Combination Antiplatelet Therapy: Implications for Pharmacists

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Objectives. To present two case reports of patients who received suboptimal oral antiplatelet therapy and to review recent changes in national guidelines for management of acute coronary syndromes.

Data Sources. Personal observation by the authors, and clinical practice guidelines and related clinical trials of the American Heart Association and the American College of Cardiology.

Summary. The American College of Cardiology and the American Heart Association revised the guidelines for administration of antiplatelet and anticoagulant therapy in patients with unstable angina and non–ST-segment elevation myocardial infarction in March 2002. Two cases observed by the authors illustrate the consequences of suboptimal antiplatelet therapy when a combination of two antiplatelet drugs should have been administered.

Conclusion. Evidence from recent randomized controlled trials led to changes in the national guidelines for administration of oral antiplatelet therapy in patients with acute coronary syndromes. Pharmacists should be aware of these changes and counsel patients about appropriate administration of antiplatelet drugs.

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The following two case reports involving patients who received suboptimal antiplatelet therapy point out disparities between national guidelines and actual clinical practice that led to undesirable consequences in both patients.

Case Reports

Patient No. 1

A 61-year-old African-American man with a history of coronary artery disease, hypertension, diabetes mellitus type 2, and a left ventricular ejection fraction of 35% based on echocardiography was admitted to the hospital with progressing angina 2 months after the echocardiogram was obtained. He underwent percutaneous coronary intervention, with stents placed in the right coronary and circumflex arteries. He was discharged the next day with the following drug regimen: aspirin 325 mg/day, carvedilol 3.125 mg twice/day, glyburide 10 mg twice/day, hydrochlorothiazide 25 mg/day, and clopidogrel loading dose 300 mg once, then 75 mg/day.

Eleven days after discharge, the patient’s wife found him on the floor, and he was taken to the emergency department. His blood pressure was 110/50 mm Hg, pulse 80 beats/minute. He was afebrile. An electrocardiogram revealed ST depression in V2-V5, with T-wave inversion in V5-V6. The first set of cardiac biomarkers revealed a creatine kinase level of 3445 IU/L.
(normal 30–180 IU/L), with an MB fraction of 7.5% (normal <5%) and a troponin T level of 8.86 ng/ml (normal < 0.2 ng/ml). Other pertinent laboratory test results were white blood cell count 23.6 x 10^9/mm^3, hematocrit 28.8%, hemoglobin 9.6 g/dl, platelets 357 x 10^9/mm^3, sodium 133 mEq/L, potassium 4.4 mEq/L, chloride 92 mEq/L, bicarbonate 24 mEq/L, glucose 263 mg/dl, blood urea nitrogen 24 mg/dl, and serum creatinine 2 mg/dl.

The patient was taken to the cardiac catheterization laboratory, and angiography revealed total occlusion of both stents, which were subsequently restented. He received heparin, eptifibatide, and intravenous nitroglycerin.

An interview with the patient’s wife revealed that the patient never filled his prescription for the clopidogrel; he and his wife considered it unnecessary and expensive.

The assessment was acute non-ST-segment myocardial infarction secondary to acute stent closure resulting from inadequate antiplatelet therapy. The plan consisted of restenting, administering eptifibatide, and restarting aspirin plus clopidogrel. The patient was discharged 3 days later, with a drug regimen consisting of isosorbide dinitrate 10 mg 3 times/day, hydralazine 10 mg 4 times/day, carvedilol 6.25 mg twice/day, aspirin 325 mg/day, clopidogrel 75 mg/day, and insulin.

Patient No. 2

A 42-year-old Caucasian woman with a history of coronary artery disease had received multiple interventions, such as left anterior coronary artery stent placement. She underwent percutaneous coronary intervention of in-stent restenosis. She came to the emergency department approximately 6 weeks later after awakening with crushing substernal chest pain. The pain radiated to both arms and was accompanied by shortness of breath, diaphoresis, nausea, and lightheadedness. She rated her pain, which was similar to her previous anginal pain, as 9 on a scale of 0–10. Her medical history was significant for hypertension, hyperlipidemia, cigarette smoking, coronary artery disease (stent placements in the right coronary artery 5 years earlier and left anterior descending coronary artery within the last year, in addition to the percutaneous coronary intervention described above). Her ejection fraction according to echocardiography performed about 2 months earlier was 40%.

Family history revealed that her mother had experienced an acute myocardial infarction at age 54, and her father had coronary artery disease and hypertension. The patient had once smoked 50 packs/year but had not smoked for over a year and consumed no ethanol; she was married and unemployed at the time.

On admission to the hospital, the patient’s drug regimen consisted of aspirin 325 mg/day, atorvastatin 10 mg/day, metoprolol 50 mg twice/day, benazepril 40 mg/day, and clopidogrel 75 mg/day for 4 weeks after her stent 2 months earlier and after her percutaneous coronary intervention a month after that.

