Effect of Medicine and Adverse Drug Reactions of Vonoprazan Fumarate Tablets in Patients with Reflux Esophagitis

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To investigate the drug effects of vonoprazan fumarate tablets on reflux esophagitis and their adverse drug reactions is the objective of the study. A total of 102 patients with reflux esophagitis admitted to the Department of Gastroenterology of the Affiliated People's Hospital of Ningbo University from June 2021 to November 2022 were selected and randomly grouped, with 51 cases in the observation group and 51 cases in the control group. The observation group received vonoprazan fumarate tablets and the control group received rabeprazole for 8 w. The drug effects of the two groups were analyzed, including the duration of symptom relief, changes in esophageal motility, the level of serum gastric hormone, the injury degree of esophageal mucosa and the level of inflammatory factors. Adverse drug reactions were analyzed in the two groups. After medication, the symptom remission time, changes in esophageal motility, serum gastric hormone level, esophageal mucosa injury degree and inflammatory factor level in observation group were better than those in control group ($p<0.05$). The total incidence of dizziness, rash, diarrhea and other adverse drug reactions in the observation group was 3.92 %, which was significantly lower than that in the control group (9.8 %, $p<0.05$). In conclusion, vonoprazan fumarate tablets has obvious effect on the treatment of reflux esophagitis with low adverse reactions, which is worthy of clinical promotion.

Key words: Vonoprazan fumarate tablets, reflux esophagitis, drug effect, adverse reactions

Reflux Esophagitis (RE) is a kind of esophageal mucosal injury caused by repeated reflux of intestinal juice and gastric juice to the esophagus. Its clinical manifestations are burning pain, heartburn, acid regurgitation, dysphagia and so on after the sternum. It may lead to esophageal stenosis, bleeding and other chain reactions, which brings great trouble to the life of patients[1]. RE occurs mostly in the middle and lower part of the esophagus and the age of onset is usually 40-60 y old. The cause of RE is still inconclusive and it is generally believed to be caused by vomiting stimulation, adverse drug reactions, inappropriate dietary stimulation or other intrinsic reasons. There are many clinical drugs of RE[2]. The Western drugs are mainly omeprazole, itopride, rabeprazole, vonoprazan fumarate tablets, mosapride, Oryz-Aspergillus pancrease tablets, aluminum and magnesium plus suspension, flupentixol and melitracen, etc. The traditional Chinese drugs are mainly Zhizi Gancao Chi decoction, Shugan Tiaowei decoction, Shugan and Wei decoction, etc. Western medicine is mainly devoted for the treatment of RE by inhibiting individual gastric acid, reducing the stimulation of reflux on the human esophagus and improving gastrointestinal motility. This study focused on the analysis of two drugs, vonoprazan fumarate tablets and rabeprazole. Rabeprazole belongs to the acid-suppressive drugs and its pharmacology is to improve the symptoms of RE by producing an acid-fast reaction in gastric acid. Vonoprazan fumarate tablets, belonging to the acid-suppressive class are potassium-competitive acid blockers that inhibit gastric acid activity by inhibiting enzyme activity in the competitive form of potassium during the drug response[3]. For the two different acid-inhibiting drugs used in the treatment of RE, it was found that the drug efficacy and adverse drug reactions of RE were compared, which has a positive role in guiding clinical medication.

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MATERIALS AND METHODS

General information:

A total of 102 RE patients who were treated in the Department of Gastroenterology, People's Hospital Affiliated to Ningbo University from June 2021 to November 2022 were selected and randomly divided into the observation group (n=51) and the control group (n=51). In the observation group, there were 27 males and 24 females, aged from 32 to 64 y, with an average age of (42±3.68) y. The course of disease was 5 mo to 7 y, with an average course of (2.58±0.62) y. In the control group, there were 26 males and 25 females, aged 30-65 y, with an average age of (41±3.88) y. The course of disease was 6 mo to 7 y, with an average course of (2.68±0.42) y. There was no significant difference in the basic data between the two groups ($p>0.05$). Informed consent was obtained from the patients and all cases were collected in accordance with the ethical guidelines of the hospital.

