EASTERN DENTISTS INSURANCE COMPANY
Clinical Dentistry Advisor

Aspirin Alert Update for Dentistry As Cardioprotective and As an Emergency Drug

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Through its antiplatelet action, low-dose aspirin can prevent the arterial thrombosis in both high risk patients with known occlusive vascular disease and in low-risk healthy patients with no known history of vascular disease. (1) The use of aspirin in patients with annual risks of serious vascular events within the 4 to 8 percent range prevents at least 10 to 20 fatal and nonfatal vascular events for every 1,000 patients taking the drug for 1 (one) year. (1) In addition, it is estimated that aspirin, and perhaps other platelet inhibiting drugs, reduce the risk of nonfatal myocardial infarction, nonfatal stroke, or death from vascular causes by about 25%. (2) Evidence suggests that daily doses of aspirin in the range of 75 mg to 100 mg are optimal for the long-term prevention of serious vascular events in high-risk patients. (2,3) In patients with lower annual risks of vascular events (<4%), aspirin reduces the risk of myocardial infarction by about 30%. (4) However, it probably has no significant effect on the risk of stroke. (4)

There are three special alerts of clinical importance relative to the aspirin patient:

(1) Sudden aspirin withdrawal may elevate the risk of myocardial infarction;

(2) Ibuprofen may interfere with aspirin's cardioprotection; and

(3) There is a strong advisory warning against the discontinuation of dual aspirin/clopidogrel (Plavix®) antiplatelet therapy in patients with coronary artery stents.

SPECIAL ALERT #1:
SUDDEN ASPIRIN WITHDRAWAL MAY ELEVATE THE RISK OF MYOCARDIAL INFARCTION.

It was reported in 2004 (5) that patients with acute coronary syndrome (ACS) who were previously on aspirin therapy, but had discontinued aspirin use, had worse short-term outcomes than individuals not previously on aspirin therapy. Fischer et al. (6) have also reported similar findings and have suggested that discontinuation of aspirin by daily aspirin users may increase the risk of myocardial infarction. A Harvard Health Letter in 2005 (7) also stated that quitting aspirin "cold turkey" could be dangerous and that studies have linked aspirin withdrawal to heart attacks. The study by Fischer et al. (6) showed that the risk of acute myocardial infarction (AMI) was one and a half times greater for subjects who stopped taking non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, from 1 to 29 days compared to nonusers. The risk was highest in subjects with rheumatoid arthritis or systemic lupus erythematosus. Current or past NSAID use (discontinued therapy > 60 days prior to evaluation) was not associated with any increased risk of AMI. Their study (6) concluded that the risk of AMI is increased during several weeks after cessation of NSAID or aspirin therapy.

Collett et al. (5) stated that temporary withdrawal of aspirin is common and acute rebound effect with coronary thrombosis is a suspected result of the withdrawal. They studied a cohort of 1,358 patients admitted for suspected ACS. There were 930 nonusers, 355 prior users, and 73 recent withdrawers. Nonusers were defined as patients taking no oral antiplatelet agents (OAA) during the 6 months prior to admission and having no history of vascular disease. Prior users were patients who took either aspirin (97%) or other another OAA as chronic therapy to prevent acute vascular events without cessation within the three weeks before admission. Recent withdrawers were patients who had withdrawn OAA within the 3 weeks

before admission. There was no difference regarding the incidence of death or MI at 30 days between nonusers and prior users (10.3% versus 12.4%). The withdrawers had higher 30 day rates of death or MI (21.9% versus 12.4%) and bleedings (13.7% versus 5.9%) than prior users. Five percent of the patients admitted with ACS had withdrawn OAA within 3 weeks before admission. OAA was found to be an independent predictor of both mortality and bleedings at 30 days. It was concluded that prior users of OAA and patients with recent interruption of OAA displayed worse clinical outcomes than nonusers.

