Allopurinol May Act as Anti-Ischemic in Angina

BY SHARON WORCESTER

FROM THE LANCET

High-dose allopurinol, a safe and inexpensive xanthine oxidase inhibitor used for decades for the treatment of gout, also appears to be an effective anti-ischemic drug in patients with angina pectoris, according to findings from a randomized, placebo-controlled study.

VITALS

Major Finding: Allopurinol in patients with angina pectoris improved time to ST depression from 232 seconds at baseline to 249 seconds and 298 seconds in the placebo and treatment groups, respectively, for an absolute improvement of 43 seconds (19%).

Data Source: A randomized, placebo-controlled, double-blinded, crossover study of 65 patients.

Disclosures: The study was funded by the British Heart Foundation. The University of Dundee and one of the study authors have applied for a patent for the use of xanthine oxidase inhibitors to treat anginal chest pain. Dr. Noman and the other authors declared no conflicts of interest. Dr. Antony and Dr. Dargie indicated that they have no financial conflicts.

In 65 patients in the double-blind crossover study, allopurinol was shown during a standard exercise test to significantly improve median overall time to ST depression—the primary end point of the study—by a point estimate (the absolute difference between allopurinol and placebo) of 43 seconds, for a 19% improvement. It also significantly improved median exercise time and time to chest pain by point estimates of 58 and 38 seconds, respectively, Dr. Awsan Noman of the University of Dundee, Scotland, and colleagues reported online June 8 in The Lancet.

Time to ST depression improved from 232 seconds at baseline to 249 seconds and 298 seconds in the placebo and treatment groups, respectively; total exercise time improved from 301 seconds at baseline to 307 seconds and 393 seconds in the two groups, respectively; and time to symptoms improved from 234 seconds at baseline to 272 seconds and 304 seconds in the two groups, respectively, the investigators reported (Lancet 2010 June 8 [doi:10.1016/S0140-6736(10)60391-1]).

The patients were aged 18-85 years and had angiographically documented coronary artery disease, a positive exercise tolerance test, and stable chronic angina pectoris for at least 2 months prior to enrollment. They were randomized to receive allopurinol daily or placebo for 6 weeks. Allopurinol in the first phase of the study was given at a dose of 100 mg once daily in the first week, 300 mg once daily in the second week, and 300 mg twice daily in weeks 3-6; the 600-mg daily dose was used in the crossover phase, which immediately followed the first phase, because it was shown to be the most effective dose for improving endothelial function and oxidative stress, they said.

The findings suggest that "endogenous xanthine oxidase activity contributes somehow to exercise-induced myocardial ischaemia," the investigators wrote, adding that the magnitude of the anti-ischemic effect of allopurinol in this study appeared similar to that seen with other antianginal drugs.

Allopurinol significantly improved median overall time to ST depression, the study's primary end point.

DR. NOMAN

"Allopurinol might now be regarded as a potential drug for angina," the investigators wrote, citing numerous advantages over other available antianginal drugs, including lower cost, a favorable long-term safety record over more than 40 years of use in gout patients, and better tolerability; allopurinol does not reduce blood pressure or heart rate, and does not cause side effects such as headache and tiredness common with nitrates and beta-blockers, they noted.

Further study is needed to better characterize the "the precise place of allopurinol in the management of angina pectoris," but it may be a particularly appealing drug for use in developing countries where the availability of more expensive treatments is limited, they concluded.

Stable angina is the most frequent initial presentation of coronary heart disease; the condition can lead to acute coronary syndrome, particularly in higher risk groups; and it also has high rates of residual symptoms and impaired quality of life even in well-managed patients.

Nonetheless, the condition has received little attention, compared with unstable angina and other acute coronary syndromes, Dr. Renjith Antony and Dr. Henry J. Dargie of the Scottish Advanced Heart Failure Service, Golden Jubilee National Hospital, West Dunbartonshire, Scotland, said in an editorial.

The report by Dr. Noman and colleagues is interesting and welcome in that it will "focus attention on the unmet needs of patients with the most common, and frequently troublesome, manifestation of coronary heart disease," they wrote (Lancet 2010 June 8 [doi:10.1016/S0140-6736(10)60578-8]). ■

Two NSAIDs Were Associated With Increase in Heart Risks

BY DIANA MAHONEY

FROM CIRCULATION: CARDIOVASCULAR QUALITY AND OUTCOMES

The nonsteroidal anti-inflammatory drugs rofecoxib and diclofenac were linked to increased cardiovascular mortality and morbidity in a nationwide cohort of otherwise healthy Danish residents, while naproxen appeared to be associated with the least cardiovascular risk, researchers reported.

