—Original—

Effect of Dotinurad on Serum Uric Acid Concentration in Chronic Kidney Disease Patients Treated with Febuxostat

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Background: Febuxostat is recommended for treatment of severe hyperuricemia in chronic kidney disease (CKD). We previously reported a significant positive correlation between fractional excretion of uric acid (FEUA) and estimated excretion of uric acid (eEUA) in patients receiving febuxostat and proposed that the addition of uricosuric agents could further decrease serum uric acid (sUA) levels by enhancing FEUA and eEUA in patients treated with febuxostat.

Methods: This retrospective study included 34 patients with CKD who were categorized into three groups (G3-G5) according to their estimated glomerular filtration rate (eGFR). The effects on sUA, FEUA, and eEUA of adding dotinurad (0.5 mg/day) to febuxostat (10 mg/day) were evaluated in these patients. Specifically, we examined changes in sUA, FEUA, and eEUA in each group after the addition of dotinurad.

Results: Dotinurad significantly increased FEUA in all groups and notably decreased sUA in groups G3 and G4 but not in group G5. There was no significant change in eEUA in any group. Dotinurad maintained the significant positive correlation between FEUA and eEUA in patients receiving febuxostat.

Conclusions: This study is the first to show the effect of combining dotinurad with febuxostat in lowering sUA levels in G3 and G4 patients. Additional research is required in order to clarify the pharmacological mechanisms of dotinurad in patients with CKD. (J Nippon Med Sch 2024; 91: 352–356)

Key words: hyperuricemia, CKD, dotinurad, febuxostat

Introduction

Uricosuric agents and urate synthesis inhibitors are used to treat hyperuricemia. In patients with normal renal function, 90% of uric acid is reabsorbed via the proximal renal tubules and then returned to renal blood flow[1,2]. Uricosuric agents block reabsorption of uric acid in proximal renal tubules, which increases urinary excretion of uric acid and subsequently decreases serum uric acid (sUA) concentration. Xanthine oxidase inhibitors, which reduce uric acid production, are commonly prescribed to patients with hyperuricemia, as they inhibit urate synthesis. Among the two types of drugs, urate synthesis inhibitors are recommended for patients with chronic kidney disease (CKD) associated with hyperuricemia[3].

Among inhibitors of urate synthesis, it is recommended to prescribe febuxostat, a xanthine oxidase inhibitor[3]. We recently suggested that the combination of uricosuric agents and febuxostat could be effective in increasing fractional excretion of uric acid (FEUA) and estimated urinary excretion of uric acid (eEUA) in patients with CKD[4]. However, it is unclear whether the addition of a uricosuric agent would benefit patients receiving febuxostat.

In this study, we examined the effect of adding dotinurad, a uricosuric agent, on laboratory variables related to uric acid urinary excretion. The variables studied in-

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cluded FEUA and eEUA, as well as sUA concentration, in patients receiving febuxostat. We further assessed the additional effects of dotinurad on renal dysfunction.

Methods

Study Design

We conducted a retrospective analysis of correlations between clinical laboratory variables related to urinary excretion and reabsorption of uric acid through proximal renal tubules. The analysis was done before and after additional dotinurad was administered to CKD patients receiving febuxostat, as detailed below.

Definitions

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2. Hyperuricemia was defined as an sUA concentration greater than 7.0 mg/dL.

Patients

We identified 148 outpatients treated for CKD and hyperuricemia in our hospital during the period from January 2020 to April 2023, 34 of whom received febuxostat 10 mg daily. Because their sUA concentration exceeded 6.0 mg/dL despite receiving febuxostat for longer than 2 months, dotinurad 0.5 mg/day was administered for 1 month. We evaluated the effect of adding dotinurad after 1 month. We collected clinical information from our hospital's electronic medical records to calculate eGFR, FEUA, estimated 24-h urinary excretion of creatinine (eECr), and eEUA. Other information collected included age, gender, underlying diseases, and laboratory data. Patients regularly taking losartan and diuretics were excluded.

Ethical Approval

All procedures involving human participants in this study adhered to the ethical standards of the Nippon Medical School Chiba Hokusoh Hospital (IRB approval number: H-2023-044). The study adhered to the principles of the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical standards.