A more recent review (8) updated the risks associated with discontinuing aspirin antiplatelet therapy and the bleeding risks associated with continuing aspirin during surgical procedures. The article (8) confirms the possibility of a pharmacological rebound phenomenon which could lead to adverse ischemic events, and supports the warning against premature discontinuation of aspirin issued previously. (5,6) In an analysis of data obtained from 50,279 patients, Biondi-Zoccai et al. (9) reported that the increased risk of major adverse cardiac events attributed to aspirin withdrawal/non-adherence was approximately three-fold.

Burger et al. (10) reported that up to 10.2% of acute coronary syndromes follow interruption of aspirin therapy in a mean delay of 8.5 days, a delay consistent with rebound platelet activity. The delay was longer for a cerebrovascular event (approximately 14.3 days) and for peripheral arterial syndromes (about 25.8 days). Burger et al. (10) also reported that acute thrombotic complications are not immediate and usually follow interruption of aspirin therapy after a mean delay of 8 to 25 days, a time lapse consistent with normal platelet turnover required to replace the platelet pool in circulation and suggestive of a rebound phenomenon.

Special Alert #2: Ibuprofen may interfere with aspirin's cardioprotection.

In a statement released on September 8, 2006 (11), the Food and Drug Administration (FDA) notified consumers and health care professionals that the administration of ibuprofen for pain relief to patients taking aspirin for cardioprotection may interfere with aspirin's cardiovascular benefits. The report stated that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg daily). This could result in diminished effectiveness of aspirin as used for cardioprotection and stroke prevention. The FDA added that although ibuprofen and aspirin can be taken together, it is recommended that consumers talk with their health care providers for additional information.

In addressing situations where these drugs would be used concomitantly, the FDA provided the following information:

1. Patients who use immediate release aspirin (not enteric-coated aspirin) and take a single dose of ibuprofen 400 mg should dose the ibuprofen at least **30 minutes or longer after aspirin ingestion, or more than 8 hours before aspirin ingestion,** to avoid attenuation of aspirin's effect.

2. Recommendations about the timing of ibuprofen 400 mg in patients **taking enteric-coated, low-dose aspirin** could not be made based on available data. One study, however, showed that the antiplatelet effect of enteric-coated low-dose aspirin was attenuated when ibuprofen 400 mg was dosed 2,7, and 12 hours after aspirin. (12)

3. With occasional use of ibuprofen, there was likely to be minimal risk from any attenuation of the antiplatelet effect of low-dose aspirin, because of a long-lasting effect of aspirin on platelets.

4. At this time, there was no clear data regarding the potential effect of chronic ibuprofen dosing greater than 400 mg on the antiplatelet effect of aspirin.

5. Acetaminophen appeared to not interfere with the antiplatelet effect of low-dose aspirin. (12)

6. Other over-the-counter (OTC) NSAIDs, i.e., naproxen-sodium, should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin until proven otherwise. One study of naproxen and low-dose aspirin (13) has suggested that naproxen may interfere with aspirin's antiplatelet activity when they are co-administered. However, naproxen 500 mg administered two hours before or after aspirin 100 mg did not interfere with aspirin's antiplatelet effect. (13)

Other non-steroidal, anti-inflammatory drugs (NSAIDs) may be involved in blunting the antiplatelet effects of

aspirin. Gladding et al. (14) compared the *ex vivo* antiplatelet effects of six NSAIDs to determine whether these agents antagonize the effects of aspirin. The NSAIDs were:

- tiaprofenic acid
- ibuprofen
- indomethacin
- naproxen
- sulindac
- celecoxib (Celebrex)

Platelet function was assessed by Platelet Function Analyzer 100 closure time in normal subjects in a randomized, blinded, multiple crossover study. Closure time is a measure of platelet aggregation, and the longer the closure time, the greater the antiplatelet effect. Platelet function was measured 12 hours after the administration of each NSAID. The NSAIDs and the doses were:

- naproxen 550 mg
- ibuprofen 400 mg
- celecoxib (Celebrex) 200 mg
- indomethacin 25 mg
- sulindac 200 mg
- tiaprofenic acid 300 mg

The NSAID was then given 2 hours before aspirin 300 mg and platelet function was reassessed 24 hours later. At 12 hours after the administration of naproxen, closure time was significantly prolonged. The other NSAIDs did not cause significant prolongations.

