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Target-controlled infusion of propofol for sedation in patients with non-invasive ventilation failure due to low tolerance: a preliminary study

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Abstract *Purpose:* Non-invasive ventilation (NIV) in critically ill patients is associated with a high failure rate. This prospective study assessed the feasibility and safety of target-controlled infusion (TCI) of propofol for conscious sedation during NIV in patients with NIV failure due to low tolerance. *Methods:* Ten patients with NIV failure due to discomfort, agitation and/or refusal to continue with this ventilatory support were included; seven had acute respiratory failure and three had acute hypercapnic respiratory failure. Patients were sedated by TCI of propofol during NIV sessions. Blood gas analysis, cardiorespiratory and ventilatory parameters, propofol concentration (Cpt) required, comfort and adverse events were recorded. *Results:* Patients received a total of 85 NIV sessions, totalling 180 h of NIV under TCI of propofol (mean Cpt, 0.82 ± 0.25 μg/ml). NIV under TCI of propofol significantly improved arterial blood gas analyses: mean Pa/FiO_2 ratio increased from 167 ± 68 pre-session to 195 ± 68 post-session ($p < 0.05$), mean $PaCO_2$ decreased from 57.8 ± 15.3 to 49 ± 9.8 mmHg ($p < 0.05$) and mean pH increased from 7.36 ± 0.04 to 7.4 ± 0.03 ($p < 0.05$). Three patients required endotracheal intubation, two due to evolution of underlying disease and one because of a seizure disorder. Eight patients were discharged from the intensive care unit and two died. *Conclusions:* This preliminary study shows that in a selected population, TCI of propofol can facilitate acceptance of NIV. Within the limits of a pilot study, TCI of propofol seems to be safe and effective for the treatment of NIV failure due to low tolerance.

Keywords Non-invasive ventilation · Target-controlled infusion · Propofol · Sedation · Acute respiratory failure

Introduction

The ability of non-invasive ventilation (NIV) to reduce intubation and mortality has been clearly established in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) [1] and cardiogenic pulmonary oedema (CPE) [2, 3]. Randomised controlled trials in patients with acute de novo respiratory failure (ARF) show reduced mortality with NIV in highly selected populations such as patients with immunosuppression [4].

Despite the advantages of NIV in critically ill patients, this procedure is associated with a large number of failures, including patient refusal to continue uncomfortable sessions [5]. Antonelli et al. [6] showed that mask intolerance or inadequate patient co-operation led to intubation in 9% of patients with ARF. In another study

[7], Delclaux found up to 14% of patients in ARF were unable to tolerate face-mask ventilation. Carlucci and co-workers reported that when NIV was discontinued early (i.e. while the physician wished to continue it) the reason for discontinuation was the patients' refusal to continue in 22% [8]. In this situation, the traditional option is to stop NIV and intubate the patients.

Some authors have reported the use of sedative agents to achieve adequate compliance with NIV. In a preliminary study [9], Constantin et al. showed that remifentanil-based sedation during NIV is effective and safe in selected patients with NIV failure. In another study, Akada et al. [10] investigated the effect of dexmetomidine in 10 patients in whom NIV was difficult because of agitation. Like in Constantin's study [9], Akada et al. used a continuous intravenous weight-adjusted infusion. To avoid an accumulation phenomenon, we preferred target-controlled infusion (TCI) of propofol.

TCI is a modern way of administering anaesthetics based on a pharmacokinetic protocol assisted by a computerised mathematical calculation of drug concentration. The 'diprifusor' TCI system (Diprifusor® Fresenius Vial; Brezins, France) [11] has been developed as a standardised infusion system for the administration of propofol by TCI and is now widely used in clinical practice [12]. TCI allows rapid and precise adjustment of the propofol concentration according to the clinical response of the patient. Physiological studies on the effects of sub-hypnotic concentrations of propofol on respiratory mechanics, pharyngeal function and airway protection have suggested the possibility of carrying out NIV while patients are under sedation [13–15].

The purpose of this study was to assess, for the first time, the feasibility and safety of TCI of propofol for conscious sedation during NIV in critically ill patients with NIV failure due to low tolerance, with the aim of avoiding endotracheal intubation (ETI).

