

# PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the  
University of Virginia Children's Hospital

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Volume 13 Number 2

February 2007

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## Use of Aspirin in Children with Cardiac Disease

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The history of aspirin begins with the use of willow or meadowsweet bark in many early cultures to relieve pain and reduce fever. Hippocrates wrote about the beneficial effects of willow bark powder to ease pain and reduce fever. The active component of willow bark extract, salicylic acid, was isolated in the early 1800's, but administration of the compound produced gastric irritation and bleeding. In 1897, Arthur Eichengrun and Felix Hoffman buffered the compound to produce acetylsalicylic acid (ASA), which reduced the adverse effects when ingested. Once in the blood, the drug was then rapidly hydrolyzed to active salicylic acid. On March 6, 1899, ASA was patented by Bayer with the brand name Aspirin.<sup>1,2</sup>

Over the past century, aspirin has become a mainstay as a nonprescription treatment for pain, fever, and inflammation after injury. While it has a long history of use in children, the association of aspirin with Reye's syndrome in the 1980's led to its limitation to only those children with medical conditions requiring its anti-inflammatory or antiplatelet effects. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of aspirin and its current uses in children with cardiac disease.

### Mechanism of Action

Aspirin directly and irreversibly binds to and acetylates specific serine residues on cyclooxygenase types 1 and 2 (COX-1 and COX-2). These isoenzymes catalyze the first step in prostanoic acid biosynthesis, the conversion of arachidonic acid to prostaglandin H<sub>2</sub>. Inactivation of these enzymes by aspirin results in inhibition of prostaglandin and thromboxane A<sub>2</sub> synthesis. The latter effect is mediated through COX-1 inhibition, and results in aspirin's ability to inhibit platelet aggregation at relatively low doses. This effect on platelet function lasts for the life of the platelet. At high doses, aspirin also inhibits COX-2 mediated formation of prostacyclin (prostaglandin I<sub>2</sub>), resulting in further inhibition of platelet aggregation.<sup>1-4</sup>

### Pharmacokinetics

Aspirin is rapidly absorbed from the stomach and small intestine, primarily by passive diffusion across the gastrointestinal (GI) tract. It is then rapidly hydrolyzed to salicylic acid by esterases in the GI mucosa and plasma. Aspirin has an average half-life in the plasma of 15 to 20 minutes. Oral or rectal administration of immediate-release aspirin typically results in peak plasma levels of salicylic acid within 1 to 2 hours. Salicylic acid is widely distributed throughout the body, with the highest concentrations found in the plasma, liver, renal cortex, heart, and lungs.<sup>3,4</sup>

Salicylic acid is metabolized via conjugation in the liver to form salicyluric acid and several other metabolites. In adults, the plasma half-life is approximately 6 hours.<sup>3</sup> A pharmacokinetic study of 10 children given a single dose of aspirin (mean 9.43±0.34 mg/kg) revealed an average half-life of 3.43 hours.<sup>5</sup> The metabolism of salicylic acid is saturable, with the rate of total body clearance decreasing at higher serum concentrations. In cases of overdose, the half-life may increase to more than 20 hours. Unchanged salicylic acid and its metabolites are excreted in the urine. Alkalinization of the urine increases drug excretion.<sup>3</sup>

### Aspirin Use in Kawasaki Disease

In 2004, two expert panels published recommendations for the management of Kawasaki disease.<sup>6,7</sup> This condition, an acute vasculitis, occurs most commonly in children and in 15 to 25% of untreated cases, results in the development of coronary artery aneurysms. In the consensus guidelines from the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy, treatment with intravenous immune globulin (IVIG) is recommended, along with high-dose aspirin (80-100 mg/kg/day) during the acute phase of the illness for its anti-inflammatory effects, followed by low-dose aspirin (3-5 mg/kg/day) for its antiplatelet effect for 7 weeks or longer.<sup>6</sup> In children with coronary

aneurysms, long-term anticoagulation with warfarin and low-dose aspirin is recommended.

Later that same year, the American Heart Association published an update of their treatment guidelines for Kawasaki disease.<sup>7</sup> The panel members recommended the same treatment regimen of IVIG and aspirin as described in the ACCP guidelines. High-dose aspirin (80-100 mg/kg/day) is recommended during the acute phase of the illness, with a duration of treatment determined by the prescriber (ranging from 48 hours to 14 days). After the acute phase, low-dose aspirin (3-5 mg/kg/day) is recommended until follow-up at 6-8 weeks has shown no coronary changes. For children who develop coronary enlargement, the authors recommended continuing aspirin therapy, with a duration determined by the prescriber.

