Commentary

Remifentanil for analgesia-based sedation in the intensive care unit

Ralf Kuhlen[1] and Christian Putensen[2]

[1]Professor of Anesthesia and Intensive Care Medicine, Department of Anesthesia, University Hospital Aachen, Germany
[2]Professor of Anesthesia and Intensive Care Medicine, Department of Anesthesia and Intensive Care Medicine, University of Bonn, Germany

Correspondence: Ralf Kuhlen, rkuhlen@ukaachen.de

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Abstract

Providing effective analgesia and adequate sedation is a generally accepted goal of intensive care medicine. Due to its rapid, organ independent and predictable metabolism the short acting opioid remifentanil might be particularly useful for analgesia-based sedation in the intensive care unit (ICU). This hypothesis was tested by two studies in this issue of *Critical Care*. The study by Breen *et al*. shows that remifentanil does not exert prolonged clinical effects when continuously infused in renal failure patients, although the weak acting metabolite remifentanil acid accumulates. The study by Muellejans *et al*. reports a multicenter trial comparing a remifentanil versus a fentanyl based regimen in ICU patients. With both substances a target analgesia and sedation level was reached, and no major differences were found when frequent assessments of the sedation level and according readjustments of doses were performed. These results are in accordance with other studies suggesting that the adherence to a clear analgesia-based sedation protocol might be more important then the choice of medications itself.

Keywords analgesia, sedation, remifentanil, organ failure

Providing effective analgesia and adequate sedation is a generally accepted goal in the intensive care unit (ICU). Most critically ill patients – especially those who are mechanically ventilated – are treated with various analgesics and sedative drugs, which have primarily been investigated for their short-term use for anaesthesia during surgical interventions. Recent studies suggest that longer term administration of these drugs might be associated with significant risks and adverse effects. Therefore, we must learn that their use has to undergo a risk–benefit assessment as strict as is required for other treatments.

In this issue of *Critical Care* two investigations further promote our understanding of analgesics and sedatives in critically ill patients by investigating the use of remifentanil for analgesia-based sedation protocols in the ICU setting [1,2].

Breen and colleagues [2] investigated the clinical effects of continuous remifentanil infusion for up to 72 hours supplemented by propofol in ICU patients with impaired or normal renal function. They found that scheduled down-titrations of the remifentanil infusion at 8, 24, 48 and 72 hours resulted in statistically significant but clinically irrelevant differences in time to offset of sedative effect, as assessed on the basis of clinical signs. This observation in an ICU setting substantiates data suggesting that remifentanil clearance is clinically independent of renal function because of its esterase dependent metabolism [3]. The metabolite remifentanil acid is known to accumulate in renal failure [3], but because this metabolite is approximately 1/4600 less potent than remifentanil [4] this should not result in any clinical effect. This hypothesis was supported by Breen and colleagues [2], who found no correlation between remifentanil acid and time to offset of analgesic and sedative effects in patients with renal dysfunction. No differences in adverse events related to the study drug were found, although the number of adverse events was higher in the renal failure group, probably reflecting their increased

ICU = intensive care unit.

morbidity. Remifentanil was found to be as safe in renal failure patients as in patients with normal renal function. Half of the patients did not need any propofol when remifentanil was used as the primary agent.

This observation in favour of an analgesia-based sedation regimen using remifentanil is in accordance with the results of the study by Muellejans and colleagues [1], who compared remifentanil with fentanyl for analgesia-based sedation in a double-blind, multicentre, randomized controlled trial mainly in postoperative ICU patients. Those investigators reported that both remifentanil and fentanyl were able to achieve the targeted sedation level of 4 on the Sedation–Agitation Scale [5] (reflecting a calm and easily arousable state, in which the patient is able to follow commands) in almost 90% of the duration of sedation. However, there was clearly less variability in the remifentanil group, suggesting a more constant and predictable effect of remifentanil. Again, the analgesia-based regimen provided comfort without supplementation with propofol in approximately 60–65% of the patients in either group, with a lower total propofol dose needed in the remifentanil treated group. Rapid recovery from sedation and low transition times to extubation (about 1 hour) were found for both groups, without any apparent difference. This is somewhat surprising because, due to its short-acting nature, remifentanil was thought to result in faster times to recovery, as has been shown in trauma and major surgery patients [6]. This observation further supports the idea that clear differences in the pharmacokinetics of sedative substances might be less important when goal-directed use of those agents is employed [7]. This was the case in the study reported by Muellejans and colleagues [1], because frequent assessments and reassessments were scheduled by the study protocol in order to adhere to the strict goal of maintining an Sedation–Agitation Scale score of 4. Because of its rapid metabolism, pain was more frequently experienced in patients after remifentanil was stopped than in the fentanyl group. This indicates the need for a strict analgesia protocol, anticipating the rapid offset of pharmacological effect when using short-acting remifentanil.

