Original Article
Effect of febuxostat on reducing blood uric acid level and its drug action in patients with hyperuricemia

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Abstract: Objective: To explore the therapeutic performance of febuxostat and allopurinol in the treatment of hyperuricemia. Methods: A total of 82 patients with hyperuricemia admitted to our hospital were enrolled in the study. According to a random number table, the patients were divided into the study group with febuxostat (n = 41) and the control group with allopurinol (n = 41). Six mL of fasting venous blood was taken from the two groups before treatment (T0), 2 months (T1), 4 months (T2), and 6 months after treatment (T3). The serum uric acid, blood urea, serum creatinine and urine nitrogen were detected by a fully automatic biochemical analyzer. The clinical efficacy and adverse reactions of the two groups were observed and analyzed. Results: There was no significant difference in the cure rate between the study group and the control group (P>0.050). However, the effective outcome in the study group was 53.66% (22 cases), which was higher than that (29.27%, 12 cases) in the control group (P = 0.025). The incidence of adverse reactions in the study group was lower than that in the control group (P = 0.023). There was no significant change in blood urea in the two groups (P>0.050). Uric acid, serum creatinine and urine nitrogen decreased with time in both groups. The uric acid, serum creatinine and urinary nitrogen levels in the two groups were highest at T0. The values at T2 were lower than that at T1, and the value at T3 was lower than that at T2 (P<0.001). At T1, T2 and T3, uric acid, serum creatinine and urine nitrogen in the study group were better than that in the control group (P<0.001). Conclusion: The clinical efficacy of febuxostat in the treatment of hyperuricemia is superior to allopurinol, and its ability of lowering uric acid levels is also better.

Keywords: Febuxostat, hyperuricemia, blood uric acid, allopurinol

Introduction

Hyperuricemia is a disease caused by disorders of purine metabolism, which can easily induce gouty acute arthritis, joint deformity and other diseases. The kidney is often affected. Chronic interstitial nephritis or kidney stones are induced [1]. Hyperuricemia is common in middle aged and elderly people. According to statistics, the incidence of hyperuricemia in the United States has reached 18% [2]. Hyperuricemia is mainly divided into primary and secondary types. A few primary diseases are caused by enzyme defects. The other pathogenesis is not clear. It is usually accompanied by chronic diseases such as diabetes and atherosclerosis. Secondary disease is caused by a variety of causes such as kidney disease and blood diseases [3, 4]. Early hyperuricemia has no obvious special symptoms, but the course of disease develops extremely fast. Once it evolves and other acute diseases are induced, it can pose a great threat to patients [5]. According to statistics, once complication of hyperuricemia occurs, its mortality will increase linearly [6]. At present, the main purpose of treating hyperuricemia is to control uric acid in clinical practice. The most commonly used medicine is allopurinol [7].

Allopurinol is a very traditional anti-uric acid combination drug, and its clinical efficacy in hyperuricemia has been confirmed [8-10]. However, with deepening of research, more and more scholars have found that the drug mechanism of allopurinol is similar to purine. Other active enzymes involved in purine metabolism may be negatively affected, causing more adverse reactions [11, 12]. For some patients with renal impairment, its toxic side effects are more obvious [13]. Therefore, in recent years, researchers are devoting themselves to explore new treatments for hyperuricemia. Tan et al [14] proposed that the uric acid transporter

URAT1 can treat hyperuricemia better than allopurinol. Hu et al [15] showed that (E)-2-(4-bromophenyl)-1-(2,4-dihydroxyphenyl) ethyl ketoxime is a potential therapeutic agent for hyperuricemia. However, as the research has not been perfected, it is difficult to popularize in clinical practice.

Febuxostat is a newly developed xanthine oxidase inhibitor. It not only has a strong inhibitory effect on uric acid synthesis, but also has many elimination approaches. In addition, it has little side effects on patients [16]. At present, it has been shown that febuxostat has a good therapeutic effect on hyperuricemia [17]. However, the exact mechanism is not clear, and there is still very little research in comparison with allopurinol. This experiment provides a more accurate reference and guidance for clinical application by comparing the usage of febuxostat and allopurinol in the treatment of hyperuricemia.

Materials and methods

General methods

A total of 82 patients with hyperuricemia admitted to Chuxiong Medical and Pharmaceutical College were enrolled in the study. According to a random number table, the patients were divided into the study group with febuxostat (n = 41) and the control group with allopurinol (n = 41). There were 36 males and 5 females in the study group, aging from 49 to 69 years. The average age was (53.27 ± 8.67) years. There were 34 males and 7 females in the control group, aging from 50 to 69 years. The average age was (53.84 ± 9.12) years old. This experiment was approved by the Ethics Committee of Chuxiong Medical and Pharmaceutical College, and all subjects signed informed consent.

