The effectiveness of benzbromarone versus febuxostat in gouty patients: a retrospective study

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Abstract

Background Benzbromarone and febuxostat have different mechanisms in reducing serum urate. Nevertheless, the effectiveness of benzbromarone versus febuxostat in reducing serum urate in gouty patients classified with different types of hyperuricemia remain unclear.

Methods In this retrospective study from January 1, 2018 to September 30, 2020, subjects were retrieved if they were newly treated with benzbromarone 25mg daily or febuxostat 20mg daily with 24-hour urinary uric acid and 24-hour urinary creatinine measured. Baseline data and follow-up information after 28 ± 3 days treatment were collected from medical records. Subjects were classified into four types according to their 24-hour urinary uric acid and fractional excretion of uric acid.

Results A total of 73 subjects with gout were finally enrolled. Among them, 50 were treated with benzbromarone. The percent changes in serum urate from the baseline were -33.71 ± 13.59% in benzbromarone group and -29.45 ± 10.62% in febuxostat group without significant difference between the two groups (P = 0.188). In subgroup analysis, no differences were found between the two groups among subjects classified as renal underexcretion, the combined type, or “normal” type. In patients with eGFR ≥ 70 mL/min/1.73m^2, the rate of serum urate lowering was higher in those treated with benzbromarone than febuxostat. Renal function did not change significantly from the baseline for both drugs.

Conclusion Benzbromarone 25mg daily and febuxostat 20mg daily had comparable effectiveness in lowering serum urate among different types of hyperuricemia. Benzbromarone was more effective than febuxostat in lowering serum urate in subjects with eGFR ≥ 70 mL/min/1.73m^2.

Introduction

Gout is the most common inflammatory arthritis that is caused by elevated serum urate and subsequent deposition of monosodium urate crystals. Hyperuricemia is a disease with genetic predisposition, which is caused by the decreased excretion of urate by the kidneys or the gut and/or overproduction of uric acid in the liver[1, 2]. Maintaining serum urate levels < 6 mg/dL could reduce gouty tophus and decrease frequency of gout flares[3].

Based on the findings that ATP-binding cassette transporter, sub-family G, member 2 (ABCG2) has an important role in intestinal urate excretion[4, 5], hyperuricemia was now proposed to be classified into four types, namely the renal underexcretion type, the renal overload type, the combined type, and the “normal” type according to 24h urinary uric acid excretion and fraction excretion of uric acid (FE_{UA})[5, 6].

Benzbromarone, an uricosuric agent, is a first-line urate lowering drug according to the Chinese gout management guideline and is the most prescribed urate lowering drug in China[6]. Benzbromarone is primarily used in subjects with renal underexcretion. Its urate-lowering effect maintains even in gouty

patients with mild to moderate renal dysfunction[7, 8]. Benzbromarone is never approved by Food and Drug Administration and has been withdrawn from European market due to its hepatoxicity[9]. Nevertheless, in Asian and some European countries, it has been prescribing without evident safe concern for many years[8, 10].

Febuxostat, a xanthine oxidoreductase inhibitor, is another first-line urate lowering drug in China[6]. Febuxostat is primarily metabolized in the liver and no dose reduction is required in subjects with renal dysfunction[11]. Its urate-lowering effect is not reduced with renal impairment, and even though the renal function can be improved after febuxostat treatment[12]. Thus, in clinical practice, febuxostat is preferably used in patients with renal dysfunction and/or overproduction of uric acid.

Nevertheless, the urate-lowering effect of xanthine oxidoreductase inhibitors and uricosuric drug in gouty patients with different types of hyperuricemia is unknown. In this retrospective study, we aim to investigate the effectiveness of benzbromarone versus febuxostat in lowering serum urate in subjects with different types of hyperuricemia.

Methods

Subjects

This retrospective study was performed at Rheumatology Department of Zhongshan Hospital, Shanghai, China. Outpatients diagnosed with gout were retrieved electronically from January 1, 2018 to September 30, 2020. Subjects were identified if they were newly prescribed benzbromarone 25mg daily or febuxostat 20mg daily with 24-hour urinary uric acid and 24-hour urinary creatinine measured. Initially, a total of 138 patients were retrieved. Among then, 50 subjects were excluded without follow-up information of 28 ± 3 days treatment. Then another 15 individuals were further excluded since their follow-up data were measured with cessation of drugs 1 week before the measurement. Finally, 73 subjects were included for analysis. The baseline data were not statistically significant between the 73 subjects included and the other 65 subjects excluded (Supplementary Table 1). All the subjects included were without malignance or taking medications influencing renal handling of uric acid such as diuretics, aspirin, cyclosporine, and pyrazinamide. This study was approved by the Ethics Committee of Zhongshan Hospital in Shanghai and complied with the ethical principles of the 1975 Declaration of Helsinki. Due to the retrospective nature of the study, patient informed consent was exempted.

