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Fabienne Tamion
Karine Hamelin
Annie Duflo
Christophe Girault
Jean-Christophe Richard
Guy Bonmarchand

Gastric emptying in mechanically ventilated critically ill patients: effect of neuromuscular blocking agent

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F. Tamion (✉) · K. Hamelin · C. Girault
J.-C. Richard · G. Bonmarchand
Medical Intensive Care Unit,
Hospital Charles Nicolle,
Rouen University,1 rue de Germont,
76031 Rouen, France
e-mail: fabienne.tamion@chu-rouen.fr
Tel.: +33-2-32888261
Fax: +33-2-32888214

A. Duflo
Department of Biochemistry,
Hospital Charles Nicolle,
Rouen University,1 rue de Germont,
76031 Rouen, France

Abstract *Objective:* To assess gastrointestinal function in critically ill patients receiving muscle relaxant and to test clinical tolerance to enteral nutrition. *Design and setting:* Prospective study in an intensive care unit. *Patients:* 20 critically ill patients requiring sedation with muscle relaxant to obtain adequate mechanical ventilation. *Measurements and results:* Patients were randomly selected to receive infusions of opioid sedation during the first session (session 1) and the same sedation with muscle relaxation (cisatracurium) during the second session (session 2). Gastric emptying was assessed by the paracetamol absorption technique. Following the paracetamol absorption 200 ml enteral feed was given, and the residual gastric volume was measured 1 and 2 h after feeding. The maximum plasma concentration (Cmax) was 14 mg/l (range 5–26) when patients received sedation, and 12 mg/l (range 5–30) when they received muscle relaxant. The target time for reaching the maximum plasma concentration (Tmax) was 30 min (range 20–60) and 35 min (range 20–60), respectively, in sessions 1 and 2. There was no significant difference between the two session as regards Tmax, Cmax, or AUC_{0-120}. The residual volumes were 110±65 ml (H1) and 95±76 ml (H2) during session 1 and 125±85 ml (H1) and 105±90 ml (H2) during session 2. *Conclusions:* Enteral feeding is one of the most effective methods of supporting nutritional needs in the critically ill patient. We conclude that in critically ill patients requiring sedation gastric emptying is not improved by neuromuscular blocking agent.

Keywords Gastric emptying · Paracetamol test · Neuromuscular blocking agent · Sedation · Enteral feeding · Critically ill patients

Introduction

Adequate nutritional status in critically ill patients is associated with lower morbidity and mortality [1, 2]. Nutritional support must be an established part of care in critically ill patient with enteral nutrition as a priority [3]. Enteral feeding offers advantages over parental nutrition and is the preferred route particularly when there is a functioning gastrointestinal tract [4, 5, 6]. Complete bypass of the gut leads to adverse structural and functional modifications of the mucosal barrier [5, 7, 8, 9]. The benefit of enteral nutrition is based on factors such as the stimulation of epithelial cell metabolism by direct contact with nutrients, an increase in mucosal blood flow, and an increase in immunoglobulin and enterotrophic gastrointestinal secretion [10, 11, 12]. Preventing mucosal atrophy is certainly an important goal in critically ill patients. The associated increase in gut permeability can induce bacterial translocation from the gut lumen into the circulation, as reported in some animals studies [13]. In humans the advantages of enteral nutrition is the decrease in septic complications, multiple-or-

Table 1 Demographic data for patients (*ARDS* adult respiratory distress syndrome)

Patient no.	Age (years)	Sex	SAPS II	Clinical diagnosis	Final outcome
1	70	M	58	ARDS, sepsis	Nonsurvivor
2	65	M	62	ARDS, sepsis	Nonsurvivor
3	29	M	60	ARDS, sepsis	Survivor
4	64	M	53	Pneumonia	Survivor
5	39	M	61	ARDS, sepsis	Survivor
6	74	M	59	Pneumonia	Survivor
7	75	F	50	Pneumonia	Survivor
8	45	M	55	ARDS, sepsis	Nonsurvivor
9	44	F	60	ARDS, sepsis	Nonsurvivor
10	40	F	48	Bronchospasm	Survivor
11	48	M	55	ARDS, sepsis	Survivor
12	52	F	54	ARDS, sepsis	Nonsurvivor
13	64	M	45	Idiopathic lung fibrosis	Nonsurvivor
14	53	F	51	Bronchospasm	Survivor
15	48	F	52	ARDS, sepsis	Survivor
16	72	F	55	Pneumonia	Survivor
17	68	M	48	ARDS, sepsis	Survivor
18	71	F	51	ARDS, sepsis	Nonsurvivor
19	58	M	61	Idiopathic lung fibrosis	Nonsurvivor
20	61	M	60	Pneumonia	Survivor