Inclusion and exclusion criteria

Inclusion criteria: Patients consistent with the clinical manifestations of hyperuricemia [18]; patients diagnosed as hyperuricemia by uric acid examination: male >420 μmol/L, female >360 μmol/L; patients with complete medical records; patients who were willing to cooperate with the medical staff.

Exclusion criteria: Patients with tumors or other cardiovascular and cerebrovascular diseases; patients with other chronic diseases; autoimmune diseases, organ failure, kidney dysfunc-

tion or other serious complications; patients with hemodialysis, peritoneal dialysis and kidney transplantation; patients with drug allergies, physical disability, mental illness or who cannot take care of themselves; patients transferred to other facilities.

Methods

Both groups of patients were treated with routine hyperuricemia. Approach: under the low purine diet, digoxin, diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists, β receptor blockers, and aldosterone receptor antagonists were administered. For some patients with coronary heart disease, statins were used. On the basis of this, 40 mg/d of febuxostat (Jiangsu Hengrui Pharmaceutical Co., Ltd., GYZZ H20130081) was administered in the research group of patients. The uric acid concentration was observed. After 2 weeks of treatment, if the uric acid levels still did not reach the normal standard, the dosage was increased to 80 mg/time/d. Allopurinol (Guangdong PiDi Pharmaceutical Co., Ltd., GYZZ H44021368) was added to the control group based on the routine treatment. The initial dose was 100 mg/time/d. After 1 week of treatment, the dose was 100 mg/time, 2 times a day. After 3 weeks of treatment, the dose was 100 mg/time, 3 times a day. This dose is administrated until the end of the course of treatment. The total course of treatment in both groups was 6 months. Six mL of fasting venous blood was taken from the two groups before treatment (T0), 2 months of treatment (T1), 4 months of treatment (T2), and 6 months of treatment (T3). It sat for 30 minutes at room temperature, and then was centrifuged for 10 minutes (4,000 rpm). The upper serum was collected. The serum uric acid, blood urea nitrogen, serum creatinine and urine nitrogen were detected by a fully automatic biochemical analyzer.

Outcome measures

For the clinical efficacy of treatment in the two groups of patients, the hyperuricemia rehabilitation guide was referred to [19]. Markedly effective: the patient's clinical symptoms were significantly improved, and the blood uric acid indicator was completely normal; Effective: the clinical symptoms were improved to some extent, and the blood uric acid was improved but did not reach the normal standard;

Table 1. General information [n (%)]

	Study group (n = 41)	Control group (n = 41)	T or X²	P
Age	53.27 ± 8.67	53.84 ± 9.12	0.290	0.773
BMI (cm/kg²)	24.12 ± 4.04	23.70 ± 4.12	0.466	0.642
Course of disease (d)	8.42 ± 2.85	8.84 ± 3.16	0.632	0.529
Gender			0.391	0.532
Male	36 (87.80)	34 (82.93)		
Female	5 (12.20)	7 (17.07)		
Smoking			1.123	0.289
Yes	38 (92.68)	35 (85.37)		
No	3 (7.32)	6 (14.63)		
Drinking			0.249	0.618
Yes	31 (75.61)	29 (70.73)		
No	10 (24.39)	12 (29.27)		
Ethnicity			1.012	0.314
Han	40 (97.56)	41 (100.00)		
Minority	1 (2.44)	0 (0.00)		
Marital status			0.554	0.457
Married	36 (87.80)	38 (92.68)		
Unmarried	5 (12.20)	3 (7.32)		
Combined Diseases			0.213	0.899
Coronary heart Disease	16 (39.02)	15 (35.59)		
Diabetes	14 (34.15)	16 (39.02)		
Hypertension	11 (26.83)	10 (24.39)		
Living Environment			0.576	0.448
Town	29 (70.73)	32 (78.05)		
Country	12 (29.27)	9 (21.95)		

Ineffective: the clinical symptoms and the blood uric acid level were not improved.

The response rate of the two groups of patients = (Markedly + effective)/total cases ×100%. Drug safety in both groups: the adverse reactions during the course of medication were compared between the two groups, including rash, liver damage, and cytopenia. The incidence of adverse reactions in the two groups was calculated, including, rash, liver damage, cytopenia, hyperlipidemia, gastrointestinal reactions, allergies, cardiovascular diseases, etc. The incidence of adverse reactions = the number of patients with adverse reactions occurred/the total number of patients ×100%. The biochemical indicators of the two groups were: serum uric acid, blood urea, serum creatinine and urine nitrogen at T0, T1, T2 and T3.

