The Risks and Safety of Clopidogrel in Pediatric Arterial Ischemic Stroke

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Background and Purpose—The purpose of this study was to determine safety and tolerability of clopidogrel in children with arterial ischemic stroke (AIS). Clopidogrel is the alternative antiplatelet medication when aspirin is not tolerated or fails. The possible risks and safety of clopidogrel in children with AIS have not been assessed.

Methods—This is a prospective consecutive cohort study of children with AIS who were started on clopidogrel. Seventeen children were included.

Results—Two children developed subdural hematomas while on clopidogrel in conjunction with aspirin. Two others had headache or hand numbness. No other side effects like rash or gastrointestinal upsets were reported.

Conclusions—We found clopidogrel to be relatively well tolerated in the pediatric population. In combination with aspirin and in the presence of other risk factors, intracranial bleeding may be seen. (Stroke. 2006;37:1120-1122.)

Key Words: antiplatelet agents ■ child ■ clopidogrel ■ stroke

Long-term antiplatelet therapy with aspirin (ASA) is widely recommended as secondary prevention for children with arterial ischemic stroke (AIS).1–3 The failure rate of ASA is reported to be 6.6% to 15%.4,5 ASA resistance has been reported in 5% to 60% adults.6–7 Some children are unable to tolerate ASA because of gastric or respiratory side effects. Clopidogrel is currently the alternative antiplatelet medication for children. However, the risks, tolerability, and side effects of clopidogrel (Plavix) in children with AIS have not been reported. The goals of the current study were to assess the safety and tolerability of clopidogrel treatment.

Methods

Children 1 month to 18 years of age with AIS, seen from January 2000 to June 2004, comprised the study cohort. The diagnosis of AIS required neuroimaging (computed tomography or MRI) findings of focal infarction confined to an established arterial territory with or without focal neurological deficits. All children were followed from the time of their initial diagnosis and were treated with either anticoagulants or antiplatelet agents for prevention of recurrent stroke, depending on underlying stroke etiology and risk of recurrence. Children who could not tolerate or failed ASA were started on clopidogrel. Aspirin intolerance was defined as development of ASA-related significant adverse effects (eg, severe gastrointestinal upset, allergic reactions, asthma, and tinnitus) necessitating discontinuation. Aspirin failure was defined as children who had recurrent AIS or transient ischemic attack (TIA) while taking ASA. Recurrent AIS is defined as a confirmed cerebral ischemic event on neuroimaging with or without associated focal neurological signs. Recurrent TIA is defined as occurrence of new onset transient focal neurological signs without neuroimaging evidence of ischemic infarction. In addition, immunosuppressive therapy was administered to patients with central nervous system vasculitis and acetazolamide to some patients with Moyamoya disease.

We aimed for a dose of clopidogrel of 1 mg/kg per day up to the maximum of 75 mg (one tablet). When appropriate, tablets were rounded to the nearest one half, one third, or one fourth tablet.

Risks and complications related to clopidogrel therapy either alone or in conjunction with ASA were assessed during follow-up visits at 3- to 6-month intervals. Risks or complications were classified as "minor," including bruising, nose bleeding, rash, or gastrointestinal irritations, or "major," including gastrointestinal bleeding, intracranial hemorrhage, hemorrhage requiring blood transfusion, and bone marrow suppression.

Results

Seventeen children were included (8 children on clopidogrel alone, 9 in conjunction with ASA). Patient characteristics are presented in the Table. The mean age was 8.8 years (range 1.5 to 17 years). The reasons for treatment with clopidogrel were either ASA failure, including recurrent stroke or TIA while receiving ASA therapy (13 patients), or attributable to side effects of ASA, including gastrointestinal upset (1 patient), increased asthma attacks (2 patients), or allergic reaction (1 patient).

One child reported hand numbness. Onset of symptoms predated clopidogrel therapy and were unchanged after discontinuation. Neuroimaging did not reveal any new ischemic infarction. Symptoms were attributed to acetazolamide therapy. Another child reported headaches, which also predated clopidogrel therapy and continued after medication withdrawal.

No patient reported any major side effects during clopidogrel treatment alone. However, significant intracranial...
hemorrhage was reported in 2 patients (25%) on ASA and clopidogrel combination. One patient with Moyamoya disease and marked cerebral atrophy developed a significant subdural hematoma 6 weeks after revascularization surgery when therapy with clopidogrel and ASA were restarted (Figure). Both medications were withdrawn and no further progression of hemorrhage was noted. Another patient with Progeria and intracranial arterial stenosis also developed a subdural hematoma while on clopidogrel and ASA combination. He too had marked cerebral atrophy and hypertension. Both medications were withdrawn.

**Discussion**

Clopidogrel (Plavix), a thienopyridine derivative, selectively inhibits the binding of ADP to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation. It thus reduces the formation of arterial and venous thrombi. 

