European Review for Medical and Pharmacological Sciences 2016; 20: 756-761

Allopurinol ameliorates cardiac function in non-hyperuricaemic patients with chronic heart failure

J. XIAO[1], S.-B. DENG[2], Q. SHE[2], J. LI[1], G.-Y. KAO[1], J.-S. WANG[1], Y. MA[1]

[1]Department of Cardiology, Chongqing Medical Emergency Center, Chongqing, China
[2]Department of Cardiology, the Second Affiliated Hospital of Chongqing University of Medical Sciences, Chongqing, China

Abstract. – OBJECTIVE: This study sought to observe the effects of allopurinol on the cardiac function of non-hyperuricaemic patients with chronic heart failure and determine the safety of allopurinol for clinical applications.

PATIENTS AND METHODS: A group of 125 consecutive cases of non-hyperuricaemic patients with chronic heart failure who were treated at Chongqing Emergency Medical Centre between July 2011 and June 2012 were enrolled and were randomly divided into allopurinol (300 mg/day) group (n=62) and control group (n=63). During the six months treatment period, levels of cardiac function, brachial artery endothelial function, inflammatory cytokines, and biochemical markers were routinely examined.

RESULTS: After three months of allopurinol treatment, patients exhibited an increase in flow-mediated vasodilatation (FMD) of brachial artery, whereas, after six months of treatment, the cardiac function classification was improved; plasma levels of brain natriuretic peptide and tumour necrosis factor-α were decreased; left ventricular internal diameter was diminished; and the ejection fraction was increased ($p<0.01$ for all the parameters) in patients. Serum uric acid level was decreased during the treatment period for both groups, with no significant difference between the two groups. Liver and kidney dysfunction was not observed among the study participants, and no significant increase in creatine kinase level was detected for either treatment group.

CONCLUSIONS: For non-hyperuricaemic patients with chronic heart failure, the addition of six months of allopurinol therapy was safe and effective. Moreover, in these patients, allopurinol treatment not only can significantly ameliorate the left ventricular function and reduce the level of inflammatory factors but could also improve endothelial function.

Key Words:
Allopurinol, Oxidative stress, Heart failure, Uric acid.

Introduction

Many mechanisms contribute to the development of heart failure, including the presence of inflammatory factors, endothelial dysfunction, and oxidative stress[1]. Among these mechanisms, oxidative stress plays an important role in the pathophysiological process of cardiac remodelling and dysfunction[2,3]. Previous studies have demonstrated that in failing myocardial tissue, there are high levels of expression and activation of xanthine oxidase, which mediates myocardial hypertrophy and dilatation by catalyzing the generation of large quantities of reactive oxygen species (ROS)[3-5]. Allopurinol, a competitive inhibitor of xanthine oxidase[6] is currently used for the clinical treatment of gout. However, allopurinol can also significantly decrease the generation of ROS[7]; suppress hypertrophy and dysfunction of the ventricular chambers of failing hearts[8-10]; reduce the hospitalization and mortality rate of patients with chronic heart failure[11-13]; improve vascular endothelial function[14,15]; and enhance peripheral blood flow[16]. Furthermore, the aforementioned benefits occur independently of reduction in uric acid level. However, previous studies have suggested that allopurinol is unable to improve cardiac function or clinical events among the general population of patients with heart failure but instead can only benefit hyperuricaemic heart failure patients[17]. In addition, several potential adverse effects of allopurinol treatment merit attention[18]. Therefore, this study sought to evaluate the clinical benefits of allopurinol treatment in non-hyperuricaemic patients with chronic heart failure and assess the safety of allopurinol for clinical applications.

