

# Cisapride decreases gastric content aspiration in mechanically ventilated patients

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**Objective:** To determine the effect of the prokinetic agent cisapride in the prevention of aspiration of gastric contents.

**Design:** A prospective randomized two-period crossover study.

**Setting:** Fourteen-bed polyvalent intensive care unit in a University Hospital.

**Patients:** Eighteen intubated, mechanically ventilated patients who were seated in a semirecumbent position were studied.

**Method:** Tc-99m sulfur colloid (80 megabecquerels) was administered via nasogastric tube on 2 consecutive days. Patients randomly received cisapride (10 mg, via nasogastric tube) one day and a placebo the other. Bronchial secretions were obtained before and for 5 consecutive h after Tc-99m administration. The radioactivity was measured in a standard amount (1 ml) of bronchial fluid using a gamma counter and expressed as counts per min (cpm) after correction for decay.

**Results:** Sixteen out of 18 (88%) patients had increased radioactivity in bronchial secretions. The radioactivity increased over time both with and without cisapride, although it was lower in patients receiving cisapride than in those receiving a placebo. The cumulative bronchial secretion radioactivity obtained when patients received cisapride was significantly lower than when patients received a placebo:  $7540 \pm 5330$  and  $21965 \pm 16080$  cpm, respectively ( $P < 0.05$ ).

**Conclusion:** Our results suggest that aspiration of gastric contents exists even in patients who are kept in a semirecumbent position. Moreover, cisapride decreases the amount of gastric contents aspiration in intubated and mechanically ventilated patients and may play a role in the prevention of ventilator associated pneumonia. Cisapride, even with the patient in the semirecumbent position, did not completely prevent gastric content aspiration.

## Introduction

The aspiration of gastric contents induces or exacerbates bronchoconstriction and it is the most commonly recognized pathogenic factor for the development of pneumonia, especially in ventilator-associated pneumonia (VAP) [1,2].

The incidence of aspiration of gastric contents is high in intensive care unit (ICU) patients and even higher in intubated and mechanically ventilated patients. Gastrointestinal tract dysmotility is a relatively common condition in critically ill patients and is associated with gastric contents aspiration [3,4]. Additional risk factors for gastric content aspiration included enteral feeding, naso or oral-gastric tubes and position of the patients. Enteral feeding via a nasogastric tube may also result in increased gastric

volume, reflux and Gram-negative bacterial overgrowth in the stomach [5]. Wide bore nasogastric tubes themselves probably impair the function of the lower esophageal sphincter, thereby facilitating aspiration and bacterial contamination of the tracheobronchial tree [6]. Moreover, an important risk factor in causing the aspiration of gastric contents seems to be the supine position. A semirecumbent position of mechanically ventilated patients could help in part to prevent the aspiration of gastric contents into airways, but aspiration still remains a problem [7]. Orozco-Levi and colleagues [8] showed a significant increase in radioactivity count in oropharyngeal contents after Tc99m isotope instillation through nasogastric tube. This gastroesophageal reflux was irrespective of body position. In contrast, the radioactivity

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**Table 1**

Patient characteristics							
No	Sex	Age	Diagnosis	APACHE II	Medications	MV	Outcome
1	F	58	SBH	22	Midazolam	5	S
2	M	54	ICH	20	–	5	D
3	M	54	COPD	28	Midazolam	5	D
4	F	70	COPD	30	Propofol	8	S
5	M	48	Head injury	24	Fentanyl, Midazolam	10	S
6	M	19	GBS	14	Fentanyl	5	S
7	M	40	Head injury	29	Fentanyl, Midazolam	6	D
8	M	67	Head injury	28	Fentanyl, Midazolam	7	S
9	M	76	ICH	28	Midazolam	6	D
10	M	41	Drug overdose	12	–	4	S
11	M	74	ICH	25	Midazolam, Fentanyl	4	D
12	M	74	Cardiac failure	27	Lorazepam	4	D
13	F	64	ICH	25	Midazolam	6	S
14	M	25	Head injury	17	Lorazepam, Fentanyl	5	S
15	M	26	Trauma	22	Fentanyl	5	S
16	M	55	Head injury	24	Propofol	8	S
17	M	62	ICH	27	–	6	S
19	M	35	Head injury	19	Propofol, Fentanyl	8	S
Mean		52		23		6	
SD		17		5		1.7	

