Intensive Care Med (1996) 22: 1339–1344

ORIGINAL

D. K. Heyland
G. Tougas
D. King
D. J. Cook

Impaired gastric emptying in mechanically ventilated, critically ill patients

Received: 11 December 1995
Accepted: 14 August 1996

D.K. Heyland (✉)[1] · D. King · D.J. Cook
Department of Clinical Epidemiology & Biostatistics, McMaster University, Faculty of Health Sciences, Hamilton, Ontario, Canada K7L 3N

G. Tougas
Department of Medicine, Division of Gastroenterology, McMaster University, Faculty of Health Sciences, Hamilton, Ontario, Canada

D.J. Cook
Department of Medicine, Division of Critical Care, St. Joseph's Hospital, Hamilton, Ontario, Canada

* *Present address:*
[1] Anagada 3, Kingston General Hospital, 76 Stuart Street, Kingston, Ontario, K7L 2V7, Canada, FAX: +1 (613) 548 2402

Abstract *Objective:* To measure gastric emptying in critically ill patients using an acetaminophen absorption model and determine which variables are associated with impaired gastric emptying.
Design: A prospective, cohort study.
Setting: A medical/surgical ICU at a tertiary care hospital: Hamilton General Hospital, Hamilton, Ontario.
Patients and participants: We recruited 72 mechanically ventilated patients expected to remain in the ICU for more than 48 h. Our results were compared to those in healthy volunteers.
Intervention: Within 48 h of admission to the ICU, 1.6 g acetaminophen suspension were administered via a nasogastric tube into the stomach. Blood samples were drawn a $t = 0$, 30, 60, 90, and 120 min for measurement of plasma acetaminophen levels determined by the enzymatic degradation method.
Measurements and results: Maximal concentration of acetaminophen was 94.1 (75.3) μmol/l compared to 208.4 (33.1) μmol/l in a control population ($p < 0.0001$). The time to reach the maximal concentration was 105 min (60–180) compared to 30 min (15–90) in controls ($p < 0.0001$). The area under the time-acetaminophen concentration curve $t = 120$ was 9301 (7343) μmol/min per l compared to 11 644 (1336) μmol/min per l in the controls ($p = 0.28$). The variables associated with delayed gastric emptying were age, sex and use of opioids for analgesia and sedation.
Conclusions: Gastric emptying is delayed in critically ill patients. The important consequences of this phenomenon include intolerance to enteral nutrition and gastric colonization. Strategies to minimize the use of narcotics may improve gastric emptying. Studies to examine the effect of gastrointestinal prokinetic agents on gastric emptying are needed.

Key words Gastrointestinal motility · Gastric emptying · Critical care · Opioids · Prokinetic drugs · Enteral nutrition

Introduction

Critical illness is characterized by multiple factors which can alter the structure and function of the gastrointestinal tract. These alterations may include changes to splanchnic blood flow, mucosal injury and disturbance in gastrointestinal immune function and motility. Gastrointestinal motility is a major, natural defense mechanism against infection of the gut [1]. Microorganisms are relatively scarce in the esophagus, stomach, duodenum and jejunum due to powerful,

peristaltic contractions (known as migrating motor complexes), which periodically flush the luminal contents of the proximal gut towards the colon. As movement of the intestinal contents slows in the terminal ileum, the quantity of bacteria rises tremendously [2]. Patients who have impaired gastrointestinal motility are at risk of bacterial overgrowth of the upper gut with potentially pathogenic organisms and increased translocation, conditions associated with a higher incidence of acquired infection in the intensive care unit (ICU) [3, 4].

Furthermore, our previous observations of enteral feeding practices suggest that large volume gastric residuals frequently preclude the successful implementation of enteral nutrition [5], especially when feeds are administered early in the course of critical illness [6]. To correlate these findings with a physiological phenomenon and to determine the extent of the problem, we measured gastric emptying in critically ill patients early in the course of their stay in the ICU and compared the results with those derived from healthy volunteers. Additionally, we performed a statistical analysis to evaluate which variables correlate with impaired gastric emptying in critically ill patients.

Materials and methods

We conducted this study in the Hamilton General Hospital ICU, a 15-bed unit which serves as a regional facility for trauma and neurosurgery. We included mechanically ventilated patients who, at admission, were expected to be in the ICU for more than 48 h. We excluded patients who were already receiving enteral nutrition, patients who were pregnant, had bowel perforation or obstruction, gastroesophageal surgery in the last week or a clinically significant gastrointestinal bleed in the last 48 h.