Statistical method

All the experimental results were statistically calculated using SPSS 24.0 statistical software (Beijing NDTimes Technology Co., Ltd.). All the graphs were drawn using Graphpad8 (Shenzhen Tianruiqi Software Technology Co., Ltd.) and a secondary proof was performed. The enumeration data were expressed in the form of (rate), and the chi-square test was used for comparison between groups; the measurement data was expressed in the form of (mean ± standard deviation), and the t-test was used for comparison between groups. The comparison among multiple time points was conducted by Repeated measure ANOVA with hoc post bonferroni test. P<0.050 indicated statistically significant.

Results

No significant differences in baseline data

There were no significant differences in age, BMI, course of disease, gender, smoking, drinking habits, ethnicity, marital status, combined disease and living environment between the two groups (P>0.050), which shows that the two groups were comparable (**Table 1**).

No significant differences in response rate

There was no statistical significance in the response rate between the study group and the control group (P>0.050). There was no significant difference in the patients assessed with 'effective' or 'ineffective outcomes' between the study group and the control group (P> 0.050). However, the patients assessed with 'markedly effective' in the study group was 53.66% (22 cases), which was higher than that (29.27%, 12 cases) in the control group (P = 0.025) (**Table 2**).

Patients in study group showed less adverse reactions

In the study group, cytopenia occurred in 1 patient (2.44%), gastrointestinal reaction occurred in 1 patient (2.44%), and the incidence

Table 2. Clinical efficacy [n (%)]

	Study group (n = 41)	Control group (n = 41)	X^2	P
Markedly Effective	22 (53.66)	12 (29.27)	5.025	0.025
Effective	16 (39.02)	24 (58.54)	3.124	0.077
Ineffective	3 (7.32)	5 (12.20)	0.554	0.457
Response rate	92.68	87.80	0.554	0.457

Table 3. Adverse reaction in two groups of patients [n (%)]

	Study group (n = 41)	Control (n = 41)	X^2	P
Rash	0 (0.00)	1 (2.44)		
Liver injury	0 (0.00)	2 (4.88)		
Cytopenia	1 (2.44)	2 (4.88)		
Hyperlipidemia	0 (0.00)	1 (2.44)		
Gastrointestinal Reaction	1 (2.44)	2 (4.88)		
Hypersensitivity	0 (0.00)	1 (2.44)		
Cardiovascular Disease	0 (0.00)	0 (0.00)		
Incidence rate	2 (4.88)	9 (21.95)	5.145	0.023

of adverse reactions was 4.88%. In the control group, rash occurred in 1 patient (2.44%), liver injury occurred 2 patients (4.88%), cytopenia occurred in 2 patients (4.88%), hyperlipidemia occurred in 1 patient (2.44%), gastrointestinal reaction occurred in 2 patients (4.88%), allergies occurred in 1 patient (2.44%), and the incidence of adverse reactions was 21.95%. The incidence of adverse reactions in the study group was lower than that in the control group (P = 0.023) (**Table 3**).

The uric acid and urinary nitrogen levels in the study group were lower than the control group

There was no significant change in blood urea in the two groups (P>0.050). Uric acid, serum creatinine and urine nitrogen decreased with time. It was at the highest level at T0. The value at T2 was lower than that at T1, and the value at T3 was lower than that at T2 (P<0.001). The differences between the two groups showed that there was no significant difference in blood urea at T0, T1, T2 and T4 between the two groups (P>0.050). There was no significant difference in serum creatinine at T0, T1 and T2 between the two groups (P>0.050). The serum creatinine in the study group at T3 was lower than that in the control group (P<0.001). There was no significant difference in urine nitrogen at T0 and T1 between the two groups (P>0.050). Urine nitrogen in the study group at T2 and T3

was lower than that in the control group (P<0.001). There was no significant difference in uric acid at T0 between two groups (P>0.050). The uric acid and urine nitrogen in the study group at T1, T2 and T3 were lower than those in the control group (P<0.050) (**Table 4**).

Discussions

As a new non-purine selective xanthine oxidase inhibitor, febuxostat has the same efficacy as traditional hyperuricemia allopurinol. As there are few comparative studies with allopurinol, the promotion of its clinical application is still controversial. The application value of febuxostat among hyperuricemia treatment was compared in this experiment through rigorous inclusion and exclusion criteria, advanced reagents and instruments.

