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Efficacy and safety of allopurinol in patients with hypoxanthine-guanine phosphoribosyltransferase deficiency

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Abstract

Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency is a genetic disease of purine metabolism resulting in uric acid overproduction. Allopurinol, which inhibits the enzyme xanthine oxidase and reduces uric acid synthesis, is widely used for the treatment of gout and uric acid overproduction. The aim of the study was to analyze the long-term efficacy and safety of allopurinol in patients with HPRT deficiency. Nineteen patients (13 with Lesch-Nyhan syndrome and 6 with partial HPRT deficiency) were treated with allopurinol (mean dose, 6.4 mg/kg body weight per day; range, 3.7-9.7 mg/kg body weight per day) and followed up for at least 12 months (mean follow-up, 7.6 years). The efficacy of allopurinol was evaluated by serial measurement of purine metabolic parameters and renal function as well as by clinical manifestations. Safety was assessed by recording adverse events. Treatment with allopurinol normalized serum urate level in all patients and resulted in a mean reduction in serum urate of 47%. Allopurinol treatment was associated with a mean 74% reduction in urinary uric acid-to-creatinine ratio. In contrast, allopurinol treatment increased mean hypoxanthine and xanthine urinary excretion rates 5.4- and 9.5-fold, respectively, compared with baseline levels. The decrease in uric acid excretion in complete and partial HPRT-deficient patients was not accompanied by a stoichiometric substitution of hypoxanthine and xanthine excretion rates. Allopurinol-related biochemical changes were similar in patients with either complete or partial HPRT deficiency. Renal function remained stable or improved with treatment. Three patients had urolithiasis during allopurinol treatment. In 2 patients, xanthine stones were documented and they required allopurinol dose adjustments aimed at reducing excessive oxypurine excretion rates. No allopurinol hypersensitivity reactions occurred. Neurologic manifestations were not influenced by allopurinol therapy. In conclusion, allopurinol is efficacious and generally safe for the treatment of uric acid overproduction in patients with HPRT deficiencies. Xanthine lithiasis, developing as a consequence of allopurinol therapy, should be preventable by adjustment of allopurinol dose.

1. Introduction

Hypoxanthine-guanine phosphoribosyltransferase (HPRT, EC 2.4.2.8) deficiency is a genetic disorder of purine metabolism resulting from mutation in the X chromosome–linked *HPRT* gene encoding the enzyme HPRT. All HPRT-deficient patients show hyperuricemia and/or hyperuricosuria. Complete deficiency of HPRT activity underlies the Lesch-Nyhan syndrome (MIM [mendelian inheritance in man] 300322), which is characterized by hyperuricemia, dystonia, choreoathetosis, mental retardation, and self-mutilation behavior [1,2]. Partial deficiency of HPRT activity (MIM 300323) [3,4] is associated with variable neurologic manifestations, depending on the residual enzyme levels. Increased uric acid synthesis in HPRT deficiency is a consequence of decreased purine base reuse for nucleotide synthesis and enhanced de novo purine synthesis due to the excessive availability of the regulatory substrate 5-phosphoribosyl 1-pyrophosphate. Uric acid overproduction imparts increased risks for nephrolithiasis, renal insufficiency, gouty arthritis, and tophi. To prevent

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these undesired consequences, treatment with the xanthine oxidase inhibitor allopurinol, hydration, and urine alkalinization is recommended [4].

Allopurinol is a hypoxanthine analogue and is a substrate and inhibitor of xanthine oxidase (EC 1.2.3.2), which catalyzes conversion of both hypoxanthine to xanthine and xanthine to uric acid [5]. Allopurinol is oxidized to oxipurinol, an even more potent xanthine oxidase inhibitor. Allopurinol is effective in reducing hyperuricemia in patients with Lesch-Nyhan syndrome, but long-term clinical usefulness of this agent has not been systematically assessed. Moreover, the efficacy and safety of allopurinol have not been analyzed in patients with partial HPRT deficiency.