Dr. Emil Loldrup Fosbøl of Gentofte University Hospital in Hellerup, Denmark, and colleagues reported that patients in the study taking the nonselective NSAID diclofenac (Voltaren, Cataflam) had a 91% increased risk of cardiovascular death, compared with patients with no NSAID history, and patients taking the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib (Vioxx), which was withdrawn from the market in 2004 because of poor cardiovascular safety, had a 66% increased risk.

The investigators also observed a small, dose-dependent trend for increase in cardiovascular risk associated with ibuprofen, while no such relationship was observed with naproxen, they wrote (Circ. Cardiovasc. Qual. Outcomes 2010 June 8 [doi: 10.1161/CIRCOUTCOMES.109.861104]).

The epidemiologic study included data for 1,028,437 individuals, median age 39, collected from 1997 through 2005. Approximately 45% of the cohort had a history of some NSAID use during this time.

To determine whether specific NSAIDs carried a risk of cardiovascular adverse events, the investigators compared cause-specific mortality and hospitalizations for individuals with and without a history of NSAID use. They estimated the risk of cause-specific death associated with exposure to NSAIDs (ibuprofen, naproxen, diclofenac, rofecoxib, and celecoxib) using two statistical methods: case-crossover and Cox proportional-hazard regression analysis.

In the case-crossover analyses, diclofenac use was associated with a significant increase in the risk of cardiovascular death, coronary death, or nonfatal myocardial infarction, as well as fatal or nonfatal stroke, with a clear dose-dependent relationship, the authors wrote. The dose-dependent association is especially worrying, according to the authors, "because diclofenac more often is used in high doses compared with the other drugs."

The crossover analyses also showed a significant relationship between rofecoxib treatment and an increased risk of cardiovascular death and the composite of coronary death or nonfatal MI and a nonsignificant trend for increased risk of fatal or nonfatal stroke, while no such relationships were observed for celecoxib (Celebrex), the authors reported. Additionally, high doses of ibuprofen were associated with a significant increased risk of coronary death or nonfatal MI and fatal or nonfatal stroke, they wrote.

In the Cox proportional hazard analysis, diclofenac was linked with increased risk of cardiovascular death in high doses and a dose-dependent increased risk of coronary death or nonfatal MI and fatal or nonfatal stroke; rofecoxib demonstrated a similar but statistically nonsignificant pattern for fatal and nonfatal stroke and an increased risk of coronary death or nonfatal MI and cardiovascular death; and celecoxib showed a "small and statistically insignificant trend" toward increased risk of coronary death, nonfatal MI, and fatal/nonfatal stroke, according to the authors.

Ibuprofen showed a dose-dependent association with coronary and stroke event risk in the Cox analyses, with a decreased risk of coronary death, nonfatal MI, and stroke in low doses and trend for increased risk in high doses, and, as in the crossover analysis, "naproxen was associated with a trend for neutral or decreased risk of all the examined end points," they wrote.

In repeat analyses conducted on a population of NSAID users and sex-, age-, and time-matched NSAID nonusers, a trend for a higher increase in cardiovascular risk was associated with use of all of the NSAID drugs, the authors reported. ■

Disclosures: *The authors report no financial conflicts relevant to this investigation.*

Risk of Cardiovascular Events in Users of Selected NSAIDs, Compared With Nonusers

	Cardiovascular death		Coronary death or nonfatal MI		Fatal or nonfatal stroke	
	Events	HR	Events	HR	Events	HR
Diclofenac	218	1.20*	229	1.83*	195	2.00*
Ibuprofen	453	0.88*	465	1.31*	412	1.47*
Rofecoxib	78	1.64*	61	1.84*	33	1.12

*Significantly different from sex-, age-, and time-matched non-NSAID users.

Note: Based on a case-control historic study of 1,028,437 healthy Danish individuals; HR, hazard ratio.

Source: Circulation: Cardiovascular Quality and Outcomes