HHS Public Access

Author manuscript

Eur J Intern Med. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Eur J Intern Med. 2018 February ; 48: 75–79. doi:10.1016/j.ejim.2017.10.007.

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 deficiency (APRTd) 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 APRTd patients.

Materials and methods—Patients listed in the APRTd Registry of the Rare Kidney Stone Consortium, currently receiving allopurinol therapy were invited to participate. The trial endpoint was the 24-hour 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 method.

Results—Eight of the 10 patients invited completed the study. The median (range) 24-hour 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

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Conflict of Interests

The results presented in this paper have not been published previously in whole or part, except in abstract form. None of the authors declared financial or other conflicting interests.

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 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 APRTd 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 APRTd, should be confirmed in a larger sample.

Keywords

chronic kidney disease; kidney stones; nephrolithiasis; xanthine oxidoreductase inhibitors; crystal nephropathy

Introduction

Adenine phosphoribosyltransferase deficiency (APRTd; 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]

APRTd 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 cases reported to date have already developed end-stage kidney failure at diagnosis,[4] which frequently is not recognized or 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 APRTd. 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 APRTd 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 generally use doses higher than 300 mg/day. Recently, our

group developed a novel 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 APRTd.[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 APRTd.

Materials and Methods

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.

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 the urinary DHA excretion in individuals with APRTd. These doses were chosen as they are currently recommended in the management of APRTd. 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.

Participants

Study participants were recruited from a group of patients with confirmed APRTd, 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 APRTd was based upon the determination of known biallelic pathogenic *APRT* mutations or absent APRT enzyme 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 APRTd); 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.

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 hours; allopurinol 1-2 hours and oxypurinol, the active allopurinol metabolite, 15-16 hours).[10, 11] Twenty-four hour and first morning void urine samples were collected at baseline and at the end of allopurinol and febuxostat treatment periods (days 7, 21 and 42), respectively. To minimize 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-hour urine sample and adhere to the same diet when they collected the other two 24-hour 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.

Laboratory testing

During the study, all participants were asked to donate three pairs of 24-hour urine and first morning void specimens as described in Table 1. All urine samples were collected without additives or preservatives and stored at room temperature and returned to the laboratory on days 8, 22 and 43, the same days the 24-hour collections were completed. Immediately before aliquoting, the 24-hour collection bottles were inverted 3 times and the urine samples were then frozen and stored at −80°C.

Urinary DHA and adenine were measured using the UPLC-MS/MS assay developed by our group, as previously described.[9] Prior to the UPLC-MS/MS analysis, the urine samples were diluted 1:15 (*v/v*) with 10 mM NH_4OH, followed by the addition of internal standard. The samples were subsequently mixed for 3 min and centrifuged at 3100 rpm for 10 min at 4°C before injection into the UPLC-MS/MS system. The lower limit of detection for DHA is 20 ng/mL, the lower limit of quantification 100 ng/mL and the upper limit of quantification 5000 ng/mL. The intra- and inter-day accuracy and precision coefficients of variation have been shown to be well within +/−15% for quality control samples. The 24-hour urinary DHA and adenine excretion was measured and the urinary DHA- and adenine-to-creatinine ratios in first morning void urine samples were calculated. Urine and serum creatinine concentrations were measured with an isotope dilution mass spectrometry (IDMS) standardized laboratory method. Glomerular filtration rate (eGFR) was estimated from serum creatinine values using the Chronic Kidney Disease Epidemiology Collaboration equation.[12] Plasma uric acid was measured at baseline and at the conclusion of both allopurinol and febuxostat therapy, applying standard laboratory methods.

Outcome measures

The primary trial endpoint was the 24-hour urinary DHA excretion and the urinary DHA-to-creatinine ratio after two weeks of treatment with the two study drugs, allopurinol (daily dose 400 mg) and febuxostat (daily dose 80 mg).

Statistical Analysis

The urinary DHA excretion is expressed as mg/24 hr and as DHA-to-creatinine ratio in mg/mmol). Data are presented as a median (range). Differences in the median urinary DHA

excretion and the urinary DHA-to-creatinine ratio between periods off pharmacotherapy and on the two study drugs, allopurinol and febuxostat, were assessed using the Wilcoxon signed-rank test.