Since 1984, we have studied 30 patients with HPRT deficiency at the La Paz University Hospital (Madrid, Spain) [6]. This experience has afforded an opportunity to assess the efficacy and safety of allopurinol treatment in these patients.

2. Subjects and methods

2.1. Patients

We analyzed the course of 19 HPRT-deficient patients who were followed up at the La Paz University Hospital periodically (every 3, 6, or 12 months) for at least 12 months. We estimated that 12 months was the minimum period needed to evaluate the efficacy and safety of allopurinol (Table 1). These patients were referred to the La Paz University Hospital from all over Spain, including the Canary Islands and Mallorca, as a result of our report of a patient with partial HPRT deficiency in 1985 who was the first patient in whom HPRT activity was determined in Spain [7].

2.1.1. Diagnosis of HPRT deficiency

Deficiency of HPRT was diagnosed in 19 patients. These patients were included in the study on the basis of all of the following 3 criteria:

(a) Clinical signs: clinical symptoms and signs typical of an HPRT-deficient state.
(b) Biochemical abnormalities: purine metabolism was examined by the determination of plasma and urinary uric acid, creatinine, hypoxanthine, and xanthine [8], and, in some instances, by quantification of urinary radioactivity after the infusion of tracer doses of [8-^{14}C]adenine to radiolabel the adenine nucleotide pool [9].
(c) Enzyme deficiency: decreased HPRT activity in erythrocyte lysates and simultaneously increased adenine phosphoribosyltransferase (EC 2.4.2.7) activity [10]. In 16 patients, residual HPRT activity was determined in intact erythrocytes [6].

In 16 families of the 19 reported patients, the genetic defects accounting for enzyme deficiency were also established [11].

Table 1
Characteristics of patients with HPRT deficiency included in the study

Patient	Age [a]	Clinical characteristics at consultation	Clinical group [b]
Classic Lesch-Nyhan syndrome			
1	6 y	Choreoathetosis, spasticity, mental retardation	4
2	5 y	Choreoathetosis, spasticity, self-mutilation, mental retardation	4
3	4 y	Choreoathetosis, spasticity, self-mutilation	4
4	19 mo	Psychomotor retardation, crystalluria	4
5	11 mo	Psychomotor retardation, spasticity	4
6	5 mo	Psychomotor retardation	4
7	27 y [c]	Choreoathetosis, spasticity, self-mutilation, mental retardation	4
8	18 mo	Psychomotor retardation, spasticity	4
9	3 y	Psychomotor retardation, acute pyelonephritis	4
10	19 mo	Psychomotor retardation, encephalopathy	4
11	10 mo	Motor retardation, nephrocalcinosis	4
12	11 mo	Motor retardation	4
13	1.5 y	Motor retardation	4
Partial HPRT deficiency			
14	5 mo	Hyperuricemia and crystalluria	1
15	13 y	Acute renal failure, dystonia	2
16	35 y	Mental retardation, hyperuricemia, dystonic gait	2
17	33 y	Mental retardation, hyperuricemia, dystonic gait	2
18	14 y	Severe dystonia, extrapyramidal syndrome	3
19	7 mo	Psychomotor retardation, crystalluria	3

[a] Age at the first visit to the La Paz University Hospital.
[b] According to the clinical classification proposed by García Puig et al [6]: 1, absence of neurologic manifestations; 2, neurologic manifestations that slightly or moderately limit a normal life, although subjects can carry an independent life; 3, life is dependent on others but can perform activities; 4, neurologic manifestations characteristic of Lesch-Nyhan syndrome.
[c] Diagnosed at 9 years and referred to the La Paz Hospital at 27 years.

2.1.2. Clinical follow-up

One of us (JGP) followed all the patients for the entire study period (1984-2006). A copy of the clinical report given at each visit to the patient and his family was kept in the medical record. Informed consent was obtained from the patients and/or from the parents of the patients. The ethics committee of the La Paz University Hospital approved the protocol.