Inclusion and exclusion criteria:

Inclusion criteria meet the Western medicine diagnostic criteria of RE "2020 Chinese Expert Consensus on gastroesophageal reflux disease", with clinical symptoms such as acid reflux, heartburn and stomach regurgitation, aggravation of symptoms after eating and positive transesophageal provocation test; esophageal stenosis or esophageal mucosal injury can be identified under endoscopy and patients who were willing to sign the informed consent.

Exclusion criteria include psychiatric patients; patients with leukemia, Acquired Immunodeficiency Syndrome (AIDS), cancer and other immune system diseases; patients with heart, liver, kidney dysfunction and pregnant or lactating patients.

Medication methods:

During the medication period, all patients were prohibited to smoke and drink, eat spicy and acidic foods, avoid excessive satiety and adhere to light diet. Avoid immediate exercise after meals, stay in bed, 3 h before sleep, no food and drink, bed pillow height of 15 cm is appropriate. Vonoprazan fumarate tablets (Takeda Pharmaceutical Company Limited, Hikari Plant, JX20190049, 20 mg) were taken orally in the observation group, 20 mg once daily for 8 w. Patients in the control group were treated with rabeprazole enteric-coated tablets orally, once a day, 20 mg each time, for 8 w. Rabeprazole enteric coated tablets were produced by Shuanghe Pharmaceutical (Hainan) Co., Ltd., with the specification of 20 mg per tablet, 14 tablets per box and the national drug approval number is H20133326.

Observation indicators:

Efficacy evaluation of two drugs: The symptom relief time, esophageal motility changes, serum gastric hormone levels, the degree of esophageal mucosal injury and inflammatory factor levels were observed. The symptom relief time was mainly to record the relief of burning pain, heartburn, acid regurgitation, dysphagia and other symptoms after medication and its time was recorded in detail. The changes of esophageal motility were monitored by esophageal manometer before and after medication. The main targets of monitoring were Lower Esophageal Sphincter (LES) pressure, reflux time in different positions and percentage of total reflux time. Serum gastric hormone levels were generally considered in terms of serum Gastrin (GAS), Motilin (MTL) and Pepsinogen I (PGI), and the values of each index before and after medication were recorded. Esophageal mucosal injury was evaluated by endoscopy before and after treatment. According to Los Angeles (LA) classification, ≥1 esophageal mucosal injury with a long diameter less than 5 mm was defined as grade A. Grade B was defined as ≥1 esophageal mucosal injury with a long diameter greater than 5 mm. Mucosal injury appeared fusion and less than 75 % of the circumference was defined as grade C. Mucosal lesions appeared confluent and were rated as grade D at 75 % or more of the circumference. 3 ml of venous blood was collected and Tumor Necrosis Factor alpha (TNF-α), Interleukin-6 (IL-6) and Interleukin-8 (IL-8) were detected by the laboratory.

Evaluation of adverse reactions of two drugs: Adverse drug reactions such as dizziness, rash and diarrhea were recorded in the two groups.

Statistical treatment:

Statistical Package for the Social Sciences (SPSS) 16.0 statistical software was used to process the relevant data and t-test or Chi square (χ^2) test was used for the comparison between the observation group and the control group and $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Efficacy evaluation of two drugs was explained by comparison before and after treatment.

Comparison of the remission time of symptoms after medication was shown in Table 1. After treatment, the relief time of symptoms in the observation group was faster and the relief time of burning pain, heartburn, acid regurgitation, dysphagia and other symptoms was shorter than that in the control group. This suggests that vonoprazan fumarate tablets are more effective than rabeprazole as shown in Table 1.

Comparison of esophageal dynamic changes before and after medication was shown in Table 2. According to the esophageal pressure detector before and after medication, there were no significant differences in the indexes of esophageal dynamics between the two groups before medication ($p>0.05$). After treatment, the LES pressure in the observation group was higher than that in the control group and the decubitus position, orthostatic position and total reflux time were lower than that in the control group ($p<0.05$). This indicated that fumarate was more effective than rabeprazole (Table 2).