Patients were recruited for this study within their first 72 h of admission to the ICU before the institution of enteral nutrition. After informed consent had been obtained from family members, the patient underwent an assessment of gastric emptying at 18:00 p.m. the same day. To measure gastric emptying, the stomach contents were first removed by nasogastric suction, after which the suction was discontinued for the duration of the acetaminophen sampling. Via a nasogastric tube (position confirmed by X-ray to be in the stomach), 1.6 g (50 ml) of liquid acetaminophen were then instilled into the stomach followed by 20 cc of water to flush the tube. Blood samples for acetaminophen levels were drawn at the time the acetaminophen was given (time = 0) and 30, 60, 90, and 120 min later. Plasma acetaminophen levels were determined by the enzymatic degradation method. We measured the maximum plasma concentration (μmol/l), time to reach maximal concentration (min) and area under the plasma concentration-time curve $t = 120$ (μmol/min per l).

Acetaminophen absorption has been previously used as an index of gastric emptying in other studies [7, 8] including studies conducted in the critical care setting [9–12]. As acetaminophen is absorbed in the small intestine rather than the stomach, its rate of absorption following oral administration reflects the rate of gastric emptying. This model has been validated by studies showing that the changes in plasma acetaminophen concentration reflect the rate of gastric emptying as determined by an In-113 DPTA chelate scintiscanning technique [13, 14]. One study assessed the inter- and intra-subject variability of gastric emptying in healthy volunteers measured by acetaminophen absorption. Intra-subject variability was not statistically significant for any measurements, while inter-subject variability was significant for all parameters [15]. Thus, the acetaminophen drug model is simple, valid and reproducible.

We collected the following demographic data on each study patient: age, sex, diagnosis, simplified acute physiology score (SAPS) and medication use. Motility agents and enteral feeds were not administered during the study period. All patients received sucralfate via the nasogastric tube for stress ulcer prophylaxis; doses were held during the assessment of acetaminophen absorption. In this study, we did not assess clinically important patient outcomes, nor did we assess the link between gastric motility and pneumonia. Rather, the results from critically ill patients were compared to the assessments of gastric emptying in healthy normal volunteers (age 22–26 years) using a similar methodology previously published [16]. After an overnight fast, volunteers received 1.5 g acetaminophen(tablets) with 100 ml of water, and serial determinations of acetaminophen concentrations were undertaken.

The primary outcomes of the study were the area under the plasma concentration curve for acetaminophen, the peak concentration of acetaminophen (reported as the mean and standard deviation) and time to peak concentration of acetaminophen (reported as median and interquartile range). We used a Z test to compare the means from the two groups. For time to peak concentration of acetaminophen, the median was used as an estimate of the mean and the standard deviation was estimated to be one-fifth of the range [17].

Analysis of variance models were used to test the effect of the following covariates on acetaminophen absorption: age, sex, use of opioids, operative versus non-operative admitting diagnosis, and Simplified Acute Physiology Score. We also examined the effect of dose of morphine or morphine-equivalent in the preceding 24 h period on acetaminophen absorption. For the multivariate regression, we used a backward elimination algorithm, which deletes terms from the model iteratively until all terms in the model are significant at the 0.05 level [18]. Variables with a significance level less that 0.05 were deemed to be statistically significant.

This study was approved by our local Institutional Review Board.

Results

Consecutive, eligible critically ill patients were screened for participation in this study. We enrolled 72 patients; 39% were female; the average age was 54.0 ($\pm$ 19.1) years; 47% were postoperative, 83% were receiving opioids and the mean Simplified Acute Physiology Score was 9.5 ($\pm$ 3.0). The primary admitting diagnosis of study patients was as follows: head trauma 14 (19%), surgical including multiple trauma 19 (26%), neurosurgical 20 (28%), and medical 19 (26%). The control population was 12 healthy, non-smoking, male volunteers with an average age of 22.8 years [16].

In our critically ill cohort, the maximal concentration of acetaminophen was 94.1 ($\pm$ 75.3) μmol/l compared to 208.4 ($\pm$ 33.1) μmol/l in the control population ($p < 0.0001$); the time to reach the maximal concentration was 105 min (60–180) compared to 30 (15–90) in controls ($p < 0.0001$) and the area under the time-acetaminophen concentration curve $t = 120$ was

9301 (± 7343) compared to 11,644 (± 1336) in the controls ($p = 0.28$, see Table 1). There was no statistically significant difference in acetaminophen adsorption between postoperative and medical critically ill patients (see Table 2).