Physical examination indicated that she was hemodynamically stable; her blood pressure was 118/82 mm Hg, heart rate 72 beats/minute, with no respiratory distress. Cardiovascular examination revealed a regular rate and rhythm without murmur, rubs, or gallops. She had normal S1 and S2 heart sounds, no jugular venous distention, clear lungs, and no edema.

Electrocardiography revealed ST elevation of 3 mm in the anterior leads with reciprocal changes in the inferior leads. Initial laboratory test results were normal. In the emergency department she received aspirin, heparin, nitroglycerin, and morphine. She continued to experience substernal chest pain with ST elevation, and preparations were made to take her to the catheterization laboratory immediately for diagnostic left heart catheterization and possible coronary intervention. Left heart catheterization revealed that her left main, right, and circumflex coronary arteries were angiographically normal, but the left anterior descending coronary artery had a 100% stenosis proximally.

Percutaneous coronary intervention of the left anterior descending coronary artery was performed, with new stents placed proximal and distal to the previous stent. The patient received tirofiban for 24 hours after the procedure. No residual stenosis was noted. Clopidogrel and aspirin were restarted without complications, and the plan was to continue administering both antiplatelet agents indefinitely.

The assessment was that the patient was experiencing repeated episodes of myocardial ischemia and infarction, and that inconsistent clopidogrel therapy as well as possible resistance to aspirin may have been contributing to her unstable course.

Discussion

Changes in the American College of Cardiology and American Heart Association Guidelines

The American College of Cardiology and the
American Heart Association revised the guidelines for administration of antiplatelet and anticoagulant therapy for unstable angina and non–ST-segment elevation myocardial infarction in March 2002.1 The guidelines incorporate a system of classifying the level of benefit and evidence based on randomized controlled trials. Briefly, the system ranks evidence into three levels (Table 1): A—the highest class, in which data are derived from many randomized controlled trials involving large numbers of patients; B—intermediate, in which data are derived from a limited number of trials involving comparatively small numbers of patients or from well-conceived data analyses of nonrandomized studies or observational data registries; and C—the lowest class, in which the consensus of expert opinion is the primary source of information. Usually, this source is used only when data from randomized controlled trials are not available.

The system incorporates the levels of evidence into three classes of recommendations: class I—conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective; class II—conditions for which conflicting evidence and/or a divergence of opinion exists regarding the usefulness or efficacy of a procedure or treatment; class II A—in which weight of evidence or opinion is in favor of usefulness or efficacy; class II B—in which usefulness or efficacy is less well established by evidence or opinion; class III—conditions exist for which evidence and/or general agreement indicate that a procedure or treatment is not useful or effective and in some cases may be harmful.

Major changes in the new guidelines from the original published guidelines2 of 2000 are as follows:

1. Rather than specifying a thienopyridine, the revised guidelines recommend clopidogrel specifically. The rationale for this change is that clopidogrel has fewer adverse effects than ticlopidine (diarrhea, abdominal pain, nausea, vomiting, or neutropenia in approximately 2.4% of patients, severe neutropenia in 0.8% of patients, and rarely, thrombotic thrombocytopenia purpura) and requires less monitoring. Clopidogrel also has a more rapid onset of activity than ticlopidine; however, in emergency situations a loading dose of 300 mg is often given.

### Table 1. American College of Cardiology and American Heart Association Guidelines for Administration of Antiplatelet and Anticoagulant Therapy in Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction (revised March 2002)