Measurement Of Serum Parameters

The levels of serum urate, creatinine, alanine aminotransferase, and aspartate aminotransferase were all performed using automatic biochemical analyzer at the Department of Clinical Laboratory of Zhongshan Hospital, Fudan University (Cobas c702, Roche Diagnostics, Basel, Switzerland). The estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) was calculated according to the Chronic Kidney Disease–Epidemiology Collaboration formula[13].

24-hour urine was collected for measurement of 24h-hour urinary uric acid and creatinine (Labospect 008 AS, Hitachi, Tokyo, Japan). FE_{UA} was calculated as follows: (24-hour urinary uric acid * serum creatinine) / (24-hour urinary creatinine * serum uric acid).

Serum urate and creatinine were originally measured in mmol/L, which were converted to mg/dL by dividing 59.5 and 88.4, respectively. Urinary uric acid and creatinine were transformed to mg/24h from their original mmol/24h by dividing 5.95 and 8.84, respectively.

All patients were stratified into four types according to their 24-hour urinary uric acid and FE_{UA}. Renal underexcretion type was defined as 24-hour urinary uric acid ≤ 600 mg/day and FE_{UA} < 5.5%; Renal overload type was classified as 24-hour urinary uric acid > 600 mg/day and FE_{UA} ≥ 5.5%; the combined type was specified as 24-hour urinary uric acid > 600 mg/day and FE_{UA} < 5.5%; the “normal” type was characterized by 24-hour urinary uric acid ≤ 600 mg/day and FE_{UA} ≥ 5.5%.

Statistics

Results

Baseline characteristics of the study population

Of the 73 subjects enrolled, 69 (94.52%) were men. The mean age of the subjects were 47.88 ± 15.73 years of age without significant difference between benzbromarone and febuxostat groups (P = 0.876). Baseline serum urate concentrations were also comparable between the two groups (P = 0.076). All subjects involved were with eGFR > 40 mL/min/1.73m^2. Serum creatinine was significantly higher febuxostat group than benzbromarone group (P < 0.001); correspondingly, serum eGFR was significantly lower in febuxostat group (P = 0.001). 24h urinary uric acid, FE_{UA}, alanine transaminase, and aspartate aminotransferase were similar between the two groups. The majority of the patients were classified as renal underexcretion (Table 1).

The urate-lowering effect

For both drugs, serum urate decreased significantly from the baseline (P < 0.001 for both group). No significant difference in serum urate was observed between the two groups after urate-lowering treatment (P = 0.054) (Table 2). The percent changes (mean ± SD) in serum urate from the baseline were -33.71 ± 13.59% and -29.45 ± 10.62% for benzbromarone and febuxostat, respectively, showing no significant differences between the two groups (Figure 1a).

In multivariate linear regression model, after adjusting for baseline eGFR, the percent change in serum urate from the baseline remained comparable between the two groups (unstandardized B = 5.56, P = 0.108).

The percentages of patients achieving a serum uric acid levels < 6.05mg/dL were 58.0% (29/50 patients) (95% confidence interval, 43.8% to 72.2%) in benzbromarone group and 47.8% (11/23 patients) (95% confidence interval, 25.7% to 69.9%) in febuxostat group, respectively, indicating no statistically difference between the two groups (P = 0.417) (Figure 1b).

Subgroup analysis

Since in renal overload type, only 1 patient was treated with febuxostat 20mg daily, subgroup analysis was not performed in this subgroup. In subjects of the combined type, the rate of serum urate lowering from the baseline was numerically higher in benzbromarone group than febuxostat group, but without significant difference (P = 0.105). The rate of serum urate lowering was also comparable between the two groups in subjects stratified with renal underexcretion, or “normal” type (renal underexcretion, P = 0.440; “normal” type, P = 0.636) (Table 3). Similar trend remained after adjusting for baseline eGFR (Supplementary Table 2).