Methods

The experimental protocol was approved by our institutional review board for human subjects. Written informed consent was obtained from each study participant or their next of kin.

Patient selection

The study cohort consisted of 10 adult patients with acute respiratory failure under NIV.

Inclusion criteria included: NIV failure due to patient refusal to continue NIV sessions because of discomfort, claustrophobia or marked agitation. Exclusion criteria are detailed in the electronic supplementary material (ESM).

Study design

Non-invasive ventilation settings are detailed in the ESM.

Propofol infusion

During NIV sessions, propofol was infused through a dedicated catheter. The observer's assessment of alertness and sedation (OAA/S) scale [16] was used to subjectively assess the level of sedation observed by the physician (Table 1).

Table 1 Patients' clinical characteristics

Patient no.	Age (years)	Sex	Cause of ICU admission	SAPS	NIV indication	BMI (kg/m^2)	Clearance of creatinine[a] (ml/min)	Outcome
1	72	F	Pneumonia	33	AHRF	21	81	Alive
2	76	M	Pneumonia	36	AHRF	19	75	Alive
3	30	M	Pneumonia	51	ARF	27	114	Alive
4	80	M	Convulsive status epilepticus	65	AHRF post extubation	18	96	Alive
5	62	M	COPD exacerbation	34	AHRF	24	115	Alive
6	48	M	Pneumonia/sarcoidosis	27	ARF	22	102	Alive
7	68	M	Pneumonia	33	ARF	24	112	Dead
8	45	M	Pneumocystis pneumonia	32	AHRF	18	110	Alive
9	35	M	Pneumonia/immunodeficiency diseases	25	AHRF	20	95	Alive
10	33	F	Pneumonia	42	ARF	25	130	Dead
Mean (±SD)	55 (±18)	–	–	37 (±11)	–	22 (± 3)	103 (± 16.8)	–

SAPS simplified acute physiology score, *ARF* acute hypoxemic respiratory failure, *AHRF* acute hypercapnic respiratory failure, *BMI* body mass index

[a] At baseline, calculated by Cockcroft and Gault's method

Score	Responsiveness	Speech	Facial expression	Eyes
5	Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis
4	Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half of the eye)
3	Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half of the eye or more)
2	Responds only after mild prodding or shaking	Few recognizable words	-	-
1	Does not respond to mild prodding or shaking	-	-	-

Fig. 1 The observer's assessment of alertness/sedation scale. *Responsiveness* indicates responsiveness to calling the patient's name and/or using physical stimuli; *speech*, while asking the patient to repeat a standard sentence; *facial expression*, degree of facial relaxation; and *eyes*, ability of subject to focus eyes and ptosis [16]

For the first NIV session, the target effect-site concentration of propofol (Cpt) was initially set at 0.4 μg/ml. The Cpt was increased in increments of 0.2 μg/ml until the sedation goal was achieved. The objective was to obtain an OAA/S level of 4 or 3 (response to verbal stimulation). Once the desired level of sedation was obtained, the Cpt necessary was used as a basis for the following NIV session (Fig. 1).

At the end of the NIV session, sedation was interrupted and at recovery (opening eyes and shaking hand to verbal command) patients were removed from the ventilator.

The protocol excluded use of sedative or analgesic drugs.

Data collection

Severity of illness was assessed by the simplified acute physiology score (SAPS II) [17].

All patients had an arterial catheter. Blood gas analysis was performed before and at the end of each NIV session, or every second hour if the NIV session lasted longer. Because of the limits of the pharmacokinetic model, the duration of the NIV session could not exceed 6 h.

The nurses in charge of the patients were asked to systematically report the duration of each NIV session and the duration of nursing and medical care required for each ventilation session. Patients evaluated their comfort themselves after each NIV sessions (excellent, good, satisfactory, medium, or uncomfortable).

Adverse events, including time of over-sedation (defined as time beyond the target level of sedation), haemodynamic instability, hypoxemia, vomiting and air leakage were recorded. The level of sedation was estimated every 10 min by nurses.

Patients in whom NIV was not successful underwent endotracheal intubation (ETI) and received mechanical ventilation. The predetermined criteria for ETI are detailed in the ESM. The primary outcome variable was the need for ETI and mechanical ventilation at any time during the study. Secondary outcome variables included the development of complications.

