ICU

MANAGEMENT & PRACTICE

SPECIAL SUPPLEMENT

VOLUME 18 - ISSUE 4 - WINTER 2018

Sedation practices in the ICU

Report of a symposium presented at LIVES 2018: 31st congress of the European Society of Intensive Care Medicine, Paris, France

Chairs: **Michael Sander**, *Germany*
& **Jean-Daniel Chiche**, *France*

Safety first: insights from clinical pharmacists
Rob Shulman *(London, UK)*

What a difference a drug makes?
Jean-Daniel Chiche *(Paris, France)*

Good past—better future?
Marc Leone *(Marseille, France)*

Knowledge and practice in sedation and analgesia in the ICU have advanced greatly in recent years. The risks of delirium and of over-sedation and effect on outcomes are well-known. Simple measures such as protocols and sedation strategies can improve outcomes for patients. Technical advances have enabled the use of new techniques in the operating theatre and promise to improve sedation practice in the ICU.

This symposium discussed sedation and analgesia from expert angles, including medication safety in sedation and analgesia, prescribing and using sedation and analgesia, and concluded with a look to the future of sedation and analgesia in the ICU.

Supplement in collaboration with Aspen Pharma

Rob Shulman
Lead Pharmacist, Critical Care
University College Hospitals
NHS Foundation Trust
London, UK

robert.shulman@nhs.net

Safety first: insights from clinical pharmacists

A critical care pharmacist's perspective and advice on medication safety around sedative and analgesic therapy in the ICU.

Medication errors occur at every stage of the drug therapy process. A recent report on medicines processes in English hospitals identified notably high error rates in prescribing (8.8%) and preparation and administration (78.6%) (Elliott et al. 2018).

Medication errors in ICU

ICU patients are at particular risk of errors around preparation and administration of intravenous therapies due to the high number of infused drugs. Furthermore, the nature of the ICU environment with the nurses often being interrupted at the bedside and the need for drug concentration calculations contributes to this risk. A multinational observational study found an error rate in parenteral drug administration of around 7% (Valentin et al. 2009). A similar ratio was highlighted in a single-centre observational study of ICU nurses, who knew they were being observed, and the author found an administration error rate of 6.6% (Tissot et al. 1999). A study in which nurses did not know they were being observed had an error rate of administration of 33%, excluding errors of wrong time (van den Bemt et al. 2002).

The 2009 24-hour observational study included 113 ICUs in 27 countries (Valentin et al. 2009). From 1328 patients and 12,000 medicines administrations 861 errors affecting 441 patients were reported. One-third of patients received one or more medication error, of which 19% had one error, and 14% had one or more error. Although most errors did not affect patient status, in 28% of cases medication errors led to temporary change in the patient status. Also, seven patients experienced permanent harm and five died. Looking at the involved drug categories, it appeared that 9% of administrations of sedatives and analgesics were associated with errors (181/2136); resulting in one death and one incident of permanent harm (Valentin et al. 2009). Another study, called the PROTECTED-UK study, analysed data from 21 ICUs from a 2-week period where pharmacists identified all their contributions to care, including noting errors, optimisations and consultations. Out of 20,517 prescriptions, 1 in 6 had such a contribution, and 1 in 15 prescriptions had an error (Shulman et al. 2015; Rudall et al. 2017). The data showed that 5.5% of all errors identified were around sedation and analgesia. Of contributions to care relating to sedation and analgesia (384/3294) 50% were errors, 45% optimisations and 5% consults (Shulman R, pers. comm.).