Informed Consent

All participants included in this study provided written informed consent.

eGFR

eGFR was determined by using the equation recommended by the Japanese Society of Nephrology[5]: eGFR (mL/min/1.73 m^2)=194 × [Cr (mg/dL)]$^{-1.094}$ × [Age (years)]$^{-0.287}$ (× 0.739, for women).

FEUA

The FEUA was determined using the equation FEUA = (U_{UA}/S_{UA}) / (U_{Cr}/S_{Cr}) × 100 (%).

U_{UA}: urinary concentration of uric acid (mg/dL)

S_{UA}: serum concentration of uric acid (mg/dL)

U_{Cr}: urinary concentration of creatinine (mg/dL)

S_{Cr}: serum concentration of creatinine (mg/dL)

Estimated Creatinine Excretion in 24-H Urine (eECr)

eECr was calculated using the equation recommended by the Japanese Society of Hypertension[6]: eECr (mg/day) = [Body weight (kg) × 14.89] + [Height (cm) × 16.14] − [Age (years) × 2.043] − 2,244.45.

Estimated 24-Hour Uric Acid Excretion (eEUA)

eEUA was determined using the equation eEUA (mg/day) = [eECr (mg/day)] / U_{Cr} (mg/dL)] × U_{UA} (mg/dL).

U_{UA}: urinary concentration of uric acid (mg/dL)

U_{Cr}: urinary concentration of creatinine (mg/dL)

eECr: estimated creatinine excretion in 24-h urine (mg/day)

Analysis of Laboratory Variables

Patients enrolled in this study (n = 34) were divided into three groups (G3-G5) according to their eGFR levels. Group G3 comprised patients with an eGFR of >30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2. Group G4 included patients with an eGFR of >15 mL/min/1.73 m^2 to ≤30 mL/min/1.73 m^2. Group G5 consisted of patients with an eGFR less than 15 mL/min/1.73 m^2. We retrospectively investigated the effects of an additional dose of dotinurad (0.5 mg/day) on sUA, FEUA, eEUA, and eGFR in patients receiving febuxostat. The patterns of changes in sUA, FEUA, eEUA, and eGFR after an additional dose of dotinurad were compared among the groups. We examined the correlation of FEUA with eEUA before and after administering an additional dose of dotinurad. Finally, we assessed the effect of additional dotinurad on this correlation.

Statistical Analysis

All analyses were conducted using R version 4.0.0 (R Core Team, 2020) and IBM SPSS Statistics version 29. The Kolmogorov-Smirnov test was used to check the data for normality. We used the Kruskal-Wallis test to compare average age across all groups. Fisher's exact test was used to compare the prevalences of comorbidities such as hypertension, diabetes mellitus, and dyslipidemia across groups. We used the Wilcoxon signed-rank test to analyze paired samples of sUA, FEUA, eEUA, and eGFR before and after administering dotinurad. Because of the skewed distribution of the data, the correlation between FEUA and eEUA was analyzed with Spearman's rank correlation test. A *P*-value of <0.05 was considered to indicate statistical significance.

Table 1 Clinical characteristics of the patients

Group	G3	G4	G5	
Total, n	10	14	10	
Age (years, mean ± SD)	65.8 ± 8.3	64.4 ± 14.4	67.5 ± 18.5	(*P*=0.729)
Gender, n (%), male	9 (90)	13 (93)	8 (80)	(*P*=0.804)
female	1 (10)	1 (7)	2 (20)	
Hypertension, n (%)	9 (90)	11 (79)	8 (80)	(*P*=0.863)
Diabetes mellitus, n (%)	4 (40)	4 (29)	3 (30)	(*P*=0.899)
Dyslipidemia, n (%)	8 (80)	10 (71)	8 (80)	(*P*=1.000)
eGFR (mL/min/1.73 m^2)	42.8 ± 7.0	22.0 ± 7.2	14.0 ± 7.9	

Table 2 eGFR before and after administration of dotinurad 0.5 mg/day in all groups. There was no significant change in eGFR in any group after the start of dotinurad

eGFR (mL/min/1.73 m^2)	G3 (n=10)	G4 (n=14)	G5 (n=10)
Pre-dotinurad	42.8 ± 7.0	22.0 ± 7.2	14.0 ± 7.9
Post-dotinurad	40.1 ± 8.0	21.3 ± 4.2	10.7 ± 4.3
	P=0.167	*P*=0.972	*P*=0.440