2.1.3. Treatment

Allopurinol was the only urate-lowering drug given to HPRT-deficient patients. The most commonly used dose was 5 mg/kg per day. Allopurinol was given orally as a single daily dose, or in 2 divided doses, every 12 hours, according to the patient or caregiver preference. Compliance was assessed by questioning the patient and/or parents: “what is the allopurinol dose that he takes everyday?” Treatment objectives were (*a*) a serum urate (sUA) concentration

≤7.0 mg/dL and greater than 4.5 mg/dL and (*b*) urinary uric acid-to-creatinine ratio of less than 1.0 mg/mg. These 2 targets were expected to reduce risks for flares of gouty arthritis and urolithiasis. Where appropriate, allopurinol dose was changed to achieve the target sUA. All patients were prescribed bicarbonate (50 mg/kg of body weight per day, in 3 divided doses) to increase urinary oxypurine solubility. Some patients received drugs other than allopurinol for conditions associated with HPRT deficiency, such as anemia (folic acid; patients 4, 18, and 19; Table 1) or neurologic manifestations (benzodiazepines).

2.1.4. Studied variables

The following variables were examined to assess allopurinol efficacy and safety at each visit:

(a) Biochemical determination of purine metabolites: in each patient, we determined sUA, urinary uric acid-to-creatinine ratio, and urinary hypoxanthine and xanthine concentrations. Total purine excretion was the sum of hypoxanthine, xanthine, and uric acid excretion. A morning urine sample was obtained in patients with Lesch-Nyhan syndrome because 24-hour urine samples were difficult to collect from these patients. Uric acid was determined in the morning of its collection. In most partial HPRT-deficient patients, a 24-hour urine sample was obtained at each visit. During time collection, 24-hour urine samples were preserved below 10°C and, after laboratory arrival, carefully homogenated and processed in the same morning. An aliquot of each morning urine sample or of the homogenated 24-hour urine sample was maintained at −20°C for oxypurine determination. Each sample was carefully homogenated the day of the assay.

(b) Renal function: serum creatinine was used to assess renal function, and glomerular filtration rate (GFR) was estimated by the formulas of Schwartz and Gauthier [12] or Cockroft and Gault [13]. Correlation between calculated GFR and the creatinine clearance was performed when 24-hour urine samples were obtained. Kidney ultrasound was performed periodically.

(c) Safety assessment: we monitored and recorded adverse events, including those that could be related to allopurinol therapy, such as acute arthritis, changes in tophus size, urolithiasis, hypersensitivity reactions, and gastrointestinal symptoms.

2.2. Analytical methods

HPRT and adenine phosphoribosyltransferase activities in erythrocyte lysates were determined by high-performance liquid chromatography [10]. Residual HPRT activity in 16 patients was determined in intact erythrocytes [6]. Uric acid and creatinine in plasma and urine were measured in a multichannel autoanalyzer (Modular P800, Roche, Mannheim, Germany; and Hitachi 704, Hitachi, Tokyo, Japan). Urinary hypoxanthine and xanthine were determined by high-performance liquid chromatography [8] while patients consumed a self-selected diet. Renal calculi were analyzed by infrared spectroscopy (Spectrum RXI FT-IR System, Perkin Elmer, Norwalk, CT).

2.3. Statistical analysis

The significance of the differences in purine metabolism and GFR values between baseline and allopurinol therapy and between patients with the Lesch-Nyhan syndrome and those with partial HPRT deficiency were assessed by means of nonparametric tests such as the Wilcoxon (paired data, basal vs allopurinol therapy) or Mann-Whitney rank sum test (patients with Lesch-Nyhan syndrome vs those with partial HPRT deficiency). A P value of less than .05 was taken to indicate a statistically significant difference. All P values are 2-tailed. Values given are means ± SD.

3. Results

Patients were classified into 2 groups: classic Lesch-Nyhan syndrome (clinical group 4) and partial HPRT deficiency (including clinical groups 1-3). Classification was based on clinical, biochemical, enzymatic, and molecular data. Because self-injury does not emerge until 2 to 3 years of age and can be delayed until late adolescence, patients who did not self-injure were classified as having Lesch-Nyhan syndrome if they had nondetectable enzyme levels and a null mutation (ie, Table 1, patient 5) or another family member was diagnosed with Lesch-Nyhan syndrome on the basis of the full neurobehavioral syndrome (ie, Table 1, patient 1).