Comparison of serum gastric hormone levels before and after treatment was shown in Table 3. Gastric hormone levels are important indicators of RE. RE is often accompanied by gastric dysfunction. Gastric hormone levels are important markers of gastric function. For RE patients, a higher GAS value within the normal range indicates that the stomach is able to secrete GAS effectively and is a manifestation of normal physical indicators. The higher the MTL value within the normal range, the more normal it is to promote and affect gastrointestinal motility and gastrointestinal function, the lower the PGI within the normal range, the more normal the index of the degree of gastric mucosal secretion. After different drugs in this study, the growth rate of GAS and MTL values in the observation group was higher than that in the control group, and the PGL value was lower in the observation group. This indicates that vonoprazan fumarate tablets are superior to rabeprazole in improving gastric hormone levels (Table 3).

Comparison of the degree of esophageal mucosal injury before and after treatment was shown in Table 4. Esophageal mucosal injury is one of the important indicators of RE. The degree of esophageal mucosal injury before treatment was almost the same in both groups. However, 90.2 % of the patients in the observation group returned to normal, while only 68.6 % of the patients in the control group returned to normal. This showed that the esophageal mucosal injury was improved in both groups after treatment, but the observation group was significantly better than the control group ($p<0.05$, Table 4).

Comparison of inflammatory factors before and after treatment was shown in Table 5. TNF-a, IL-6 and IL-8 are regarded as the main inflammatory factors in RE. Before medication, the values of the three indexes were almost the same. After treatment, all three indicators decreased in both groups. However, the three indicators in the observation group decreased more significantly. This indicates that patients in the observation group had fewer inflammatory factors after medication and that vonoprazan fumarate tablets in the observation group were better than rabeprazole in the control group in terms of anti-inflammatory (Table 5).

Evaluation of adverse reactions of the two drugs was explained here. After treatment, adverse drug cases occurred in both groups. There were 2 cases in the observation group, with an overall incidence of 3.92 % and the drug safety was high. There were 5 cases in the control group, with an overall incidence of 9.8 % and the drug safety was low. This indicates that vonoprazan fumarate tablets have high drug safety and low adverse reaction rate (Table 6).

Vonoprazan fumarate tablets are a new class of Potassium (K^+) Competitive Acid Blockers (P-CAB) that can prematurely stop gastric acid secretion by inhibiting the binding of K^+ to Adenosine Triphosphatase (ATPase, proton pump) in the last

TABLE 1: COMPARISON OF SYMPTOM RELIEF TIME BETWEEN THE TWO GROUPS AFTER TREATMENT ($\bar{x}\pm s$)

Group	n	Symptom relief time/week			
		Pain of burning	Heartburn	Sour regurgitation	Difficulty swallowing
Observation group	51	1.36±0.28	3.42±0.33	1.56±0.24	1.22±0.18
Control group	51	3.18±0.38	5.21±0.24	3.55±0.31	2.44±0.25
p		<0.05	<0.05	<0.05	<0.05

TABLE 2: COMPARISON OF ESOPHAGEAL DYNAMICS BEFORE AND AFTER MEDICATION (x̄±s)

Group	n	LES (kPa)		PNRRT (%)		PNURT (%)		PTRT (%)	
		BM	AF	BM	AF	BM	AF	BM	AF
Observation group	51	1.52±0.31	2.62±0.59	11.66±2.96	3.36±0.38	7.62±2.08	1.98±0.22	10.82±2.12	2.27±0.18
Control group	51	1.53±0.31	1.84±0.52	11.62±2.92	7.02±0.64	7.58±2.11	4.18±0.43	10.94±2.16	4.65±0.39
t		0.16	7.27	0.11	8.92	0.13	9.78	0.12	8.98
p		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: LES: Lower Esophageal Sphincter; PNRRT: Percentage Number of Recumbent Reflux Time; PNURT: Percentage Number of Upright Reflux Time; PTRT: Percentage of Total Reflux Time; BM: Before Medication and AF: After Medication

TABLE 3: COMPARISON OF SERUM GASTRIC HORMONE LEVELS BEFORE AND AFTER TREATMENT (x̄±s)