Results

Eight of the 10 patients who were invited to participate in the clinical trial completed the study. One participant discontinued participation due to pregnancy and one did not accept the invitation. One individual inadvertently reversed the order of the allopurinol and febuxostat treatment periods, but as he had otherwise adhered to the protocol, his data were included in the analysis.

Clinical characteristics of the participating patients are presented in Table 2. Only one individual had stage 3 CKD; the others had CKD stage 1 or 2. The median (range) 24-hour urinary DHA excretion was 116 (75–289) mg at baseline. Following 14 days of allopurinol therapy, the DHA excretion was 45 (13-112) mg and was below the lower limit of quantification (100 ng/mL) in all 8 cases after 14 days of febuxostat treatment (P=0.036). At the end of febuxostat therapy, 4 participants had urinary DHA below detectable limits (<20 ng/mL) and the other 4 had a median urinary DHA excretion of 13 (10-13) mg/24 hr (P=0.036) (Table 3). The median urinary DHA-to-creatinine ratio in first morning void urine samples was 16.1 (8.2-34.5) mg/mmol at baseline, 5.3 (1.1-8.4) mg/mmol on allopurinol (P=0.036) and below lower limit of quantification at the completion of febuxostat treatment in all participants (P=0.036) (Table 4). Four of these individuals with a quantifiable value had a median urinary DHA-to-creatinine ratio of 1.0 (0.8-1.1) mg/mmol. The urinary adenine excretion, which was 32 (18-46) mg/24 hr at baseline, increased to 96 (26-139) mg/24 hr on allopurinol and to 112 (54-158) mg/24 hr at the end of febuxostat treatment. The plasma uric acid concentration was 257 (180-454) μmol/L at baseline, and decreased to 179 (131-295) μmol/L following two weeks of of allopurinol and to 137 (88-221) μmol/L at the end of the febuxostat treatment period. No adverse events were observed.

Six of the 8 participants had their urinary DHA excretion re-evaluated when they had resumed allopurinol therapy in the daily dose of 400 mg, at a median of 6 (2-12) months following study completion. The median (range) 24-hour urinary DHA excretion of these 6 individuals was 33 (9-88) mg, compared with 45 (13-112) mg at the completion of allopurinol therapy during the study period. The median urinary DHA-to-creatinine ratio in first morning void urine samples from these 6 patients was 3.0 (1.0-3.7) mg/mmol 6 months following study completion and 5.3 (1.1-8.4) mg/mmol during the study. Individual patient data are displayed in Table 5.

Discussion

In this pilot study, a marked reduction in urinary DHA excretion was observed with both allopurinol and febuxostat therapy in patients with APRTd. However, febuxostat decreased the urinary DHA excretion much more effectively than allopurinol. Importantly, urinary DHA excretion remained substantial despite conventional doses of allopurinol, suggesting that higher doses may be required to adequately control dihydroxyadeninuria.

As this is the first published study designed to compare the effect of allopurinol and febuxostat on the urinary DHA excretion in patients with APRTd, no prior data are available for comparison. The more powerful reduction in urinary DHA excretion observed during febuxostat treatment may simply reflect more effective XOR inhibition compared with allopurinol in the doses prescribed. This notion is supported by both a larger increase in urinary adenine excretion and greater reduction of plasma uric acid concentration when the participants changed from allopurinol to febuxostat. Whereas a carry-over effect of allopurinol cannot be excluded, this would be very unlikely due the short half-life of allopurinol and its active metabolite, oxypurinol. Thus, it can be assumed that urinary DHA had returned to baseline before the febuxostat treatment commenced. Lack of compliance during allopurinol therapy only is a highly unlikely explanation of the differences in urinary DHA excretion observed between the two study drugs. Since dose-equivalence studies comparing allopurinol and febuxostat for lowering DHA are not available, underdosing of allopurinol rather than a true difference in the efficacy of the two drugs in XOR inhibition may have contributed to the superior effect on urinary DHA excretion observed with febuxostat treatment. Moreover, higher doses of allopurinol might have led to a more complete inhibition of DHA generation and should be studied in this patient population. Doses of allopurinol up to 800 mg/day are approved by US Food and Drug Administration and the European Medicines Agency but have not been tested in a systematic way. Studies in patients with gout have shown that febuxostat, in a dose of 80-120 mg daily, resulted in a greater proportion of individuals achieving serum uric acid levels <6 mg/dL (357 μmol/L), compared with allopurinol 300 mg daily, or approximately 80% vs. 40%.[13, 14]