Compared with placebo plus aspirin, closure time was significantly reduced when ibuprofen, indomethacin, naproxen, and tiaprofenic acid were given before aspirin. It was concluded that ibuprofen, indomethacin, and naproxen all block the antiplatelet effect of aspirin. Sulindac and celecoxib (Celebrex) did not demonstrate any significant antiplatelet effect or reduce the antiplatelet actions of aspirin. It was suggested that sulindac and celecoxib may be the NSAIDs of choice in patients requiring aspirin and NSAIDs concomitantly.

Gengo et al. (15) measured the magnitude and duration of inhibition of platelet aggregation following doses of aspirin or ibuprofen alone or taken in combination in a group of healthy volunteers. Ten subjects underwent three randomized treatment sessions: aspirin 325 mg alone, ibuprofen 400 mg alone, and finally ibuprofen 400 mg followed by aspirin 325 mg 2 hours later. There was a significant reduction in both magnitude and duration of aspirin's inhibitory effect on platelet aggregation when ibuprofen was given prior to aspirin administration.

In addition, a confirmatory study was performed. Over 27 months, patients treated with aspirin (325 mg daily) for secondary stroke prophylaxis while taking an NSAID were identified. Of eighteen patients who were taking either ibuprofen 200-800 mg per dose or naproxen 220-500 mg per dose along with aspirin, none showed inhibition of platelet aggregation. All showed inhibition of platelet aggregation following discontinuation of the NSAID. And 13 of the 18 experienced a recurrent ischemic episode while taking NSAID and aspirin concomitantly. The Gengo et al. study (15) concluded that ibuprofen and naproxen prevent the irreversible inhibition of platelet aggregation produced by aspirin needed for secondary stroke prophylaxis, and the interaction can have clinical consequences for patients taking aspirin.

Special Alert #3:
Strong advisory warning against the discontinuation of dual aspirin/clopidogrel (Plavix®) antiplatelet therapy in patients with coronary artery stents.

Aspirin and clopidogrel (Plavix®) in combination is the primary prevention strategy against stent thrombosis after placement of drug-eluting metal stents in coronary patients. (16) Premature discontinuation of this drug combination strongly increases the risk of a catastrophic event of stent thrombosis leading to myocardial infarction and/or death, so says a science advisory issued in 2007 from the American Heart Association (AHA) in collaboration with the American Dental Association (ADA) and other professional health care organizations. (16) The advisory stresses a 12-month therapy of aspirin and Plavix® combination after placement of a drug-eluting stent in order to prevent thrombosis at the stent site. The AHA also stressed educating both the patient and the health care provider about the hazards of premature antiplatelet drug discontinuation. Any elective surgery should be postponed for one year after stent implantation, and if surgery must be performed, consideration should be given to continuing the antiplatelet therapy during the perioperative period in high-risk patients with drug-eluting stents.

The advisory panel was concerned that antiplatelet therapy is sometimes prematurely discontinued within the first year after stent implantation, either by the patient or by a health care provider who may not realize the consequences of discontinuation of the antiplatelet combination. According to the panel, the leading adverse event resulting from discontinuation is stent thrombosis, leading to acute myocardial infarction (MI) or death.

The recommendations from the AHA advisory panel (16) were summarized for the dental professional according to the following:

1. Dental professionals and other health care providers who perform invasive or surgical procedures and are concerned about periprocedural and postoperative bleeding must be made aware of the potential catastrophic risks of premature discontinuation of dual antiplatelet (aspirin and Plavix®) therapy. The dental professional should contact the patient's cardiologist if issues regarding the patient's antiplatelet therapy are unclear, in order to discuss optimal patient management strategy.

2. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of dual antiplatelet therapy. The course of this therapy is suggested as 12 months after drug-eluting stent implantation if they are not at high risk of bleeding.

The latest report (17) from the Cleveland Clinic and the Brigham and Women's Hospital recommends that dual antiplatelet therapy with aspirin and clopidogrel be extended for greater than 1 (one) year, and perhaps indefinitely, in all patients receiving drug-eluting stents. Their recommendation was based on a current body of randomized and observational evidence that patients with acute coronary syndrome, a prior history of ischemic events, or percutaneous coronary intervention with bare metal stents or drug-eluting stents have improved cardiovascular outcomes with more robust or longer duration antiplatelet therapy.

Another recent report (18) looked at the consequences of short-term discontinuation of antiplatelet therapy in patients with drug eluting stents. Antiplatelet therapy is often discontinued in patients with drug-eluting stents who are undergoing surgical procedures. The objective of the study was to examine the safety of short-term discontinuation of antiplatelet therapy. The authors searched the literature for reported cases of late stent thrombosis and identified 161 cases of late stent thrombosis. A total of 19 cases occurred in patients who were receiving dual antiplatelet therapy (aspirin-Plavix®) at the time of the event. If patients stopped both drugs, the median time to event was 7 days. If patients had previously stopped Plavix® with no ill effect and subsequently stopped aspirin, the median time to event was also 7 days from the time of aspirin cessation. If Plavix® was stopped but aspirin maintained, the median time to event was 122 days. Among the 48 patients who stopped both agents, 36 cases (75%) occurred within 10 days. Among the 95 patients who discontinued the Plavix®, but continued aspirin, only 6 cases (6%) occurred within 10 days. In conclusion, if aspirin therapy was maintained, short-term discontinuation of Plavix® may be relatively safe in patients with drug-eluting stents.

Aspirin As An Emergency Drug

According to emergency room physicians, chewing and swallowing two to four baby aspirin tablets (81 mg each) or a single standard 325 mg aspirin tablet during a suspected heart attack (acute coronary syndrome) reduces the risk of death from a myocardial infarction (MI). (19) Presently, in individuals with a history of acute coronary syndrome (ACS) who may or may not be taking daily cardioprotective aspirin but who suddenly experience chest pain, giving aspirin immediately is an accepted protocol for paramedics, for hospital emergency rooms, and for other pre-hospital situations. (20) Where did the evidence come from that aspirin can be this effective as a life saver, and what is its mechanism of action during an ongoing heart attack?

One of the first reports of aspirin use in heart attacks was in 1983 from a study completed by the Veterans Administration Hospitals. (21) Using 1,266 men, half receiving aspirin (324 mg) daily for 12 weeks and half receiving placebo daily for 12 weeks, the incidence of nonfatal acute MI was 51% lower in the aspirin group compared to the placebo group. The incidence of fatal MI was also 51% lower in the aspirin group compared to

the placebo group. The study results suggested that perhaps a single dose of aspirin given during an episode of acute MI could have life-saving properties. (21)

Next there was a report on the benefits of aspirin by the Second International Study of Infarct Survival, a study known as ISIS-2. (22) In that report, 17,187 patients entering 417 hospitals up to 24 hours after the onset of suspected acute MI were randomized with placebo control, one month of 160 mg daily aspirin tablets. The aspirin produced a highly significant reduction in 5-week vascular mortality. There were 804/8,587 (9.4%) deaths due to MI among the patients receiving aspirin tablets, and 1,016/8,600 (11.8%) deaths among the placebo users. This amounted to an overall reduction of mortality of patients with acute MI of 23% by aspirin, a difference which was statistically significant.