Group	n	GAS (pg/ml)		MTL (pg/ml)		PGI (μg/ml)	
		BM	AF	BM	AF	BM	AF
Observation group	51	89.72±15.66	179.56±20.44	218.28±16.36	346.66±32.42	138.72±16.35	96.45±8.76
Control group	51	89.86±15.58	120.63±18.55	217.96±16.85	288.5±28.762	138.62±16.52	121.63±10.53
t		0.18	5.35	0.14	6.24	0.16	4.35
p		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: BM: Before Medication and AF: After Medication

TABLE 4: COMPARISON OF THE DEGREE OF ESOPHAGEAL MUCOSAL INJURY BEFORE AND AFTER TREATMENT (%)

Group	n	Normal		Type A		Type B		Type C		Type D	
		BM	AF	BM	AF	BM	AF	BM	AF	BM	AF
Observation group	51	0	46 (90.2)	36 (70.6)	4 (7.8)	9 (17.6)	2 (3.9)	5 (9.8)	0	1 (2)	0
Control group	51	0	35 (68.6)	35 (68.6)	11 (21.6)	11 (21.6)	3 (5.9)	4 (7.8)	2 (0.39)	1 (2)	0
t			3.18								
p			<0.05								

Note: BM: Before Medication and AF: After Medication

TABLE 5: COMPARISON OF INFLAMMATORY FACTOR LEVELS BEFORE AND AFTER MEDICATION (ng/l, x̄±s)

Time	Group	n	TNF-α	IL-6	IL-8
Before medication	Observation group	51	56.42±5.88	71.62±7.46	62.45±6.36
	Control group	51	56.38±5.91	71.54±7.36	62.48±6.28
	t		7.76	9.24	8.14
	p		>0.05	>0.05	>0.05
After medication	Observation group	51	16.56±1.52	32.62±3.14	21.18±2.44
	Control group	51	30.08±2.94	48.26±4.52	32.28±3.14
	t		0.18	0.16	0.17
	p		<0.05	<0.05	<0.05

TABLE 6: COMPARISON OF ADVERSE REACTIONS BETWEEN THE TWO DRUGS (%)

Group	n	Dizzy	Rash	Diarrhea	Overall adverse reaction rate
Observation group	51	1	0	1	2 (3.92)
Control group	51	1	1	3	5 (9.8)
χ^2					<0.001
p					<0.05

step of gastric acid secretion in gastric wall cells. It has a strong and long-lasting inhibitory effect on gastric acid secretion[4].

Excessive secretion of gastric acid can cause peptic ulcers, acid reflux and other symptoms, which may aggravate the symptoms of reflux esophagitis. Oral administration of vonoprazan fumarate can lead to a peak blood concentration in humans after 2 h and increase intragastric pH above 4 after 4 h. It only needs to be taken once a day to provide rapid and lasting acid suppression. Vonoprazan fumarate tablets were first developed by Takedas in Japan and launched in December 2014. The drug belongs to a new class of inhibitors of potassium competitive acid blockers[5]. P-CABs are lipophilic, weakly basic, have a high dissociation constant and are stable at low pH values. Therefore, vonoprazan fumarate tablets have a rapid, robust and long-lasting inhibition of gastric acid secretion. It also has a premature termination effect on gastric acid secretion by inhibiting the binding of Potassium (K) to Hydrogen (H), K-ATPase (proton pump)[6].

Rabeprazole belongs to the class of drugs that inhibit secretion and is an alternative drug to benzimidazole. Although rabeprazole has no anticholinergic and anti H_2-histamine functions, it can adhere to the surface of gastric parietal cells and inhibit gastric acid secretion by inhibiting the H^+, K^+-ATPase pathway[7]. This enzyme system acts as an acid proton pump, so rabeprazole relies on proton pump inhibitors in the stomach to block the production of gastric acid in a dose-dependent manner. Animal studies have demonstrated that rabeprazole can be eliminated from plasma and gastric mucosa shortly after administration. Characteristics of rabeprazole inhibition on gastric acid secretion-The effect of rabeprazole begins to take effect 1 h after taking 20 mg of rabeprazole orally, the blood concentration of rabeprazole reaches the peak within 2-4 h and the gastric acid can be inhibited 23 h after the first oral administration, and the effect can be up to 48 h[8]. Rabeprazole inhibits H^+/K^+-ATPase. The inhibition of gastric acid secretion was slightly enhanced by increasing the dose of rabeprazole appropriately.

