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Planejamento de ensaio clínico randomizado para avaliação da eficácia do uso de alopurinol no acidente vascular encefálico agudo

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Mestre em Pesquisa Clínica.

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Palavras-chave: acidente vascular cerebral; alopurinol; ensaio clínico randomizado; reposicionamento.

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Orientador: Prof. Dr. Edison Iglesias de Oliveira Vidal

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Faculdades Integradas de Jaú

Botucatu, 28 de Fevereiro de 2019.

DEDICATÓRIA

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“O saber a gente aprende com os mestres e os livros. A sabedoria, se aprende é com a vida e com os humildes”.

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RESUMO

ARAUJO, C. F. M. **Planejamento de ensaio clínico randomizado para avaliação da eficácia do uso de alopurinol no acidente vascular encefálico agudo**. 2019. 113 f. Dissertação (Mestrado) – Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu, 2019.

O acidente vascular cerebral (AVC) é uma das mais importantes afecções clínicas atualmente. A Organização Mundial de Saúde (OMS) define o AVC como sendo um comprometimento neurológico focal ou global que subitamente ocorre com sintomas persistindo para além de 24 horas, ou levando à morte, com provável origem vascular. O AVC agudo é responsável por uma carga substancial de morbidade e mortalidade no mundo representando a segunda causa global de anos de vida perdidos por incapacidade e respondendo por cerca de 10% de todas as mortes. No Brasil e nos Estados Unidos, o risco estimado de AVC ao longo da vida foi de 19,1% e 23,7%, respectivamente. A doença pode gerar sequelas e incapacidades resultando em grande impacto econômico e social. O alopurinol é uma droga inibidora da xantina oxidase (XO), a enzima que catalisa a conversão da hipoxantina em xantina e da xantina em ácido úrico a partir da degradação de purinas. Trata-se de medicamento antigo, seguro, disponível amplamente e com custo baixo utilizado principalmente para a prevenção de crises de gota. Além de seus efeitos sobre a redução dos níveis séricos de ácido úrico, sabe-se que o alopurinol também possui efeitos promissores em condições cardiovasculares. Esses efeitos têm o potencial de contribuírem para o tratamento de pacientes com AVC isquêmico agudo. Atualmente, o alopurinol não faz parte do tratamento padrão de pacientes com esse quadro no SUS ou internacionalmente, porém constitui um medicamento promissor a ser melhor estudado. Sabe-se que a condução de ensaios clínicos com medicamentos antigos para descoberta de novas aplicações para as mesmas não é considerada interessante para a indústria farmacêutica, pois após a perda da patente usualmente não há recompensa financeira suficiente para os altos gastos incorridos durante a condução dos ensaios. De tal modo normalmente fica a cargo de universidades e institutos de pesquisa com financiamento público realizar estudos clínicos com medicamentos já aprovados e com longo tempo de uso a fim de descobrir novas aplicações. Inovar com novos usos de medicamentos antigos já conhecidos representa uma oportunidade rara para o sistema público de saúde oferecer mais benefícios à população a um baixo custo. Sendo assim, propomos o presente ensaio clínico randomizado multicêntrico para avaliar a eficácia do alopurinol para prevenção de incapacidades e mortalidade no AVC agudo.

Palavras-chave: alopurinol; acidente vascular cerebral; AVC agudo; ensaio clínico randomizado.

ABSTRACT

ARAUJO, C. F. M. **Planning of a randomized clinical trial to evaluate the efficacy of allopurinol in acute stroke.** 2019. 113 f. Thesis (Master) – Faculty of Medicine of Botucatu, Universidade Estadual Paulista, Botucatu, 2019.

Stroke is one of the most important clinical conditions currently. The World Health Organization (WHO) defines stroke as a focal or global neurological impairment that suddenly occurs with symptoms persisting beyond 24 hours or leading to death with probable vascular origin. Acute stroke accounts for a substantial burden of morbidity and mortality in the world accounting for the second overall cause of Disability-Adjusted Life Year and accounting for about 10% of all deaths. In Brazil and the United States, the estimated lifetime risk of stroke was 19.1% and 23.7%, respectively. The disease can generate sequelae and incapacities resulting in great economic and social impact. Allopurinol is a xanthine oxidase (XO) inhibitor, the enzyme that catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid from purine degradation. It is an old, safe, widely available and low cost drug used primarily for the prevention of gout attacks. In addition to its effects on the reduction of serum uric acid levels, it is known that allopurinol also has promising effects under cardiovascular conditions. These effects have the potential to contribute to the treatment of patients with acute stroke. Currently, allopurinol is not part of the standard treatment of patients with this condition in Brazilian Public Health System or internationally, but it is a promising drug to be better studied. It is known that the conduct of clinical trials with old medicines to discover new applications for them is not considered interesting for the pharmaceutical industry, since after the loss of the patent usually there is not enough financial reward for the high expenses incurred during the conduction of the essay. Thus, it is usually the responsibility of publicly funded universities and research institutes to conduct clinical trials of long-term and approved drugs in order to discover new applications. Innovating with new uses of old medicines already known represents a rare opportunity for the public health system to offer more benefits to the population at a lower cost. Therefore, we propose the present multicenter randomized trial to evaluate the efficacy of allopurinol for the prevention of disabilities and mortality in acute stroke.