Corresponding Author: Yu Ma, MD; e-mail: yr7964@sina.com

Patients and Methods

Case Selection and Grouping

For this study, 125 consecutive cases of non-hyperuricaemic patients with chronic heart failure who were treated at Chongqing Emergency Medical Centre between July 2011 and June 2012 were enrolled. Among these patients, there were 71 cases of coronary artery disease (CAD) that had been verified by coronary angiography, including 37 cases of anterior myocardial infarction, 21 cases of inferior wall myocardial infarction, and five cases of lateral myocardial infarction; 29 cases of dilated cardiomyopathy (DCM), strictly excluding cardiomyopathies caused by ischemia, alcohol, or various other factors; and 25 cases of other diseases. The patients were randomly divided into an allopurinol group (62 patients), who received standard drug therapy against heart failure supplemented with 300 mg/day of allopurinol (Chongqing Qingyang Pharmaceuticals, China Food and Drug Administration approval number H50021422) and a control group (63 patients), who received standard drug therapy against heart failure; the treatment period was six months. Following inclusion criteria were used for this study: (1) 43-71 years of age; (2) class II to class III heart failure according to the New York Heart Association (NYHA) classification scale; (3) normal serum levels of uric acid; (4) a stable health condition which included treatment with standard anti-heart failure drugs, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers, digoxin, and/or diuretics, as well as statins (among a subset of the CAD patients); and (5) agreement to participate in this study accompanied by a signed informed consent form. Exclusion criteria used for this study were: (1) verified or suspected hypertension and/or diabetes; (2) an autoimmune disease and/or hepatic or renal insufficiency; and (3) an allopurinol allergy. This study was approved by the Ethics Committee of Chongqing Emergency Medical Centre.

Collection and Testing of Blood Samples

A peripheral venous blood sample was obtained from each patient at the time of enrolment in the study and after six months of treatment. Plasma was separated from these blood samples and used for testing. Enzymatic approaches were applied to determine various biochemical parameters of each plasma sample, using an automatic biochemistry analyzer, whereas plasma levels of tumour necrosis factor-α (TNF-α) and brain natriuretic peptide (BNP) were measured by enzyme-linked immunosorbent assay (ELISA).

Testing of Brachial Artery Endothelial Function

At study enrolment and after three months of treatment, colour ultrasonography diagnostic examinations were performed on age- and gender-matched DCM patients to assess brachial artery endothelial function and determine the baseline internal diameter (D_0), reactive hyperaemia diameter (D_1), and nitroglycerine-influenced diameter (D_2) of this brachial artery. The percentage change in flow-mediated vasodilation (FMD) was calculated using the formula FMD (%)=(D_1-D_0)/D_0×100%, whereas the change in vascular diameter after the sublingual administration of nitroglycerine (NTG) was calculated using the formula NTG-MD(%)=(D_2-D_0)/D_0×100%.

Evaluation of Left Ventricular Function

At the time of enrolment and after six months of treatment, the left ventricular function of each patient in both treatment groups was evaluated using the NYHA classification system. In addition, for each patient, left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were determined, and left ventricular ejection fraction (LVEF) was measured using the biplane Simpson method.

Evaluation of Safety and Follow-up

Drug safety was evaluated by monitoring the liver function, kidney function, and creatine kinase levels of study participants at the enrolment time and after six months of treatment. Patients were followed-up for the subsequent six to eighteen months to observe the long-term effects of allopurinol on cardiac events. For the purpose of this study, cardiac events were defined as cardiovascular death and hospitalization for heart failure.

Statistical Analysis

The SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used to establish a database. Data are expressed as means ± standard deviation (±*s*). Independent-samples t-tests were employed for between-group comparisons of count data, and χ^2 tests were utilized for between-group comparisons of rates. Count data before and after the treatments were compared using paired-samples

Table I. Clinical data comparison of the allopurinol and control groups.

Index	Control group (n=63)	Allopurinol group (n=62)
Age	55.3 ± 14.7	48.5 ± 12.4
Male (%)	47 (74.6)	45 (72.6)
Aetiology		
CAD (%)	36 (57.1)	35 (56.5)
DCM (%)	14 (22.2)	15 (24.2)
Other (%)	13 (20.7)	12 (19.3)
Course (year)	6.2 ± 3.9	5.8 ± 2.3
Pharmacotherapy		
ACEIs (%)	82.6	81.3
ARBs (%)	19.4	16.9
β-blockers (%)	90.3	96.5
Diuretics (%)	80.6	93.3
Digoxin (%)	58.4	56.7
Statins (%)	35.5	32.7

t-tests. Parameter relationships were assessed by linear regression analysis. $p<0.05$ was considered statistically significant.

Results

Clinical Data

There were no significant differences between the two treatment groups with respect to the various baseline conditions that were examined, including age, gender, aetiology, disease course, and clinical indicators. The two treatment groups also featured similar percentages of patients who used various types of standard anti-heart failure drugs, including ACEIs and β-blockers (Table I).

