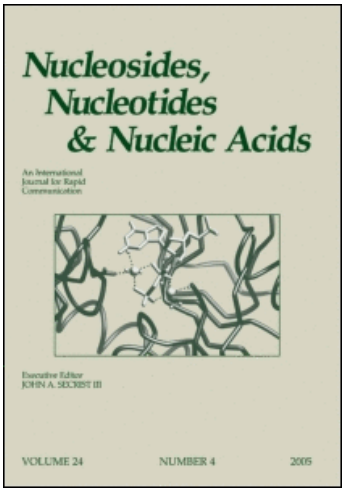

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Efficacy and Safety of Allopurinol in Patients with the Lesch-Nyhan Syndrome and Partial Hypoxanthine- Phosphoribosyltransferase Deficiency: a Follow-up Study of 18 Spanish Patients

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EFFICACY AND SAFETY OF ALLOPURINOL IN PATIENTS WITH THE LESCH-NYHAN SYNDROME AND PARTIAL HYPOXANTHINE-PHOSPHORIBOSYLTRANSFERASE DEFICIENCY: A FOLLOW-UP STUDY OF 18 SPANISH PATIENTS

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□ *Allopurinol is used widely for the treatment of purine disorders such as gout, but efficacy and safety of allopurinol has not been analyzed systematically in an extensive series of patients with HPRT deficiency. From 1984 to 2004 we have diagnosed 30 patients with HPRT deficiency. Eighteen patients (12 with Lesch-Nyhan syndrome or complete HPRT deficiency, and 6 with partial HPRT deficiency) were treated with allopurinol (mean dose, 6.44 mg/Kg of weight per day) and followed-up for at least 12 months (mean follow-up 7,6 years per patient). Mean age at diagnosis was 7 years (range, 5 months to 35 years). Treatment with allopurinol was associated to a mean reduction of serum urate concentration of 50%, and was normalized in all patients. Mean urinary uric acid excretion was reduced by 75% from baseline values, and uric acid to creatinine ratio was close or under 1.0 in all patients. In contrast, hypoxanthine and xanthine urinary excretion rates increased by a mean of 6 and 10 times, respectively, compared to baseline levels. These modifications were similar in patients with complete or partial HPRT deficiency. In 2 patients xanthine stones were documented despite allopurinol dose adjustments to prevent markedly increased oxypurine excretion rates. Neurological manifestations did not appear to be influenced by allopurinol therapy. Allopurinol is a very efficacy and fairly safety drug for the treatment of uric acid overproduction in patients with complete and partial HPRT deficiency. Allopurinol was associated with xanthine lithiasis.*

Keywords Allopurinol; Lesch Nyhan syndrome; HPRT; Hypoxanthine; Xanthine; Uric acid

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INTRODUCTION

Hypoxanthine phosphoribosyltranseferase (HPRT, EC 2.4.2.8) deficiency is a genetic disease of purine metabolism. Increased uric acid synthesis is a consequence of decreased purine reutilization for nucleotide synthesis and, thus, enhanced de novo purine synthesis to maintain the nucleotide pool. Uric acid overproduction leads to an increased risk of nephrolithiasis, renal insufficiency, gout arthritis, and tophi. To prevent these undesired complications allopurinol treatment, hydration and urine alkalinization have been recommended.[1] Allopurinol is very effective in reducing hyperuricemia in patients with Lesch-Nyhan syndrome,[2–6] but its clinical usefulness has not been assessed systematically in an extensive series of patients. Moreover, the efficacy and safety of allopurinol has not been analyzed in patients with partial HPRT deficiency. Since 1984 we have studied at La Paz University Hospital 30 patients with HPRT deficiency. The availability of one of the most extensive series published in the literature[7] enabled us to assess the efficacy and safety of allopurinol in these patients.

