# Painkiller undermines aspirin's anti-clotting action

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Millions of Americans take Celebrex for arthritis or other pain. Many, if they are middle-aged or older, also take a low-dose aspirin tablet daily to reduce the risk of heart attack and stroke. Yet they may be getting little protection, because Celebrex keeps the aspirin from doing its job effectively, a new study suggests.

In laboratory studies, University of Michigan researchers found that several coxibs, the drug class to which Celebrex belongs, interfere with aspirin's ability to discourage blood clots, if the aspirin is taken in low doses. Celebrex, also known as celecoxib, is the only coxib currently on the market. The results appear online in the Proceedings of the National Academy of Sciences.

Doctors frequently advise daily low-dose aspirin (81 mg) for patients who have heart conditions, notably a serious form of angina known as unstable angina, or for patients who are at risk of second heart attacks. Aspirin is well-known for its ability to discourage formation of blood clots that can lead to heart attack and stroke. In addition, arthritis patients who take Celebrex regularly are often put on low-dose aspirin because this is thought to counteract Celebrex's own potential clot-promoting effect.

"There are many people who take low-dose aspirin, perhaps as many as half of men over 50. If they are also prescribed Celebrex for arthritis or other pain, our results suggest that the Celebrex will probably interfere with the aspirin's action," says William L. Smith, Ph.D., the study's

senior author, Minor J. Coon Professor of Biological Chemistry and chair of the biochemistry department at the U-M Medical School.

"The greatest risk is having people take Celebrex who are taking aspirin for cardiovascular problems that are known to be mitigated by aspirin, including patients with unstable angina or those at risk for a second heart attack," he says. In unstable angina, small clots form in arteries and interfere with blood flow.

Previous studies of healthy subjects found no ill effect on blood clotting when Celebrex was combined with aspirin at higher doses, specifically a daily "regular" aspirin tablet (324 mg), Smith notes.

So it may be that a higher aspirin dose, or spreading out the time between taking low-dose aspirin and Celebrex, will allow aspirin to be effective. Aspirin's undesirable effects on the gastrointestinal tract at higher doses when taken long-term would have to be taken into account.

First, though, the effect seen in the U-M study needs to be replicated in studies of low-dose aspirin and Celebrex in people, perhaps in older patients who have conditions such as rheumatoid arthritis, says Smith. If the effect holds true in people, it will be important to determine if a balance in dose and/or dose regimens can be found so that aspirin and Celebrex can both be effective.

## Research details

The researchers used biochemical measurements and X-ray crystallography to discover that celecoxib binds to COX-1, an enzyme that promotes clotting, and slows aspirin's COX-1-blocking action. In animal studies, the researchers found more clumping of platelets - the initial stage of clotting - in blood from animals given Celebrex and low-dose aspirin than in animals given only low-dose aspirin.

More information: Proceedings of the National Academy of Sciences, advance publication online Dec. 1, www.pnas.org/cgi/doi/10.1073/pnas.0909765106

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