Mean age at diagnosis was 7 years (3 years for patients with the Lesch-Nyhan syndrome [range, 5 months to 9 years] and 16 years for partial HPRT-deficient patients [range, 5 months to 35 years]).

HPRT activities in erythrocyte hemolysates were undetectable (<0.01 nmol/h per milligram of hemoglobin) in all patients with the Lesch-Nyhan syndrome. In partial HPRT-deficient patients, HPRT activity ranged from undetectable to 9.38 nmol/h per milligram of hemoglobin (reference range, 64-124 nmol/h per milligram of hemoglobin). Adenine phosphoribosyltransferase activity ranged from 40 to 141 nmol/h per milligram of hemoglobin (reference range, 19-38 nmol/h per milligram of hemoglobin). HPRT activity was also determined in intact erythrocytes and expressed as the percentage of ^{14}C hypoxanthine converted into ^{14}C inosine monophosphate under conditions of enrichment for the HPRT co-substrate 5-phosphoribosyl 1-pyrophosphate. In patients with Lesch-Nyhan syndrome, HPRT activity ranged from 0.1% to 1.1%, and in partial HPRT-deficient subjects from 0.2% to 54.1%.

Genetic studies were performed in the 16 families of the 19 patients and showed 10 point mutations: 2 in a noncoding region causing splice errors and 8 in coding regions. Of the

Table 2
Purine metabolism during allopurinol therapy in 19 patients with HPRT deficiency

	Baseline	Allopurinol
Serum		
Urate (mg/dL) (n = 19)	10.0 ± 2.6	5.3 ± 1.1**
Urine		
Uric acid/creatinine (mg/mg) (n = 19)	2.7 ± 1.3	0.7 ± 0.3 **
Hypoxanthine (μmol/g creatinine) (n = 15)	654 ± 312	3510 ± 1430 **
Xanthine (μmol/g creatinine) (n = 15)	246 ± 150	2328 ± 1202 **
Total purines (μmol/g creatinine) (n = 15)	16793 ± 8793	9831 ± 2957 *

Normal values for sUA levels depend on age and sex. Normal values for urinary uric acid-to-creatinine ratio are less than 1.0 after 3 years of age. Normal values for urinary total purines markedly depend on uric acid excretion, which is extremely dependent on age and diet. Normal total purine excretion on a purine-free diet for adult controls is 2529 ± 542 μmol/g creatinine. Normal values for hypoxanthine and xanthine excretion rates are 128 ± 95 μmol/g creatinine and 110 ± 105 μmol/g creatinine, respectively. "Baseline" indicates not receiving allopurinol; "allopurinol," values obtained at the last visit during treatment with allopurinol.

* $P < .05$ (baseline vs allopurinol).

** $P < .0001$ (baseline vs allopurinol).

coding region mutations, 7 predicted an amino acid change in the translated protein, and one a premature stop codon. Two insertions and 4 deletions were also found.

The total follow-up period on allopurinol ranged from 12 months to 17 years (mean, 7.6 years). Only 12 patients tolerated bicarbonate. Allopurinol doses ranged from 50 to 600 mg/d. The mean allopurinol dose at the last visit was 6.4 ± 2.1 mg/kg of body weight per day (range, 3.7-9.7 mg/kg of body weight per day).

3.1. Purine metabolism

Treatment with allopurinol significantly modified purine metabolism (Table 2). All patients showed, under basal conditions, hyperuricemia (range, 6.9-14.6 mg/dL) for their age. Allopurinol therapy normalized sUA in all patients and decreased sUA to a mean of 47% of baseline value.