MATERIALS AND METHODS

From 1984 to 2004 we have diagnosed at La Paz University Hospital 30 patients with HPRT deficiency. Nineteen suffered from the Lesch-Nyhan syndrome and 11 patients were diagnosed as having a partial enzyme defect. We analyzed the evolution of 18 patients that met these 2 criteria: (a) diagnosed as having HPRT deficiency and (b) followed-up at La Paz University Hospital periodically (every 3, 6, or 12 months) for at least 12 months. Among the 18 patients included in this study, 12 suffered the Lesch-Nyhan syndrome and 6 partial HPRT deficiency. The allopurinol dose commonly used was 5 mg/Kg of body weight per day, orally. This dose was given as a single dose every 24 hours, or in two divided doses, every 12 hours. Treatment objectives were: (a) a serum urate concentrations below 7.0 mg/dL and (b) a normal urinary uric acid to creatinine ratio (below 1.0). These 2 objectives were intended to prevent gout arthritis and renal lithiasis. Allopurinol dosage was periodically adjusted depending on the individual serum urate concentration and urinary excretion of uric acid, hypoxanthine and xanthine. HPRT and APRT activities in the hemolysate were determined by high performance liquid chromatography.[8] The residual HPRT activity in 16 patients was determined in intact erythrocytes.[7] Uric acid and creatinine in plasma and urine were measured in a multichannel auto analyzer. Urinary hypoxanthine and xanthine were determined by high-performance liquid chromatography[9] while patients consumed a self-selected diet. Renal calculi were analyzed by infrared spectroscopy

(Spectrum RX I FT-IR System de Perkin Elmer, Norwalk, CT, USA). The significance of the differences between baseline conditions and allopurinol therapy and between patients with the Lesch-Nyhan syndrome and partial HPRT deficient patients were assessed by means non-parametric tests such as the Wilcoxon o Mann-Whitney rank-sum test A P value of.05 or less was considered to indicate a statistically significant difference. All P values are two tailed. Values are given as means ± SD.

RESULTS

The mean age at diagnosis of the 18 HPRT deficient patients 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]). The allopurinol dose given to the 18 patients ranged from 50 to 600 mg/day. The mean allopurinol dose at the last visit was 6.44 ± 1.97 mg/Kg of body weight per day. The total follow-up period on allopurinol range from 20 months to 16 years and 3 months (a mean of 91 months per patient or 7.6 years per patient). All patients showed, under basal conditions, hyperuricemia (above 7.0 mg/dL; range, 6.9 to 14.6 mg/dL). Allopurinol therapy decreased serum urate to a mean of 50% of baseline values and brought it to normal levels in 17 patients. Urinary uric acid to creatinine ratio decreased a mean of 75% of baseline values (Table 1). All patients, except one showed a baseline uric acid to creatinine ratio above 1.0. In all of them uric acid to creatinine ratio decreased to close or less than 1.0 with allopurinol. Mean urinary hypoxanthine and xanthine excretion rates increased on allopurinol 5.7 and 10.4 times, respectively (Table 1). However, due to the decrease in uric acid excretion, mean total purine excretion markedly decreased (40%). The

TABLE 1 Modifications of Purine Metabolism by Allopurinol Therapy in 18 Patients With HPRT Deficiency. Baseline, Values Off Allopurinol. Allopurinol, Values Obtained at the Last Visit While Being Treated With Allopurinol

	HPRT Deficiency	
	Baseline	Allopurinol
Serum		
Urate (mg/dL)	10.1 ± 2.6	5.3 ± 1.1[a]
Urine		
Uric Acid/Creatinine	2.7 ± 1.4	0.6 ± 0.3[a]
Hypoxanthine (μmol/g creat)	654 ± 312	3714 ± 1732[a]
Xanthine (μmol/g creat)	246 ± 150	2564 ± 1434[a]
Total Purines (μmol/g creat)	16793 ± 8793	10168 ± 3489[b]

[a] $p < 0.0001$ (baseline versus allopurinol).
[b] $p < 0.05$ (baseline versus allopurinol).