Changes in Cardiac Function

For the study participants, plasma BNP levels were significantly correlated with NYHA functional class and LVEF ($p<0.01$). After six months of treatment, the patients in the allopurinol group exhibited significantly improved NYHA functional classes, decreased plasma BNP levels, reduced left ventricular internal diameters, and increased LVEF values ($p<0.01$ for these parameters). But the patients in the control group displayed improved NYHA functional classes ($p<0.05$) without a significant increase in LVEF values. No significant change from pretreatment baseline was observed for blood sugar and blood pressure in either group after six months of treatment (Table II).

Changes in Brachial Artery Endothelial Function

Relative to baseline levels, the FMD levels of DCM patients in the control group did not change significantly after three months of treatment ($p>0.05$), whereas the FMD levels in the experimental group increased significantly after three months of drug treatments that incorporated allopurinol therapy ($p<0.01$). No significant change in NTG-MD values was observed for both groups after three months of treatment (Table III).

Changes in Plasma TNF-α Levels

Compared to the baseline, the plasma TNF-α levels of patients in the control group were not significantly changed after six months of treatment, whereas the plasma TNF-α levels of patients in the allopurinol group were significantly decreased after six months of allopurinol-enhanced treatment ($p<0.01$) (Table IV).

Table II. A comparison of cardiac function in the allopurinol and control groups after six months of treatment.

Index	Baseline (n=125)	Control group (n=63)	Allopurinol group (n=62)
NYHA	2.45 ± 0.50	2.33 ± 0.41*	2.02 ± 0.30$^{**\#}$
BNP (pmol/L)	1157.4 ± 554.4	911.2 ± 406.5	544.7 ± 377.8$^{**\#}$
LVEDD (mm)	66.0 ± 8.3	64.8 ± 9.7*	62.5 ± 9.8$^{**\#}$
LVESD (mm)	54.3 ± 10.4	52.7 ± 11.5*	49.1 ± 12.3$^{**\#}$
LVEF (%)	37.7 ± 12.0	40.1 ± 11.3	44.5 ± 12.7$^{**\#}$
Systolic pressure (mmHg)	113.5 ± 18.4	113.4 ± 14.2	114.5 ± 17.6
Diastolic pressure (mmHg)	74.2 ± 11.1	71.8 ± 9.8	73.8 ± 11.6
Fasting plasma glucose (mmol/L)	5.15 ± 0.47	5.24 ± 0.56	5.21 ± 0.39

$^{*}p<0.05$ compared to baseline; $^{**}p<0.01$ compared to baseline; $^{\#}p<0.01$ compared to control group.

Table III. A comparison of brachial artery endothelial function in the allopurinol and control groups after three months of treatment.

Index	Baseline (n=29)	Control group (n=14)	Allopurinol group (n=15)
D0 (mm)	3.58 ± 0.57	3.55 ± 0.44	3.69 ± 0.45
D1 (mm)	3.75 ± 0.54	3.70 ± 0.42	4.07 ± 0.39
FMD (%)	4.75 ± 2.40	4.23 ± 3.52	10.46 ± 4.28$^{**\#}$
D2 (mm)	4.20 ± 0.48	4.17 ± 0.40	4.29 ± 0.45
NTG-MD (%)	17.52 ± 2.87	17.46 ± 5.16	15.95 ± 6.02

$^{**}p<0.01$ compared to baseline; $^{\#}p<0.01$ compared to control group.

Table IV. A comparison of blood biochemical indicators in the allopurinol and control groups after six months of treatment.

Index	Baseline (n=125)	Control group (n=63)	Allopurinol group (n=62)
UA (μmol/L)	321.4 ± 42.5	327.9 ± 58.1	305.6 ± 52.9
TNF-α (ng/L)	27.2 ± 16.0	26.5 ± 11.1	20.3 ± 14.0$^{**\#}$
ALT (U/L)	28.4 ± 13.6	26.9 ± 9.0	27.5 ± 11.2
Cr (μmol/L)	81.3 ± 18.6	85.7 ± 19.2	82.8 ± 25.1
CPK (U/L)	79.1 ± 41.6	85.1 ± 32.0	88.3 ± 34.9

$^{**}p<0.01$ compared to baseline; $^{\#}p<0.01$ compared to control group.

Safety Analysis

Baseline serum uric acid levels were within the normal range for both treatment groups. After six months of treatment, the allopurinol group demonstrated no significant decrease in serum uric acid levels or increase in creatine kinase levels. Moreover, no sign of hepatic or renal dysfunction was observed in the allopurinol group (Table IV). One patient discontinued treatment due to allergic dermatitis.