Statistical analysis

Statistical analysis is detailed in the ESM.

Results

The study cohort consisted of 10 adult patients with ARF under NIV (mean age, 55 ± 18 years; two women and eight men). The characteristics of the patients, reasons for admission to the ICU and NIV indications are shown in Table 2. Seven patients, including five who were immunocompromised, presented with hypoxemic ARF, and three had acute exacerbation of COPD with marked agitation caused by hypercapnia.

The patients received a total of 85 NIV sessions with a mean duration of 2 h (128 ± 88 min) for a total of 180 h. The mean number of sessions/patient was 9 (range, 3–20).

Loss of consciousness was obtained with a mean calculated propofol concentration of 0.82 μg/ml (±0.25). Comfort was evaluated as "good" or "excellent" by all of the patients. At this low hypnotic concentration, no significant heart rate, heart rhythm or arterial blood pressure changes were observed. No modification of ventilator settings was required for clinical reasons and no increase in air leak was recorded. The medical consumption time was 3.9% of the ventilatory time, mainly during the first NIV session.

Some patients presented episodes of over-sedation, but 98.9% of the total infusion time was passed at the desired level of sedation. Recovery was prompt in all patients. For one patient (patient 4) during the first NIV session, SpO_2 decreased from 96 to 84% suggesting respiratory depression and some degree of airway obstruction. Effect-site concentration was reduced immediately, allowing respiratory parameters to normalise within 2 min. This

Table 2 Ventilator settings

Patient no.	pH[a]	$PaCO_2$[a] (mmHg)	NIV setting[b] (cmH_2O) IPAP/EPAP	PaO_2/FiO_2[a]	Intubation (during study)
1	7.31	64	14/6	190	No
2	7.22	72.4	14/6	162	No
3	7.44	48.3	10/6	122	Yes
4	7.32	50.4	14/6	87	Yes For seizure
5	7.35	48.3	14/6	97	No
6	7.37	53.5	12/6	58	No
7	7.39	39.75	12/6	128	No
8	7.29	76.5	16/6	260	No
9	7.23	63.3	16/6	256	No
10	7.31	46.3	10/6	86	Yes
Mean (±SD)	7.32 (±0.06)	57.8 (±15.3)	–	144 (±67)	–

IPAP inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure
[a] Before the first session of NIV
[b] Mean of values at the end of all sessions

patient was an elderly man who had been premedicated with lorazepam for agitation before admission to the ICU. No apnoea or significant desaturation during NIV session was observed for any of the other patients. No patient presented signs of aspiration pneumonia during follow-up in the ICU. No other side-effect, directly or indirectly related to propofol, was reported.

Three patients required ETI during the study: two due to evolution of the underlying disease with inability to maintain a PaO_2/FiO_2 ratio >80 and one because of a seizure disorder. Eight patients were discharged from the ICU and two patients died (one due to refractory hypoxemia and one due to therapeutic limitations).

NIV under TCI of propofol significantly improved arterial blood gas analyses: mean Pa/FiO_2 ratio increased from 167 ± 68 pre-session to 195 ± 68 at the end of the sessions ($p < 0.05$), mean $PaCO_2$ decreased from 57.8 ± 15.3 to 49 ± 9.8 mmHg ($p < 0.05$) and mean pH increased from 7.36 ± 0.04 to 7.4 ± 0.03 ($p < 0.05$).

Discussion

Since the description of ARF and its treatment with NIV and sedation with morphine and midazolam by Rocker et al. [18], the conventional approach to ventilation has been to use ETI in cases of low tolerance. In a pilot study, Constantin et al. [9] reported the feasibility and safety of remifentanil-based sedation to treat NIV failure due to low tolerance. However, in that study, the required level of sedation was not achieved in three of the 13 patients with the maximum allowed dose of remifentanil. In order to avoid high doses of opioids, which decrease respiratory drive, Constantin et al. used a combination of propofol and remifentanil. However, despite all their efforts, $PaCO_2$ increased, probably because the use of opioids or hypnotics as a continuous intravenous weight-adjusted infusion resulted in an accumulation phenomenon. For this reason, we preferred to use TCI of propofol. In Akada's study [10], the NIV was used in postoperative respiratory failure or CPE as continuous positive airway pressure (CPAP) in a continuous way. As in our work, the PaO_2/FiO_2 ratio and the $PaCO_2$ improved and all patients were successfully weaned from NIV.