gan failure, and length of hospital stay compared with parenteral nutrition [2, 14]. However, impaired gastric emptying is a common cause of intolerance to enteral feeding [15]. Several mechanisms can alter the gastrointestinal function in critically ill patients [16]. Slow gastric emptying may be caused by failure of systemic hemodynamics, artificial ventilation, and drugs such as narcotics or catecolamines [17]. Opioids which are frequently used for the sedation of critically ill patients reduce the rate of the gastric emptying [18, 19]. Slow gastric emptying has been reported under continuous opioid treatment with neuromuscular blocking agents [20]. The effect of neuromuscular blocking agents on gastric emptying in critically ill patient remains unclear. Also, patients with neuromuscular blocking frequently receive parenteral nutrition because of a preconception that they would not tolerate enteral feedings.

The aim of the study was to compare gastric emptying in critically ill patients under sedation or under sedation plus neuromuscular blocking agent and to assess the short-term effects on gastric emptying.

Materials and methods

Patient selection

Adult intensive care patients were enrolled if they required sedation and a neuromuscular blocking agent. Exclusion criteria were: a history of gastrointestinal disease, the use of drugs known to interfere with gastrointestinal motility (metoclopramide, cisapride, erythromycin), and preexisting hepatic failure as assessed by presence of bleeding disorders. Twenty mechanically ventilated patients with a were studied (12 men, 8 women; mean age 57±13 years). All patients had acute renal failure (creatinine levels: 184±125 mmol/l). The majority presented with septic shock and adult respiratory distress syndrome (ARDS); other underlying diseases included respiratory failure with severe bronchospasm or idiopathic fibrosis. All patients were ventilated in pressure-controlled mode. Their hemodynamics were stable with vasopressor support. On admission the mean Simplified Acute Physiology Score II (SAPS II) was 54.9±9. The patients' main characteristics (age, sex, SAPS II, diagnosis, outcome) are presented in Table 1 and their hemodynamic and inotropic therapy in Table 2. All patients received vasopressor support, which improved their mean arterial pressure (mean 72±5 mmHg). The study was approved by the Clinical Research Ethics Committee of our hospital. Formal consent was obtained from the patients' relatives.

Table 2 Characteristics of patients in session 1 (fentanyl, midazolam) and session 2 (fentanyl, midazolam plus cisatracurium)

	Session 1	Session 2
Mean arterial pressure (mmHg)	72±5	80±7
Creatinine Level (mmol/l)	204±125	198±123
PaO_2/FIO_2 (torr)	102±48	105±50
Blood sugar level (mmol/l)	12±1.2	14±1.3
Patients on inotropes (*n*)		
Dopamine	3	3
Dobutamine and norepinephrine combined	5	5
Epinephrine	8	8

Groups of patients

Each patient participated in both study sessions (Fig. 1). The effects of opiate sedation (fentanyl/midazolam) on gastric emptying were compared with those of the same sedation associated with a neuromuscular blocking agent (cisatracurium). After enrollment each patient was allocated first to receive opiate sedation (session 1) and in a second stage the same sedation as well as cisatracurium (session 2). Intravenous opiate sedation with fentanyl (1–5 μg/kg per hour) and midazolam (2–10 mg/h) were administered in doses sufficient to produce optimal Ramsay sedation scores [21]. Intravenous mus-