There are several differences in the actions of the two study drugs. Whether these differences, beyond the greater inhibitory effect of febuxostat on XOR, contribute to the greater efficacy of febuxostat in patients with APRTd is not known. Allopurinol is a purine analogue that inhibits enzymes involved both in purine and pyrimidine synthesis and metabolism. In addition to inhibiting XOR, allopurinol and its metabolites also impede purine nucleoside phosphorylase (PNP), a mediator of purine metabolism, and orotidine-5′-monophosphate decarboxylase (OMPDC), which is required in the synthesis of pyrimidines.[15] Febuxostat is a non-purine inhibitor of XOR only.[16] Allopurinol, a relatively weak inhibitor of XOR and a purine analogue, also undergoes metabolism by XOR, which results in the production of its most active metabolite, oxypurinol. It is oxypurinol that binds very tightly to the reduced form of XOR, resulting in a robust competitive inhibition of XOR. Febuxostat, on the other hand, is a potent inhibitor of XOR, blocking both the reduced and oxidized forms of the enzyme. We cannot comment on whether these differences in pharmacologic properties contribute to the marked discrepancy in the effectiveness of the two drugs in decreasing urinary DHA excretion.

Recent work has shown that allopurinol in doses less than 400 mg/day may not effectively diminish new stone formation or stabilize kidney function in APRTd patients[1, 4, 6]. Therefore, we have recommended a daily dose of at least 400 mg which is the dose we elected to use in the current study. However, as the level of reduction in urinary DHA excretion required for optimal prevention of adverse renal outcomes is unknown,[4, 17] it is not clear if the difference in urinary DHA excretion observed between the two drugs in the current study is clinically significant. Nevertheless, the urinary DHA excretion remains

substantial despite allopurinol 400 mg daily, unlike with febuxostat 80 mg, suggesting that higher doses of allopurinol may be required to adequately control dihydroxyadeninuria. Finally, febuxostat may also have some safety benefit as its association with hypersensitivity is extremely rare as compared with allopurinol. Rarely, allopurinol-associated hypersensitivity may be manifested as the Stevens-Johnson syndrome.

The novel, rapid and robust UPLC-MS/MS-based urinary DHA assay was instrumental in this study. This assay has the potential to greatly improve pharmacotherapy monitoring in patients with APRTd and will form the basis for future studies of the optimal reduction in urinary DHA excretion required for prevention of adverse renal outcomes. Although the assay is not yet commercially available, we do offer urinary DHA measurements for all patients participating in our studies and for other individuals on a case-by-case basis.

Limitations inherent in this study include a small number of participants which is to be expected for a rare disease. Measuring hard endpoints, including incidence of stones or changes in eGFR would take years or even decades to complete due to the small number of participants and low event rate. Other notable limitations are lack of a cross-over design and measurement of urinary DHA at the end of the second washout period. However, a long-lasting pharmacodynamic effect of allopurinol would be unlikely due to the short half-life of the active metabolite, oxypurinol. While the study was not blinded to the participants, laboratory personnel were blinded to the drug treatment assignments. As 7 of 8 participants had well-preserved eGFR, we were unable to examine whether febuxostat is more effective in patients with advanced CKD. Before we discovered the robust result of febuxostat presented here, we were reluctant to discontinue allopurinol therapy in patients with more advanced CKD. Since febuxostat is largely metabolized by the liver, and the active allopurinol metabolites are cleared by the kidneys, the former may be easier to dose adequately and perhaps is safer in individuals with CKD.[18]

The study has several important strengths, including the use of a new mass spectrometry-based method for accurate quantification of urinary DHA excretion in the participants. The participation of a well characterized population of APRTd patients and the abundant clinical data from the APRT Deficiency Registry of the RKSC also add strength to this work.

In conclusion, this clinical trial revealed a marked decrease in urinary DHA excretion in patients with APRTd using conventional doses of both allopurinol and febuxostat. Interestingly, febuxostat was significantly more efficacious than allopurinol in reducing DHA excretion in the prescribed doses. These results need to be confirmed in a larger patient sample. Furthermore, it will be important to include higher doses of allopurinol in the range of 600-800 mg daily in future studies. The clinical significance of the difference in urinary DHA excretion observed between these drugs warrants further study, as the effect on long-term renal outcomes may be improved with enhanced inhibition of DHA excretion.