TCI is the computer-assisted intravenous administration of drugs. This improvement in the technique of intravenous drug administration has been made possible by the development of multicompartment models. The pharmacokinetic (PK) model, which describes the distribution and elimination of drugs given intravenously, is pre-programmed in the Diprifusor® (Gepts modified by Marsh). The TCI system uses information including gender and weight to predict the blood drug concentration associated with delivery of a given amount of the drug. From its pharmacokinetic model, the TCI system determines the initial loading dose needed to achieve the target concentration and the infusion rate needed to maintain it. TCI devices strictly control the drug concentration at the effect site and avoid accumulation phenomena that may delay patient recovery.

Possibly the most important advantages of TCI are prompt titration of a variable infusion regimen during the procedure and the avoidance of side-effects due to over- and under-dosage. The pharmacokinetic properties of propofol are characterised by a rapid onset and short duration of action. The rapid recovery of patients after stopping propofol infusion makes it an attractive option, particularly in this kind of short procedure. Moreover, propofol also has amnesic properties.

The covariates of this PK model used in Diprifusor are weight and gender without consideration of age. The

Marsh's model is very effective in patients with normal BMI, without co-morbidities and young patients. As a matter of fact, other models such as Schnider's should fit the ICU environment better [19]. Adopting new pharmacokinetic models could be a way to increase the safety of this technique in intensive care units.

The very low concentration used (0.82 ± 0.25 μg/ml) allows continued patient co-operation and does not compromise spontaneous respiration, even in high-risk patients. Moreover, TCI propofol-based sedation does not increase $PaCO_2$.

Physiological studies [15, 20] show that propofol causes a reduction in the ventilatory response to acute hypoxia. Sundman et al. [13] showed that sub-hypnotic concentrations of propofol alter pharyngeal function with a risk of impaired airway protection and aspiration. However, TCI is used routinely for perioperative sedation and many clinical studies validate its use in patients breathing spontaneously [21–27]. None of our patients presented any adverse effects such as vomiting, signs of aspiration pneumonia or gastric dilation. In one patient, SpO_2 decreased during the first NIV session, suggesting some degree of airway obstruction. However, no apnoea was observed and respiratory parameters normalised within 2 min after reduction of the Cpt.

Although the pharmacokinetic model used in the Diprifusor® does not take into account age, in our protocol the required level of sedation was quickly achieved, without major over-sedation. Furthermore, 98.8% of the total infusion time was passed at the desired level of sedation. The mean duration of NIV sessions under sedation was longer than the usual duration, reflecting good tolerance. The nursing time spent with the patient was appreciably reduced.

There are some limitations to the study. First, the Cpt necessary was variable for each patient. Thus, for the first session it was necessary to carry out a titration. Thereafter, however, TCI of propofol provided a constant level of sedation during the entire NIV session. Second, we selected patients in whom NIV had failed due to difficulties in application and not due to the severity of ARF. An important limitation of the study was the small number of patients, which may not have allowed us to detect all possible complications. However, it would appear that only a minority of failures of NIV could be related to difficulties in application of the technique, especially after having improved all the other variables. Finally, these results were obtained in an ICU where clinicians are experienced in routine NIV therapy and the use of TCI of propofol. Thus, within the constraints of a pilot study, this report describes that TCI of propofol can be an adjuvant way to help with NIV adherence in selected patients with NIV failure due to low tolerance. Indeed, all of the patients in our study would have required immediate ETI if this procedure had not been tried.

In conclusion, this is the first study to our knowledge to evaluate TCI of propofol during NIV. The results of this preliminary study show that this technique is effective and safe in selected patients with NIV failure due to low tolerance. Within the limits of pilot study, TCI of propofol during NIV reduces patient discomfort with no significant effects on respiratory function. TCI of propofol may facilitate acceptance of NIV. The use of TCI of propofol to treat NIV failure is an interesting alternative if a reduction in ETI is confirmed in controlled randomised trials.

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