

• CLINICAL RESEARCH •

The effect of famotidine on gastroesophageal and duodeno-gastro-esophageal refluxes in critically ill Patients

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Abstract

AIM: To investigate the effect of famotidine on gastroesophageal reflux (GER) and duodeno-gastro-esophageal reflux(DGER) and to explore it's possible mechanisms. To identify the relevant factors of the reflux.

METHODS: Nineteen critically ill patients were consecutively enrolled in the study. Dynamic 24 hours monitoring of GER and DGER before and after administration of famotidine was performed. The parameters of gastric residual volume, multiple organ disorder syndrome (MODS) score, acute physiology and chronic health evaluation II (APACHE II) score and PEEP were recorded. Paired *t* test; Wilcoxon signed ranks test and Univariate analysis with Spearman's rank correlation were applied to analyse the data.

RESULTS: Statistical significance of longest acid reflux, reflux time of pH<4 and fraction time of acid reflux was observed in ten critically ill patients before and after administration. *P* value is 0.037, 0.005, 0.005 respectively. Significance change of all bile reflux parameters was observed before and after administration. *P* value is 0.007, 0.024, 0.005, 0.007, 0.005. GER has positive correlation with APACHE II score and gastric residual volume with correlation coefficient of 0.720, 0.932 respectively.

CONCLUSION: GER and DGER are much improved after the administration of famotidine. GER is correlated with APACHE II score and gastric residual volume.

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INTRODUCTION

The incidence of GER and DGER is relatively high in critically ill patients. It was reported that the incidence of DGER was 48 % and that of GER 74 %. GER and DGER are important causes of esophageal inflammation, ulcer, upper GI bleeding^[1], bronchospasm^[2] and aspiration pneumonia^[3]. In our study using 24 hours' acid and bile reflux monitoring, the effect of famotidine on GER and DGER was recorded and the relationship between reflux, gastric residual volume, positive

end expiratory pressure (PEEP), APACHE II and MODS scores were studied.

MATERIALS AND METHODS

General conditions

Clinical data: From June, 2001 to February, 2002 nineteen critically ill patients were enrolled including ten males and nine females with age ranging from thirty to seventy-five. Among them there were eleven cerebral trauma patients, four acute cerebrovascular accident, one intracranial neoplasm and three respiratory failure with lung infection. Criteria for enrollment were: fasting for at least 6 hours, on mechanical ventilator support, no enteral nutrition through nasogastric tube (NGT) before, and serum bilirubin level less than 2.0 mg/dl. Exclusion criteria included active gastrointestinal bleeding, esophageal and fundic varices, mechanical ileus, previous thoracic or abdominal radiotherapy, esophageal or gastric surgery, cholecystectomy, previous GERD or gastrointestinal dynamic disorders, esophageal or upper small intestinal Crohn's disease. Also excluded were patients receiving cisapride, erythromycin, atropine, theophylline, metoclopramide and acid suppressants within three days.

Drug and equipments

Famotidine (trade name of Xin Fa Ding, Shanghai Sine pharmaceutical company.), pH monitor of dynamical Digitrapper MK III and Bilitec 2000 all produced by Medtronic Synectics Medical Company (Sweden).

Methods

The level of PEEP, the score of MODS and APACHE II (Knaus, 1985) were recorded on the day of study. The electrode of pH monitor was calibrated in buffers of pH 7.01 and 1.07. The Bilitec 2000 probe was calibrated in calibrating fluid. Then two probes were taped together and inserted into patients' stomach through nostril. Gastroesophageal junction was determined by pH gradient change. After exclusion of torsion by chest X-ray film the probes were taped to the patients' faces. During the study all patients were kept supine and received TPN nutritional support. All data was analysed by specific software provided by Medtronic Synectics Medical Company. Pathologic acid reflux was defined as the fraction time of pH less than 4, greater than 4 %^[4]. The pathologic bile reflux was defined as the fraction time of light absorption value more than 0.14, greater than 4 %^[5]. MODS and APACHE II score was reevaluated on the second day. Acid and bile reflux monitoring were repeated after the administration of famotidine of 40 mg.iv.q12 h. On the third day nasogastric tube was inserted into the stomach and the gastric residual volume was recorded during the famotidine administration.

