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Original Article

Comparison of the effect of allopurinol and febuxostat on urinary 2,8-dihydroxyadenine excretion in patients with APRT deficiency: A clinical trial

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ABSTRACT

Introduction: Adenine phosphoribosyltransferase (APRT) deficiency is a rare, but significant, cause of kidney stones and progressive chronic kidney disease. The optimal treatment has not been established. The purpose of this pilot study was to compare the effect of the xanthine oxidoreductase inhibitors allopurinol and febuxostat on urinary 2,8-dihydroxyadenine (DHA) excretion in APRT deficiency patients.

Materials and methods: Patients listed in the APRT Deficiency Registry of the Rare Kidney Stone Consortium, currently receiving allopurinol therapy, were invited to participate. The trial endpoint was the 24-h urinary DHA excretion following treatment with allopurinol (400 mg/day) and febuxostat (80 mg/day). Urinary DHA was measured using a novel ultra-performance liquid chromatography - electrospray tandem mass spectrometry assay.

Results: Eight of the 10 patients invited completed the study. The median (range) 24-h urinary DHA excretion was 116 (75–289) mg at baseline, and 45 (13–112) mg after 14 days of allopurinol therapy ($P = 0.036$). At the end of the febuxostat treatment period, 4 patients had urinary DHA below detectable limits (< 20 ng/mL) compared with none of the participants following allopurinol treatment ($P = 0.036$). The other 4 participants had a median 24-h urinary DHA excretion of 13.2 (10.0–13.4) mg at the completion of febuxostat therapy ($P = 0.036$).

Conclusion: Urinary DHA excretion in APRT deficiency patients decreased with conventional doses of both allopurinol and febuxostat. Febuxostat was, however, significantly more efficacious than allopurinol in reducing DHA excretion in the prescribed doses. This finding, which may translate into improved outcomes of patients with APRT deficiency, should be confirmed in a larger sample.

1. Introduction

Adenine phosphoribosyltransferase (APRT) deficiency (OMIM 102600) is a rare autosomal recessive disorder of adenine metabolism resulting in the generation and renal excretion of large amounts of the poorly soluble and nephrotoxic metabolite 2,8-dihydroxyadenine (DHA) [1,2]. Adenine accumulates in affected patients due to the abolished APRT enzyme activity and is converted by xanthine oxidoreductase (XOR; xanthine dehydrogenase/oxidase) to DHA in excessive quantities [3].

APRT deficiency patients frequently develop serious renal complications, including recurrent radiolucent kidney stones and progressive chronic kidney disease (CKD) caused by DHA crystal nephropathy. At least 15% of patients reported to date have already developed end-stage

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Table 1
Assessment and treatment schedule of study participants.

Protocol activity	First visit	Wash-out period 1	Allopurinol (400 mg/day)	Wash-out period 2	Febuxostat (80 mg/day)
	Day 1	Days 1–7	Days 8–21	Days 22–28	Days 29–42
Physical examination	X				
Serum Cr measurement	X				
24-H urine samples collected[a]		Day 7	Day 21	NA	Day 42
First morning void urine sample[a]		Day 7	Day 21	NA	Day 42
Adverse events			Monitored continuously		

Abbreviations: Cr, creatinine. NA, not assessed.
[a] 2,8-Dihydroxyadenine and creatinine were measured in these urine samples.

kidney failure at diagnosis [4], which frequently is not confirmed until after kidney transplantation when disease recurrence in the allograft has occurred [5].