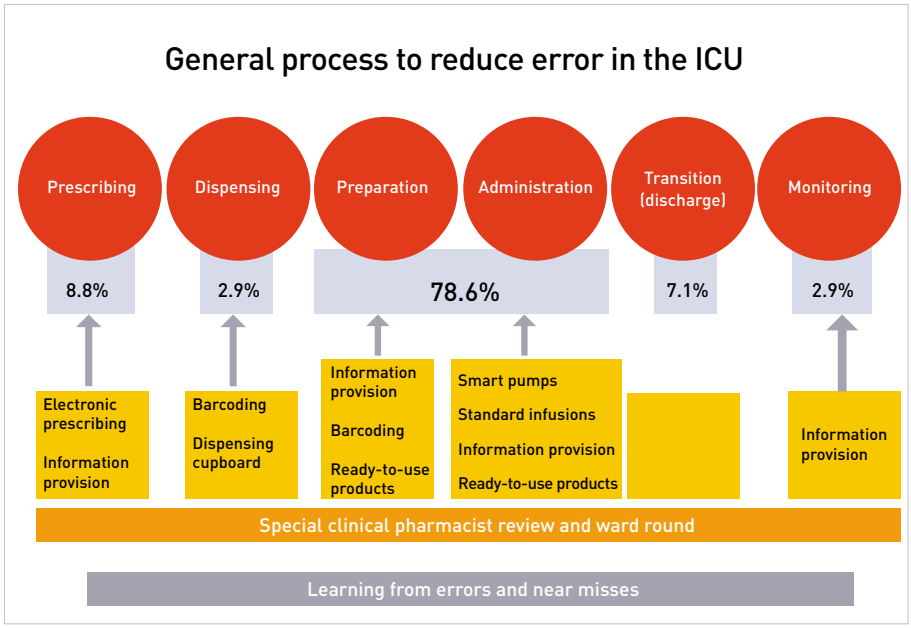

Figure 1. General processes to reduce medication error in the ICU

Data source: Elliott et al. 2018

What can go wrong with sedation and analgesia in the ICU?

Potential errors include selecting the wrong drug, wrong dose, incorrect preparation, contamination in preparation of the product, administration at the wrong rate and compatibility issues. There may be inadequate monitoring of sedation and/or delirium, over- or under-sedation, and errors related to unlicensed use of medications. Commonly used drugs that are not licensed include clonidine (sedation) and haloperidol (delirium) and lidocaine for analgesia.

Table 1. Risk assessment of injectable medicines: example of noradrenaline and milrinone

Risk factors	Noradrenaline 4mg, 8mg, 16mg in 50mL infusion		Milrinone 20mg in 50mL infusion	
	Current status	Ready-to-use syringes	Current status	Ready-to-use syringes
Therapeutic risk	Yes	Yes	Yes	Yes
Use of a concentrate	Yes	No	Yes	No
Complex calculation	Yes	Yes	Yes	Yes
Complex method	Yes	No	Yes	No
Reconstitution of powder in a vial	No	No	No	No
Use of a part vial or ampoule, or use of more than one vial or ampoule	Yes	No	Yes	No
Use of a pump or syringe driver	Yes	Yes	Yes	Yes
Use of non-standard giving set/device required	Yes	No	No	No
Total number of product risk factors	**Six**	**Three**	**Six**	**Three**

Six or more risk factors = high-risk product (Red). Risk reduction strategies are required to minimise these risks.
Three to five risk factors = moderate-risk product (Amber). Risk reduction strategies are recommended.
One or two risk factors = lower-risk product (Green). Risk reduction strategies should be considered.
Source: National Patient Safety Agency (2007)

How to prevent medication errors in the ICU?

Several interventions at the different phases of drug therapy can help to mitigate errors (**Figure 1**).

Prescribing

Electronic prescribing is widely used in critical care. A 2005 study that analysed errors before and after introduction of electronic prescribing found that error rates went down, but that the types of errors were potentially more harmful than with handwritten prescribing (Shulman et al. 2005). Nevertheless, both electronic prescribing and information provision at the point of prescription can reduce errors. Electronic systems can include preset standards of infusions, such as the UK Intensive Care Society's standard concentrations for infusions used in critical care (Intensive Care Society 2017).

> **having pharmacists knowledgeable about intensive care can make a big difference**

Dispensing

Solutions to reduce selection errors include robotic dispensing, barcode readers and dispensing cupboards that are barcoded.

