Allopurinol modulated serum troponin level in renal stone patients

Nivel de troponina sérica modulada por alopurinol en pacientes con cálculos renales

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Received/Recibido: 11/28/2021 Accepted/Aceptado: 02/15/2022 Published/Publicado: 03/30/2022 DOI: http://doi.org/10.5281/zenodo.6578732

Abstract

Cardiovascular diseases are aggravated by various factors, including chronic use of certain medications. There are worldwide reported cases of sudden strokes or myocardial infarction in previously non-ischemic patients while using medications for other chronic diseases, such as diabetes, gout, hypertension, and endocrine diseases. The mechanism is quite complicated, and the underlying causes were obscure. In line with this reported toxicity are patients with hyperuricemia on uric acid lowering therapy. The goal of the present investigation was to assess the cardiotoxic effect of allopurinol based on the levels of troponin that were quantified by fully automated COBAS technique in apparently healthy renal stone patients. To do so, serum samples were collected from these patients at baseline (before starting allopurinol therapy), and at the end of the course of the therapy. The troponin level was significantly elevated after allopurinol therapy compared to baseline. The study concluded that allopurinol could have a significant cardiotoxic effect in heart tissues and should be used cautiously in patients with pre-existing ischemic cardiac diseases.

Keywords: troponin, allopurinol, xanthine oxidase, cardiac diseases.

Resumen

Las enfermedades cardiovasculares se ven agravadas por varios factores, incluido el uso crónico de ciertos medicamentos. Se han reportado casos en todo el mundo de accidentes cerebrovasculares repentinos o infarto de miocardio en pacientes previamente no isquémicos mientras usaban medicamentos para otras enfermedades crónicas, como diabetes, gota, hipertensión y enfermedades endocrinas. El mecanismo es bastante complicado y las causas subyacentes son oscuras. En consonancia con esta toxicidad reportada están los pacientes con hiperuricemia con tratamiento para reducir el ácido úrico. El objetivo de la presente investigación fue evaluar el efecto cardiotóxico del alopurinol en función de los niveles de troponina, cuantificados mediante la técnica COBAS totalmente automatizada en pacientes con cálculos renales aparentemente sanos. Para ello, se recolectaron muestras de suero de estos pacientes al inicio (antes de comenzar la terapia con alopurinol) y al final del curso de la terapia. El nivel de troponina incrementó significativamente en los pacientes que recibieron tratamiento con alopurinol en comparación con el valor inicial. El estudio concluyó que el alopurinol podría tener un efecto cardiotóxico significativo en los tejidos cardíacos y debería usarse con precaución en pacientes con enfermedades cardíacas isquémicas preexistentes.

Palabras clave: troponina, alopurinol, xantina oxidasa, cardiopatías.

Introduction

Gout, a form of inflammatory arthritis depicted by recurrent attacks of a red, tender, hot, and swollen joint, is due to constantly increased concentration of uric acid in the blood produced by a genetic defect or certain cancer medicines. Allopurinol is a xanthine oxidase (XO) inhibitor primarily used in the management of gout[1-3]. It works by reducing uric acid production in the body[4]. The urilithiasis may be seen as a clinical condition of an fundamental pathological procedure prompting to crystallization within the renal system. Renal stones may be encompassed of calcium salts, uric acid, cystine, and various other insoluble complexes. Gout attacks and kidney stones can both be caused by high uric acid levels[1-3]. Allopurinol is used to evade gout attacks rather than to treat them once they happen. Renal illness, hypertension, and gout have all been linked to hyperuricemia[5]. The effect of allopurinol, a urate-lowering drug, on renal function is unknown, particularly in patients with chronic kidney disease who are more likely to experience a hypersensitive reaction[6]. Hyperuricemia is linked to hypertension, inflammation, the advancement of renal disease, and cardiovascular disease. However, little information on the effects of allopurinol in patients with chronic renal disease is available[5,6].

High levels of uric acid can accumulate and cause tiny, sharp crystals to form in and around joints[6]. This also happens if kidneys do not filter it out quickly enough. Allopurinol is an agent that reduces uric acid concentrations in the blood, is used in the treatment of Gout and kidney stones[5,6]. Allopurinol adverse drug reactions are simple and well tolerable and rarely produce the deleterious effect [7]. The patients should seek medical attention, if patients had a severe allergic response to allopurinol, shouldn't use this medication[8]. If any signs of swelling in throat or face, burning in eyes, blood in urine, painful urination, or skin rash (no matter how small)[5,6]. Allopurinol can cause a decrease in the number of white blood cells that protect the body against infections[5-7].

