

## **Concomitant Use of Ibuprofen and Aspirin: Potential for Attenuation of the Anti-Platelet Effect of Aspirin**

Healthcare professionals should be aware of an interaction between low dose aspirin (81 mg per day) and ibuprofen which might render aspirin less effective when used for its anti-platelet cardioprotective effect. Healthcare professionals should advise consumers and patients regarding the appropriate concomitant use of ibuprofen and aspirin.

### **Summary**

- Existing data using platelet function tests suggest there is a pharmacodynamic interaction between 400mg ibuprofen and low dose aspirin when they are dosed concomitantly. The FDA is unaware of data addressing whether taking less than 400 mg of ibuprofen interferes with the antiplatelet effect of low dose aspirin.
- The clinical implication of this interaction may be important because the cardioprotective effect of aspirin, when used for secondary prevention of myocardial infarction, could be attenuated.
- For single doses of ibuprofen, the pharmacodynamic interaction can be minimized if ibuprofen is given at least 8 hours before or at least 30 minutes after immediate release aspirin (81mg; not enteric coated).
- The clinical implication of the interaction has not been evaluated in clinical endpoint studies.
- There is no clear data regarding the potential effect of chronic ibuprofen dosing of greater than 400mg on the antiplatelet effect of aspirin.
- The timing of dosing of ibuprofen and low-dose aspirin is important for preserving the cardioprotective effect of aspirin.

### **Recommendations for Concomitant Use**

- Health care providers should counsel patients about the appropriate timing of ibuprofen dosing if the patients are also taking aspirin for cardioprotective effects.
- With occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low dose aspirin.
- Patients taking immediate release low-dose aspirin (not enteric coated) and ibuprofen 400mg should take the ibuprofen at least 30 minutes after aspirin ingestion, or at least 8 hours before aspirin ingestion to avoid any potential interaction.
- Other nonselective OTC NSAIDs should be viewed as having potential to interfere with the antiplatelet effect of low-dose aspirin unless proven otherwise.
- Analgesics that do not interfere with the antiplatelet effect of low dose aspirin should be considered for populations at high risk for cardiovascular events.

- Recommendations about concomitant use of ibuprofen and enteric-coated low dose aspirin cannot be made based upon available data. One study showed that the antiplatelet effect of enteric-coated low dose aspirin is attenuated when ibuprofen 400mg is dosed 2, 7, and 12 hours after aspirin.<sup>6</sup>

## **Discussion**

### ***Background***

Ibuprofen has been marketed in the United States as an anti-inflammatory, analgesic, and antipyretic drug for decades. It is widely available in a variety of strengths and formulations for children and adults as single-ingredient over-the-counter (OTC) and prescription products, and can also be found in combination OTC and prescription products.

Chemically, ibuprofen is a propionic acid derivative and a member of the class of non-steroidal anti-inflammatory drugs (NSAIDs). The NSAIDs include aspirin, and several other classes of organic acids, including the propionic acid derivatives naproxen and ketoprofen, acetic acid derivatives diclofenac and indomethacin, and the enolic acid piroxicam, and newer agents such as celecoxib.

### ***How does ibuprofen work and why does it interact with aspirin?***

All NSAIDs work by inhibiting the enzyme cyclooxygenase (COX). Aspirin inhibits COX irreversibly, while all non-aspirin NSAIDs are reversible inhibitors of COX. There are two forms of cyclooxygenase; namely, COX-1 found in blood vessels, stomach and kidney, and COX-2, which is induced in settings of inflammation by cytokines and inflammatory mediators. A putative COX-3 has been suggested but not proven in humans.<sup>1</sup> All currently available OTC NSAIDs are nonselective COX inhibitors, and inhibit both COX-1 and COX-2 to varying degrees. The antipyretic, analgesic, and antiinflammatory actions of NSAIDs are related to their ability to inhibit COX-2. Side effects such as gastrointestinal (GI) bleeding and renal toxicity are a result of the inhibition of COX-1 and are well known complications of NSAID therapy<sup>2,3,4</sup>. By inhibiting COX-1, the NSAIDs prevent the formation of thromboxane from arachadonic acid, and thereby prevent thromboxane-induced platelet aggregation. Aspirin has an irreversible anti-platelet effect, while other NSAIDs, including ibuprofen, have a reversible anti-platelet effect.<sup>5</sup> Low dose aspirin is effective in the secondary prevention of cardiovascular events because of its antiplatelet effect. Because they bind at similar sites on COX, concurrent use of aspirin and ibuprofen may change the pharmacodynamic effect of either drug depending on the timing of dosing of each drug.