Preparation

Most ICUs prepare intravenous (IV) infusions at the bedside. Ready-to-use products reduce handling and preparation complexity. The case for pre-filled syringes is strong. It is generally accepted that 10% too high or too low dose is acceptable (Wheeler et al. (2008). Ferner et al. (2001) studied concentrations in discarded bags of N-acetylcysteine (NAC) administered to 66 patients. Of these 63% were outside of 10% of the intended dose, 39% outside of 20% and 9% outside of 50%. Parshuram et al. (2003) randomly sampled 232 opioid infusions in a Paediatric Intensive Care Unit and found that 65% were outside of 10% of the intended dose and 6% had two-fold errors or greater. In 2008, the same author tested a scenario of 464 morphine calculations and preparation and found that 35% were outside of 10% of the intended dose, and 8% had two-fold errors or greater (Parshuram et al. 2008).

The UK National Patient Safety Agency produced a risk assessment tool for preparation and administration of injectable medicines in clinical areas (NPSA 2007). **Table 1** shows risk assessment for noradrenaline and milrinone; using pre-filled syringes halved the number of risk factors.

Purchasing pre-filled syringes or ready-to-use infusion vials reduces the number of manipulations of the product and improves safety.

Contaminated propofol

Propofol has been associated with healthcare-associated infections; a review of 58 studies identified 103/1405 (7.3%) incidents of contaminated propofol in theatres and 36/894 (4%) incidence of contaminated propofol in ICUs (Zorrilla-Vaca et al. 2016). Not all propofol formulations contain disodium edetate or EDTA, which reduces microbial growth; Fukada and Ozaki (2007) studied microbial growth in propofol preparations and found that propofol with disodium edetate suppressed bacterial growth more than propofol without. Taking a purchasing for safety approach to propofol, ICUs should consider using prefilled syringes and formulations that contain EDTA.

Figure 2 shows microbial growth in commercially available formulations; Fukada and Ozaki (2007) found that propofol with EDTA suppressed the growth of MSSA, MRSA, *E. coli*, and *K. pneumoniae* to a greater extent than propofol without EDTA.

Clinical pharmacist role

Having clinical pharmacists review and attend ward rounds has been shown to reduce errors.