People who once had renal stones are more prone to having another. Drinking plenty of water and changing diet is typically enough to keep this from happening. If kidney stones continue to form, medication can be taken as a preventative measure. Within five years, 30 to 50 persons out of 100 who have had a kidney stone can expect to get another. About ten out of every hundred individuals will suffer kidney stones regularly. Since there are various causes for kidney stones, it is important to evaluate the reason for the renal stone formation. Renal stones may be encompassed of calcium salts, uric acid, cystine, and various other insoluble complexes. Calcium stones account for about 80% of all kidney stones. Uric acid stones account for around 5% to 10% of all kidney stones. The rest are formed of struvite, cystine, or other uncommon materials[5-10]. The participants of most of the clinical trials[3-6] conducted on allopurinol therapy were subjects with cardiovascular diseases. All these trials[3-6] has confirmed a positive role for allopurinol on cardiovascular diseases. Nonetheless, its worthy to mention that the principle clinical indication for allopurinol is in apparently healthy subjects (hyperuricemia, gout, and renal stone patients), the case in which allopurinol might induce a reverse action on heart. The goal of the present investigation was to assess the cardiotoxic effect of allopurinol based on the levels of troponin that were quantified by fully automated COBAS technique in apparently healthy renal stone patients.

Material and methods

A study was conducted to measure the level of serum troponin renal stone patients treated with allopurinol. This study included 15 clinically treated renal stone patients (9 males and 6 females) who were treated with allopurinol (300 mg/day) for 6 months. The patients' demographic characteristics are listed in Table 1.

Table 1. Demographic characteristics of the studied groups

	Allopurinol Therapy (n=15)	
Parameters	**Before**	**After**
Age (years)	39.41±3.8	-------
BMI (kg/m²)	28.2±3	28.5±2.8
Duration of treatment	6 months	-------
Gender (Male/Female)	9/6	-------

*P<0.05, BMI=body mass index, kg=kilogram, m^2=square meter

All participants signed a consent form of agreement. Those with a history of chronic conditions (such as hepatic or renal insufficiency, heart failure, myocardial infarction, atherosclerosis, angina pectoris, hypertension, and thyroid disease) or who were using any chronic medications were excluded. The study did not include pregnant women or nursing mothers.

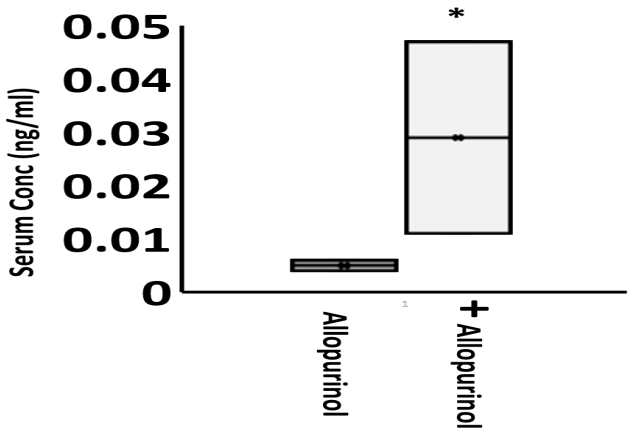
After fasting overnight, six mL of venous blood were withdrawn from patients, before and after 6 months of allopurinol treatment for quantification of biochemical markers. The blood was allowed to coagulate at room temperature, and the serum was separated in a plane tube after centrifugation. Samples were stored at -20 °C until analysis. The fasting serum troponin level was measured using an enzymatic approach (Cobas 6000, Roche-Diagnostic).

Results

Following allopurinol administration for 3 months at 300mg/day dose, allopurinol has significantly ($p<0.05$) increased serum troponin level (0.029±0.02) compared to baseline levels (0.005±0.001) (Figure 1).

The data were expressed as mean ± standard deviation. Unpaired t-test conducted to indicate the difference. A statistically significant difference was defined as $P< 0.05$. GraphPad Prism 5.0 was used to generate statistical results (GraphPad Software Inc., La Jolla, CA, USA).

Figure 1. Allopurinol elevated serum troponin level. Chronic allopurinol used at a dose of 300 mg/day for 6 months increased troponin concentration; as compared to same subject baseline levels, data expressed as mean ± SD, *p<0.05.