Allopurinol treatment significantly decreased uric acid excretion in all patients. All patients, except one (Table 1, patient 17), showed a baseline uric acid-to-creatinine ratio of greater than 1.0 mg/mg. In all patients, except one (Table 1, patient 13), the uric acid-to-creatinine ratio decreased to less than 1.0 mg/mg with allopurinol. Urinary uric acid-to-creatinine ratio decreased a mean of 74% from baseline values (Table 2).

Treatment with allopurinol significantly increased urinary hypoxanthine and xanthine excretion (Table 2). Compared with baseline values, mean hypoxanthine and xanthine concentrations increased on allopurinol 5.4 and 9.5 times, respectively (Table 2). However, because of decreased uric acid excretion, mean total purine excretion decreased by 41%. In healthy subjects, hypoxanthine and xanthine excretion accounts for only a small percentage of total urinary purines, with urinary uric acid accounting for almost all excreted purines (>97%). Mean baseline urinary purine distribution in HPRT-deficient patients was as follows: uric acid, 94.6%; hypoxanthine, 3.9%; and xanthine 1.5%. Treatment with allopurinol markedly modified this distribution. When excluding 4 patients with the Lesch-Nyhan syndrome for whom baseline urinary hypoxanthine and xanthine were not determined, mean total urinary purine distribution on allopurinol therapy was as follows: uric acid, 40.6%; hypoxanthine, 35.7%; and xanthine 23.7%.

Under baseline conditions, mean sUA was not significantly different between patients with complete and partial HPRT deficiency (Table 3). The mean decrease in sUA during allopurinol therapy was similar in patients with the Lesch-Nyhan syndrome (−4.6 mg/dL) and in those with partial HPRT deficiency (−4.9 mg/dL) (Table 3).

Baseline urinary excretion of hypoxanthine, xanthine, and total purines was markedly elevated in HPRT-deficient

Table 3
Purine metabolism in 13 patients with Lesch-Nyhan syndrome and 6 patients with partial HPRT deficiency

	Lesch-Nyhan syndrome		Partial HPRT deficiency	
	Baseline	Allopurinol	Baseline	Allopurinol
Serum				
Urate (mg/dL)	9.7 ± 2.7	5.1 ± 1.1**	10.6 ± 2.5	5.7 ± 1.1*
Urine				
Uric acid/creatinine (mg/mg)	2.9 ± 1.4	0.8 ± 0.3 **	2.2 ± 1.1	0.5 ± 0.3 *
Hypoxanthine[a] (μmol/g creatinine)	734 ± 308	4118 ± 991*	535 ± 305	2598 ± 1577 *
Xanthine[a] (μmol/g creatinine)	311 ± 151[†]	2830 ± 1236 *,[†]	147 ± 85	1575 ± 682 *
Total purines[a] (μmol/g creatinine)	18982 ± 9576	11541 ± 2183 *,[†]	13510 ± 6942	7266 ± 1923

Normal values for sUA levels depend on age and sex. Normal values for urinary uric acid-to-creatinine ratio are less than 1.0 after 3 years of age. Normal values for urinary total purines markedly depend on uric acid excretion, which is extremely dependent on age and diet. Normal total purine excretion on a purine-free diet for adult controls is 2529 ± 542 μmol/g creatinine. Normal values for hypoxanthine and xanthine excretion rates are 128 ± 95 μmol/g creatinine and 110 ± 105 μmol/g creatinine, respectively.

[a] Urinary hypoxanthine, xanthine, and total purines were determined in 9 patients with Lesch-Nyhan syndrome.

* $P < .05$ (baseline vs allopurinol).

** $P < .001$ (baseline vs allopurinol).

[†] $P < .05$ (patients with Lesch-Nyhan syndrome vs patients with partial HPRT deficiency).

patients. No significant differences were encountered between patients with the Lesch-Nyhan syndrome and those with partial HPRT deficiency with the exception of urinary xanthine, which was significantly higher in patients with Lesch-Nyhan syndrome (Table 3). Allopurinol treatment was associated with a significant decrease in total urinary purine excretion of a similar magnitude in patients with the Lesch-Nyhan syndrome (−7441 μmol/g creatinine) and with partial HPRT deficiency (−6244 μmol/g creatinine). However, the mean percentage of decrease was more pronounced in the latter (46%) than in the former (39%). The decrease in uric acid excretion accounted for the decrease in total urinary purines because hypoxanthine and xanthine excretion rates were similarly increased by allopurinol therapy in patients with the Lesch-Nyhan syndrome and in those with partial HPRT deficiency (Table 3).