In the univariate regression analysis, variables associated with impaired gastric emptying in the critically ill group were age, sex, use of opioids and dose of opioids (see Table 3). The older the patient, the greater the time to maximal concentration of acetaminophen. For area under the time/absorption curve and maximal concentration of acetaminophen, results were higher for females. For all three parameters, the admitting diagnosis was just short of statistical significance: surgical/trauma patients had worse gastric emptying than other admitting diagnoses. Patients who were not on opioids had a better gastric emptying, as evidenced by a quicker time to maximal concentration, a greater area under the time/absorption curve and a higher maximal concentration of acetaminophen. Finally, higher doses of opioids were associated with lower acetaminophen absorption and, thereby, a greater impairment of gastric emptying. In the multivariate analysis, only age and the use of opioids remained significant.

Table 1 Results of acetaminophen absorption, compared (a measure of gastric emptying) in critically ill patients to those of healthy volunteers: maximum plasma concentration (C_{max}, μmol/l), time to reach C_{max} (t_{max}, min) and the area under the plasma concentration-time curve $t = 120$ (AUC_{120}, μmol/min/l)

	Critically ill patients ($n = 72$)	Healthy volunteers [16] ($n = 12$)	p value
C_{max} ^	94.1 (± 75.3)	208.4 (± 33.1)	0.0001
t_{max}*	105 (60–180)	30 (15–90)	0.0001
AUC_{120} ^	9301 (± 7343)	11 644 (± 1336)	0.28

^ mean and standard deviation
* mean and interquartile range

Table 2 Results of acetaminophen absorption in medical and post-operative critically ill patients: maximum plasma concentration (C_{max}, μmol/l), time to reach C_{max} (t_{max}, min) and area under the plasma concentration-time curve $t = 120$ (AUC_{120}, μmol/min/l)

	Medical ($n = 38$)	Postoperative ($n = 34$)	p value
C_{max} ^	102.5 (78.7)	84.7 (71.4)	0.32
t_{max}*	90 (60–180)	120 (60–180)	0.064
AUC_{120} ^	10,037 (7680)	8479 (6968)	0.37

^ mean and standard deviation
* mean and interquartile range

Table 3 The results of the univariate analyses of possible predictors of gastric emptying. The dependent variables are: maximum plasma concentration (C_{max}, μmol/l), time to reach C_{max} (t_{max}, min), and area under the plasma concentration-time curve $t = 120$ (AUC_{120}, μmol/min/l). (*SAP* simplified acute physiology; *Surg* surgical/multiple trauma; *Neurosx* neurosurgical, *Med* medical); * Note A negative parameter estimate means that the association is negative (i.e., a 1 mg/24 h change in morphine dose is associated with a 0.4 decrease in C_{max} and a 38.2 decrease in AUC_{120}). A positive parameter estimate means that the association is positive (i.e. 1 year increase in age is associated with a 0.73 min increase in the time to reach maximum acetaminophen concentration)

Independent variables	t_{max} (min)	C_{max} (μmol/l)	AUC_{120} (μmol/min/l)
Age	Parameter estimate: 0.73 $p = 0.04$	Parameter estimate: 0.61 $p = 0.20$	Parameter estimate: 42.1 $p = 0.36$
Sex	Male: 109 Female: 114 $p = 0.75$	Male: 78.5 Female: 118.7 $p = 0.03$	Male: 7,780 Female: 11,550 $p = 0.04$
Operative diagnosis	Yes: 116 No: 106 $p = 0.44$	Yes: 84.7 No: 102.5 $p = 0.32$	Yes: 8,479 No: 10,037 $p = 0.37$
SAP score	Parameter estimate: − 0.14 $p = 0.95$	Parameter estimate: 5.6 $p = 0.06$	Parameter estimate: 516.7 $p = 0.08$
Primary diagnosis	Head trauma: 75.0 Surg/trauma: 123.2 Neurosx: 118.5 Med: 116.8 $p = 0.07$	Head trauma: 113.3 Surg/trauma: 57.8 Neurosx: 107.0 Med: 102.7 $p = 0.10$	Head trauma: 10,729 Surg/trauma: 6,103 Neurosx: 9,756 Med: 10,969 $p = 0.16$
Use of opioids	Yes: 118 No: 75 $p = 0.02$	Yes: 84.2 No: 143.6 $p = 0.01$	Yes: 8,180 No: 14,908 $p = 0.003$
Dose of morphine (or equivalent)	Parameter estimate: 0.09 $p = 0.52$	Parameter estimate: − 0.4* $p = 0.03$	Parameter estimate: −38.2* $p = 0.04$