M, male; F, female; S, survival; D, death; ICH, intracerebral hemorrhage; GBS, Guillain Barr syndrome; SBH, subarachnoid brain hemorrhage; COPD, chronic obstructive pulmonary disease; MV, days of mechanical ventilation.

count values in bronchial secretions were higher in the supine position than in semirecumbency, which suggests that the semirecumbent position helps prevent in part gastric content aspiration. Apart from position, agents, such as erythromycin and cisapride, increase the gastric motility and they could accelerate gastric emptying and prevent gastric aspiration [9,10].

Cisapride is a very effective prokinetic agent that acts by increasing the physiological release of acetylcholine from the postganglionic nerve endings of the myenteric plexus without any associated dopamine antagonism [10].

In this study, we assessed the effect of cisapride in the prevention of pulmonary aspiration of gastric contents in mechanically ventilated patients maintaining the benefit of a semirecumbent position.

## Materials and methods

### Patients

Eighteen mechanically ventilated patients (15 men and three women, mean age  $52.33 \pm 17.90$  years) were included

in this study. The protocol was approved by the Medical Ethics Committee of The University Hospital of Ioannina and consent was obtained from the patients' relatives. Patients with gastrectomy, ileus, respiratory infections, sepsis and hemodynamic instability (low blood pressure needing high doses of inotropes, or wide fluctuation of blood pressure over time) were excluded from the study. The demographic data and the underlying clinical conditions of these patients are summarized in Table 1.

### Protocol

All patients had a 5 mm diameter nasogastric tube in place for enteral nutritional support and received sucralfate 2g twice daily for stress ulcer prophylaxis. The position of the nasogastric tube was radiographically checked before the study. Sedation and all the other medications were kept unchanged throughout the study (Table 1). Nobody was given paralytic agents, antibiotics or inotropes. The enteral nutrition and other medications via nasogastric tube were withheld 8h before the onset and during the study. The body position of the patients was semirecumbent at a 45 degree angle, and they were put in this position at least 8h before the study.

All patients were intubated and mechanically ventilated with an assist-control mode. A low level of positive end-expiratory pressure (PEEP) was used (PEEP:  $5 \pm 1.7$  cmH<sub>2</sub>O). The volume, pressure and the leaking of the cuff of the endotracheal tube was checked, before and at the end of every day of the study. The minimal volume and pressure necessary to prevent air leaking around the cuff were used. The study lasted 2 consecutive days for each patient. Eighteen hours before the study, the patients received, at 6 h intervals, a cisapride suspension (Alimix, Janssen Pharmaceutica, Beerse, Belgium; 1 mg/ml) in a dose of 10 mg, or a placebo given as a bolus randomly via nasogastric tube. The next morning, 60 megabecquerels of Tc99m sulfur colloid were carefully administered via the tube as described by Chernow and colleagues [11]. Bronchial secretions were taken at zero time (baseline radioactivity) and then once an hour for 5 consecutive h. The secretions were taken in a sterile container by bronchial suction. The suction catheter was placed at the level of the carina. The distance of the carina from the tip of the endotracheal tube was measured on a chest X-ray. Just after the end of this procedure, patients who had previously received cisapride were given placebo and vice versa. On the second day, the procedure was repeated in the same way. Blood samples were taken from the first five patients in the study, before and 5 h after isotope instillation and checked for radioactivity. Just before starting the procedure, bronchial secretion, oropharyngeal and gastric samples were taken for microbiological cultures. A gentle suction of gastric content was performed just before the administration of the isotope.