3.2. Renal function

To assess renal function at baseline and after at least 12 months of uninterrupted allopurinol therapy, we used serum creatinine and height to calculate the GFR according to the formula of Schwartz and Gauthier [12] in infant and adolescent patients. In adult patients, GFR was calculated with the Cockroft-Gault formula, which takes into account age, weight, and serum creatinine. There was a significant correlation between calculated GFR and 24-hour creatinine clearance ($r = 0.855$, $P < .0001$). Calculated GFR was used to compare the influence of allopurinol on the renal function in partial HPRT-deficient patients and in those with Lesch-Nyhan syndrome.

Glomerular filtration rate remained stable or increased during allopurinol therapy (Table 4). Four patients with Lesch-Nyhan syndrome showed a calculated GFR of less than 60 mL/min per 1.73 m^2 at diagnosis, but in every case, GFR increased to more than 60 mL/min per 1.73 m^2 with allopurinol treatment. Renal function changes in patients with partial HPRT deficiency and low baseline GFR markedly differed. One patient aged 33 years (Table 4, patient 17) had a serum creatinine level of 2.1 mg/dL and a creatinine clearance of 51 mL/min per 1.73 m^2 when brought to our attention. Five years later, serum creatinine increased to 3.4 mg/dL and GFR decreased to 30 mL/min per 1.73 m^2. He was intermittently noncompliant with allopurinol therapy, based on his sUA levels in the noncompliant periods (12.8 mg/dL) and low urine hypoxanthine and xanthine excretion rates (323 and 205 μmol/g creatinine, respectively). His brother, aged 35 years (Table 4, patient 16), showed a baseline serum creatinine of 1.4 mg/dL and GFR of 61 mL/min per 1.73 m^2. After 5 years on allopurinol therapy, with good compliance, his renal function appeared to improve (serum creatinine of 1.1 mg/dL and GFR of 75 mL/min per 1.73 m^2).

Table 4
Glomerular filtration rate in patients with Lesch-Nyhan syndrome and partial HPRT deficiency at baseline and after allopurinol therapy

Patient	GFR (mL/min per 1.73 m^2)	
	Baseline (age)	Allopurinol (age)
Lesch-Nyhan syndrome		
1	87 (6 y)	137 (18 y)
2	98 (5 y)	127 (17 y)
3	92 (6 y)	123 (18 y)
4	66 (19 m)	109 (15 y)
5	48 (11 mo)	133 (11 y)
6	54 (5 mo)	125 (10 y)
7		63 (28 y)[a]
8	82 (18 mo)	102 (7 y)
9	75 (3 y)	93 (10 y)
10	59 (20 mo)	92 (4 y)
11	79 (8 mo)	135 (4 y)
12	32 (1 y)	83 (3 y)
13	87 (20 mo)	129 (3 y)
Mean ± SD	72 ± 20 (n = 12)	116 ± 19 * (n = 12)
Partial HPRT deficiency		
14	60 (5 mo)	113 (10 y)
15		85 (22 y)[a]
16	61 (35 y)	75 (40 y)
17	51 (33 y)	30 (38 y)
18	133 (13 y)	136 (20 y)
19	59 (7 mo)	109 (18 y)
Mean ± SD	73 ± 34 (n = 5)	93 ± 41 (n = 5)

[a] Value not included in the mean.
* $P < .05$ (baseline vs allopurinol).