Ventilation associated pneumonia (VAP) (refer to informal guide for the diagnosis and treatment of nosocomial pneumonia set by CMA, pulmonary division in 1999) was also observed.

Statistics analysis

All results were expressed as $\bar{x} \pm s$ (M). Data were analyzed by

pair-matching *t* test, Wilcoxon signed rank test, Spearman's rank correlation.

RESULTS

Scoring

The ranges of PEEP, APACHE II and MODS were 5 mmHg to 15 mmHg, 10 to 26 points and 8 to 18 points respectively in nineteen critically ill patients. No significant differences were found in PEEP, APACHE II and MODS in ten patients before and after administration of famotidine.

Results of esophageal acid reflux

The parameters of acid reflux in ten patients were showed in Table 1. The incidence of pathological acid reflux before famotidine administration was 80 % (8/10) and 30 % (3/10) after famotidine administration. There were significant differences in longest reflux time, reflux time of pH less than 4 and fraction time of reflux.

Table 1 Acid reflux comparison before and after famotidine administration

	Before administration	After administration	<i>P</i> value
Reflux frequency	81.60±110.57 (49.50)	39.50±59.44(22.00)	0.059
Frequency of long reflux (>5 min)	13.90±13.08 (9.50)	7.60±9.79 (6.00)	0.052
Longest reflux time (min)	34.80±64.12 (12.00)	9.30±10.20 (7.50)	0.037
pH<4 reflux time (min)	146.80±293.46 (34.50)	27.10±45.68 (14.00)	0.005
pH<4 fraction time(%)	18.43±19.64 (11.43)	0.44±0.55(0.18)	0.005

Results of esophageal bile reflux

The parameters of bile reflux in ten patients were shown in Table 2. The incidence of pathological bile reflux before administration was 60 % (6/10) and 20 % (2/10) after famotidine administration. All the parameters were improved after famotidine administration.

Table 2 Bile reflux comparison before and after famotidine administration

	Before administration	After administration	<i>P</i> value
Reflux frequency	37.20±19.00 (34.50)	14.30±12.04 (11.50)	0.007
Frequency of long reflux (>5 min)	13.30±5.93 (13.50)	5.40±7.88(2.00)	0.024
Longest reflux time (min)	111.20±142.42 (18.00)	17.90±30.63 (5.50)	0.005
Absorption>0.14 reflux time (min)	308.00±413.02 (49.50)	32.60±49.40 (11.00)	0.007
Absorption>0.14 fraction time (%)	26.00±27.33 (15.30)	0.64±10.39 (0.29)	0.005

Esophageal mixed reflux

The incidence of mixed reflux in ten critical ill patients was 50 % (5/10) before famotidine administration and was 20 % (2/10) after famotidine administration. The total incidence of mixed reflux in nineteen patients was 36.84 % after the administration.

Correlation analysis

Before administration reflux time of pH<4 was positively related to APACHE II score with Pearson correlation coefficient of 0.72 (Figure 1). After administration fraction time of acid reflux and APACHE II score were positively related to gastric residual volume with Pearson correlation coefficient of 0.932 and 0.467 respectively (Figure 2,3).

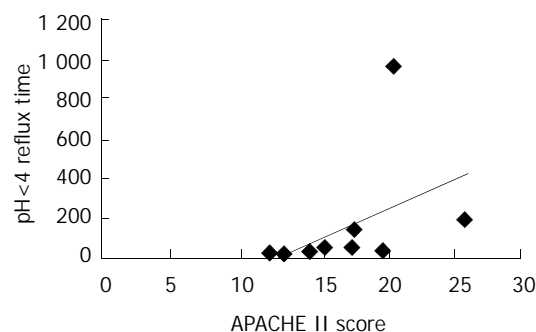


Figure 1 The relationship between pH<4 reflux time and APACHE II score before famotidine administration.

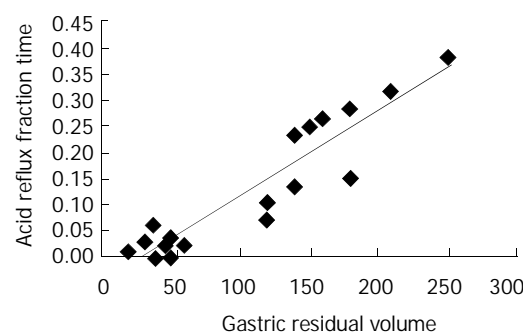


Figure 2 The relationship between acid reflux fraction time and gastric residual volume after famotidine administration.