### Measurements

The activity of Tc99m was measured, using a gamma counter (Gamma Counting system, Crystal TM II, 5400 Series, Packard Instrumental Company), in a standard amount (1 ml) of bronchial secretions. The amount of radioactivity is expressed as counts per min (cpm) after correction for decay according to the equation of radioactive decay law:

$$N = N_0 \cdot e^{-\lambda t}$$

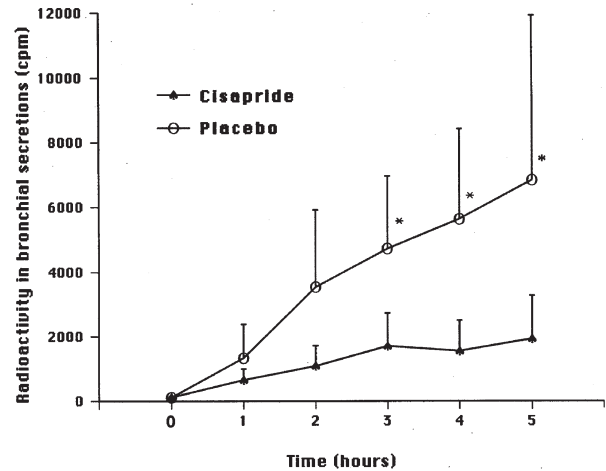
where  $N_0$  is the number of parent nuclei present at  $t=0$ ,  $N$  is the number remaining nuclei at time  $t$ ,  $\lambda$  is a constant of proportionality, called the decay constant, which is different for different isotopes and  $e$  is the base of natural logarithm [12].

During the procedure, monitoring was performed with a two-lead electrocardiogram (ECG) and a 12-lead ECG was performed before and soon after the end of every procedure.

### Statistics

The differences between groups were tested for significance by analysis of variance (ANOVA) test for repeated

**Figure 1**



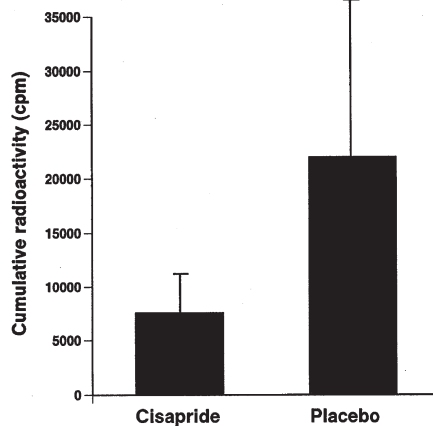
The radioactivity of bronchial secretions over time. The values at zero time represent the baseline radioactivity. Asterisk (\*) denotes statistical significance between cisapride and placebo.

measures. Results are expressed as mean  $\pm$  SD. A  $P$  value less than 0.05 was considered significant.

### Results

Sixteen out of 18 patients (88%) demonstrated an increased radioactivity in bronchial secretions and it increased over time both in patients receiving cisapride or placebo. When patients received cisapride, the radioactivity increased from  $120 \pm 18$  cpm (baseline radioactivity at zero time) to  $1930 \pm 1340$  cpm at the fifth hour ( $P < 0.05$ ). When patients received a placebo the radioactivity increased from  $115 \pm 22$  cpm (baseline radioactivity at the zero time) to  $6825 \pm 5100$  cpm 5 h later ( $P < 0.01$ ). There was no significant difference in baseline radioactivity of bronchial secretions whether the patients were given cisapride or placebo. The change in radioactivity of bronchial secretions over time is demonstrated in Fig 1. The difference in radioactivity during cisapride and placebo administration became statistically significant after the third hour ( $P < 0.05$ ). The cumulative bronchial secretion radioactivity obtained when patients received cisapride was significantly lower than when patients received a placebo ( $7540 \pm 5330$  and  $21965 \pm 16080$  cpm, respectively;  $P < 0.05$ ; Fig 2).

The microbiological cultures showed that 10 patients had identical microorganisms colonizing the stomach, oropharyngeal area and bronchus. Five patients had the same microorganisms only in the oropharyngeal content and bronchial secretion, and different ones in the gastric content. Three patients had different microorganisms in stomach, oropharynx and bronchus. Two of the studied patients developed VAP during their stay in ICU; both patients had the

**Figure 2**

The cumulative radioactivity of bronchial secretions with and without cisapride.

stomach, oropharynx and bronchus colonized with the causative bacteria of VAP, which were detected by quantitative cultures of protected brush specimens.

There was no significant difference in cuff pressure between measurements before and at the end of the study.