3.3. Clinical and adverse effects of allopurinol therapy

Allopurinol treatment did not overtly modify neurologic symptoms and signs, although, in this study, we did not attempt a thorough assessment of the neurologic evolution of HPRT-deficient patients during allopurinol therapy. Concerning symptoms related to uric acid overproduction, some parents reported at diagnosis reddish sandy urine in the diapers, similar to “brick dust,” particularly when a febrile process coexisted (Table 1, patients 3, 6, 14, and 19). Among the 19 patients, 3 reported renal lithiasis (Table 1, patients 3, 6, and 19) during allopurinol therapy. Two patients with the Lesch-Nyhan syndrome (Table 1, patients 3 and 6) passed xanthine stones as detected by infrared spectroscopy. One of these patients (Table 1, patient 3) required extracorporeal lithotripsy on his right kidney. This was followed by the elimination of 20 xanthine calculi. The second patient passed a xanthine stone and a subsequent renal ultrasound disclosed 2 additional calculi. The third patient (Table 1, patient 19) with partial HPRT deficiency had bilateral renal lithiasis but the composition of the calculi could not be determined.

In 4 patients with the Lesch-Nyhan syndrome, tophaceous deposits in the ears were suspected, but fine needle aspiration did not show monosodium urate crystals, and we concluded that they had chronic chondritis due to recurrent trauma. Thus, the adverse event most frequently occurring in HPRT-deficient patients on allopurinol therapy was xanthine urolithiasis (2/19 patients). No patient experienced

allopurinol hypersensitivity or gastrointestinal symptoms leading to allopurinol discontinuation.

4. Discussion

This study reports the efficacy and safety of allopurinol in 19 patients with HPRT deficiency. Allopurinol treatment reduced sUA from hyperuricemic to normal levels (mean decrease, 4.7 mg/dL) and decreased urinary uric acid-to-creatinine ratio to less than 1.0 mg/mg (mean, 0.7 mg/mg). Allopurinol therapy appeared to preserve or improve renal function. Follow-up of 19 patients with HPRT deficiency allowed us to conclude that, with the exception of xanthine urolithiasis, allopurinol treatment for these patients is safe and effective with regard to the metabolic abnormalities.

The present series of 19 patients is one of the largest in the literature that has examined the course of this enzyme defect. Christie et al [14] reported in 1982 a series of 19 patients with the Lesch-Nyhan syndrome, some of whom were followed for 16 years. However, the data were obtained from different physicians, and purine concentrations before and after allopurinol therapy are missing in some patients. In addition, no mention is made regarding renal function and its follow-up. Concerning partial HPRT deficiency, the most extensive available series is the seminal article published by Kelley et al [4] in 1969, which included 18 patients, 12 of whom were treated with allopurinol. The short-term efficacy of allopurinol was well demonstrated: allopurinol administration to 5 patients for 6 days resulted in a mean decrease in sUA of 8 mg/dL.

The strengths of our study are the number of studied patients and the length of observation at the same institution by the same team. For 22 years (1984-2006), we have followed 19 patients with HPRT deficiency (mean follow-up, 7.6 years per patient). This has allowed an extensive evaluation of allopurinol efficacy and safety in HPRT-deficient patients. Several isolated clinical reports of patients with HPRT deficiency have described xanthine lithiasis [15-23], or acute gout [24], or have discussed the influence of allopurinol on biochemical variables [25-27]. In 8 patients with HPRT deficiency, Kelley et al [4] showed that allopurinol (400-800 mg/d) decreased sUA levels between 48% and 76% after only 48 hours, an effect attributed to a greater sensitivity to the inhibitory effect of allopurinol on xanthine oxidase in HPRT-deficient patients as compared with patients with gout. This hypothesis has been questioned and, in fact, Christie et al [14] believe that patients with the Lesch-Nyhan syndrome require higher doses of allopurinol than patients with gout to normalize sUA. In the review of Christie et al [14], doses given ranged from 6.7 to 38.1 mg/kg per day, with total doses of 100 to 800 mg/d. In our study the mean allopurinol dose administered was 6.4 mg/kg per day, with total doses ranging from 50 to 600 mg/d to achieve an sUA level between 4.5 and 7.0 mg/dL. Higher allopurinol doses would have reduced sUA levels further but would also have increased hypoxanthine and xanthine urinary excretion rates, which are less soluble that uric acid in urine.

