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BJAN-D-20-00104_Case Report

Effects of allopurinol on pain and anxiety in fibromyalgia patients: a pilot study

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Abstract

Allopurinol is a potent inhibitor of the enzyme xanthine oxidase used in the treatment of hyperuricemia and gout. The aim of this pilot study was to investigate the effects of allopurinol on pain and anxiety in women displaying fibromyalgia refractory to conventional therapy. This prospective case series enrolled 12 women with previous diagnosis of fibromyalgia refractory to conventional therapy. Patients received an add-on therapy with oral allopurinol 300 mg twice daily for 30 days. Patients were submitted to evaluation for pain and anxiety scores before treatment, 15 and 30 days thereafter. This pilot study has demonstrated that oral administration of allopurinol 300 mg twice daily caused a significant reduction on pain scores up to 30 days of treatment in women with fibromyalgia. No effect was observed regarding anxiety scores. Randomized clinical trials are warranted and should further investigate allopurinol and more selective purine derivatives in the management of acute or chronic pain

conditions.

KEYWORDS

Allopurinol; Chronic pain; Fibromyalgia; Anxiety; Purines

Introduction

Fibromyalgia is a chronic syndrome characterized by widespread pain and tenderness, accompanied by disturbed sleep, chronic fatigue, cognitive dysfunction, depressive symptoms, and multiple additional functional disturbances. Fibromyalgia usually requires a multimodal therapeutic approach to optimize treatment efficacy, and its management is still challenging since many patients fail to achieve sufficient relief from conventional treatments.[1]

It is well known that purines exert multiple effects on pain transmission. Adenosine and its analogs are involved in multiple biological effects, including modulation of pain transmission at peripheral and central sites.[2] The purine derivative allopurinol is a potent inhibitor of the enzyme xanthine oxidase used primarily in the treatment of hyperuricemia and gout. Notably, previous studies have shown that allopurinol produces dose-dependent antinociceptive effects against several chemical and thermal pain models in rodents.[3] We hypothesized that the inhibition of xanthine oxidase by allopurinol, thereby reducing purine degradation, could be a valid strategy to enhance purinergic activity and treat pain in humans. The aim of this pilot study was to investigate an add-on therapy with oral allopurinol on pain and anxiety in women displaying fibromyalgia refractory to conventional therapy.

Material and methods

A prospective case series was performed in a tertiary care hospital in South Brazil. The protocol was designed to be a pilot study for a larger clinical trial and was approved by the Institution's Research and Ethics Committee (HCPA/UFRGS – CAAE #229000100007; Brazilian Registry of Clinical Trials – ReBEC #RBR-8h7dmq). A total of twelve female patients were enrolled into the study, with American Society of Anesthesiologists (ASA) physical status I–II, and ages ranging from 18 to 65 years old, being excluded the illiterate or who does not understand Portuguese language, those who refused to participate of the study or who had already participated in other studies. Participants received a written and oral explanation of the study and signed an informed consent form. Patients were allocated to receive oral allopurinol 300 mg twice daily for 30 days following initial evaluation. No other medication was added

during the follow-up. All patients were maintained on their current medications protocol and no additional changes in the dosage regimen were allowed during follow-up, except for the use of rescue analgesics. Patients were evaluated for primary and secondary outcomes at baseline, 15 and 30 days after enrollment. The description of the present study was based on CARE guidelines.

Patients were asked to report any pain in four self-assessment instruments – a Verbal Scale (VPS), a Visual Analogue Scale (VAS), a Numerical Scale (NPS) and the McGill modified questionnaire, described in detail elsewhere.[4] In the first one, the reported pain was graded from 1 to 4, according to intensity: (1) none, (2) mild, (3) moderate, or (4) severe. VAS is widely used as a measure of self-reported pain assessment. The scale consists of a 100-mm line that pictorially represents a continuum between two extremes: no pain (score of 0) and extreme pain (score of 100). In order to stratify the data of VAS, cutoff points were established considering previous literature,[4] with moderate to severe pain corresponding to scores above 30-mm.[4] For NPS, patients were asked to report their pain in numbers ranging from zero (no pain) to 10 (extreme pain). Finally, The McGill questionnaire was used to measure the multidimensional pain experience (sensory, affective, and evaluative dimensions).[4]

The measurement of anxiety levels was performed through the State-Trait Anxiety Inventory for Adults (STAI).[4] The questionnaire contains two separate 20-item, self-report rating scales for measuring trait- and state-anxiety. Total scores for situational and baseline questions separately range from 20 to 60 or 80, with higher scores denoting higher levels of anxiety. Mean of anxiety scores at baseline was used to determine the cutoff point, so that individuals with scores above the average were classified as the high anxiety group and those with scores equal to or below the average as the low anxiety group.[4]

Data were stored in Excel software and analyzed by STATA 12.0. Numerical variables were given as mean ± Standard Deviation (SD). Data were submitted to Shapiro-Wilk test for normality evaluation. Statistical analysis between time points was performed using one-way ANOVA followed by Bonferroni's multiple comparison test for numerical data and Pearson's X^2 test for categorical data; $p < 0.05$ was considered for statistically significant differences.

Results

As depicted in Table 1, allopurinol caused a significant reduction in pain scores measured by verbal, numerical and visual analogue pain scales both 15 and 30 days after treatment ($p < 0.05$). No significant

effects were observed on pain scores measured by the McGill questionnaire (Table 1). As shown in Table 2, we did not detect any significant difference in both trait and state anxiety scores after 15 and 30 days of treatment ($p > 0.05$). Notably, no significant adverse events were observed following a 30-day trial of allopurinol in the present population and there were no dropouts.