Table 3 FEUA, eEUA, and sUA levels in the G3 group before and after administration of dotinurad 0.5 mg/day. FEUA and sUA significantly changed but eEUA did not

		FEUA (%)	eEUA (mg/day)	sUA (mg/dL)
G3 (n=10)	Febuxostat (10 mg/day)	5.1 ± 2.1	441 ± 250	7.5 ± 1.2
	Addition of dotinurad (0.5 mg/day)	7.6 ± 4.0	515 ± 382	6.2 ± 1.1
		**P*=0.017	*P*=0.445	**P*=0.005

Results

Clinical Characteristics of Patients

The characteristics of the 34 enrolled patients are summarized in **Table 1**. We found no significant difference in age among the groups and no significant difference in the gender distribution or numbers of patients with hypertension, diabetes mellitus, or dyslipidemia across the groups.

Effect of Additional Dotinurad on eGFR

Administration of additional dotinurad (0.5 mg/day) did not significantly affect eGFR in any group (**Table 2**).

Effect of Additional Dotinurad on FEUA, eEUA, and sUA

Administration of additional dotinurad (0.5 mg/day) significantly increased FEUA in all groups and significantly reduced sUA in G3 and G4 but not in G5. Dotinurad did not have a significant effect on eEUA in any group (**Table 3-5**).

Effect of Additional Dotinurad on the Correlation between FEUA and eEUA

FEUA and eEUA were significantly positively correlated in patients treated with febuxostat before (**Fig. 1a**) and after dotinurad administration (**Fig. 1b**).

Discussion

We previously reported a significant positive correlation between FEUA and eEUA[4]. Our research indicates that additional administration of uricosuric agents may further decrease sUA levels by enhancing FEUA and eEUA in patients receiving febuxostat[4]. The present study analyzed data from 34 CKD patients who were previously treated with febuxostat 10 mg daily. Patients regularly taking diuretics or losartan were excluded to eliminate the effects of drugs that affect uric acid excretion. These patients subsequently received an additional dose of dotinurad, a uricosuric agent, at a daily dose of 0.5 mg.

Table 4 FEUA, eEUA, and sUA levels in the G4 group before and after administration of dotinurad 0.5 mg/day. FEUA and sUA significantly changed but eEUA did not

		FEUA (%)	eEUA (mg/day)	sUA (mg/dL)
G4 (n=14)	Febuxostat (10 mg/day)	5.3 ± 1.8	233 ± 139	7.9 ± 0.82
	Addition of dotinurad (0.5 mg/day)	7.0 ± 3.4	246 ± 112	7.1 ± 1.2
		*P=0.030	P=0.638	*P=0.003

Table 5 FEUA, eEUA, and sUA levels in the G5 group before and after administration of dotinurad 0.5 mg/day. FEUA significantly increased, but sUA and eEUA showed no significant change

		FEUA (%)	eEUA (mg/day)	sUA (mg/dL)
G5 (n=10)	Febuxostat (10 mg/day)	8.7 ± 4.5	209 ± 106	7.4 ± 1.6
	Addition of dotinurad (0.5 mg/day)	12.2 ± 4.8	198 ± 86	6.4 ± 1.3
		*P=0.037	P=0.799	P=0.173