Acknowledgments

Part of this work was presented in an abstract form at the American Society of Nephrology Kidney Week in San Diego in November 2015.

Funding

This study was supported by the Rare Kidney Stone Consortium (U54DK083908), part of the Rare Diseases Clinical Research Network (RDCRN), which is an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS). This consortium is funded through a collaboration between NCATS, and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The study sponsor had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

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Highlights

- Both allopurinol and febuxostat effectively reduced urinary DHA excretion in APRTd patients.
- Febuxostat was significantly more efficacious than allopurinol in the prescribed doses.
- This finding which may translate into improved outcomes should be confirmed in a larger sample.
- Allopurinol doses in the range of 600-800 mg daily may be required to control dihydroxyadeninuria.

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-hour urine samples[1]		Day 7	Day 21	NA	Day 42
First morning urine sample collected[1]		Day 7	Day 21	NA	Day 42
Adverse events	Monitored continuously				

Abbreviations: Cr, serum creatinine. NA, not assessed.

[1] 2,8-Dihydroxyadenine and creatinine were measured in these urine samples.

Table 2

Clinical characteristics of study participants.

Patient	Age (years)	Gender	eGFR (ml/min/1.73m^2)	Age at diagnosis (years)	Major clinical feature
1	33	Female	103	0.5	Crystalluria
2	61	Male	90	23	Asymptomatic
3	28	Male	103	0.8	Kidney stones
4	38	Female	87	3.3	LUTS
5	52	Male	99	24.2	Kidney stones
6	62	Female	83	33.1	Kidney stones
7	67	Female	37	52.2	CKD
8	56	Male	80	32.9	Kidney stones

Abbreviations: eGFR, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation; CKD, chronic kidney disease; LUTS, lower urinary tract symptoms.

Table 3

Twenty-four hour urinary 2,8-dihydroxyadenine (DHA) excretion at baseline and at the completion of allopurinol and febuxostat treatment periods.

Patient	Baseline	Allopurinol	Febuxostat
	DHA/24 hr (mg)	DHA/24 hr (mg)	DHA/24 hr (mg)
1	89	32	13*
2	126	54	13*
3	233	112	10*
4	151	35	ND
5	289	90	13*
6	106	27	ND
7	75	13*	ND
8	95	75	ND

Abbreviations: ND, not detectable (limit of detection <20 ng/mL).

*Below limit of quantification (<100 ng/mL)

Table 4

2,8-Dihydroxyadenine-to-creatinine ratio in first morning void urine samples baseline and at the completion of allopurinol and febuxostat treatment periods.

Patient	Baseline	Allopurinol	Febuxostat
	DHA/Cr (mg/mmol)	DHA/Cr (mg/mmol)	DHA/Cr (mg/mmol)
1	12.5	4.4	0.9*
2	22.8	7.0	ND
3	34.5	5.4	1.1*
4	8.2	2.8	0.8*
5	17.4	8.4	1.1*
6	13.9	5.6	ND
7	15.2	1.1*	ND
8	16.9	5.1	ND

Abbreviations: Cr, creatinine; DHA, 2,8-dihydroxyadenine; ND, not detectable (limit of detection <20 ng/mL).

*Below limit of quantification (<100 ng/mL).

Table 5

Twenty-four hour 2,8-dihydroxyadenine (DHA) excretion and DHA-to-creatinine ratio in first morning void urine samples on allopurinol therapy (400 mg/day) during and following the study.

Patient	Allopurinol[1]		Allopurinol[2]	
	DHA/24 hr (mg)	DHA/Cr (mg/mmol)	DHA/24 hr (mg)	DHA/Cr (mg/mmol)
2	54	7.0	47	3.5
4	35	2.8	27	3.0
5	90	8.4	88	3.0
6	27	5.6	18*	2.3
7	13*	1.1*	9*	1.0*
8	75	5.1	39*	3.7

[1] Allopurinol treatment period;

[2] during allopurinol treatment following study completion. Abbreviations: Cr, creatinine; ND, not detectable (limit of detection <20 ng/mL).

* Below limit of quantification (<100 ng/mL).