The etiology of RE is complex and some studies believe that its pathogenesis is closely related to abnormalities of the lower esophageal sphincter, decreased esophageal thrust, decreased esophageal defense function, gastric hypersensitivity and high gastric acid secretion. After the occurrence of RE, patients showed discomfort such as nausea, acid regurgitation, heartburn, burning pain and dysphagia. Endoscopic examination showed different degrees of esophageal mucosal damage[9]. In clinical practice, in addition to the patient's chief complaint, endoscopy should also be performed to check the esophageal mucosal injury and venous blood should be collected to check the inflammation. Studies have shown that RE is treated with omeprazole, itopride, mosapride, Oryz-Aspergillus enzyme tablets, aluminum and magnesium plus suspension, flupentixol and melitracen and other different drugs, and the curative effect is not ideal[10].

Acid-suppressive therapy is the main method of RE treatment. Vonoprazan fumarate tablets and rabeprazole belong to acid inhibition drugs. It is of great significance to compare the two drugs as objects. Rabeprazole can be attached to gastric parietal cells after oral administration and can reduce the content of gastric acid through drug interaction with ATPase and protect the esophageal mucosa from further damage, so as to achieve the purpose of improvement. Vonoprazan fumarate tablets are novel potassium-competitive acid blockers. Vonoprazan fumarate tablets have more obvious advantages than other acid inhibitors, mainly reflecting in its faster onset of action, its proton pump inhibition, without acid activation, its ability to directly enter the human stomach at high concentrations and its stability in acid. Vonoprazan fumarate tablets showed almost the same pharmacodynamic activity at different pH values and had strong acid-fast decomposition ability. Acid inhibition is closely related to GAS, MTL and PGI[11]. The author believes that the core of acid inhibition is the regulation of GAS, MTL and PGI. GAS mainly promotes the secretion of digestive juice, enhances gastrointestinal peristalsis and promotes gastric acid secretion to achieve the purpose of regulating gastric emptying. The secretion of MTL is an effective hormone to control gastric emptying, which prevents the reflux of gastric contents in the esophagus by promoting the contraction of small intestinal muscle and gastric fiber. Studies have shown that reflux esophagitis is associated with high levels of gastric hormones in individuals and PGI is secreted by cervical mucus cells and principal cells of the fundic gland, which has a positive effect on human gastrointestinal peristalsis[12]. In this study, GAS and MTL in patients treated with vonoprazan fumarate tablets were higher than those in patients treated with rabeprazole. Vonoprazan fumarate

tablets are superior to rabeprazole in improving intestinal function, inhibiting acid and promoting gastric contents excretion. The basic feature of RE is esophageal mucosal injury, which must have inflammatory factors. TNF-a, IL-6 and IL-8 are pro-inflammatory factors and their high expression in RE is often positively correlated with esophageal mucosal injury. Comparison of the anti-inflammatory effect of vonoprazan fumarate tablets and rabeprazole is an important index to judge the efficacy of RE. In this study, vonoprazan fumarate tablets had a faster decline in the three inflammatory cytokines than rabeprazole. Vonoprazan fumarate tablets had a relatively low incidence of adverse drug reactions and the safety of vonoprazan fumarate tablets was generally acceptable.

In conclusion, both vonoprazan fumarate and rabeprazole belong to the acid inhibition class and both have a certain effect on the treatment of RE. However, vonoprazan fumarate is superior to rabeprazole in relieving symptoms, improving esophageal motility and reflux frequency, improving gastric function, inhibiting inflammatory factors and adverse drug reactions, and the overall effect is significantly better than that of rabeprazole. In the treatment of RE, vonoprazan fumarate should be the first choice.

Conflict of interests:

The authors declared no conflict of interest.

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