Discussion

Using a well established model of gastric emptying, our study shows that critically ill patients have impaired gastric emptying early in the course of their illness compared to healthy volunteers. Moreover, the use of opioids is associated with impaired emptying in a dose-dependent phenomenon. However, our choice of a control group may have biased the results for the following reasons: 1) The control group was much younger than the critically ill patients. Increasing age correlated significantly with impaired gastric emptying in our study population. 2) The control group swallowed their acetaminophen and the cephalic phase of swallowing may increase gastric emptying whereas in critically ill patients this cephalic phase is absent and 3) The control group received 100 ml of liquid with their dose of acetaminophen while the critically ill patients received only 50 ml. Differences in volume may have influenced gastric emptying. Nevertheless, the results of our analysis are consistent with the work of Nimmo and colleagues [19], who have previously demonstrated that narcotic analgesics significantly inhibit gastric emptying, and Dive and colleagues [20] who also demonstrated that gastroduodenal motility is severely impaired in mechanically ventilated patients. Using a manometer to record antroduodenal motility, Dive et al. demonstrated that the activity front of the migrating motor complex of the stomach was absent in adult patients.

By restoring gastric motility, critically ill patients may better tolerate enteral nutrition. The early administration of enteral nutrition to critically ill patients is associated with a decreased catabolic response to injury, maintenance of bowel mucosal integrity, decreased translocation, improved wound healing and reduced septic morbidity [21]. However, attempts to feed in the stomach are often frustrated by gastrointestinal intolerance, especially in the early course of a patient's illness. Large volume gastric residuals and vomiting are the most common reasons feeds are interrupted or discontinued [5, 6]. Using a radioisotope liquid meal, Ott and colleagues [22] measured gastric emptying over a 3-week period in head-injured patients. Patients who initially had normal or rapid gastric emptying tolerated enteral feeds earlier than those who experienced delayed gastric emptying (8.5 vs 13.7 days, $p < 0.001$). By improving gastric motility, can we improve tolerance to enteral nutrition and, thereby, favorably influence the outcome of critically ill patients?

It has been hypothesized that the loss of peristaltic activity of the stomach may be one of the major determinants of gastric colonization in the critically ill population. Atherton and White [23] initially suggested this relationship between dysmotility, gastric colonization and pneumonia. They described ten mechanically ventilated patients with paralytic ileus who developed microbial overgrowth of the stomach. In six patients, the same gram-negative bacilli were subsequently found in the trachea, and in three patients the sequence of transmission from the stomach to the trachea was clearly documented. Several other studies have subsequently documented this sequence of transmission – retrograde transmission of contaminated stomach contents to the lungs [24–28]. Inglis and colleagues further described the association of impaired gastrointestinal motility and colonization of the stomach [29] and the trachea [30] in critically ill patients. The presence of duodeno-gastric reflux (indicated by the presence of conjugated bilirubin in the stomach secretions) was shown to correlate with the isolation of gram-negative bacteria in the stomach and the trachea in mechanically ventilated patients. Several studies have examined the association between body position, presence of a nasogastric tube, the development of gastroesophageal reflux and the incidence of aspiration pneumonia in critically ill patients [31–33]. These studies suggest that the supine body position and the presence of a nasogastric tube increase gastroesophageal reflux; the more gastroesophageal reflux, the greater is the likelihood of finding gastric contents in endobronchial secretions.

The foregoing results are consistent with our understanding of the gastropulmonary route of infection [24] and raises the question: Would restoring gastrointestinal motility (increasing lower esophageal sphincter tone, decreasing gastroesophageal regurgitation, improving gastric emptying and gastroduodenal coordination) reduce gastric colonization and subsequent pulmonary infection in critically ill patients?

Strategies to improve gastric motility in critically ill patients include minimizing the use of opioids and using gastrointestinal prokinetic agents. Opioids are frequently used to provide adequate analgesia and sedation to critically ill patients [34, 35]. As suggested by our study and demonstrated in others [19], opioids significantly impair gastric emptying and probably contribute to feeding intolerance and bacterial overgrowth. In a randomized study of 21 brain-injured patients requiring sedation, McArthur and colleagues compared the effect of morphine and midazolam to propafol on gastric emptying [12]. In this study, there was no significant difference in gastric emptying, as assessed by acetaminophen absorption and by residual volumes following a 200 ml test feed. More studies on 'opioid-reducing' sedation strategies are needed to determine which drugs and doses have the least impact on gastrointestinal motility.