### ***What types of aspirin are currently available Over-the-Counter?***

Aspirin is available over-the-counter as a tablet, buffered tablet, effervescent tablet, or caplet in immediate-release formulations and as a tablet in enteric-coated formulations in strengths ranging from 81 mg to 500 mg.

### ***What is the interaction between aspirin and ibuprofen in single dose studies?***

It has been demonstrated in published and unpublished human ex vivo studies, that ibuprofen interferes with the antiplatelet activity of low dose aspirin (81 mg; not enteric coated) when they are ingested concurrently.<sup>6</sup> The mechanism by which this

occurs may be through competitive inhibition of the acetylation site of cyclooxygenase in the platelet. Both ibuprofen (reversible inhibition) and aspirin (irreversible inhibition) occupy nearby sites on cyclooxygenase, such that the presence of ibuprofen interferes with aspirin binding. Once the ibuprofen releases from the binding site, COX will not be inhibited because some aspirin available to bind will have been excreted due to aspirin's short half-life. This ibuprofen interference attenuates the expected aspirin-mediated irreversible inhibition of thromboxane B<sub>2</sub> (TXB<sub>2</sub>) production and attenuates the expected inhibition in platelet aggregation.

There are no clinical endpoints studies conducted specifically to evaluate the interaction. Attenuation of 90% or more of the antiplatelet effect of aspirin has been defined as clinically significant<sup>7</sup> by some investigators. Unpublished single dose trials with ibuprofen 400 mg indicate that interference with aspirin's antiplatelet activity, as measured by TXB<sub>2</sub> levels and platelet activation studies, occurs when ibuprofen is taken within 30 minutes after immediate release aspirin dosing. The interaction also occurs when a single dose of ibuprofen 400 mg is taken within 8 hours prior to aspirin dosing. At least 8 hours should elapse after ibuprofen dosing, before giving aspirin, in order to avoid significant interference.

***What is the interaction between aspirin and ibuprofen in a multiple dose study?***

One published study demonstrated that if immediate-release aspirin 81 mg is given daily for an 8 day run-in, followed by ibuprofen 400 mg dosed at 1, 7, and 13 hours after the daily aspirin dose for the next 10 days, then no interference is found with the aspirin-induced inhibition of thromboxane, when measured as TXB<sub>2</sub> production ex vivo.<sup>7</sup>

***How can the data regarding the interaction between aspirin and ibuprofen from the single and multiple dose studies be interpreted?***

It thus appears that taking low-dose immediate release aspirin at least 30 minutes before ibuprofen will preserve the anti-platelet effect of aspirin.

***Does the same interaction occur with enteric-coated aspirin?***

A published study showed that with no aspirin run-in period, enteric-coated aspirin 81 mg given daily with ibuprofen 400 mg dosed 2, 7, and 12 hours after aspirin, leads to interference with aspirin-induced inhibition of thromboxane, when measured as TXB<sub>2</sub> production ex vivo.<sup>6</sup> This seems to contradict the observations of other studies using non-enteric-coated aspirin but may be explained by the absorption of enteric-coated aspirin being delayed compared to non-enteric-coated aspirin. More data are needed to reach a conclusion about the interaction between a single daily enteric-coated low dose aspirin and multiple daily doses of ibuprofen.