As stated in the guidelines, aspirin should always be used in conjunction with IVIG; when used alone, it has not been shown to reduce the incidence of coronary aneurysms.<sup>8</sup> Although the recommendations of these expert panels regarding aspirin dosing are consistent, the benefit of high-dose aspirin in the acute phase remains controversial.<sup>8-10</sup> In 2002, Saulsbury compared high-dose and low-dose aspirin during the acute phase in 70 children with Kawasaki disease.<sup>9</sup> All patients received IVIG. The duration of fever was not significantly different between the groups (47±8 hours in the high-dose group versus 34±5 hours in the low-dose group; p=0.13). In a review of 162 children with Kawasaki disease treated during the acute phase with IVIG alone, Heish and colleagues found that 153 patients (94%) responded to treatment.<sup>10</sup> Based on their results, the authors concluded that the omission of high-dose aspirin during the acute phase did not alter the expected outcomes.

#### Prophylaxis after Cardiac Surgery

Children who have undergone surgery for congenital heart defects may require long-term antiplatelet therapy to prevent thrombosis. In the guidelines from the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy, low-dose aspirin (1-10 mg/kg/day) is recommended for primary prophylaxis in neonates with Blalock-Taussig shunts. The ACCP panel also recommends the use of aspirin, at doses of 6-20 mg/kg/day, as an alternative anticoagulant in children with mechanical valves who fail to respond to warfarin or have contraindications to its use.<sup>6</sup>

Although there is not a clear consensus in the literature regarding anticoagulation after Fontan surgery,<sup>11,12</sup> the ACCP Conference panel

recommends either aspirin (5 mg/kg/day) or heparin followed by warfarin as primary prophylaxis.<sup>6</sup> In a recent review of their Fontan patients, Barker and colleagues from the University of Michigan found a 9% incidence of cerebrovascular events (CVE) following surgery.<sup>13</sup> Seventy-nine percent of their patients received aspirin, 11% received warfarin, and 10% were not given anticoagulants. The patients receiving aspirin had a CVE rate of 2.4/1,000 patient-years, compared to a rate of 13.7/1,000 patient-years in those not receiving anticoagulation.

#### Drug Interactions

The concomitant use of aspirin with other anticoagulants or non-steroidal anti-inflammatory agents may place patients at risk for bleeding. In addition to the additive anticoagulant properties of aspirin and warfarin, aspirin can displace warfarin from its protein binding sites, resulting in greater free drug, prolongation of the prothrombin time, and an increase in the International Normalized Ratio (INR). Patients requiring multi-drug regimens should be closely monitored.<sup>3</sup>

Aspirin can also displace other highly protein-bound drugs, such as phenytoin and valproic acid, increasing the concentration of free drug. The renal clearance of acetazolamide and methotrexate is inhibited by aspirin, which can result in elevated serum concentrations of those drugs, predisposing the patient to toxicity. The use of aspirin is generally considered contraindicated in patients receiving high-dose methotrexate. Aspirin may also increase the effects of oral hypoglycemic agents.<sup>3</sup>

The efficacy of beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics may be reduced in patients taking aspirin, as a result of sustained prostaglandin inhibition and decreased renal blood flow. Aspirin may also decrease the efficacy of uricosuric agents (probenecid and sulfapyrazone).<sup>3</sup>

#### Adverse Effects

Aspirin is typically well tolerated. The most commonly reported adverse effects with aspirin include stomach pain and heartburn. Patients and their families should be aware of the need to report worsening of these symptoms, as well as vomiting of blood or bloody stools, which might indicate GI ulceration or perforation.

Hypersensitivity reactions, ranging in severity from urticaria to angioedema, bronchospasm, and anaphylactic shock are rare, but have been reported in children as well as adults. Other

adverse effects include rhabdomyolysis, interstitial nephritis, renal insufficiency, and hepatic dysfunction. Chronic aspirin use has been associated with iron deficiency anemia.<sup>3</sup>

High doses of aspirin may produce salicylism, with tinnitus, headache, confusion, hyperventilation, dehydration, diaphoresis, vomiting, and diarrhea. These symptoms may occur when plasma salicylate concentrations are within the range of 110-200 mg/dL. Severe toxicity (salicylate concentrations  $\geq$  300 mg/dL) may produce salicylism along with hyperthermia and severe metabolic acidosis in children, or respiratory alkalosis (due to hyperventilation) followed by metabolic acidosis in adults. Hypokalemia, hypoglycemia, cerebral edema and pulmonary edema may also occur. Treatment of overdose consists of gastric emptying, supportive care, and dialysis, if needed.<sup>1-3</sup>

### Reye's Syndrome

The routine use of aspirin as an OTC antipyretic and analgesic is no longer recommended in children because of the potential association with Reye's syndrome. This syndrome was first reported by Drs. Reye, Morgan, and Baral in 1963.<sup>14</sup> They described 21 children with encephalopathy and fatty degeneration of the viscera. The syndrome typically follows a viral illness, most often influenza or varicella. The patient often experiences a recovery period of 1-3 days, followed by severe vomiting and encephalopathy. Serum transaminases, bilirubin, and ammonia levels are often significantly elevated. Pathologic changes include microvesicular steatosis and swelling of the mitochondria with disruption of the cristae.<sup>15,16</sup>