Subjects were further analyzed according to their baseline eGFR. In subjects with eGFR ≥ 70 mL/min/1.73m^2, the rate of serum urate lowering was significant higher in benzbromarone group than febuxostat group (-34.55 ± 13.03% versus -23.60 ± 7.71%, P = 0.027). No significant difference in the rate of serum urate lowering were observed between the two groups in patients with eGFR < 70 mL/min/1.73m^2 (-29.90 ± 16.19% versus -32.57 ± 10.85, P = 0.632) (Table 3).

The renal function

Renal function was comparable with the baseline for both groups (benzbromarone group, P = 0.587; febuxostat group, P = 0.129; respectively) (Table 2). Whereas, the rate of serum creatinine lowering and eGFR increase from the baseline were higher in febuxostat group than benzbromarone group (for serum creatinine, P = 0.005; for eGFR, P = 0.003) (Figure 2).

Safety

1 patient in benzbromarone group (1/50) and 1 in febuxostat group (1/23) experienced an increase in both serum alanine transaminase and aspartate transaminase. The other 3 patients in benzbromarone group (3/50) had a mild increase in alanine transaminase. All of which were within 2 upper limit of normal.

Discussion

In this retrospective cohort study, we did not observe significant difference in effectiveness in lowering serum urate between the benzbromarone and febuxostat groups. The comparable effectiveness remained among subjects of renal underexcretion type, the combined type, or “normal type”. In gouty patients with eGFR ≥ 70 mL/min/1.73m^2, benzbromarone was more effective in lowering serum urate than febuxostat. Even though renal function did not change significantly from the baseline in both

groups, subjects taking febuxostat 20mg daily experienced a higher rate of eGFR increase than benzbromarone 25mg daily.

In our study, benzbromarone 25mg daily shows comparable effectiveness in lowering serum urate with febuxostat 20mg daily. Their comparable effectiveness in Chinese gouty patients has also been described in another prospective cohort study[12]. In our cohort, the two groups had the inherent heterogeneity in the baseline characteristics. Clinically, subjects with lower eGFR were prone to be prescribed febuxostat. Thus, as a real-world study, it's reasonable that the baseline eGFR was significantly lower in the febuxostat group than benzbromarone group. In order to minimize the influence of baseline renal function on the effectiveness of the two drugs, multivariate linear regression was conducted. Still, benzbromarone and febuxostat showed similar urate-lowering effect.

In subgroup analysis with individuals stratified by different types of hyperuricemia. The urate-lowering effect of the two drugs remained comparable in subjects stratified with renal underexcretion, the combined type, or "normal" type. Benzbromarone is an urate anion transporter 1 (URAT1) inhibitor and functions in inhibiting reabsorption of urate in proximal tubule, thus increases urate excretion in the kidneys[14]. Febuxostat binds to xanthine oxidoreductase, an rate-limiting enzyme in purine metabolism, thus obstructs substrate binding to this enzyme, and inhibits generation of uric acid[15]. Due to the different mechanisms in reducing serum urate, clinically, benzbromarone and febuxostat are preferably prescribed to subjects of renal underexcretors and overproducers, respectively. In our analysis, we found that even in patients with renal underexcretion of uric acid, febuxostat 20mg daily was as effective as benzbromarone 25mg daily in reducing serum urate. The effectiveness of febuxostat in lowering serum urate in underexcretors has also been described previously[16]. Thus, febuxostat may be another consideration for subjects with renal underexcretion.

In patients of the combined type, the urate-lowering effect of benzbromarone was numerical higher than febuxostat but without statistical difference. In this kind of subjects, hyperuricemia was resulted from the overproduction of uric acid in the liver, or the decreased excretion of urate in the intestine, combined with renal underexcretion of urate[5]. Since the small number of patients included in our study, the effectiveness of benzbromarone 25mg daily versus febuxostat 20mg daily in subjects of the combined type should be further investigated with larger population.

As the baseline renal function was better in subjects treated with benzbromarone than febuxostat, subjects were further analyzed according to their eGFR. In subjects with eGFR $\geq$ 70 mL/min/1.73m^2, the urate-lowering effect of benzbromarone 25mg daily was significantly better than febuxostat 20mg daily. While, the two drugs had comparable effectiveness in lowering serum urate in subjects with eGFR < 70 mL/min/1.73m^2. Previously, it has been reported that benzbromarone was as effective as febuxostat in reducing serum urate in hyperuricemia patients with eGFR 20–60 mL/min/1.73m^2[7]. In this study, we found that in gouty patients with eGFR $\geq$ 70 mL/min/1.73m^2, benzbromarone was more effective in

reducing serum urate than febuxostat. Studies with prospective design are needed to further confirm this effect of benzbromarone with long term observation.