***What is the relationship between these observations and clinical outcomes?***

There has not been a prospective, randomized clinical trial with pre-identified cardiovascular endpoints that could provide data to clarify the clinical consequence of such concomitant dosing with ibuprofen and low dose aspirin. Epidemiological data on the cardiovascular event clinical outcome of concomitant dosing has been equivocal.<sup>8,9,10,11,12,13,14</sup>

### ***Do other nonprescription pain relievers show a similar interaction with aspirin?***

Acetaminophen appears to not interfere with the antiplatelet effect of low dose aspirin.<sup>6</sup> FDA is unaware of studies that have looked at the same type of interference by ketoprofen with low dose aspirin. One study of naproxen and low-dose aspirin has suggested naproxen may interfere with aspirin's anti-platelet activity when they are co-administered.<sup>15</sup> However, naproxen 500 mg administered two hours before or after the administration of aspirin 100 mg did not interfere with aspirin's antiplatelet effect. There is no data looking at doses of naproxen less than 500mg. Naproxen is available OTC only as 220mg. Prescription strengths of naproxen are 250, 375, and 500mg.

### **Conclusions**

- There may be a pharmacodynamic interaction between ibuprofen and aspirin when they are dosed concomitantly. This interaction may interfere with the antiplatelet activity of the aspirin, as measured by TXB<sub>2</sub> levels and platelet activation.
- The clinical implication of this interaction is unclear, but may be important since the cardioprotective effect of aspirin, when used for secondary prevention of myocardial infarction, could be minimized or negated.
- A negative clinical impact on aspirin's cardioprotection is unlikely from an occasional dose of ibuprofen because the effect of aspirin taken daily is long-lasting.
- Ibuprofen given at least 30 minutes after immediate-release aspirin or at least 8 hours before taking immediate-release aspirin does not appear to interfere with aspirin's anti-platelet effect.

### **References**

- <sup>1</sup> Chandrasekharan NV et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. *Proc Nat Acad Sci* 2002; 99: 13926-13931.
- <sup>2</sup> Insel P: Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout. *In* Hardman JG, Gilman AG, Limbird LE (eds): *Goodman's & Gilman's The Pharmaceutical Basis of Therapeutics*, 5<sup>th</sup> ed. New York, Mcgraw-Hill, 1996: 617-43.
- <sup>3</sup> Lanza FL, et al: A guideline for treatment and prevention of NSAID-induced ulcers. *Am J Gastroenterol* 1998; 93(11):2037-46.
- <sup>4</sup> Altman RD, et al: Recommendations for the medical management of osteoarthritis of the hip and knee; 2000 update. *Arthritis Rheum* 2000; 43(9): 1905-15.
- <sup>5</sup> Cheema A. Should people on aspirin avoid ibuprofen? A review of the literature. *Cardiol in Review* 2004; 12: 174-176.
- <sup>6</sup> Catella-Lawson et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *NEJM* 2001; 345: 1809-1817.
- <sup>7</sup> Cryer B et al. Double-blind, randomized, parallel, placebo-controlled study of ibuprofen effects on thromboxane B<sub>2</sub> concentrations in aspirin-treated healthy adult volunteers. *Clin Ther* 2005; 27: 185-191.
- <sup>8</sup> Curtis JP et al. Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study 2003; *BMJ* 327: 1322-1333.

- <sup>9</sup> Rodriguez, LAG. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. *Circulation* 2004; 109:3000-3006.
- <sup>10</sup> Hudson M et al. Anti-inflammatory drugs are associated with a decreased risk of recurrent acute myocardial infarction in patients on aspirin. *Arthritis Rheumatism* 2002 (Abstract); 46:S617.
- <sup>11</sup> Patel TN and Goldberg KC. Use of Aspirin and Ibuprofen Compared With Aspirin Alone and the Risk of Myocardial Infarction. *Arch Intern Med* 2004; 164:852-856.
- <sup>12</sup> MacDonald TM and Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003;361: 573-574.
- <sup>13</sup> Kurth, T et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* 2003; 108:1191-1195.
- <sup>14</sup> Kimmel SE et al. The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Coll Cardiol* 2004; 43:985-90.
- <sup>15</sup> Capone ML et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. *J Am Coll Cardiol* 2005; 45: 1302-1303.