There have been three studies of prokinetic agents in critically ill patients. Spapen and colleagues [36] randomized 21 stable, medical ICU patients receiving continuous enteral feeds to receive cisapride 10 mg

q.i.d. or placebo. After 5–7 days of treatment, gastric emptying, as measured by bedside scintigraphy, was markedly delayed and the mean gastric residuals were higher in the control group compared to patients receiving cisapride. In a randomized, double-blind, placebo-controlled study, we evaluated the effect of cisapride on gastric emptying in mechanically ventilated patients early in the course of their illness. Using an acetaminophen absorption model, we demonstrated that cisapride improves gastric emptying in both medical and surgical patients, including those patients on narcotics [37]. Finally, erythromycin, a macrolide antibiotic that mimics the effects of motilin, which stimulates smooth muscle in the gastrointestinal tract, is the only other prokinetic agent that has been evaluated in critically ill patients. In ten stable, mechanically ventilated patients, 200 mg of erythromycin was administered in a randomized, cross-over design. As measured by acetaminophen absorption and antral manometry, erythromycin was shown to improve gastric motility [11].

In conclusion, our study documents and our discussion highlights the important relationship between gastrointestinal motility and critical illness. Strategies to minimize the use of opioids in critically ill patients may improve gastric emptying. To date, there are promising results of studies evaluating the effect of motility agents on physiologic endpoints in critically ill patients. Further research evaluating the effect of motility agents on clinically important endpoints is warranted.

References

1. Hart CA (1989) Defence against colonization and infection. In: Van Saene HKF, Stoutenbeek CP, Ledingham IMcA(eds) Update in intensive care and emergency medicine – Infection control by selective decontamination. Springer, Germany pp 13–21.
2. King CE, Toskes PP (1979) Small intestine overgrowth. Gastroenterology 76: 1035–1055
3. Heyland DK, Mandell LA (1992) Gastric colonization and nosocomial pneumonia: evidence for causation. Chest 101: 187–193
4. Fink MP (1991) Gastrointestinal mucosal injury in experimental models of shock, trauma and sepsis. Crit Care Med 19: 627–641
5. Heyland D, Winder B, Cook DJ, Brylowski L, Guyatt G (1995) Enteral nutrition in the critically ill patient: a prospective survey. Crit Care Med 23: 1055–1060
6. Heyland DK, Cook DJ, Winder B, Guyatt GH (1996) How well do critically ill patients tolerate early, intragastric enteral nutrition. Clin Intensive Care 7: 68–73
7. Harasawa A, Tani N, Suzuki S, Miwa M, Sakita R, Nomiyama T, Miva T (1979) Gastric emptying in normal subjects and in patients with peptic ulcer. A study using the acetaminophen method. Gastroenterol Jpn 14: 1–5
8. Imbimbo BP, Gardino L, Palmas F, Frascio M, Canepa G, Scarpignato C (1990) Different effects of atropine and cimetropium bromide on gastric emptying of liquids and antroduodenal motor activity in man. Hepatogastroenterology 37: 242–246
9. Power I, Easton JC, Todd JG, Nimmo WS (1989) Gastric emptying after head injury. Anaesthesia 44: 563–566
10. Hu OY, Ho ST, Wang JJ et al. (1993) Evaluation of gastric emptying in severe, burn-injured patients. Crit Care Med 21: 527–531
11. Dive A, Galanti L, Jamart J, Evrard P, Gonzalez M, Installe E (1995) Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients: a double-blind, randomized, placebo-controlled study. Crit Care Med 23:1356–1362
12. McArthur CJ, Gin T, McLaren IM, Critchley JAJH, Oh TE (1995) Gastric emptying following brain injury: effects of choice of sedation and intracranial pressure. Intensive Care Med 21: 573–576
13. Clements JA, Heading RC, Nimmo WS, Prescott LF (1978) Kinetics of acetaminophen absorption and gastric emptying in man. Clin Pharmacol Ther 24: 420–431
14. Heading RC, Nimmo J, Prescott LF, Tothill P (1973) The dependence of paracetamol absorption on the rate of gastric emptying. Br J Clin Pharmacol 47: 415–421
15. Petring OU, Flachs H (1990) Inter- and intra-subject variability of gastric emptying in healthy volunteers measured by scintigraphy and paracetamol absorption. Br J Clin Pharmacol 29: 703–708
16. Rowbotham DJ, Parnacott S, Nimmo WS (1992) No effect of cisapride on paracetamol absorption after oral simultaneous administration. Eur J Clin Pharm 42: 235–236
17. Chatfield C (1988) Problem solving: a statistician's guide. Chapman and Hall, London
18. Draper NR, Smith H (1981) Applied regression analysis. Wiley, New York, pp 305–307
19. Nimmo WS, Heading RC, Wilson J, Tothill P, Prescott LF (1975) Inhibition of gastric emptying and drug absorption by narcotic analgesics. Br J Clin Pharmacol 2: 509–513
20. Dive A, Moulart M, Jonard P, Jamart J, Mahieu P (1994) Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study. Crit Care Med 22: 441–447
21. Heyland DK, Cook DJ, Guyatt GH (1993) Enteral nutrition: A critical appraisal of the evidence. Intensive Care Med 19: 435–442
22. Ott L, Young B, Phillips R, McClain C, Adams L, Dempsey R, Tibbs P, Ryo UY (1991) Altered gastric emptying in the head-injured patient: relationship to feeding intolerance. J Neurosurg 74: 738–742
23. Atherton ST, White DJ (1978) Stomach as source of bacteria colonising respiratory tract during artificial respiration. Lancet 2: 968–969
24. Tryba M (1991) The gastropulmonary route of infection: fact or fiction. Am J Med 91 (Suppl 2A): 135S–146S
25. Daschner F, Kappstein I, Engels I, Reuschenbach K, Pfisterer J, Kreig N, et al. (1988) Stress ulcer prophylaxis and ventilation pneumonia: prevention by antibacterial cytoprotective agents. Infect Control Hosp Epidemiol 9: 59–65