In our study, both benzbromarone and febuxostat had no significant influence on renal function. However, the rate of eGFR increase was higher in febuxostat group than benzbromarone group. In a prospective cohort study comparing the effect of benzbromarone and febuxostat, a significant improvement of renal function was observed after 12 weeks treatment with febuxostat[12]. Nevertheless, this reno-protective effect of febuxostat could not always be proven. In a meta-analysis including subject with CKD stage 1–5, compared with either placebo, or urate-lowering agents (allopurinol or benzbromarone), febuxostat showed no renal protective effect[17]. In subgroup analysis, the reno-protective effect was found only in subjects with CKD stage 3 and 4, or with treatment duration ≥ 6 months when compared with controls[17]. In another study involving hyperuricemia patients without end-stage renal disease, febuxostat was associated with a significant improvement in renal function compared with placebo[18]. Thus, it seems that the reno-protective effect of febuxostat is depended on the CKD stage and treatment duration. In our study, subjects include were with CKD stage 1–3, after a relative short treatment of 28 ± 3 days, a trend of renal improvement was observed with febuxostat treatment, but no difference was observed when compared with the baseline. The impact of febuxostat on renal function needs for adequate powered randomized trial including subjects with different stages of CKD to be clarified.

The increase in serum transaminase was mild without cessation of drugs. Since data were collected through medical records electronically rather than self-report, information about gout flares was not known. Nevertheless, in another prospective cohort study, benzbromarone 25mg daily had similar occurrence rate of gout flares with febuxostat 20mg daily during 12 weeks treatment[12].

The limitations of the study include the relatively short experimental period. A dose-escalation with longer period study will provide more information to guide prescriptions in choosing urate-lowering drugs. The relatively small number of subjects was another limitation of our study, the effectiveness of benzbromarone versus febuxostat in different types of hyperuricemia needs for further investigation with large number of participants.

Conclusions

In conclusion, benzbromarone 25mg daily and febuxostat 20mg daily had comparable effectiveness in reducing serum urate regardless of type of hyperuricemia. A stronger effect of benzbromarone in reducing serum urate in subjects with eGFR ≥ 70 mL/min/1.73m^2 was observed. No difference in renal function was found for both drugs. Further investigations with prospective design are needed.

Abbreviations

ABCG2：ATP-binding cassette transporter, sub-family G, member 2

FEUA：Fraction Excretion of Uric Acid

eGFR：estimated Glomerular Filtration Rate

URAT1：Urate Anion Transporter 1

CKD：Chronic Kidney Disease

Declarations

Ethics declarations

This study was approved by the Ethics Committee of Zhongshan Hospital in Shanghai and and approval number is B2021-230. This study was also complied with the ethical principles of the 1975 Declaration of Helsinki. Due to the retrospective nature of the study, patient informed consent was exempted.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LDM and ZBB designed the study, collected and analyzed the data, and wrote the manuscript. ZZJ, DXJ, JZF, CHY, and SY collected data. LZ conducted statistical analysis and wrote the manuscript. JLD designed the study, analyzed the data, and revised the manuscript. All the authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of the subjects

	Total	Benzbromarone	Febuxostat	P value
Number	73	50 (68.49%)	23 (31.51%)	
Male (%)	69 (94.52%)	46 (92.00%)	23 (100.00%)	0.163
Age (years of age)	47.88 ± 15.73	47.68 ± 15.88	48.30 ± 15.76	0.876
Serum urate (mg/dL)	8.92 ± 1.44	8.72 ± 1.30	9.36 ± 1.63	0.076
Serum creatinine (mg/dL)	1.08 ± 0.21	1.01 ± 0.20	1.24 ± 0.26	< 0.001
eGFR (mL/min/1.73m^2)	82.91 ± 21.01	87.79 ± 16.75	72.31 ± 25.46	0.001
24h urinary creatinine (mg/24h)	1452.08 ± 428.55	1362.43 ± 395.65	1646.98 ± 440.94	0.007
24h urinary uric acid (mg/24h)	527.90 (420.08, 639.08)	523.95 (410.00, 633.74)	527.90 (420.34, 806.22)	0.476
FE_{UA} (%)	4.71 ± 1.15	4.63 ± 1.16	4.87 ± 1.13	0.417
Alanine transaminase (IU/L)	29.50 (17.75, 50.50) (n=42)	31.00 (19.00, 52.00) (n=31)	26.00 (16.00, 43.00) (n=11)	0.415
Aspartate aminotransferase (IU/L)	23.00 (17.75, 32.00) (n=42)	23.00 (17.00, 32.00) (n=31)	23.00 (19.00, 28.00) (n=11)	0.819
Type of hyperuricemia				
Renal underexcretion	37 (50.68%)	26 (52.00%)	11 (47.83%)	
Renal overload	7 (9.59%)	6 (12.00%)	1 (4.35%)	
The combined type	17 (23.29%)	11 (22.00%)	6 (26.095)	
"Normal" type	12 (16.44%)	7 (14.00%)	5 (21.74%)	