Clopidogrel has been assessed in several studies in adults with stroke. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study reported a significant relative risk reduction for ischemic events of 8.7% in favor of clopidogrel. The CARESS trial found short-term combination therapy with clopidogrel and ASA was more effective than ASA alone in reducing asymptomatic embolization. No increased bleeding risk was seen when this combination was given for just 1 week. However, a recent study in adults reported an increased risk of major bleeding when ASA and clopidogrel were used together.

Clopidogrel has been found to be better tolerated than ASA and ticlopidine in the adult population. Reported side effects of clopidogrel include gastrointestinal symptoms of nausea, stomach ache, diarrhea, and constipation. Systemic symptoms include fatigue, muscle aches, headache, rash, pruritis, and purpura. Serious side effects consist of an increased risk of bleeding, intracranial hemorrhage, and severe neutropenia. Compared with ASA, clopidogrel is associated with lower rates of gastrointestinal disturbances, abnormal liver functions, and hemorrhage but more frequent rash and diarrhea. 

Our study subjects tolerated clopidogrel well, and no one developed rash or diarrhea. One child reported headaches and another reported hand numbness. However, onset of symptoms predated clopidogrel therapy and were unchanged after discontinuation. In both patients, the symptoms were unlikely to be side effects of the medication. Nevertheless, we report these symptoms as they were brought to the attention of the physician after starting clopidogrel and prompted its withdrawal.

Two patients developed significant intracranial hemorrhagic complications. One patient had recent surgery and another had hypertension, potential risk factors for development of hemorrhage. In addition, both had marked cerebral atrophy and hypertension. Both medications were withdrawn.

**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>No.</th>
<th>Underlying Diseases</th>
<th>Age at Treatment Initiation</th>
<th>Clopidogrel Dose</th>
<th>Duration of Follow-Up After Initiation of Clopidogrel Start</th>
<th>Complications</th>
<th>Stroke Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thrombotic</td>
<td>6 y</td>
<td>18.75 mg</td>
<td>0.95</td>
<td>3 y</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Cardioembolic</td>
<td>15 y</td>
<td>37.5 mg</td>
<td>0.5</td>
<td>3 y</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Arteriopathy</td>
<td>10 y 4 mo</td>
<td>37.5 mg</td>
<td>0.77</td>
<td>3 y</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Thrombotic</td>
<td>4 y 2 mo</td>
<td>37.5 mg</td>
<td>1.8</td>
<td>3 y</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Arteriopathy</td>
<td>5 y 5 mo</td>
<td>37.5 mg</td>
<td>1.5</td>
<td>3 y</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Arteriopathy (Vasculitis)</td>
<td>11 y</td>
<td>75 mg</td>
<td>0.9</td>
<td>3 y</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Multiple</td>
<td>6 y</td>
<td>25 mg</td>
<td>2.4</td>
<td>2 y</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>Idiopathic</td>
<td>16 y 3 mo</td>
<td>75 mg</td>
<td>1.1</td>
<td>2 y</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Cardioembolic</td>
<td>15 y 2 mo</td>
<td>75 mg</td>
<td>1.4</td>
<td>1.5 y</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>Arteriopathy</td>
<td>3 y 9 mo</td>
<td>18.75 mg</td>
<td>1.3</td>
<td>4 mo</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>Idiopathic</td>
<td>6 y</td>
<td>37.5 mg</td>
<td>1.3</td>
<td>2 y</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>Idiopathic</td>
<td>17 y</td>
<td>37.5 mg</td>
<td>1.5</td>
<td>1.5 y</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>Arteriopathy (Moyamoya)</td>
<td>16 y</td>
<td>75 mg</td>
<td>1.2</td>
<td>6 mo (discontinued)</td>
<td>Right hand numbness</td>
</tr>
<tr>
<td>14</td>
<td>Arteriopathy (Moyamoya)</td>
<td>10 y</td>
<td>37.5 mg</td>
<td>1.1</td>
<td>1 mo (discontinued)</td>
<td>Headache</td>
</tr>
<tr>
<td>15</td>
<td>Arteriopathy (Moyamoya)</td>
<td>1 y 6 mo</td>
<td>18.75 mg</td>
<td>1.5</td>
<td>6 mo (discontinued)</td>
<td>Bleed (post-op)</td>
</tr>
<tr>
<td>16</td>
<td>Arteriopathy</td>
<td>4 y</td>
<td>18.75 mg</td>
<td>1.6</td>
<td>1 y (discontinued)</td>
<td>Subdural bleed</td>
</tr>
<tr>
<td>17</td>
<td>Arteriopathy (Vasculitis)</td>
<td>5 y</td>
<td>37.5/18.75 mg</td>
<td>1.3</td>
<td>15 mo</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>alternate days</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Average dose 1.3 mg/kg per day; range 0.5–2.4 mg/kg per day.
Conclusion
Clopidogrel appears to be a reasonable option for children who cannot take ASA or who display ASA resistance. It should be used with caution when used in conjunction with ASA in children with multiple risk factors for intracranial hemorrhage and intracranial vasculopathies. Whether clopidogrel is effective at stroke prevention in children cannot be assessed in the current study.

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References
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