Cardiac Events

All patients were followed-up for 6 to 18 months after the conclusion of treatment (with an average follow-up duration of 9.6±2.2 months) with the exception of one patient who was lost. A total of seven patients experienced cardiac events, including two patients from the allopurinol group who were hospitalized for heart failure. From the control group, one patient died from heart failure, and four patients were hospitalized for heart failure.

Discussion

The benefits of allopurinol for patients with chronic heart failure have been confirmed by several basic research studies[5,19,20]. Our previous animal experiments have also illustrated the related mechanism[21]. Many recent clinical works have started to use allopurinol to treat heart failure patients[22-24]. These reports have demonstrated that independent of a reduction in serum uric acid levels, the long-term administration of high doses of allopurinol (>300 mg/day) can improve vascular endothelial function by lowering oxidative stress, and significantly reducing mortality and hospitalization rates among heart failure patients[11-15]. However, certain papers have also indicated that allopurinol does not improve cardiac function or cardiac-related clinical events among the general population of patients with moderate or severe heart failure but instead only provides benefits to hyperuricaemic heart failure patients[17].

Since serum uric acid is an independent risk factor for cardiovascular events[4,13,25], current study utilized a prospective controlled design to examine the effects of allopurinol on randomly selected non-hyperuricaemic patients with chronic heart failure. To account for drug safety considerations, a treatment plan was devised that incorporated a conventional dose of allopurinol (300 mg/day). Results indicated that the addition of allopurinol to standard drug regimens for six

months could significantly improve cardiac function in patients with chronic heart failure. Moreover, six months of treatment produced no significant decrease in serum uric acid levels in either the control or the allopurinol treatment group, confirming that the observed benefits of allopurinol treatment were independent of a reduction in serum uric acid levels.

A sustained increase in TNF-α level is an important indicator of the deterioration of cardiac function[26], and its expression is regulated by oxidative stress[27]. Our report provides the first confirmation that the six months of allopurinol (300 mg/day) treatment can reduce the plasma TNF-α level of heart failure patients. This effect may relate to the ability of allopurinol to reduce the ROS that are upstream regulatory factors of TNF-α. In addition, oxidative stress can lead to peripheral vascular endothelial dysfunction in heart failure patients[28]. To exclude the impact of various factors, such as diabetes mellitus, hypertension and CAD on vascular endothelial function, we selectively examined the effects of allopurinol on peripheral vascular endothelial function in heart failure patients with DCM that was not accompanied by significant complications. The results of this examination revealed that allopurinol improved endothelium-dependent vasodilation in DCM patients with heart failure but did not affect non-endothelium-dependent vasodilation. These findings are consistent with previous reports[14,15]. Although it has gradually become evident that allopurinol treatment can benefit patients with heart failure, the safety of clinical application of allopurinol must be considered[18].

Conclusions

Our results demonstrated that the administration of allopurinol (300 mg/day) for six months to treat heart failure did not appear to increase creatine kinase levels or affect hepatic or renal functions of patients. The observation time period of this study was short, and this investigation chose to examine patients with chronic heart failure who were in relatively stable condition. Thus, the findings of the current study cannot be generalized to all patients. Further studies are required to assess the specific circumstances for an individual patient that could manage the drugs and dosages to be administered for the treatment of heart failure.

Acknowledgements

This study was partially supported by Chongqing Municipal Health and Family Planning Commission Medical Research Fund, Chongqing, China (20142083).