Abbreviation: eGFR, estimated glomerular filtration rate; FE_{UA}, fraction excretion of uric acid.

Table 2. Serum urate and renal function before and after urate-lowering treatment

	Benzbromarone			Febuxostat			P value[b]
	Baseline	After treatment	P value[a]	Baseline	After treatment	P value[a]	
Serum urate (mg/dL)	8.72 ± 1.30	5.79 ± 1.47	< 0.001	9.36 ± 1.63	6.56 ± 1.27	0.001	0.054
Serum creatinine (mg/dL)	1.01 ± 0.14	1.00 ± 0.16	0.587	1.24 ± 0.26	1.14 ± 0.23	0.129	0.002
eGFR (mL/min/1.73m^2)	87.01 ± 16.66	88.35 ± 17.73	0.637	72.31 ± 25.46	79.10 ± 24.86	0.282	0.030

[a] Inter-group difference

[b] Intra-group difference after treatment

Abbreviation: eGFR, estimated glomerular filtration rate

Table 3. Subgroup analysis of the percent change in serum urate from the baseline

	Benzbromarone	Febuxostat	P value
Type of hyperuricemia			
Renal underexcretion	-32.55 ± 13.08	-29.03 ± 10.94	0.440
The combined type	-35.39 ± 10.85	-26.43 ± 8.85	0.105
"Normal" type	-34.77 ± 16.17	-30.61 ± 11.68	0.636
eGFR (mL/min/1.73m^2)			
≥ 70	-34.55 ± 13.03 (n=41)	-23.60 ± 7.71 (n=8)	0.027
< 70	-29.90 ± 16.19 (n=9)	-32.57 ± 10.85 (n=15)	0.632