Discussion

The rationale to administer allopurinol for pain and anxiety is derived from evidence in basic and clinical research on the purinergic system. Adenine-based purines have been considered important targets for the development of new drugs for pain management and the treatment of several neuropsychological disorders.[2,3] Endogenous adenosine can be released in the central nervous system and peripheral tissues, and the regulation of its levels by various pharmacological agents can alter pain processing through activation of adenosine A_1 receptors on neurons, and perhaps other receptors on adjacent structures.[2] We also have demonstrated that some guanine-based purines, especially the nucleoside guanosine, produced consistent antinociceptive and anxiolytic effects in several animal models.[5] Although adenine- or guanine-based purines have been related to some antinociceptive effects in both animals and humans,[5] it is relatively early to propose the use of most purine derivatives for clinical research and practice.

The main contribution of the present case series is to propose an alternative approach to investigate the clinical role of purines, focusing on the investigation of purine derivatives previously used in humans such as the xanthine-oxidase inhibitor allopurinol. Therefore, allopurinol, by inhibiting xanthine oxidase and production of uric acid, may cause accumulation of other purines in the central nervous system and in the periphery (for instance, adenosine and other nucleosides and nucleotides), which may account for potential analgesic and other neuromodulatory properties. The primary effect of allopurinol is inhibition of uric acid production, and the overall result is the inhibition of the metabolism of xanthine and hypoxanthine, leading to greater salvage of these purines by their conversion to inosine, adenosine, and guanosine. These findings, both in the central nervous system and periphery, have been extensively demonstrated after systemic administration of allopurinol in several studies in animals and humans.[3,5]

There are major limitations in the present study. First, this is a pilot study for a larger clinical trial and only few cases were investigated. Notably, there was no control group and patients were solely evaluated as compared to their baseline. Therefore, a placebo effect could have played a major role in

the present findings and a randomized clinical trial is pivotal to further evaluate an intrinsic analgesic effect of allopurinol in humans displaying chronic pain syndromes. We are currently carrying out a single-center, randomized, double-blinded, placebo-controlled clinical trial investigating allopurinol as an adjuvant therapy in women with refractory fibromyalgia pain.

In summary, this study has demonstrated that oral administration of the xanthine oxidase inhibitor allopurinol 300 mg twice daily caused a significant reduction on pain scores after 15 and 30 days of treatment in women with fibromyalgia. No benefit was observed against both trait and state anxiety scores. Considering that previous studies have shown some beneficial effects of some purines against pain in animals and humans, new clinical trials are still warranted to determine if allopurinol is effective in reducing pain in other clinical settings. These studies should include larger samples and longer follow-up to better determine the impact of allopurinol and perhaps more selective xanthine-oxidase inhibitors on pain scores in humans displaying acute or chronic pain.

Conflicts of interest

The authors declare no conflicts of interest.

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Table 1 Comparison among main outcomes between time-points – pain scores.

Variables	Treatment time-points			*p*[a]
	Baseline	**15 days**	**30 days**	
VPS, n (%)				
None	0 (0%)	2 (17%)	3 (25%)	
Mild	0 (0%)	3 (25%)	4 (33%)	0.039
Moderate	2 (17%)	3 (25%)	3 (25%)	
Severe	10 (83%)	4 (33%)	2 (17%)	
NPS (mean ± SD)	7.7 (1.4)	5.0 (2.8)[b]	5.2 (2.8)[b]	0.016
VAS (mean ± SD)	7.5 (1.5)	4.6 (2.8)[b]	4.7 (2.9)[b]	0.010
VAS categories, n (%)				
None–mild	0 (0%)	6 (50%)	6 (50%)	0.011
Moderate–severe	12 (100%)	6 (50%)	6 (50%)	
McGill (mean ± SD)	41.5 (14)	34.3 (17)	34.6 (19)	0.508

VPS, Verbal Pain Scale; NPS, Numerical Pain Scale; VAS, Visual Analogue Pain Scale; McGill, McGill modified pain questionnaire.

Data are shown as absolute values (percentiles) or as mean scores (standard deviation – SD). One-way ANOVA followed by Bonferroni's multiple comparison test for numerical data and Pearson's X^2 test for categorical data.

[a] $p < 0.05$ was considered significant.

[b] $p < 0.01$ as compared with baseline scores (n = 12 patients).

Table 2 Comparison among main outcomes between time-points – anxiety scores.

Variables	Treatment time-points			*p*[a]
	Baseline	**15 days**	**30 days**	
STAI trait anxiety, n (%)				
Low levels	5 (42%)	5 (42%)	4 (33%)	0.89
High levels	7 (58%)	7 (58%)	8 (67%)	
Mean scores (mean ± SD)	55.7 (11)	53.8 (10)	55.1 (9)	0.82
STAI state anxiety, n (%)				
Low levels	6 (50%)	5 (42%)	8 (67%)	0.46
High levels	6 (50%)	7 (58%)	4 (33%)	
Mean scores (mean ± SD)	52.8 (13)	52.7 (12)	50.3 (12)	0.90

STAIC, State-Trait Anxiety Inventory.

Data are shown as absolute values (percentiles) or as mean (standard deviation – SD). One-way ANOVA followed by Bonferroni's multiple comparison test for numerical data and Pearson's X^2 test for categorical data.

[a] $p < 0.05$ was considered significant, (n = 12 patients).