed the benefit of combination therapy.[21]

Gastric pH increases with food, and studies show that return to normal acidity takes longer for elderly subjects compared with young adults.[19] Reports also indicate that gastric pH is elevated in elderly subjects.[19,22–24] Elevated gastric pH is most likely to impair absorption of poorly water-soluble weak basic drugs such as dipyridamole and ketoconazole as dissolution of undissolved drug in the intestine at high pH may be too low to permit complete absorption.[25]

Ketoconazole is the best known drug that shows impaired absorption with high gastric pH. Elevated gastric pH resulted in subtherapeutic levels of ketoconazole, and the manufacturer recommends dissolving ketoconazole in acidic solution (and using a straw to avoid exposing teeth to the acidic solution) for patients with achlorhydria.[26]

Similarly, itraconazole and enoxacin absorption decreases with increased gastric pH and patients are advised to administer the medications at least two hours after taking buffered didanosine antacids, anticholinergics, antispasmodics, histamine H2-receptor antagonists, omeprazole, and sucralfate. Successful development of the acid labile antiviral agent didanosine utilized buffers to increase gastric pH that protected the drug from acid degradation.[27] Impaired dipyridamole absorption, shown in subjects with high gastric pH, led to the formulation of ER dipyridamole as a buffered product encapsulating a tartaric acid core to maintain an acidic microenvironment.

To further investigate the influence of gastric pH on dipyridamole absorption from the ER combination product, a study was designed to mimic likely clinical conditions. Bioavailability of dipyridamole from the marketed composite ER formulation was compared with an equivalent dose of immediate-release dipyridamole co-administered with low-dose aspirin in subjects with an elevated gastric pH induced by pre-treatment with the widely used proton pump inhibitor lansoprazole. The dosing regimen was chosen to approximate doses of dipyridamole and aspirin that are commercially available and may be substituted for the marketed composite extended-release capsule formulation. Lansoprazole is widely used in the elderly population and was selected as a representative antacid that is likely to be co-administered in patients prescribed antiplatelet therapy.[28]

Results showed that dipyridamole absorption was clearly dampened with the immediate-release generic dipyridamole compared with the composite ER formulation in subjects with elevated gastric pH. Corresponding mean pharmacokinetic parameters are summarized in *Table 1* for the two treatments. Peak dipyridamole concentrations (C_{max}) measured with the immediate-release formulation were less than half (43%) of those measured after the composite ER formulation. Examination of individual values revealed that the lowest C_{max} value after administration of the composite ER capsule exceeded the average C_{max} concentrations measured following the immediate-release tablets. Similarly, the extent of dipyridamole exposure that is reflected by the area under the curve $(AUC)_{0-12}$ with the immediate-release formulation was only 50% of the mean value after the composite buffered ER formulation.

Several literature reports indicate that a low gastric pH is required for dipyridamole absorption.[18,25] However, the clinical significance of reduced absorption is not well characterized, and interactions with antacids are generally not listed in prescribing information for standard dipyridamole formulations. Equivocal results of clinical trials that evaluated the efficacy of dipyridamole combined with aspirin may be explained in part by impaired absorption of the non-buffered formulation. The striking difference in outcome of the ESPRIT and ESPS-2 studies contrasts with previous reports indicating little added benefit of dipyridamole compared with aspirin alone. The ESPS-2 study, which used a buffered formulation, showed additive effects of aspirin and dipyridamole to reduce the risk of stroke by 37% compared with placebo and by 23% compared with aspirin alone in 6,600 patients at risk of stroke.[15] In contrast to decreased dipyridamole, which would be expected from age-associated increases in gastric pH, pharmacokinetic data from the ESPS-2 trial indicated that elderly subjects had higher dipyridamole exposure compared with younger study subjects.[29] The increased AUC in elderly subjects was attributed to decreased dipyridamole clearance.

In conclusion, a considerable body of evidence shows that formulation selection can be critical for dipyridamole absorption in some patient populations. In addition to issues of dose regimen compliance when comparing the efficacy of formulations requiring dosing three or four times daily, the buffering capacity of the formulation could be critical for absorption. As the use of antacids is widespread among patients at risk of stroke, improved absorption with the buffered extended-release dipyridamole formulation may be associated with efficacy in preventing stroke. ■

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