normal urinary purine distribution is: uric acid, 94.6%; hypoxanthine, 3.9%; and xanthine 1.5%. Mean total urinary purine distribution on allopurinol was: uric acid, 38.3%; hypoxanthine, 36.5%; and xanthine 25.2%. The mean serum urate decrease on allopurinol therapy was similar in patients with the Lesch-Nyhan syndrome (−4.8 mg/dL) and in subjects with partial HPRT deficiency (−4.9 mg/dL). The allopurinol induced decrease in total urinary purine excretion was of a similar magnitude in patients with the Lesch-Nyhan syndrome (−6879 μmol/g creat) and in subjects with partial HPRT deficiency (−6244 μmol/g creat). Allopurinol treatment did not appear to modify neurological symptoms. Among the 18 patients 3 reported renal lithiasis during allopurinol therapy. Two patients with the Lesch-Nyhan syndrome passed xanthine stones as detected by infrared spectroscopy. The third patient with partial HPRT deficiency had bilateral renal lithiasis but the composition of the calculi could not be determined.

DISCUSSION

This study analyzes the efficacy and safety of allopurinol in 18 patients with HPRT deficiency. Allopurinol treatment reduced serum urate concentrations to normal levels (mean decrease, 4.8 mg/dL) and decreased urinary uric acid to creatinine ratio to less than 1.0 (mean, 0.6). Allopurinol therapy did not appear to influence renal function. Thus, allopurinol is a fairly safety drug for these patients since none discontinued the drug due to adverse events, although 3 patients had renal lithiasis. The strengths of our study rely on the number of studied patients and the length of observation at the same institution by the same team. For 20 years (1984–2004) we have followed-up 18 patients with HPRT deficiency (mean follow-up, 7.6 years per patient). Allopurinol decreased serum urate concentrations to normal values in all patients (mean decrease, 4.8 mg/dL; percentage decrease from baseline values, 47.5%) except in one who showed a serum urate concentration slightly above the upper normal limit. In 8 patients with HPRT deficiency, Kelley et al.[1] showed that allopurinol (400 to 800 mg/day) decreased serum urate levels between 48% and 76% only after 48 hours. This effect was attributed to the fact that HPRT deficient patients are more sensitive to the inhibitory effect of allopurinol on xanthine oxidase than patients with gout. In contrast, Christie et al.[10] believe that Lesch-Nyhan patients need higher doses of allopurinol than gout patients to normalize serum urate levels. In this study, allopurinol also markedly reduced urinary uric acid excretion. In fact, the mean reduction of urinary uric acid to creatinine ratio was 78% and all patients showed a ratio below 1.0 following allopurinol therapy. The achieved reduction was similar to that reported by Kelley et al.[11] in 7 patients (2 with the Lesch-Nyhan syndrome and 5 partial HPRT deficiency; mean reduction, 80%). In this study, total purine excretion

was higher, although not significantly different, in Lesch-Nyhan syndrome patients than in subjects with partial HPRT deficiency (data not shown). Allopurinol decreased total purine excretion in both groups comparably and, thus, the percentual reduction of total urinary purines was higher in partial HPRT deficient patients. The decrease in total purine excretion was achieved without the introduction of a purine restricted diet, and was due to a marked reduction in uric acid excretion not accompanied by a stoichometric substitution of hypoxanthine and xanthine (hypoxanthine and xanthine excretion rates that did not completely compensate for the reduction in uric acid excretion). The observed decrease in total purine excretion in complete and partial HPRT deficient patients could be due to an effect of age and/or to an inhibitory effect of allopurinol metabolism on purine nucleotide synthesis.

Allopurinol therapy may cause xanthine stones.[12–20] In this study 3 out of 18 patients showed nephrolithiasis during the follow-up. In 2 patients xanthine was the component of the calculi and in a third patient we could not determine the calculus composition. To prevent xanthine lithiasis associated with allopurinol therapy in HPRT deficiency we adjusted the allopurinol dose to obtain: (a) a urinary hypoxanthine excretion rate higher than that of xanthine, since the later is less soluble, and (b) a serum urate concentration below 7.0 mg/dL but higher than 5.0 mg/dL. In addition, we performed a renal ultrasound study annually.[21] We can not assess the efficacy of these measures since our results have not been compared with a control series of patients. In summary, the study and follow-up of 18 patients with HPRT deficiency allow us to conclude that allopurinol is a very efficacious and fairly safe drug for the treatment of uric acid overproduction. However, allopurinol did not appear to modify the neurological manifestations associated with the enzyme defect.

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