The XOR inhibitor allopurinol is an effective therapy for preventing new kidney stone formation, renal DHA deposition and progressive crystal nephropathy in individuals with APRT deficiency. The drug decreases DHA synthesis and thereby reduces crystalluria [1,2,4,6]. Febuxostat, a selective non-purine XOR inhibitor [7], has also been reported to decrease DHA crystalluria in APRT deficiency patients [8], providing an attractive alternative treatment option for those who are intolerant of allopurinol. A reliable method to guide the titration of either XOR inhibitor has been lacking due to inability to measure urinary DHA. The monitoring of drug treatment is currently performed by urine microscopy where the absence of urinary DHA crystals is considered indicative of adequate therapy. However, this indirect method has several limitations that render it unsatisfactory as the only approach for therapeutic drug monitoring. Based on our own personal experience some patients with minimal or no crystalluria continue to form stones, while others with persistent crystalluria do not develop new stones or evidence of CKD progression. Thus, the dosing of XOR inhibitor therapy has simply been empiric and has been modified by the degree of DHA crystalluria or by clinical events such as recurrent kidneys stones or progressive CKD. In adults, allopurinol has commonly been prescribed in doses ranging from 200 to 300 mg/day [5]. Several reports of recurrent allograft DHA nephropathy despite treatment with allopurinol in this dosage range [5], has prompted us to use doses higher than 300 mg/day. Recently, our group developed a high-throughput ultra-performance liquid chromatography - electrospray tandem mass spectrometry (UPLC-MS/MS) assay for measurement of DHA in urine samples, which has the potential to greatly improve monitoring of pharmacotherapy in patients with APRT deficiency [9].

The aim of this exploratory pilot study was to compare the efficacy of allopurinol and the non-purine XOR inhibitor febuxostat in reducing urinary DHA excretion in patients with APRT deficiency.

2. Materials and methods

2.1. Ethics committee approval

The study was approved by the Icelandic National Bioethics Committee (NBC 13-115-S1), the Icelandic Medicines Agency (EudraCT No. 2013-00975-33) and the Icelandic Data Protection Authority. This clinical trial is registered at www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02752633). All study participants gave a written informed consent for their participation.

2.2. Study design and setting

This exploratory pilot study was an open-label, crossover, single-center, non-randomized clinical trial designed to compare the effect of allopurinol (400 mg/day) and febuxostat (80 mg/day) on urinary DHA excretion in individuals with APRT deficiency. These doses were chosen as they are currently recommended in the management of APRT deficiency. The study was conducted between May 2013 and May 2015 as the participants were enrolled at different times. The only study site was Landspitali - The National University Hospital of Iceland in Reykjavik, Iceland. The Data Safety Monitoring Board (DSMB) constituted by the National Institutes of Health had oversight responsibility of the Data Safety Monitoring Plan for this clinical trial. The monitoring board reviewed accrual, patterns and frequencies of all adverse events, and protocol compliance every 6–12 months.

2.3. Participants

Study participants were recruited from a group of patients with confirmed APRT deficiency, who were enrolled in the National Institutes of Health-supported APRT Deficiency Registry of the Rare Kidney Stone Consortium (RKSC, http://www.rarekidneystones.org/). Confirmation of APRT deficiency was based upon the determination of known biallelic pathogenic APRT mutations or absent APRT activity in red blood cell lysates. Participants were eligible for inclusion if they: a) were currently receiving allopurinol therapy (the recommended treatment for patients with APRT deficiency); b) were willing to interrupt their allopurinol therapy for a total of 3 weeks as outlined below; and c) were at least 18 years of age. There were no exclusion criteria if the above inclusion criteria were met. Patients with reduced kidney function were not excluded.

2.4. Study interventions

An overview of the treatment and assessment schedule is presented in Table 1. At baseline, after a 7-day washout period, all participants were prescribed 400 mg of allopurinol in a single daily dose for 14 days. Following a second 7-day washout period, all participants were prescribed 80 mg of febuxostat in a single daily dose for another 14 days. The order of the interventions was not varied as it was not considered important due to the relatively short half-life of both study drugs (febuxostat, 5–8 h; allopurinol 1–2 h and oxypurinol, the active allopurinol metabolite, 15–16 h) [10,11]. 24–H and first morning void urine samples were collected at baseline and at the end of the allopurinol and febuxostat treatment periods (on days 7, 21 and 42), respectively. To minimize a potential adverse effect of variations in dietary purine intake on the results, the participants were asked to keep a food record while they collected the first 24-h urine sample and adhere to the same diet when they collected the other two 24-h urine samples. No further measures were taken to control dietary purine intake during the study period. At the completion of the study, all patients were advised to return to their regular allopurinol dosing regimens.

2.5. Laboratory testing

During the study, all participants were asked to donate three pairs of 24-h and first morning void urine specimens as described in Table 1. All urine samples were collected without additives or preservatives and