Effects of Febuxostat on Oxidative Stress

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ABSTRACT

Purpose: We previously examined factors that affect the measured derivatives of reactive oxygen metabolites (d-ROMs), an indicator of reactive oxygen species production, and biological antioxidant potential (BAP), an indicator of antioxidant capacity, in typical health checkup examinees and reported the usefulness of measuring both indicators simultaneously. In addition, a positive correlation reportedly exists between d-ROMs and the visceral fat area measured by using computed tomography. A recent study of the relationship between uric acid levels and various obesity-related factors found that visceral fat was the factor most strongly related to uric acid levels. Uric acid is itself a potent endogenous antioxidant, but because reactive oxygen species are produced during uric acid generation, it is suggested that uric acid may have opposing effects. The objective of this study was to analyze the effect of febuxostat, a novel xanthine oxidase inhibitor, on oxidative stress.

Methods: Study subjects were 43 hyperuricemia outpatients receiving care in the internal medicine department of our institution. The subjects were divided into a new administration group (29 patients) and a switched administration group (14 patients); the latter were allopurinol-treated patients with hyperuricemia who were switched to febuxostat. In addition to measuring the patients' uric acid and creatinine levels and estimated glomerular filtration rate before and after treatment, their d-ROMs and BAP as well as the BAP/d-ROMs ratio were also measured.

Findings: Both groups exhibited significant decreases in uric acid levels, as well as significant decreases in d-ROMs and BAP. No significant changes were observed in the BAP/dROMs ratio or renal function, including creatinine levels and estimated glomerular filtration rate.

Implications: Febuxostat could significantly reduce d-ROMs. However, BAP levels were also significantly reduced concurrently. No changes were observed in the BAP/d-ROMs ratios. This regulatory mechanism is believed to have counteracted changes in the in vivo oxidative stress balance caused by febuxostat administration. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: BAP, d-ROMs, febuxostat, oxidative stress, uric acid, xanthine oxidase.

INTRODUCTION

Oxidative stress is believed to be involved in various diseases, including lifestyle-related diseases, and many reports have stated that oxidative stress also affects the onset and progression of atherosclerosis.[1–3] Numerous researchers have investigated whether hyperuricemia is an independent risk factor for the onset of cardio-cerebrovascular events; however, no definite conclusions have yet been reached.[4–9]

Uric acid is an intrinsic antioxidant substance, and reactive oxygen species are synthesized in a process whereby the reaction between xanthine and xanthine oxidase produces uric acid. Accordingly, opposing actions on oxidative stress can occur in vivo, which makes it difficult to determine whether hyperuricemia is a risk factor for cardio-cerebrovascular disease in terms of oxidative stress. How a xanthine oxidase inhibitor affects oxidative stress in vivo is a topic for investigation. The present study was thus designed to examine the effects of febuxostat, a novel xanthine oxidase inhibitor, on oxidative stress in hyperuricemic patients.

Conventionally measured indicators of reactive oxygen species production include serum thiobarbituric acid–reactive substances, oxidized LDL, 8-hydroxydeoxyguanosine, and urinary 8-iso-prostaglandin F2 alpha.[10–13] The measured principal indicators of

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antioxidant capacity include superoxide dismutase and glutathione peroxidase.[14,15] The methods for measuring these indicators are complex, however, and not suitable when many samples require analysis.

Recently, reactive oxygen metabolites (d-ROMs), an indicator of reactive oxygen species production, and the biological antioxidant potential (BAP), an indicator of antioxidant capacity have been well recognized and accepted as conventional oxidative stress markers.[16–26] Furthermore, d-ROMs and BAP can be measured by using a general automatic biochemical analyzer. We analyzed the d-ROM and BAP distribution ranges in Japanese subjects, as well as the factors regulating the measured values.[27]

SUBJECTS AND METHODS

The present study included 43 patients with hyperuricemia who received outpatient care at our institution's internal medicine department. Patients who either had no history of treatment for hyperuricemia or had discontinued treatment for ≥ 1 month were classified into the new administration group (29 patients); the switched administration group (14 patients) comprised patients who were previously treated with allopurinol either alone or combined with benzbromarone but in whom allopurinol was switched to febxostat. Treatment of Febuxostat was 20 mg once daily, except one subject of 40 mg once daily in switched administration group, and allopurinol were 100 mg once or twice daily. In addition to measuring the patients' uric acid and creatinine levels and estimated glomerular filtration rates before and after treatment, we also measured d-ROMs and BAP and the BAP/dROMs ratio. d-ROMs and BAP were measured by using an automatic biochemical analyzer (Hitachi 7180; Hitachi, Ltd, Ibaraki, Japan) according to a previously reported method.[27] A concurrent report found no problems with testing precision or reproducibility.

All analytical data are given as mean (SD); a paired *t* test was used for changes between before and after administration, and an unpaired *t* test was used to test for differences between treatments. The level of statistical significance was set at $P < 0.05$. Statistical processing was performed by using StatView 5.0 software (SAS Institute, Inc, Cary, North Carolina). The statistical and academic uses of the data were approved by the ethics committee at our institution; after approval, we obtained consent at the time of examination and provided written documents and verbal explanations stating that the test results would be used for analysis in such a way that individual names could not be identified.

RESULTS

The Table displays the background information of the new administration and switched administration groups. Both groups exhibited significant decreases in uric acid levels (from 8.6 to 5.7 mg/dL and from 7.1 to 5.7 mg/dL, respectively) (Figure 1), as well as significant decreases in d-ROMs (from 306 to 291 CARR U and from 325 to 303 CARR U) and BAP (from 2578 to 2419 μM and from 2670 to 2469 μM) (Figure 2). No changes were observed in the BAP/dROMs ratios (from 8.48 to 8.44 and from 8.59 to 8.66) (Figure 3). No significant changes were observed in creatinine levels or estimated glomerular filtration rates (Figure 4).

DISCUSSION

Oxidative stress was originally defined according to the balance between reactive oxygen species production and antioxidant capacity. The accuracies of dROMs and BAP measurements (according to a general automatic biochemical analyzer) allow for verification by routine simultaneous measurement. We therefore analyzed the dROMs and BAP distribution ranges in Japanese subjects, as well as the factors regulating the measured values in health checkup examinees, and reported the usefulness of these measurements. We also suggest an ability to maintain oxidative stress balance in vivo based on the positive correlation between d-ROMs and BAP.[27]

Although no reports in which febuxostat was used in actual clinical practice and biological oxidative stress were found, a recent animal study involving a rat model of ischemia-reperfusion kidney injury showed that the reactive oxygen species production markers nitrotyrosine, thiobarbituric acid–reactive substances, and urinary 8-isoprostane could be inhibited by administration of febuxostat.[28]

In our results, the administration of febuxostat reduced uric acid levels significantly more than allopurinol, and this finding was associated with a significant reduction in d-ROMs. However, BAP was simultaneously more significantly reduced. In light of our earlier report, this result seems to be an adaptive response of the body to an increase in reactive oxygen species production; most recently, a similar response was observed with regard to changes before and after exercise as well as a type of change within a shorter length of time.[29,30]

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