Keywords: allopurinol; stroke; acute stroke; clinical trial.

Contents

DETAILING THE RESEARCH PROJECT[1]:

1. The importance of the proposal

1.1 Stroke

Stroke accounts for a substantial burden of morbidity and mortality worldwide representing the second global cause of years of life lost and responding for about 10% of all deaths [1]. According to the last update of World Health Organization (WHO) Global Burden of Disease project in 2016 stroke was responsible almost 120 million disability adjusted life years in the world, corresponding to the second most important cause of disability on Earth [2].

Still according to recently published data from the WHO Global Burden of Disease project, the estimated global lifetime risk of stroke from age 25 onwards was 24.9%, meaning that 1 in every 4 people aged 25 years and older will suffer a stroke during the remaining years of life according to 2016 parameters [3]. In Brazil and the United States the estimated lifetime risk of stroke was 19.1% and 23.7%, respectively.

1. 2 Allopurinol

Allopurinol is a xanthine oxidase (XO) inhibitor. XO is the enzyme that catalyzes the conversion of hypoxanthine to xanthine and of xanthine to uric acid from purine degradation [4]. It is an old, safe, widely available and low-cost drug used for the prevention and treatment of gout attacks and for the prevention of tumor lysis syndrome [5]. In addition to its effects on the reduction of serum uric acid levels several lines of evidence suggest that allopurinol may exert a protective role in the managment of cardiovascular diseases [6].

Epidemiological research has indicated that chronic use of allopurinol is associated with a 9% (95%CI:1% to 17%): decreased risk of incident stroke [7]. In that study the protective association with regards to stroke was evident after 6 months of use of allopurinol and there was an increased gradient of protection against stroke with

[1]O presente produto de mestrado será utilizado na submissão para financiamento do projeto The Allopurinol in acute Ischemic Stroke (THALIS) clinical trial por meio do Programa de Pesquisa Biomédica Colaborativa EUA-Brasil, uma parceria entre o National Institutes of Health (NIH) e o Ministério da Saúde/CNPq, para a execução do ensaio clínico randomizado multicêntrico proposto. Por essa razão, o texto encontra-se em inglês.

longer uses, i.e. average 21% (95%CI: 4% to 35%) risk reduction with allopurinol use beyond 2 years. A recent systematic review of 91 clinical trials of allopurinol found a protective effect of that drug regarding the occurrence of acute myocardial infarction (OR: 0.38, 95%CI: 0.17 to 0.83) and of severe cardiovascular outcomes (OR: 0.56, IC95%: 0.36 a 0.86) [8]. In addition, animal studies have shown a protective effect of allopurinol against experimentally induced cerebral ischemia [9] and a small randomized clinical trial of allopurinol for patients with acute stroke and elevated serum uric acid levels disclosed preliminary evidence that allopurinol could increase the occurrence of favorable functional status, defined as a modified Rankin Scale (mRS) of 0 to 2 in that study, after stroke (OR: 4.7, P: 0.014) [10].

It is believed that the drug's protective cardiovascular effect stems from a number of mechanisms. For instance, it is known that purines play a central role in the cellular energy metabolism through purine nucleotides such as Adenosine Triphosphate (ATP), the main intracellular energy currency. During hypoxia, tissue ATP depletion is proportional to the duration of the ischemic period, which is followed by an increased production of hypoxanthine, itself an important degradation product of ATP [9]. The conversion of hypoxantine into uric acid by means of XO may aggravate the ischemic insult because it means that the more energy-efficient way of reconstituting ATP by using hypoxanthine as a substrate is no longer possible and hence ATP will have to be synthetized *de novo* in a much less energy efficient fashionduring reperfusion. That phenomenon leads to impairment of the cellular ability to resynthesize ATP when tissue reperfusion occurs. Therefore, allopurinol would contribute to cell protection against ischemic insults by inhibiting purine degradation. By blocking the formation of uric acid the drug would indirectly prevent excessive and irreversible loss of purines and increase the circulation of hypoxanthines. Thus, there would be a reduction in energy expenditure to restore ATP at a delicate moment of energy deficit in areas affected by ischemia.