There are 2 long-standing questions concerning HPRT deficiency. (*a*) Is residual HPRT activity inversely related to purine overproduction? and (*b*) does allopurinol therapy modify total purine synthesis, that is, during allopurinol treatment, is there a stoichiometric substitution of uric acid by hypoxanthine and xanthine [26-28]? The results of our study add new data to answer these questions.

Purine overproduction may be related to the residual HPRT activity. Some authors reported that purine overproduction is of a similar magnitude in patients with partial and complete HPRT deficiency [4,29]. In other reports, purine overproduction appeared to be more pronounced in patients with the Lesch-Nyhan syndrome than in partial HPRT-deficient patients [30,31]. In this study, total purine excretion was higher in patients with Lesch-Nyhan syndrome than in subjects with partial HPRT deficiency, although the difference was not statistically significant (Table 3). This is in agreement with the fact that the mean allopurinol dose to achieve the target sUA concentration was similar in both groups. The observation that total purine excretion is lower in patients with partial than complete HPRT deficiency is in consonance with the hypothesis that, in the former, residual HPRT activity may contribute to nucleotide synthesis and partial inhibition of de novo purine synthesis.

On the other hand, the observation that the decrease in uric acid excretion in complete and partial HPRT-deficient patients was not accompanied by a stoichiometric substitution of hypoxanthine and xanthine supports the hypothesis of an inhibitory effect of allopurinol metabolism on purine nucleotide synthesis [32].

An important finding of this study is that allopurinol significantly modified the clinical course of patients with HPRT deficiency. Nephrocalcinosis (Table 1, patients 4 and 11), acute pyelonephritis (Table 1, patient 9), bilateral urolithiasis with recurrent infections (Table 1, patient 18), renal lithiasis (Table 1, patient 12), and acute polyarthritis were some of the manifestations attributable to uric acid precipitation occurring before allopurinol was prescribed. Renal failure or sepsis secondary to urinary tract infections has also been described as causes of death in patients with HPRT deficiency and uncontrolled hyperuricemia [33,34]. However, effectiveness of a drug therapy must consider adverse effects as well as efficacy. Allopurinol increases urinary concentrations of the sparingly soluble uric acid precursor xanthine, increasing the risk for xanthine stone formation in the urinary tract. There are several reports of HPRT-deficient patients in whom xanthine stones developed on allopurinol therapy [11,15-21,28]. In one report, autopsy of a patient with the Lesch-Nyhan syndrome disclosed xanthine crystal deposition in kidneys, brain, thymus, and thyroid gland [35]. In this study, 3 of 19 patients showed nephrolithiasis during the follow-up. In 2 patients, xanthine was the major component of the calculus, and in a third patient, the composition of the calculus was not determined.

To prevent xanthine lithiasis, we suggest adjustment of the allopurinol dose to obtain an sUA concentration of less than 7.0 mg/dL but higher than 4.5 mg/dL. In addition, a yearly renal ultrasound may be useful [36].

4.1. Conclusions

In summary, the study and follow-up of 19 patients with HPRT deficiency allow us to conclude that allopurinol is an efficacious and safe drug for the long-term treatment of uric acid overproduction. However, allopurinol did not appear to modify the neurologic manifestations associated with the enzyme defect. Allopurinol dosage should be periodically adjusted, especially in children, to maintain sUA in the upper reference range of concentrations and a urinary uric acid-to-creatinine ratio of less than 1.0 mg/mg. Quantification of urinary hypoxanthine and xanthine excretion may contribute to assess compliance and to adjust the hypouricemic doses likely to avoid xanthine lithiasis.

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This work is dedicated to the memory of Dr Jarvis Edwin Seegmiller (1920-2006) whose seminal experiments showed that both gout and mental retardation could be attributed to a single defect in metabolism, HPRT deficiency.

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