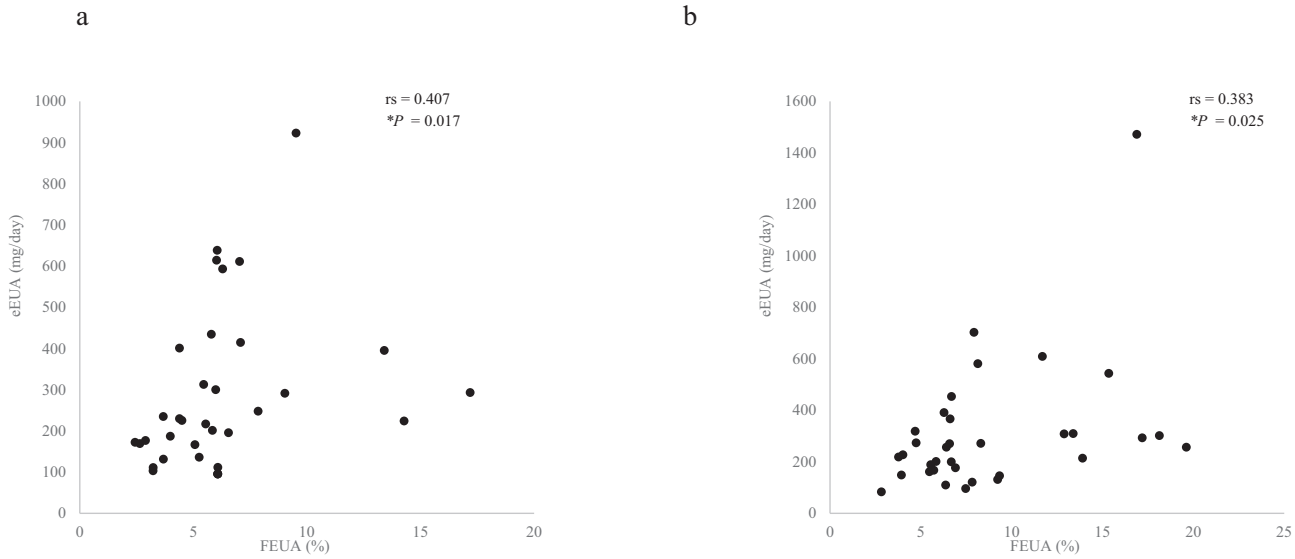

Fig. 1 Correlation between FEUA and eEUA before (a) and after (b) administration of dotinurad 0.5 mg/day in all study groups.

Analysis of FEUA showed a significant increase in 10 patients from group 3 (G3), 14 from group 4 (G4), and 10 from group 5 (G5). Conversely, sUA significantly decreased in G3 and G4 but not in G5. The effect of additional dotinurad on sUA appears to depend on eGFR. As compared with G5 patients, G3 and G4 patients may have had higher rates of glomerular sUA filtration into the renal tubular lumen. Additionally, G5 patients excrete more uric acid in stool than in urine. Consequently, the inhibitory effect of dotinurad on uric acid reabsorption was greater in G3 and G4 patients than in G5 patients.

eEUA did not significantly differ across groups (G3-G5) before or after dotinurad administration. We speculate that the interval between the start of dotinurad treatment and the evaluation of its effects may have influenced the results. The time lag in our protocol was set to 1 month. It is crucial to understand that eEUA cannot exceed the combined total of uric acid stored in the body and uric acid intake. We hypothesize that eEUA temporarily surged after the administration of dotinurad until the consumption of uric acid and the body's stored uric acid achieved equilibrium with urinary excretion.

Our previous study demonstrated a significant positive correlation between FEUA and eEUA in CKD patients receiving febuxostat[4]. The present study confirmed that this correlation persisted even after introducing dotinurad, suggesting the potential of further reduction in sUA by increasing the dosage of dotinurad. In the clinical trial, it is crucial to mention that patients with an eGFR less than 30 mL/min/1.73 m^2 did not receive dotinurad[7], making its sUA-lowering effect on G4 and G5 stages of CKD patients unclear. We recently reported that dotinurad lowered sUA in stage G4 CKD patients[8]. The present study showed the effect of dotinurad combined with febuxostat on hyperuricemia in G3 and G4 patients (**Table 3, 4**). To our knowledge, this is the first study to demonstrate the efficacy of dotinurad in G3 and G4 patients previously treated with febuxostat.

There are two main categories of drugs used to treat hyperuricemia: urate synthesis inhibitors and uricosuric agents. As CKD advances, eGFR deteriorates, leading to a decrease in the excretion of urinary uric acid. Consequently, sUA-lowering therapy with febuxostat (a urate synthesis inhibitor) is believed to approach the limit of its effectiveness without the addition of agents that act through different mechanisms. To address this, supplementary administration of dotinurad—a uricosuric agent—is helpful in further reducing sUA levels, particularly in G3 and G4 patients.

Limitations

The limitations of this study are its design and the small number of patients included. Because this is a retrospective study at a single center, more cases should be collected to corroborate the analytical findings. Additionally, Groups 3 and 5 were smaller than Group 4. Future studies should attempt to clarify the effectiveness and mechanism of this drug for CKD patients previously treated with febuxostat.

Conclusion

Dotinurad increased FEUA in all groups (G3-G5) and decreased sUA levels in patients with G3 and G4 CKD. However, it did not significantly affect sUA in G5 patients. This study is the first to demonstrate the potential of dotinurad for reducing sUA levels in G3 and G4 patients receiving febuxostat.

Conflict of Interest: None declared.

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