Abbreviation: eGFR, estimated glomerular filtration rate

Figures

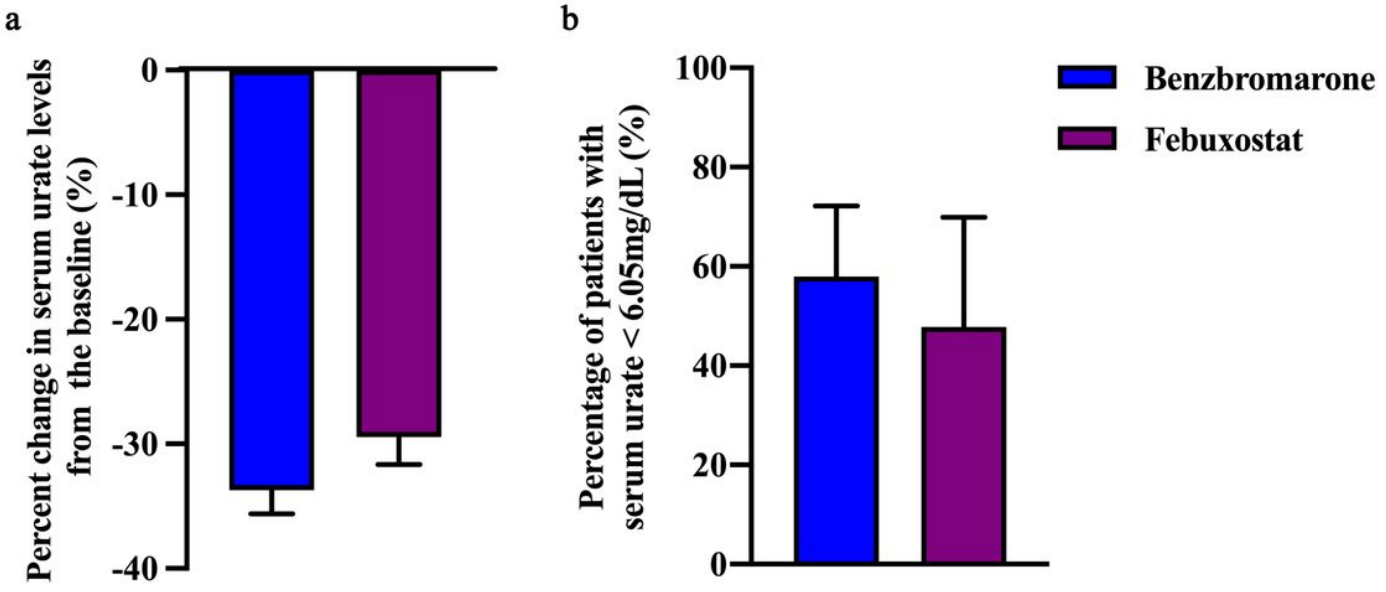

Figure 1

The urate-lowering effect. a. Percent changes in serum urate from the baseline. Data are shown as the mean ± SE. b. Percentages of patients with serum urate < 6.05 mg/dL. Data are shown as number% (95% confidence interval)

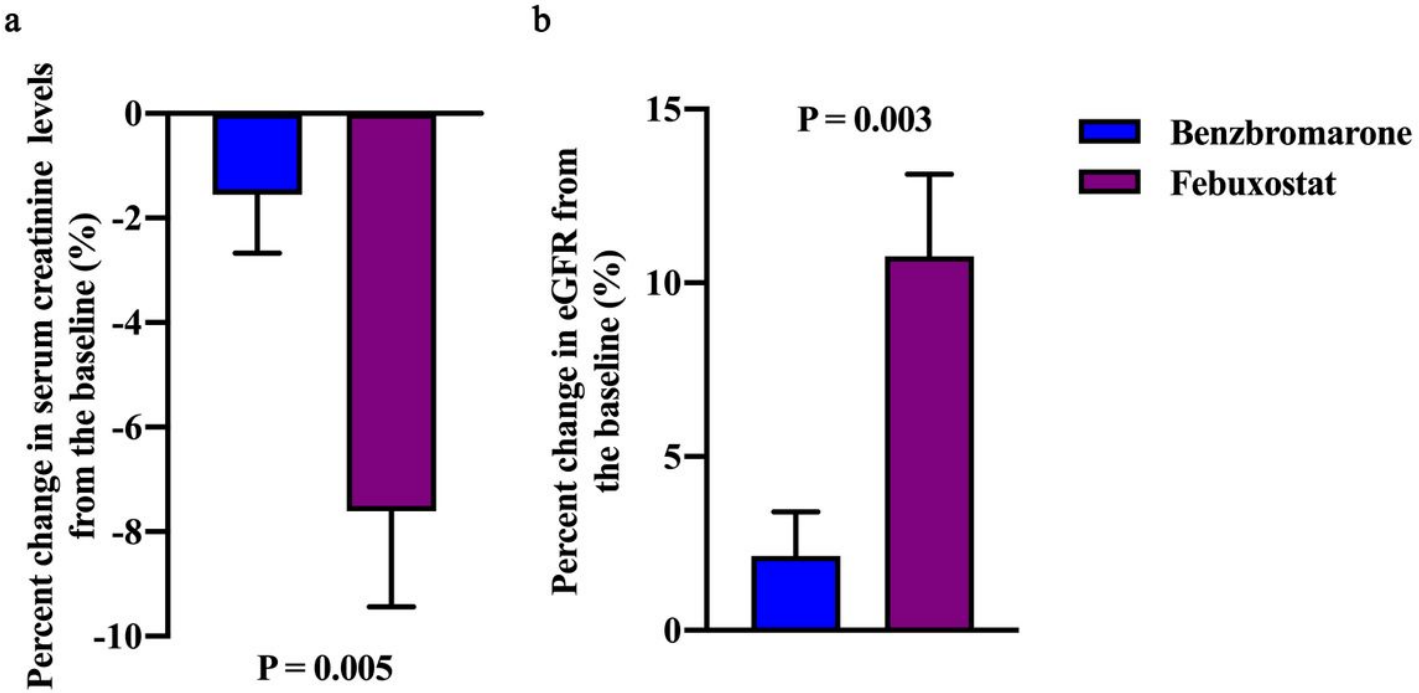

Figure 2

The renal function. Percent changes in serum creatinine (a) and eGFR (b) from the baseline. Data are shown as the mean ± SE. Abbreviation: eGFR, estimated glomerular filtration rate.

Supplementary Files

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- Supplementaldata.docx