26. Du Moulin GC, Hedley-Whyte J, Paterson DJ, Lisbon A (1982) Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonization of the airway. Lancet 1: 242–245
27. Goularte TA, Lichtenberg DA, Craven DE (1986) Gastric colonization in patients receiving antacids and mechanical ventilation: a mechanism for pharyngeal colonization. Am J Infect Control 14: 88
28. Schwartz SN, Dowling JN, Denkovic C, DeQuittner-Buchanan M, Prostko T, Yee R (1978) Sources of gram-negative bacilli colonizing the trachea of intubated patients. J Infect Dis 138: 227–231
29. Inglis TJJ, Sproat LJ, Sherratt MJ, Hawkey PM, Gibson JS, Shah MV (1992) Gastroduodenal dysfunction as a cause of gastric bacterial overgrowth in patients undergoing mechanical ventilation of the lungs. Br J Anaesth 68: 499–502
30. Inglis TAJ, Sherratt MJ, Sproat LJ, Gibson JS, Hawkey PM (1993) Gastroduodenal dysfunction and bacterial colonization of the ventilated lung. Lancet 341: 911–913
31. Ibanez J, Penafiel A, Rauriach JM, Marse P, Jorda R, Mata F (1992) Gastroesophageal reflux in intubated patients receiving enteral nutrition: effect of supine and semirecumbent positions. JPEN 16: 419–422
32. Torres A, Serr-Batlles J, Ros E, Piera C, Puig de la Bellacasa J, Cobos A, Lomena F, Rodriguez-Roisin R (1992) Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med 116: 540–543.
33. Orozco-Levi M, Torres A, Ferrer M, Peira C, El-Ebiary M, Puig de la Bellacasa J, Rodrigeuez-Roisin R (1995) Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am J Respir Crit Care Med 152: 1387–1390
34. Bion JF, Ledingham ImcA (1987) Sedation in intensive care- a postal survey. Intensive Care Med 13: 215–216.
35. Dasta JF, Fuhrman TM, McCandles C (1994) Patterns of prescribing and administering drugs for agitation and pain in patients in a surgical intensive care unit. Crit Care Med 22: 974–980
36. Spapen H, Duinslaeger L, Diltoer M, Gillet R, Bossuyt A, Huyghens (1995) Gastric emptying in critically ill intensive-care patients is accelerated by adding cisapride to a standard enteral feeding protocol. Crit Care Med 23: 481–485
37. Heyland DK, Tougas G, Cook DJ, Guyatt GH (1996) The effect of cisapride on gastric emptying in critically ill patients (Abstract) Am J Respir Crit Care Med 153: A832