Clear evidence exists that the use of treatment protocols for sedatives and analgesics is effective in terms of improving clinical outcomes, mainly by avoiding unnecessary overdosing, with prolonged mechanical ventilation and stay in the ICU [7,8]. Brook and coworkers [9] reported a shorter duration of mechanical ventilation, and shorter stay in the ICU and hospital, which was associated with fewer tracheotomies, in acute respiratory failure patients when a written protocol defining the goal of sedation was followed by nurses. In that investigation, a Ramsay score of 3 (patient awake and responds to commands only) [10] was targeted. Kress and colleagues [11] reported that a daily interruption of sedation in mechanically ventilated patients may reduce many of the complications associated with sedatives and results in improved clinical outcomes. On an average of 86% of all ICU days, those investigators found that patients who had been assessed daily were awake and able to follow commands, as compared with only 9% in the control group. Most interestingly, this was not accompanied by any subsequent negative long-term psychological effect in the patients who had been assessed on a daily basis. Moreover, long-term follow up suggested that in those patients post-traumatic stress disorders were less pronounced or even less frequent [12]. The protocol was equally effective when applied to a midazolam-based or a propofol-based sedation regimen, without any significant difference between substances; however, clear pharmacokinetic differences are obvious and have been reported to result in clinical differences when agents are compared with each other without a goal-orientated protocol [13]. It is probable that adherence to a strict and goal-orientated algorithm for defining, assessing and reassessing analgesia and sedation is more important than finding the magic bullet for a particular substance [7].

However, adherence to such a protocol might be much easier in routine clinical work when short-acting substances with low potential for overdosing are available, as is the case for remifentanil. The two observations made by Breen and coworkers [2] and Muellejans and colleagues [1] suggest that this agent may be used safely in many ICU patients, even when renal failure develops. The hypothesis that in real-world ICU conditions remifentanil would allow easier adherence to an analgesia and sedation protocol, thereby resulting in improved clinical outcomes, must be addressed in larger scale studies.

Competing interests

None declared.

References

1. Muellejans B, López A, Cross MH, Bonome C, Morrison L, Kirkham AJT: **Remifentanil versus fentanyl for analgesia based sedation to provide comfort in the ICU.** *Crit Care* 2003, **8:**R1-R11.
2. Breen D, Wilmer A, Bodenham A, Bach V, Bonde J, Kessler P Albrecht S, Shaikh S: **The offset of pharmacodynamic effects and safety of remifentanil in ICU patients with various degrees of renal impairment.** *Crit Care* 2003, **8:**R21-R30.
3. Hoke JF, Shlugman D, Dershwitz M, Michalowski P, Malthouse-Dufore S, Connors PM, Martel D, Rosow CE, Muir KT, Rubin N, Glass PS: **Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers.** *Anesthesiology* 1997, **87:**533-541.
4. Hoke JF, Cunningham F, James MK, Muir KT, Hoffman WE: **Comparative pharmacokinetics and pharmacodynamics of remifentanil, its principle metabolite (GR90291) and alfentanil in dogs.** *J Pharmacol Exp Ther* 1997, **281:**226-232.
5. Riker RR, Picard JT, Fraser GL: **Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients.** *Crit Care Med* 1999, **27:**1325-1329.
6. Soltesz S, Biedler A, Silomon M, Schopflin I, Molter GP: **Recovery after remifentanil and sufentanil for analgesia and sedation of mechanically ventilated patients after trauma or major surgery.** *Br J Anaesth* 2001, **86:**763-768.
7. Kress JP, Pohlman AS, Hall JB: **Sedation and analgesia in the intensive care unit.** *Am J Respir Crit Care Med* 2002, **166:**1024-1028.

8. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA Jr, Murray MJ, Peruzzi WT, Lumb PD; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians: **Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult.** *Crit Care Med* 2002, **30:** 119-141.
9. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH: **Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation.** *Crit Care Med* 1999, **27:**2609-2615.
10. Ramsay MA, Savege TM, Simpson BR, Goodwin R: **Controlled sedation with alphaxalone-alphadolone.** *BMJ* 1974, **2:**656-659.
11. Kress JP, Pohlman AS, O'Connor MF, Hall JB: **Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation.** *N Engl J Med* 2000, **342:**1471-1477.
12. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB: **The long term psychological effects of daily sedative interruption in critically ill patients.** *Am J Respir Crit Care Med* 2003:epub ahead of print.
13. Kress JP, O'Connor MF, Pohlman AS, Olson D, Lavoie A, Toledano A, Hall JB: **Sedation of critically ill patients during mechanical ventilation. A comparison of propofol and midazolam.** *Am J Respir Crit Care Med* 1996, **153:**1012-1018.