The results of this experiment showed that there was no difference in the clinical efficacy between the study group treated with febuxostat and the control group treated with allopurinol. However, the efficacy of the study group was higher than that of the control group. It suggested that febuxostat has the same therapeutic effect on hyperuricemia as allopurinol. Nevertheless, febuxostat was more effective. This was also consistent with the results of Chinchilla et al [20], which supports the results of this experiment. The incidence of adverse reactions in the two groups during the treatment was compared. The incidence of adverse reactions in the study group was lower than that in the control group. This suggested that the safety of febuxostat in the study group was higher than that of the control group. Further comparison of biochemical indicators showed there was no significant difference in blood urea between the two groups. Uric acid, serum creatinine and urine nitrogen in the study group were better than that in the control group. It suggested that febuxostat was superior to allopurinol in uric acid inhibition and vascular protection. It is worthy of promotion in clinical practice. The hyperuricemia treating mechanism of febuxostat is mainly to reduce the occurrence of reactive oxygen species and uric acid by inhibiting the activity of xanthine oxidase [21]. It is similar to the treatment mechanism of the two groups. The efficacy and safety of the study

Table 4. Comparison of biochemical indicators between the two groups

		T0	T1	T2	T3	F	P
Study group (n = 41)	Uric acid (µmol/L)	529.54 ± 84.51	464.51 ± 76.51[a]	405.61 ± 69.33[a,b]	364.54 ± 62.15[a,b,c]	39.091	<0.001
	Blood urea (mmol/L)	7.25 ± 2.41	7.14 ± 3.04	7.07 ± 2.69	6.97 ± 2.45	0.081	0.971
	Serum Creatinine (µmol/L)	212.64 ± 71.57	168.15 ± 65.55[a]	105.75 ± 64.85[a,b]	74.32 ± 35.51[a,b,c]	42.443	<0.001
	Urine Nitrogen (mmol/L)	13.84 ± 3.15	10.54 ± 2.15[a]	7.64 ± 3.64[a,b]	5.04 ± 1.05[a,b,c]	81.442	<0.001
Control (n = 41)	Uric acid (µmol/L)	530.44 ± 86.75	509.54 ± 81.56[a,d]	476.41 ± 76.94[a,b,d]	427.42 ± 58.43[a,b,c,d]	14.072	<0.001
	Blood urea (mmol/L)	7.28 ± 2.66	7.10 ± 3.12	7.05 ± 2.32	7.00 ± 2.52	0.086	0.968
	Serum Creatinine (µmol/L)	220.51 ± 75.15	169.15 ± 68.15[a]	104.51 ± 68.15[a,b]	89.42 ± 39.47[a,b,c,d]	69.494	<0.001
	Urine Nitrogen (mmol/L)	13.98 ± 2.98	10.34 ± 2.62[a]	9.27 ± 1.83[a,b,d]	8.84 ± 1.37[a,b,c,d]	42.643	<0.001

Note: 'a' represents it is compared with the same indicator at T0, $P<0.001$. 'b' represents it is compared with the same indicator at T1, $P<0.001$. 'c' represents it is compared with the same indicator at T2, $P<0.001$. 'd' represents it is compared with the same indicator at T3, $P<0.001$.

group was higher than that of the control group. It was speculated that the xanthine oxidase inhibitor may cause damage to liver and kidney function. Allergic reactions may occur in the circulation, causing adverse reactions in patients. Febuxostat has the action of xanthine oxidase inhibitor. Under therapeutic concentrations, it does not inhibit other enzymes generated during the process of synthesis and metabolism of purines and pyrimidines. In addition, it can be cleared by the liver and kidney [22]. This is why the incidence of adverse reactions in the study group was better than that in the control group. Secondly, febuxostat has therapeutic effect on uric acid and other indicators of patients with hyperuricemia. The reason is that febuxostat not only inhibits the metabolism of uric acid, but also accelerates the metabolic capability of uric acid through the urate transport of the proximal renal tubule. The renal tubular was controlled to reduce the uric acid reabsorption capacity. Therefore, a large amount of uric acid deposited from hyperuricemia is directly excreted from the urine. The patient's efficacy is improved. Study by Palazzuoli et al [23] also showed that febuxostat does not affect the kinetic parameters of the drug. There is no significant limit on the drug dosage. Oral bioavailability can reach more than 80%. The use restriction is lower, and drug utilization rate is higher compared with allopurinol.

In this study, the clinical application value of febuxostat was demonstrated by comparing the application of febuxostat and allopurinol to hyperuricemia. However, due to limited experimental conditions, the age span of this study was small. The specific efficacy of febuxostat on patients of different ages cannot be further confirmed. It is impossible to judge the prognosis of patients due to the short experimental period. In view of the deficiencies that allopuri-

nol eventually shows during hyperuricemia treatment, the replacement therapy with febuxostat is of great clinical significance. A long-term follow-up survey on these subjects will be conducted. In-depth research and analysis on febuxostat will be carried out to obtain the best experimental results.

In summary, the clinical efficacy of febuxostat in the treatment of hyperuricemia is slightly better than that of allopurinol. It is safer, more effective and better in inhibiting uric acid. It is worthy of promotion in clinical practice.

Disclosure of conflict of interest

None.

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