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Class</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>I</td>
<td>Antiplatelet therapy should be started promptly. Aspirin should be administered as soon as possible after patient's condition is identified and continued indefinitely.</td>
</tr>
<tr>
<td>A/B</td>
<td>I</td>
<td>In hospitalized patients for whom an early noninterventional approach is planned, clopidogrel should be added to aspirin as soon as possible after admission and administered for at least 1 month (A) and up to 9 months (B).</td>
</tr>
<tr>
<td>A/B</td>
<td>I</td>
<td>In patients for whom percutaneous coronary intervention is planned, clopidogrel should be started and continued for at least 1 month (A) and up to 9 months in patients who are not at high risk for bleeding (B).</td>
</tr>
<tr>
<td>B</td>
<td>I</td>
<td>For patients taking clopidogrel and for whom coronary artery bypass graft surgery is planned, the drug should be withheld, if possible, for at least 5 and preferably 7 days.</td>
</tr>
<tr>
<td>A</td>
<td>I</td>
<td>Anticoagulation with subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin should be added to antiplatelet therapy with aspirin and/or clopidogrel (A).</td>
</tr>
<tr>
<td>A</td>
<td>I</td>
<td>A platelet glycoprotein IIb-IIIa antagonist should be administered in addition to aspirin and heparin to patients in whom catheterization and percutaneous coronary intervention are planned. The glycoprotein IIb-IIIa antagonist also may be administered just before the percutaneous coronary intervention (A).</td>
</tr>
<tr>
<td>A</td>
<td>I</td>
<td>Aspirin 75–325 mg/day (in the absence of contraindications) should be administered.</td>
</tr>
<tr>
<td>A</td>
<td>I</td>
<td>Clopidogrel 75 mg/day (in the absence of contraindications) should be administered when aspirin is not tolerated because of hypersensitivity or gastrointestinal intolerance.</td>
</tr>
<tr>
<td>B</td>
<td>I</td>
<td>The combination of aspirin and clopidogrel should be administered for 9 months after unstable angina and non–ST-segment elevation myocardial infarction.</td>
</tr>
<tr>
<td>B</td>
<td>I</td>
<td>For long-term medical therapy, the combination of aspirin and clopidogrel is recommended for 9 months after unstable angina and non–ST-segment elevation myocardial infarction.</td>
</tr>
</tbody>
</table>
2. Based on results of the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study, it is recommended that clopidogrel be added to aspirin as soon as possible and administered for 1–9 months. Treatment for at least 1 month is strongly recommended, and up to 9 months based on average duration of treatment of patients with unstable angina to prevent recurrent ischemic events. This should not be interpreted to mean that benefit ceases after 9 months, but rather that data are limited beyond that time.

3. When percutaneous coronary intervention is planned, clopidogrel and aspirin should be given for at least 1 month and up to 9 months. When thienopyridines have a delayed onset and cessation of activity, they should be withheld for 5–7 days to minimize bleeding complications in patients for whom coronary artery bypass graft surgery is elective.

4. Anticoagulation, preferably with enoxaparin (IIA recommendation), should be administered with antiplatelet therapy with aspirin and/or clopidogrel, based on the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Events (ESSENCE) study and other combination trials.

Ensuring Administration of Optimal Treatment

What should pharmacists do to ensure that patients receive optimal treatment with antiplatelet therapy for unstable angina and non-ST-segment elevation myocardial infarction? In the inpatient setting, identifying a champion and a team of physicians, nurses, and pharmacists to lead the development of treatment algorithms and pathways would increase recognition of appropriate situations for administering combination antiplatelet therapy. All staff must understand that antiplatelet drugs work through different mechanisms, and that monotherapy with any agent is prone to failure in patients who are at high risk for developing unstable angina and non-ST-segment elevation myocardial infarction and in patients undergoing percutaneous coronary intervention with stent placement. A set of standing orders would be a useful tool so that routine consideration of combination therapy would not overlooked.

In the outpatient setting, comprehensive counseling by a pharmacist for all patients bringing prescriptions for an aspirin-clopidogrel combination would help minimize misunderstanding about potential deleterious interactions and emphasize the role for appropriate combinations. Patient counseling is imperative to enhance patient compliance and persistence with long-term regimens. Patients should understand some important points about combination oral antiplatelet therapy, as follows:

1. Combination antiplatelet therapy with aspirin and clopidogrel after percutaneous coronary intervention reduces the risk of recurrent myocardial infarction, hospitalization for angina, and need for additional procedures. This combination is safe and effective for up to 12 months.

2. The most common (~25%) symptoms occurring in patients taking clopidogrel are gastrointestinal, such as abdominal pain, dyspepsia, gastritis, and constipation; these symptoms occur about as frequently with aspirin. Combination therapy with aspirin and clopidogrel has to be discontinued in only about 2% of patients due to gastrointestinal adverse effects.

3. Rash and other skin disorders occur in up to 15% of patients taking clopidogrel, similar to the rate with aspirin. The effects on skin do not commonly lead to discontinuation of therapy.

4. Headache or dizziness led to discontinuation of combination therapy in 2–3% of patients in the CURE study.

5. The risk of major bleeding is increased with aspirin or clopidogrel; in combination, the major bleeding rate was 3.7% versus 2.7% with aspirin alone in the CURE study. The risk for bleeding with clopidogrel increased with higher dosages of aspirin.

6. Low white blood cell counts (neutropenia or agranulocytosis) occur very rarely (2/9599 patients in the CURE study) with clopidogrel and are more common (0.8%) with ticlopidine, a closely related drug. No routine monitoring is required.

Conclusion

The two case reports presented here illustrate the consequences of suboptimal antiplatelet therapy when a combination of two antiplatelet drugs should have been administered. Also, evidence from recent randomized controlled trials led to changes in the national guidelines for administration of oral antiplatelet therapy in patients with acute coronary syndromes.
Pharmacists should be aware of these changes and counsel patients about appropriate administration of antiplatelet drugs.

References