Additionally, allopurinol by preventing the excessive loss of purines through the production of uric acid, may contribute to higher levels of inosine, a purine nucleoside that may play an important role in the recovery of ischemic areas in the brain. Inosine has been shown to induce neurons to express growth-associated proteins and to lengthen their axons in culture medium and *in vivo.* In an experiment with adult mice with induced unilateral cortical infarction inosine stimulated neurons on the unaffected side of the brain to extend new projections to denervated areas [11]. That growth was

followed by a better performance on several behavioral measures after stroke in the study animals.

A third mechanism underlying the possible role of allopurinol in acute stroke involves the fact that allopurinol as an inhibitor of XO is able to reduce the oxidative stress load, which is an important mechanism of cell injury during ischemia and reperfusion. In reactions catalyzed by XO, the use of oxygen molecules as final electron acceptors results in the generation of reactive oxygen species (ROS) [12]. Indeed, the two major ROS-generating systems are nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and XO. It is known that although the basal expression of XO in humans is low, hypoxia raises the transcription of that enzyme. In this situation, the use of allopurinol may contribute to the reduction of free radical formation and the occurrence of oxidative stress-induced cellular injuries and endothelial dysfunction. Moreover, *in vitro* studies have shown that allopurinol directly eliminates free radicals by having intrinsic antioxidant properties [13]. Finally, other mechanisms whereby allopurinol could exert protective cardiovascular effects involve the improvement of endothelial function [14] and the reduction of proinflamatory molecules[15].

1.3 Knowledge gap

Despite the promising findings described above, there is still no clear evidence of the benefit of allopurinol for patients with ischemic stroke, as studies conducted in humans so far have been exceedingly rare including only small sample sizes. Currently, allopurinol is not recommended in international guidelines for the management of patients with acute stroke.

Other research groups have already realized the potential of allopurinol in the management of stroke and have been developing research in this area. For example, since 2014 a clinical trial in the UK has been underway to assess whether allopurinol may offer benefits to patients who suffered stroke when introduced about one month after the ischemic event. The Xilo-FIST (Xanthine oxidase inhibition for long-term outcomes following ischemic stroke and transient ischemic attack) study aims to assess whether allopurinol can reduce white matter hyperintensities progression and blood pressure after stroke [16]. However, the protocol of that multicenter study aimed to evaluate a number of important clinical outcomes, such as functional disability, quality of life and mortality only as exploratory outcomes, i.e. not even as secondary outcomes. We found no other ongoing clinical trials involving the use of allopurinol in

acute stroke in a search in ClinicalTrials.gov and in the WHO International Clinical Trials Registry Platform, although there are a variety of other ongoing clinical trials involving the use of allopurinol for other cardiovascular diseases.

1.4 The importance of research on new uses for old drugs

Investment in the conduction of clinical trials with old generic drugs to discover new applications for them is not economically interesting for the pharmaceutical industry, since after patent expiration there is usually no perspective of sufficient financial reward for the high expenses incurred by clinical trials [17]. Thus, it is usually the responsibility of universities and research institutes with public funding to carry out clinical trials exploring new applications for old drugs.

Despite the pharmaceutical industry's lack of interest in that field of research, there are several public health advantages in conducting studies aimed at the repurposing of old generic drugs. Those drugs have already passed all the phases required by regulatory agencies when they are first approved for commercialization with their initial indication and they usually have well-defined safety profile. Innovation through the study of new uses for old generic drugs represents a rare opportunity for public health systems to offer more benefits to the population at a low cost.

Given the arguments exposed in the previous sections we propose the present randomized clinical trial to evaluate the efficacy of allopurinol for prevention of disability and mortality in acute ischemic stroke.

2. Objectives

2.1 Primary objective

To assess the efficacy of allopurinol in preventing the combined outcome of mortality and unfavorable neurological outcomes 3 months after an episode of acute ischemic stroke.

2.2 Secondary objectives

- To evaluate the efficacy of allopurinol regarding the reduction of in-hospital mortality and at 3 months after acute stroke.

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