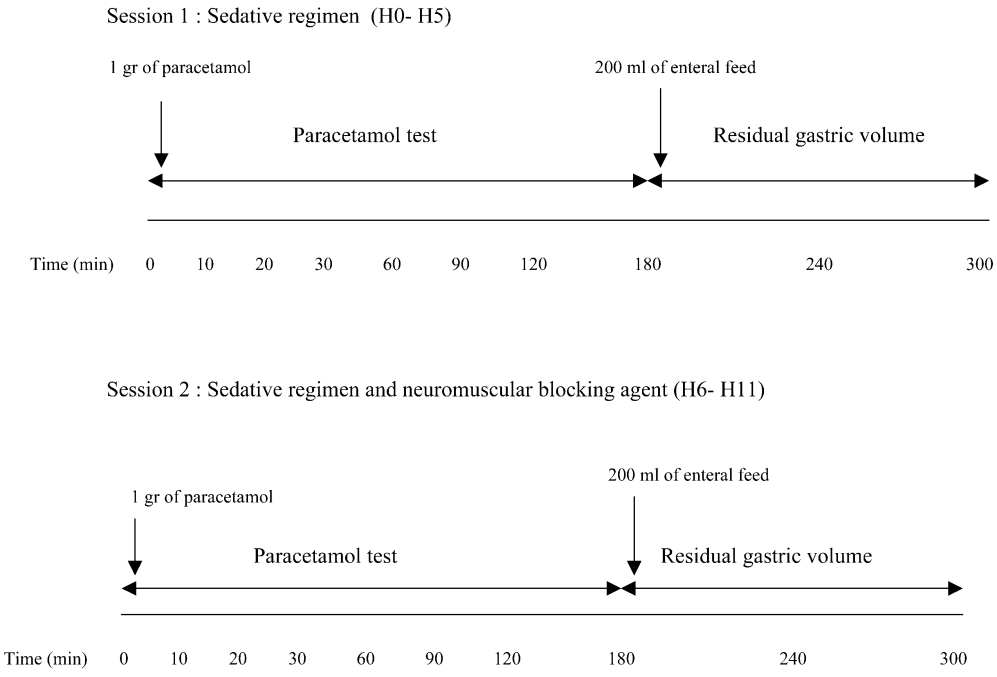

Fig. 1 Study design

cle relaxation with cisatracurium (0.2 mg/kg per hour) was administered in doses sufficient to produce two or four twitches via peripheral nerve stimulator to obtain adequate mechanical ventilation [21]. Vasopressor agent dose was the same in each sessions.

Nutritional management

No patient was fed enterally during the investigation period as an empty stomach is a prerequisite for the assessment of gastric emptying. Parenteral nutritional support was required during the study. Daily optimal energy intakes were set at 25 kcal/kg.

Pharmacokinetic protocol

After a stabilization hemodynamic period of at least 12 h gastric emptying was assessed by the paracetamol technique [22]. During this period no patient was fed enterally, and parenteral nutrition support was required. No patient received parenteral or enteral nutrition prior to the study. A 16-G gastric tube was inserted in each patient with its correct position confirmed clinically and radiographically. The stomach was emptied by aspiration, 1000 mg powered paracetamol with 10 ml water was given and followed by 20 ml water. Blood samples were taken at paracetamol administration and after 10, 20, 30, 60, 90, 120, and 180 min. The study was conducted in a fasting state during two sessions in each patient. The amount of time between the first and second sessions was 6 h. Following the final blood sample 200 ml enteral feed (Isocal, Sondalis, Nestlé, France) was given over 15 min. A rate of 800 ml/h is much faster than is usually used in practice with critically ill patients. This was a necessary feature only of the present study. The residual gastric volume was aspirated and measured 1 and 2 h after feeding.

Analytical procedures

Blood was immediately separated and the plasma was stored at –20°C until analysis. Paracetamol concentration was measured with immunoenzyme assay (Cobas Mira, Dade Behring, Paris, France).

Calculations

Peak paracetamol levels (Cmax) and the time to reach the peak concentration (Tmax) were recorded, and the area under the paracetamol serum concentration-time curve (AUC) was calculated at 60 min and 120 min by the trapezoidal method.

Statistical analysis

Results are presented as means ±SD. Patient details were compared by one-way analysis of variance. Concentration of paracetamol, the time of peak concentration, the peak concentration of paracetamol and the residual volumes that were repeated over time were compared by two-way analysis of variance. Statistical significance was considered as $p<0.05$.