In 1980, Starko published the first epidemiologic study of Reye's syndrome to evaluate a link with salicylate use.<sup>17</sup> Comparing 7 affected children with 16 controls, the investigators found that the children with Reye's syndrome had a significantly greater use of salicylates during their prodromal illness. Over the next decade, several other investigators produced similar results. In 1989, Forsyth and colleagues conducted one of the most rigorous reviews, comparing 24 Reye's syndrome patients to 48 matched controls.<sup>18</sup> In this population, 88% of the affected patients had received aspirin, compared to only 17% of the controls. Subsequent experimental studies, as well as long-term surveillance studies in the United Kingdom and Ireland, confirmed these findings.<sup>16</sup>

On December 28, 1982, the FDA first proposed a requirement for OTC and prescription salicylate-containing products to carry a warning against

use for the treatment of flu or chickenpox in children under 16 years of age because of the potential relationship with Reye's syndrome.<sup>19</sup> The following year, however, the FDA reversed its position because of the lack of evidence demonstrating a causal relationship. It wasn't until additional studies, including the Forsyth paper, became available that the labeling requirement became final for aspirin (3/7/86) and other salicylate-containing products (4/7/03).

No definitive studies have established a causal relationship between aspirin use and Reye's syndrome.<sup>15</sup> However, the available data, as well as the decline in reports of Reye's syndrome following the discontinuation of routine aspirin use in children, suggest that there is likely a link between the two. While a mechanism has not been clearly established, *in vitro* studies have suggested that impaired aspirin metabolism may play a role.<sup>16</sup>

Reye's syndrome appears to be rare in pediatric patients receiving long-term aspirin for its anti-inflammatory or antiplatelet effects, but has been reported.<sup>7</sup> In 2005, Wei and colleagues described a 10 month-old child receiving high-dose aspirin after the diagnosis of Kawasaki disease.<sup>20</sup> He exhibited poor activity, lethargy, tachycardia and tachypnea and was found to have hepatomegaly, increased serum transaminases, hyperammonemia, and a coagulopathy. A liver biopsy revealed findings consistent with Reye's syndrome. He recovered without sequelae.

Families of children taking aspirin should be aware of the need to contact their prescriber when the patient develops a viral illness, to determine if therapy should be interrupted or if further evaluation is needed. To lessen the risk for Reye syndrome, it is recommended that patients be given yearly influenza vaccines. Administration of the live varicella vaccine to children receiving chronic aspirin therapy remains controversial. If needed, another antiplatelet drug may be used for a 6-week period following vaccination to minimize patient risk.<sup>7</sup>

### Availability and Dosing Recommendations

Because of the rapid disintegration of aspirin in liquids, it is produced only in solid dosage formulations: tablets, powders, and suppositories. There are a variety of tablet formulations, including chewable, buffered, and enteric-coated products. Aspirin is also available in a wide range of dosage strengths; the most common are 81 mg, 325 mg, and 500 mg. Aspirin suppositories are available in 120, 200, 300, and 600 mg strengths, but smaller suppositories may be compounded for younger patients.<sup>3</sup>

As described previously, aspirin doses differ with the indication. High-dose aspirin (80-100 mg/kg/day) provides significant anti-inflammatory effects, while low-dose therapy (1-10 mg/kg/day) is used to provide antiplatelet effects. For pediatric patients, the chewable tablets may be halved or quartered to achieve the approximate dose and then crushed and mixed with a small amount of liquid. Aspirin may be taken with food or milk. All aspirin products should be stored in their original container and tightly sealed. When exposed to moisture, aspirin degrades to salicylic acid and acetic acid. Any aspirin product that smells like acetic acid (vinegar) should be discarded.<sup>3,6,7</sup>

### Conclusions

Although the possible link with Reye's syndrome has reduced its use as an antipyretic and analgesic, aspirin remains a useful anti-inflammatory and antiplatelet agent. In children with cardiac disease, it is often the drug of choice for long-term antiplatelet therapy.

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### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/26/07:

1. Tobramycin ophthalmic ointment was added to the Formulary.
2. The pancreatic enzyme products were streamlined to include only Ultrasec MT20, Pancrecarb MS-8, and Viokase powder.
3. Posaconazole (Noxafil<sup>®</sup>) was added to the Formulary for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 years and older who are at risk for these infections. It is a category A agent.
4. Ziprasidone mesylate intramuscular injection (Geodon<sup>®</sup>) was added for the management of acute agitation in patients with schizophrenia, with use restricted to Psychiatry.
5. The restrictions for Rifaximin (Xifaxin<sup>™</sup>) were amended to allow use in refractory Crohn's disease, pouchitis, and established small intestine bacterial overgrowth.
6. Insulin detemir (Levemir<sup>®</sup>) was added to the Outpatient Formulary.
7. Levalbuterol (Xopenex<sup>®</sup>) was rejected.

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