



Small placebo controlled study: Allopurinol may be an effective treatment option for chronic stable angina

Allopurinol is a xanthine oxidase inhibitor. Experimentally, inhibiting xanthine oxidase reduces the heart's oxygen consumption during exercise. Researchers from the University of Dundee, Scotland, wanted to test their theory that decreasing myocardial oxygen demand during exercise would increase exercise tolerance.

From January 2007 through July 2008, 65 patients with angiographically documented coronary artery disease and a history of stable angina, with a follow-up for a minimum of three months, were enrolled. 83% were males. The average age was 65 years.

Baseline exercise tolerance tests were established, and the subjects were evenly randomised to 600 mg allopurinol daily, or to placebo with standard anti-anginal therapy. Subjects underwent exercise testing after six weeks, and then were crossed over to the comparator arm.

When compared with baseline, 85% of subjects given allopurinol (51) improved their time to ST depression; while 58% of subjects

given placebo (35) showed improvement.

More of the subjects taking allopurinol showed an improvement in total exercise time (47 versus 27, 78% versus 45%), and times of chest pain (45 versus 33, or 75% versus 55%). However, treatment did not alter the reason for ending exercise tolerance testing. Allopurinol was also found to reduce the concentration of the biomarker brain natriuretic peptide from baseline, but it did not affect C-reactive protein concentrations (both of these are biomarkers for atherosclerosis). Five patients dropped out of the study. They had worse baseline angina and were on more daily nitroglycerin.

Reporting in the *Lancet*, the researchers said the results showed that exercise tolerance tests showed that patients randomised to a high dose allopurinol for six weeks significantly improved time to ST depression ($P = 0.002$), total exercise time ($P = 0.003$), and time to chest pain ($P = 0.001$), compared to subjects on placebo with standard anti-anginal therapy.

The main limitation of the study is the small

size.

An accompanying commentary stated that further work is needed to confirm the putative anti-ischemic effect of allopurinol, and also to understand the mechanism of action; however the study adds allopurinol to a growing list of drugs that tests conventional wisdom on what constitutes anti-anginal therapy. (However, it is not clear if large-scale randomised trials of allopurinol will ever come about because allopurinol is off patent.)

The senior author and the University have applied for a patent for the use of xanthine oxidase inhibitors to treat anginal chest pain.

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Sources: (1) Noman A, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet* 2010; DOI: 10.1016/S0140-6736(10)60391-1. (2) Antony R, Dargie HJ. Allopurinol for chronic stable angina: old drug, new tricks? *Lancet* 2010; DOI: 10.1016/S0140-6736(10)60578-8.

Fructose may be linked to hypertension

A cross-sectional study, from the University of Colorado and published in the Journal of the American Society of Nephrology, showed that people who consumed at least 74 grams of fructose (present in about two-and-a-half soft drinks) a day appear to have a higher risk of hypertension. Compared to lower level consumption, there were 26% to 77% greater odds of crossing various thresholds of elevated blood pressure ($P < 0.05$ for all).

There is increasing consumption of fructose in developed countries, primarily due to the addition of table sugar or high fructose corn syrup to soft drinks, fruit drinks, candy, dairy-based desserts and bakery products. The authors wanted to explore whether there was an association with the increasing prevalence of hypertension.

They studied data from 4,528 adults with no medical history of hypertension, included from a health survey from 2003 to 2006 (the National Health and Nutrition Examination Survey or NHANES). 61% had a systolic blood pressure (SBP) < 120 mm Hg. 30% were pre-hypertensive (systolic pressure 120 to 139 mm Hg). The rest had stage 1 or stage 2 hypertension (6% and 2%, respectively).

A self-administered dietary questionnaire was

used to determine fructose intake (consumption of fruits was excluded). The median fructose intake was 74 grams a day. Increasing fructose intake was found to be associated with increasing SBP (reaching borderline statistical significance of $P = 0.05$). Various factor were then adjusted for – demographics; co-morbidities; physical activity; smoking; caloric intake; dietary confounders like total carbohydrate, alcohol, salt, potassium, and vitamin C intake, and so on. Fructose intake of 74 grams per day or more was associated with higher odds of increased SBP pressure – 135/85 mm Hg with OR 1.26; 140/90 mm Hg with OR 1.30; 160/100 mm Hg with OR 1.77 ($P < 0.05$ for all). Further analysis showed that fructose intake was associated with SBP, but not diastolic blood pressure.

The authors said that there are several possible mechanisms to explain the positive association. These included stimulation of uric acid, inhibition of endothelial nitric oxide synthase system, stimulation of the sympathetic nervous system, or direct increased sodium absorption in the gut.

The authors noted that some previous studies have not found an association between fructose consumption and hypertension. The authors thought that this could be because of

the high fructose consumption in their current study. Also, some previous studies looked only at consumption of soft drink, or included consumption of naturally-occurring fructose in fruit.

The authors also state that this study does not establish a causal relationship between fructose and blood pressure, as it uses cross-sectional data, relies on self-reports, and they could not rule out the possibility of confounding by glucose in food.

Despite the limitations, the authors write that limiting fructose intake to reduce cardiovascular disease is readily feasible; but they caution that prospective studies are needed to assess whether decreased fructose intake will actually reduce the incidence of hypertension.

One of the co-authors had written a book published in 2009, which implicates fructose in various health problems, and which gives advice on how to cut fructose intake by making substitutions in daily meal plans.

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Source: Jalal D, et al. Increased fructose associates with elevated blood pressure. *J Am Soc Nephrol* 2010; DOI: 10.1681/ASN.2009111111.