Results

Pharmacokinetic study

The paracetamol kinetics is illustrated in Fig. 2. The shape of the mean concentration-time curve was similar in two sessions and concentrations of paracetamol did not differ significantly at any point (Fig. 2). Cmax was 6.5±3.8 mg/l when patients received fentanyl/midazolam (session 1) and 7.7±3.2 mg/l when they received sedation plus neuromuscular blocking agent (session 2). Tmax was 102±75 min in session 1 and 98±67 min in session 2. The mean $AUC_{0–120}$ did not change significantly between the two sessions. There was no significant difference in the time parameters for reaching the maximum plasma concentration, the peak paracetamol levels, or $AUC_{0–120}$ (Table 3). Also, patient characteris-

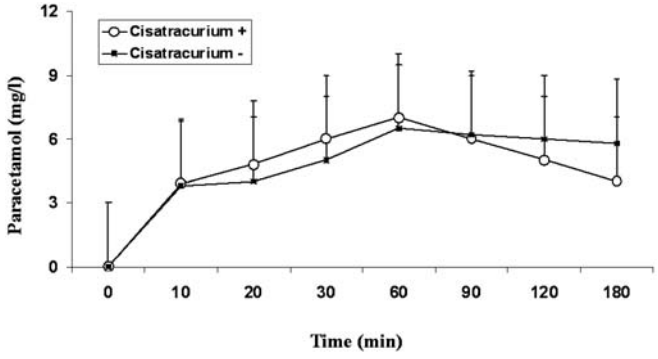

Fig. 2 Plasma paracetamol concentration after a 1-g gastric dose in patients sedated with fentanyl and midazolam (*filled squares*) and in patients sedated with fentanyl, midazolam, and cisatracurium (*open circles*). *Session 1* Sedative regimen (H0–H5); *session 2* sedative regimen and neuromuscular blocking agent (H6–H11)

Table 3 Pharmacokinetic data: Cmax, Tmax, AUC and residual volume in session 1 (fentanyl, midazolam) and session 2 (fentanyl, midazolam plus cisatracurium) Values in mean±SD (*Cmax* maximum concentration of paracetamol, *Tmax* time of maximum concentration of paracetamol, *AUC* area under the curve at 60 and 120 min)

	Session 1	Session 2
Cmax (mg/l)	6.5±3.8	7.7±3.2
Tmax (min)	102±75	98±67
AUC_{0-60} (mg min^{-1} l^{-1})	82±42	88±46
AUC_{0-120} (mg min^{-1} l^{-1})	360±262	355±256
Residual volume 1 h (ml)	110±65	125±85
Residual volume 2 h (ml)	95±76	105±90

tics did not differ significantly between the two sessions.

Nutrition

In the majority of cases enteral feeding was held for residual volumes exceeding 200 ml. The residual volumes were 110±65 ml at 1 h and 95±76 ml at 2 h in patients during session 1. The residual volumes were 125±85 ml at 1 h and 105±90 ml at 2 h in patients during session 2. Mean gastric residue did not differ in patients between the two sessions (Table 3).

Discussion

The most important finding of this study is that gut absorption capacity is maintained when neuromuscular blocking agent is administered in sedated critically ill patients. This suggests that the mechanisms required for enteral absorption are maintained despite using neuromuscular blocking agent.

The aim of the study was to test short-term intestinal absorption in patients with or without neuromuscular blocking agent. Several methods have been used to study gastric emptying, for example, radiolabeled substances, radiopaque materials, and drug absorption kinetics. Scintigraphy is considered the gold standard, but its use is often difficult in the intensive care unit. Derived values from the paracetamol concentration-time graph have been shown to be well correlated with the scintigraphic method for assessing gastric emptying. This test is a simple semiquantitative method for measuring gastric emptying and intestinal absorption, based on paracetamol pharmacological characteristics to be absorbed rapidly from the small bowel and not from the stomach [23]. The area under the paracetamol serum concentration curve is determined by the rate of gastric emptying and by the absorption capacity of the small intestine. It has been used in critically ill patients to assess intestinal function and pylorus opening. The residual volume is a common clinical method for assessing the success of enteral feeding. However, this test has not yet been validated [24].