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. Lancet 2011; 378: 704-712.
2) Migdal C, Serres M. Reactive oxygen species and oxidative stress. Med Sci (Paris) 2011; 27: 405-412.
3) Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol 2011; 301: H2181-2190.
4) Doehner W, Landmesser U. Xanthine oxidase and uric Acid in cardiovascular disease: clinical impact and therapeutic options. Semin Nephrol 2011; 31: 433-440.
5) Vergeade A, Mulder P, Vendeville C, Ventura-Clapier R, Thuillez C, Monteil C. Xanthine oxidase contributes to mitochondrial ROS generation in an experimental model of cocaine-induced diastolic dysfunction. J Cardiovasc Pharmacol 2012; 60: 538-543.
6) Aldaba-Muruato LR, Moreno MG, Hernández-Mercado E, Shibayama M, Muriel P. Secondary biliary cirrhosis in the rat is prevented by decreasing NF-□B nuclear translocation and TGF-β expression using allopurinol, an inhibitor of xanthine oxidase. Can J Physiol Pharmacol 2012; 90: 1469-1678.
7) Stone PH. Allopurinol, a new anti-ischemic role for an old drug. J Am Coll Cardiol 2011; 58: 829-830.
8) Kelkar A, Kuo A, Frishman WH. Allopurinol as a cardiovascular drug. Cardiol Rev 2011; 19: 265-271.
9) Rekhraj S, Gandy SJ, Szwejkowski BR, Nadir MA, Noman A, Houston JG, Lang CC, George J, Struthers AD. High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. J Am Coll Cardiol 2013; 61: 926-932.
10) Greenhill C. Cardiovascular disease: allopurinol reduces left ventricular hypertrophy. Nat Rev Nephrol 2011; 7: 487.
11) Struthers AD, Donnan PT, Lindsay P, McNaughton D, Broomhall J, MacDonald TM. Effect of allopurinol on mortality and hospitalisations in chronic heart failure: a retrospective cohort study. Heart 2002; 87: 229-234.
12) Wei L, Mackenzie LS, Chen Y, Struthers AD, MacDonald TM. Impact of allopurinol use on urate concentration and cardiovascular outcome. Br J Clin Pharmacol 2011; 71: 600-607.

13) Gotsman I, Keren A, Lotan C, Zwas DR. Changes in uric acid levels and allopurinol use in chronic heart failure: association with improved survival. J Card Fail 2012; 18: 694-701.

14) George J, Carr E, Davies J, Belch JJ, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation 2006; 114: 2508-2516.

15) Meléndez-Ramírez G, Pérez-Méndez O, López-Osorio C, Kuri-Alfaro J, Espinola-Zavaleta N. Effect of the treatment with allopurinol on the endothelial function in patients with hyperuricemia. Endocr Res 2012; 37: 1-6.

16) Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, Schuler G, Coats AJ, Anker SD, Hambrecht R. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002; 105: 2619-2624.

17) Nasr G, Maurice C. Allopurinol and global left myocardial function in heart failure. J Cardiovasc Dis Res 2010; 1: 191-195.

18) Ryu HJ, Song R, Kim HW, Kim JH, Lee EY, Lee YJ, Song YW, Lee EB. Clinical risk factors for adverse events in allopurinol users. J Clin Pharmacol 2013; 53: 211-216.

19) Struthers A, Shearer F. Allopurinol: novel indications in cardiovascular disease. Heart 2012; 98: 1543-1545.

20) Opie LH. Allopurinol for heart failure: novel mechanisms. J Am Coll Cardiol 2012; 59: 809-812.

21) Xiao J, She Q, Wang Y, Luo K, Yin Y, Hu R, Huang K. Effect of allopurinol on cardiomyocyte apoptosis in rats after myocardial infarction. Eur J Heart Fail 2009; 11: 20-27.

22) White WB, Chohan S, Dabholkar A, Hunt B, Jackson R. Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities. Am Heart J 2012; 164: 14-20.

23) Erdogan D, Tayyar S, Uysal BA, Icli A, Karabacak M, Ozaydin M, Dogan A. Effects of allopurinol on coronary microvascular and left ventricular function in patients with idiopathic dilated cardiomyopathy. Can J Cardiol 2012; 28: 721-727.

24) Hirsch GA, Bottomley PA, Gerstenblith G, Weiss RG. Allopurinol acutely increases adenosine triphospate energy delivery in failing human hearts. J Am Coll Cardiol 2012; 59: 802-808.

25) Málek F, Oš ádal P, Pa enica J, Jarkovský J, Vítovec J, Widimský P, Linhart A, Fedorco M, Coufal Z, Miklík R, Kr ger A, Vondraková D, Špinar J. Uric acid, allopurinol therapy, and mortality in patients with acute heart failure—results of the Acute HEart FAilure Database registry. J Crit Care 2012; 27: 737.e11-24.

26) Schlendorf KH, Kasper EK. Use of novel and conventional biomarkers for management of patients with heart failure. Curr Treat Options Cardiovasc Med 2011; 13: 475-488.

27) Finkel T. Signal transduction by reactive oxygen species. J Cell Biol 2011; 194: 7-15.

28) Tousoulis D, Briasoulis A, Papageorgiou N, Tsioufis C, Tsiamis E, Toutouzas K, Stefanadis C. Oxidative stress and endothelial function: therapeutic interventions. Recent Pat Cardiovasc Drug Discov 2011; 6: 103-114.