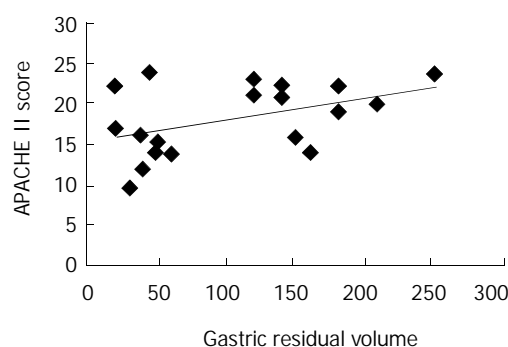


Figure 3 The relationship between APACHE II score and gastric residual volume.

Aspiration pneumonia and VAP

In our study no aspiration pneumonia and VAP were found.

DISCUSSION

The medical literatures reported that the incidence of GER and DGER could be 78.1 %^[6] and 48 %^[7] respectively in critically ill patients. Reasons for high reflux rate maybe due to the following: (1) Basic illnesses: Medical literature reported that acute or chronic cerebral injury could decrease lower esophageal sphincter pressure^[8] and delay the gastric emptying^[9] when accompanied with increased ICP. (2) Posture: Supine position is a high risk factor for GER and DGER. The incidence of GER increased from 12 % to 50 % when position was changed from semirecumbent to supine^[10]. (3) Mechanical ventilation: During ventilation swallowing hyperreflexia, inhibition of peristalsis and visceral hypoperfusion due to PEEP were observed^[11]. Similar study had not been reported in China. Researches reported that reflux of duodenal juice in gastroesophageal reflux disease was more common than pH

studies alone would suggest^[12] and the combined reflux of gastric and duodenal juices caused severe esophageal mucosal damage^[13]. We combined pH monitor with Bilited 2000^[14] to detect acid and bile reflux simultaneously. The pH step-up for electrode positioning was successfully carried out in nineteen critically ill patients^[15]. Our study showed before the administration of famotidine the incidence of pathological GER and DGER was 80 %, 60 % respectively which was in accordance with the medical literatures.

After famotidine administration acid and bile reflux were much improved. Famotidine is one of the most common drugs used in ICU. Venous injection of famotidine 40 mg twice per day would keep esophagus pH above 4 for twenty hours in our study. Parkman^[16] found increased antral phase III migrating motor complexes (MMCs) after administration of ranitidine, famotidine and omeprazole and especially in famotidine. Bortolotti noted the same finding^[17,18]. MMC III had the role of "street sweeper" in GI tract. Because of its powerful propulsion which can clean the duodenal contents reflux to stomach in the end of MMC II, MMC may have an anti-reflux role^[19]. Before MMC III there is a short duration of reversed peristalsis^[20] when MMC III is evoked by bile and pancreatic juice excretion and neutralization of acid in the duodenum^[21]. MMC III could be inhibited by continuous injection of acid in the duodenum. In conclusion famotidine improved GER through increasing gastric pH and improved DGER through increasing MMC III due to increased duodenal pH. Decreased gastric residual volume after acid inhibition may be one of the mechanisms.

In our study we also found that reflux time of pH<4 was positively correlated to APACHE II score (Figure 1). This suggests that GER and DGER occur more commonly when critical illness occurs and normal defense mechanisms are disturbed. It was reported that as part of scoring APACHE II Glasgow score was closely related to delayed gastric emptying^[22], which was consistent with our findings (Figure 3). We also found that gastric residual volume was positively related to fraction time of acid reflux (Figure 2). This may explain why famotidine may improve GER indirectly. Nasogastric tube, H₂ blocker^[23], sedatives^[24,25], muscle relaxant^[26] are known factors for ventilation associated pneumonia. But in our study there was no aspiration pneumonia or VAP. So famotidine may not increase the incidence of pneumonia. Furthermore by decreasing GER and DGER it may lessen the opportunity for aspiration. There is a need for further study in larger groups of patients to define more clearly this relationship.

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