Next, there was the Third International Study of Infarct Survival Collaborative Group (ISIS-3) which showed that the benefits of two 81 mg daily aspirin tablets were just as effective when used alone or when used with heparin in reducing mortality after acute MI. (23)

In 2002, the Antithrombotic Trialists Collaboration (24) reported that the antithrombotic effect of daily aspirin dosing at 75 mg to 150 mg daily was due to inhibition of platelet aggregation through complete inhibition of the thromboxane A2, a member of the prostaglandin family. They also reasoned that non-aspirin users could benefit from a single dose of aspirin ranging from 75 mg to 150 mg given at the time of a suspected acute MI. They reported that in clinical situations where an immediate antithrombotic effect is required such as acute MI, a loading dose of 150 mg to 300 mg is sufficient to produce rapid and complete inhibition of thromboxane-mediated platelet aggregation. (24)

Present Guidelines

Based on the above reports, the American College of Cardiology (ACC) and the American Heart Association (AHA) published guidelines for the management of patients with suspected MI. (25) The guidelines said that the prompt action of aspirin and its ability to reduce mortality rates in patients with suspected MI enrolled in the ISIS-2 study and the ISIS-3 study leads to the recommendation that aspirin be initiated immediately once the diagnosis of ACS is made or suspected. The initial aspirin dose should be between 162 mg and 325 mg. Non-enteric formulations are preferred since studies showed more rapid uptake into the blood stream after swallowing non-coated tablets.

Also, the recommendations stated do not use aspirin if there is a history of aspirin-induced allergy manifested as asthma with nasal polyps.

The ACC/AHA recommendations also stated that aspirin therapy can be started in the pre-hospital setting when an acute coronary syndrome is suspected. (25) Reports from the emergency doctors on the use of aspirin for ongoing heart attacks (Pollack and Hollander (19) and by Brady (20)) describe the present place of aspirin in emergency medicine. The first report stated that early initiation of aspirin therapy is well established in individuals having sudden chest pain. The report went on to state that the platelet plays a central role in the pathogenesis of coronary thrombosis after atherosclerotic plaque rupture, and its active inhibition forms a cornerstone of the management of ACS. (19) On basis of much clinical data, aspirin is the established antiplatelet agent. Its efficacy in management of patients with ACS is well established and is now considered standard therapy. Aspirin reduces the risk of death from new MI. The recommended initial dose of aspirin is 162 mg to 325 mg of non-enteric, non-coated formulation. In MI situations, aspirin should be continued with daily doses of 75 mg to 162 mg for an indefinite period of time. (19)

The second report by Brady (20) in the form of an editorial commented that in the patient experiencing sudden chest pain suspected as MI, dramatic reduction in morbitiy and mortality have been seen with the administration of aspirin. It is the most cost-effective treatment available in ACS management. Aspirin reduces the mortality of patients with acute myocardial infarction (AMI) by 23% without additional fibrinolytic therapy and by 42% when used with fibrinolytic therapy. The dose now recommended in the emergency room is 162 mg to 325 mg given once in the emergency department after arrival.

Aspirin In The Dental Office

Aspirin is one of the emergency drugs as part of the protocol in patients experiencing chest pains. (26) The following are some suggestions.

1. The dose for an emergency is either two to four 81 mg "baby aspirin" tablets or one single standard aspirin tablet; they should be non-enteric coated or "plain" aspirin tablets. Call 911 at the sign of chest pain and administer the aspirin tablets. (26)

2. For the most rapid uptake into the blood stream, the aspirin tablets should be chewed then swallowed with some water if available. If no water is available, have the patient chew and swallow the tablets. (27)

3. If there is only enteric-coated aspirin tablets available, the individual can take those (better than nothing) but they also must chew the tablet(s) before swallowing. (25)

4. Watch the expiration date of the aspirin product. That date will be stamped on the package and label. Aspirin does break down to inactive by-products over time, even if the bottle is sealed. Many aspirin products have about a one year expiration or one year "lifetime". Replace when necessary.

5. Keep either regular aspirin tablets (325 mg each) or "baby" aspirin of 81 mg each in your emergency drug kit.

6. Do not give to individuals with a history of aspirin allergy manifested as asthma with nasal polyps. (25)

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Provided by Eastern Dentists Insurance Company (EDIC), June 2010
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