Progress in intensive care has lead to longer survival in patients with protracted catabolic disease such as sepsis and multiple-organ dysfunction [25]. Therefore one often finds severe malnutrition in these patients, which slows recovery and lengthens hospital stay [26]. This situation demonstrates the major role of optimal nutritional support [27, 28, 29]. It is becoming increasingly clear that the consequences of enteral nutrition go beyond the supply of energy and proteins to the body [29, 30, 31]. However, impaired tolerance to gastric feeding is common in critically ill patients as a result of slow gastric emptying [32]. Gastric dysfunction has been associated with the occurrence of high gastric aspirate vomiting and abdominal distention [15]. For our pharmacokinetic study we chose a sequential cross instead of randomization of patients to crossover. No significant difference in plasma paracetamol concentrations with or without administration of neuromuscular blocking agent was observed. Nevertheless, it is possible that this experiment was too limited to demonstrate a difference. However, the plasma paracetamol concentrations and the mean AUC_{0-120} were lower than those in healthy subjects in a previous study [33].

All patients required intensive hemodynamic support. Berger et al. [34] have demonstrated that the plasma paracetamol concentration is independent of the changes in hemodynamics in cardiac surgery patients. It is well known that gastric emptying may be impaired in critically ill patients owing to the effect of medications, electrolyte abnormalities, hyperglycemia, or sepsis, all of which may be manifested clinically as a high residual volume. Opiates and artificial ventilation play a major role to reduce the rate of gastric emptying. Opioids and hyperglycemia inhibit gastric phase 3 motor activity and decrease the occurrence of antral contractions [20]. In healthy

subjects paracetamol peak absorption may be delayed up to 120 min by the simultaneous administration of opiates. The paracetamol absorption test is used for gastric emptying measurement. The concentration of paracetamol in serum also reflects several factors unrelated to emptying, such as first-pass metabolism, distribution in the body fluids, and elimination. Also, the pharmacokinetics of paracetamol vary between and within individuals. Paracetamol kinetics may be affected by changes in volume distribution or elimination because of renal or hepatic failure. Hepatic failure was an exclusion criteria, and we observed no instance of liver failure during the study; therefore it is impossible for this to be a cause of altered paracetamol metabolism. Acute renal failure was observed in all of our patients. Finally, opioids, artificial ventilation and acute renal failure could have modified paracetamol kinetics. No severe hyperglycemia capable of decreasing the occurrence of antral contractions was observed in our patients.

The second aim of our study was to evaluate the safety of enteral nutrition under sedation using neuromuscular blocking agent. Effective enteral nutritional support has been provided safely to patients undergoing highly invasive procedures such as extracorporeal respiratory assist and continuously anesthetized [35]. A quantity of 200 ml is considered the minimum residual volume that would have permitted continued feeding in normal volunteers [36]. Elevated residual volumes may be a valuable but somewhat imprecise monitor for gastric emptying and risk aspiration. Therefore 200 ml is a more reasonable quantity to use rather than lower values. Elevated residual volumes were a frequent cause of cessation of enteral feeding; limited objective data support the use of residual volumes to monitor enteral feedings. In our study only two patients received neuromuscular blocking agent, showing excessive residual volumes. These two patients presented with severe acute renal failure. Also they received hemodynamic management with inotropic drugs, but their arterial pressure was not correct. After cardiac surgery under compromised hemodynamic conditions intestinal paracetamol absorption was constantly maintained with postpyloric administration and hypocaloric enteral nutrition [1].

Enteral feeding is one of the most effective methods of supporting nutritional needs, immune function, and gastrointestinal needs in the critically ill patient. From the results of our study we conclude that in critically ill patients requiring sedation gastric emptying is not improved by neuromuscular blocking agent. Also, it was neither improved nor worsened. Similar to many reports, we observed impaired gastric emptying in critically ill patients. Also, identification of these patients may require more careful attention and more aggressive measures (prokinetics, postpyloric feeding) to maximize the delivery of enteral feeding in the critical care setting.

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