Discussion

Xanthine oxidase is an enzyme that catalyzes the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. It involves in redox reactions, mitochondrial electron transport chain, and ATP generation, resulting in ATP diminution in ischemic myocardium[1,2]. Allopurinol has been widely utilized in the treatment of gout, nephrolithiasis, and tumor lysis syndrome, and has also shown encouraging benefits in cardiovascular disease. Allopurinol's potential usefulness as an anti-ischemic agent was initially hypothesized in animal models of heart failure[3]. The area of cardiac research of allopurinol is quite important because previously conducted trials examined the impact of allopurinol on reducing myocardial damage in different surgical contexts of coronary intervention. The present study confirmed that allopurinol significantly increased the serum troponin level in normal healthy patients, who were using allopurinol for their renal stones. This area of research is interesting because allopurinol is in current use for the treatment of hyperuricemia. Cardiovascular diseases coexist with hyperuricemia and allopurinol represents the only available hypouricemic agent after febuxostat.

In ten randomized controlled trials, a comprehensive review and meta-analysis of including 594 participants were conducted to assess the effects of allopurinol in patients at risk of cardiovascular disease. Allopurinol treatment substantially increased flow-mediated dilation in these individuals, according to data analysis. Furthermore, it has been demonstrated that the advantage of allopurinol to flow-mediated dilation is unrelated to its uric acid-lowering effects. As a result, it appears that allopurinol intake is linked to a more remarkable improvement of flow-mediated dilation in people with lower serum uric acid (UA) than in people with higher UA. These findings emphasized the prospective cardiovascular advantages of allopurinol, as well as the processes involved[4].

Allopurinol has been shown to have cardioprotective benefits in lowering the occurrence of perioperative myocardial infarction in individuals receiving coronary artery bypass graft (CABG). According to a meta-analysis of six trials including 229 individuals, the incidence of myocardial infarction was greater in the control group compared to the allopurinol-treated group. It is worth noting that the impacts of allopurinol were utmost in the Rashid et al. research, in which patients were given 300 mg/day (the highest dose) and the longest period (five days) of allopurinol. Furthermore, when this study was excluded, the allopurinol effect became non-significant, a high dosage of allopurinol was tested in our randomized controlled trial (RCT)[5,6].

The oxidative stress and endothelial function improved following administration of allopurinol (600mg per day), Huang et al. demonstrated an effect following the use of allopurinol during the acute phase of an acute coronary syndrome (ACS), on oxidative stress and inflammatory response markers, like improved overall ACS therapy[7]. Furthermore, Noman et al. discovered that taking allopurinol might increase the time to ST-segment depression, the time to medial overall exercise, and the time to chest pain in those patients with coronary heart disease[8].

In the present clinical trial study, patients were given 300 mg allopurinol at the time of their diagnosis, continued for 3months. Our RCT confirmed the possible cardio destructive effects of high allopurinol treatment in inducing myocardial damage confirmed by troponin measurement. In a similar area of research, Alemzadeh-Ansari et al. demonstrated in a non-control group 254 patients with coronary disease underwent percutaneous coronary intervention (PCI) that high doses of allopurinol have no impact on creatinine kinase levels[9]. In this double-blind randomized controlled trial, 133 PCI patients received allopurinol, whereas 121 patients in the control group received a placebo. Notably, no substantial negative was observed in both trials.

In the RCT conducted by Haung et al., ACS patients were given allopurinol and were observed for 24 months. Allopurinol treatment decreased oxidative stress and inflammatory response, as measured by serum biochemical profile, and had a favorable impact on the treatment of ACS[7]. Additionally, Separham et al. demonstrated that the use of allopurinol before streptokinase resulted in decreased levels of peak creatine kinases[10].

A growing body of data demonstrates that the immune reaction is linked to cardiomyocyte apoptosis, necrosis, and cardiac hypertrophy. Neutrophils infiltrate during the commencement of infarction and are followed by monocytes/macrophages, resulting in a considerable increase in inflammatory mediators and reactive oxygen species (ROS). A high level of ROS in the ischemic myocardium may induce cardiomyocyte apoptosis. It has been suggested that increased xanthine oxidase (XO) expression and function may influence myocardial hypertrophy and deformation via an upsurge in ROS levels[11-14].

Xiao et al. demonstrated inhibition in apoptosis in heart of the rats exposed to allopurinol in the rat model[15]. Similarly, a clinical trial conducted by Rekhraj et al. reported that using allopurinol in patients with heart failure has a positive remodeling impacts[16]. Moreover, allopurinol used in CABG patients reduced mortality[17]. Positively improved patients' overall status has been reported in ischemic diseased patients[8,18,19].

Most of these studies have mentioned that allopurinol positively impacted heart diseases which contradicts our results. However, it is worthy to mention that most of these studies used allopurinol transiently for a few days or hours for surgical requirements, such as CABG, ACS.

Conclusion

The study concluded that troponin levels are increased in apparently healthy patients using allopurinol for renal stones.

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