There was no difference in the blood radioactivity before and 5 h after isotope administration, as it was the same as the background radioactivity.

No side effects of cisapride were observed during this study. No cardiac arrhythmia or QT interval prolongation was noted.

## Discussion

This study demonstrates that cisapride significantly reduced the pulmonary aspiration of gastric contents in mechanically ventilated patients although the conventional protective methods, such as semirecumbent position and regular checking of cuff leaking, even with cisapride administration are not sufficient to prevent gastric content aspiration completely.

In critically ill patients receiving mechanical ventilation gastrointestinal motility is often impaired [3,4]. The precise mechanism leading to this gastroparesis is still unknown. Medications such as opiates and dopamine [13,14], hyperglycemia [15] or increased intracranial pressure [16] have all been shown to depress the antral motor activity in experimental or clinical conditions. This situation favors not only gastroesophageal reflux but also duodenogastric reflux, thereby promoting the colonization of the stomach with gastric Gram negative pathogens [17,18]. Enteral nutrition in patients with inadequate gastric emp-

tying can increase the risk of aspiration, and expand the size of the gastric bacterial reservoir by increasing the gastric volume and the pH. Today most investigators agree that gastric colonization with potentially pathogenic microorganisms is important in the pathogenesis of VAP [17,19,20]. Moreover, nasogastric tubes themselves probably impair the function of the lower esophageal sphincter thereby promoting aspiration. In addition, the supine position of patients promotes aspiration and the semirecumbent position helps minimize the aspiration of gastric contents to lower airways [7,8].

Our results showed that aspiration in mechanically ventilated patients occurs even when they are kept in a semirecumbent position. The administration of cisapride significantly decreases aspiration in these patients. A properly inflated cuff was insufficient to prevent aspiration to lower airways. The incidence of gastric content aspiration in our group of patients was very high. One explanation could be the high percentage of neurological diseases, which are included in our patient population, because severe head injury has been associated with impaired gastric emptying [16]. Another cause of the high incidence of aspiration could be the sedation received by the majority of the patients. There is no clear explanation for the absence of gastric content aspiration in two patients. It is noteworthy, though, that one of them did not receive sedation and the other was given low-dose (5 mg/h) midazolam. Both survived, and their age, APACHE II score and the days of mechanical ventilation at the day of the study were equivalent to those of the other patients.

These findings are in agreement with other investigators who found that cisapride prevents the morphine-induced delay in gastric emptying [21]. It also significantly accelerates gastric emptying both in patients with gastroesophageal reflux disease and in patients with delayed gastric emptying caused by idiopathic or postsurgical reasons [22]. It has also been suggested that cisapride can minimize the risk of aspiration pneumonia in patients with long-term enteral feeding [23]. In critically ill patients with gastric dilatation and functional gastric paralysis the administration of cisapride showed a clinical benefit [24,25]. Moreover, cisapride increases the lower esophageal sphincter pressure in normal volunteers and in patients with reflux disease [26]. The velocity of transit in the esophagus remains unchanged with cisapride, but an increase in distal peristalsis is noted [27].

Oral cisapride usually has few side effects. Nevertheless, cardiac arrhythmias, especially torsade de pointes, and prolonged QT intervals with a potentially fatal outcome have been described in patients with concomitant use of medication that is metabolized by the cytochrome P-450 3a4 isoenzyme, eg imidazole antibiotics or macrolides [28]. Cisapride should be administered with caution in patients

who are on any medication known to prolong QT interval and in those with renal insufficiency, a history of arrhythmia or cardiac disease. None of our patients received any of the above medications and, possibly for this reason, no side effects were noted during the period of cisapride administration.

## Conclusion

In summary, our results suggest that cisapride decreases the risk of aspiration of gastric contents in intubated and mechanically ventilated patients who are kept in a semi-recumbent position. Conventional protective methods though, such as the semirecumbent position and regular checking of cuff leaking, even with cisapride administration are not sufficient to prevent gastric content aspiration completely. Further studies are needed to establish if this drug helps in the prevention of ventilator associated pneumonia, bronchitis or bronchoconstriction.

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