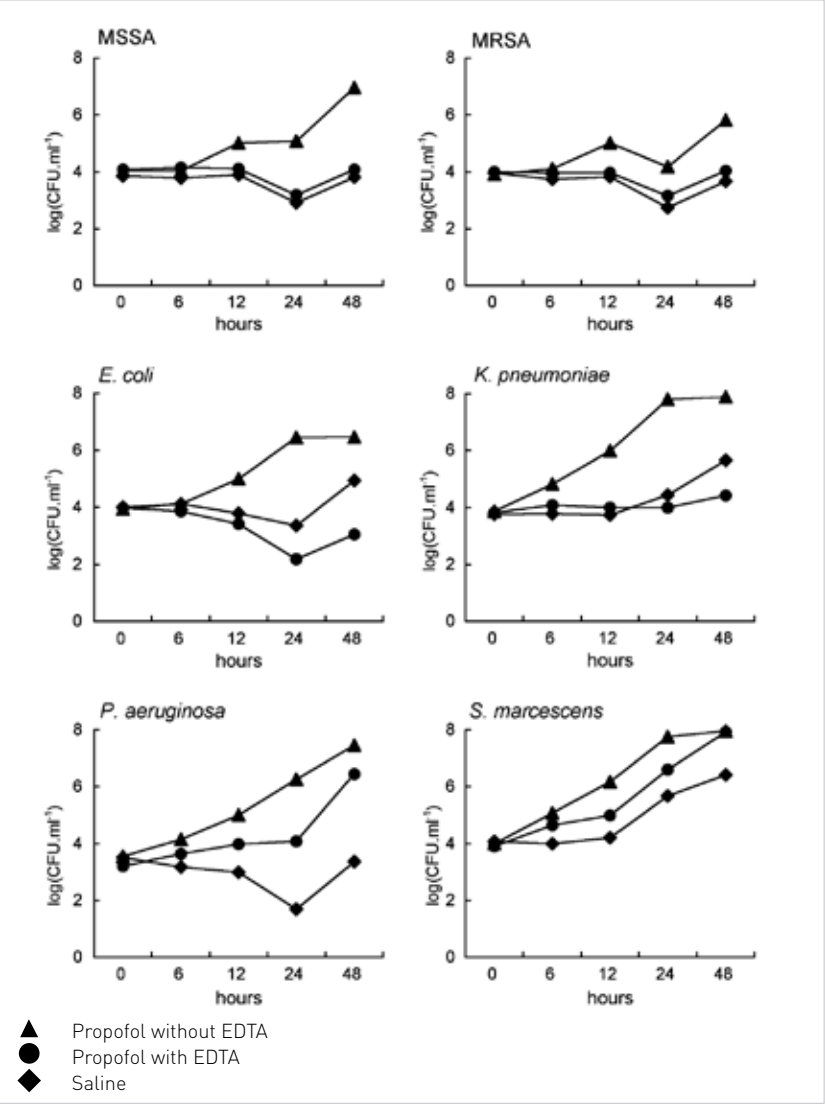

Figure 2. Microbial growth in propofol formulations with disodium edetate

Source: Fukada T, Ozaki M (2007) Microbial growth in propofol formulations with disodium edetate and the influence of venous access system dead space. Anaesthesia, 62(6):575-80.

Meaningful reviews of critical incidents and near miss events, and disseminating solutions to colleagues can all help reduce errors (Shulman et al. 2015; Leape et al. 1999; MacLaren and Bond 2009).

Conclusion

There are many initiatives which ICUs can take to mitigate against error at every stage of the drug therapy process, and ensure patient safety. These include minimising interruptions during preparation, including a specialist clinical pharmacist in the multidisciplinary team, using electronic prescribing systems with guidelines and pre-prepared products. ■

Key Points

- Medication errors are likely to occur at the preparation and administration stages particularly in Intensive Care Units
- Consider pre-filled syringes to decrease the risks related to drug preparation
- Prefer formulations of propofol that include a microbial growth retardant (e.g. EDTA)
- A clinical pharmacist in the ICU can improve medication safety
- Barcoding solutions with ready-to-use products can improve patient safety

References

Elliott R, Camacho E, Campbell F et al. (2018) Prevalence and economic burden of medication errors in the NHS in England. Rapid evidence synthesis and economic analysis of the prevalence and burden of medication error in the UK. Policy Research Unit in Economic Evaluation of Health and Care Interventions. Universities of Sheffield and York. Available from eepru.org.uk/prevalence-and-economic-burden-of-medication-errors-in-the-nhs-in-england-2

Ferner RE, Langford NJ, Anton C et al. (2001) Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example. Br J Clin Pharmacol, 52(5):573-7.

Fukada T, Ozaki M (2007) Microbial growth in propofol formulations with disodium edetate and the influence of venous access system dead space. Anaesthesia, 62(6):575-80.

Intensive Care Society; Faculty of Intensive Care Medicine (2017) Medication concentrations in adult critical care (v 2.2). Available from https://ics152.files.wordpress.com/2017/02/ics-standard-medication-concentrations-2016.pdf

Leape LL, Cullen DJ, Clapp MD et al. (1999) Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA, 282(3): 267-70.

MacLaren R, Bond CA (2009) Effects of pharmacist participation in intensive care units on clinical and economic outcomes of critically ill patients with thromboembolic or infarction-related events. Pharmacotherapy, 29(7): 761-8.

National Patient Safety Agency (2007) 0434H: Promoting safer use of injectable medicines - Risk assessment tool - 2007 - V1. Available from webarchive.nationalarchives.gov.uk/20171030132159/http://www.nrls.npsa.nhs.uk/resources/patient-safety-topics/medication-safety/?entryid45=59812&p=2

Parshuram CS, Ng GY, Ho TK et al. (2003) Discrepancies between ordered and delivered concentrations of opiate infusions in critical care. Crit Care Med, 31(10):2483-7.

Parshuram CS, To T, Seto W et al. Systematic evaluation of errors occurring during the preparation of intravenous medication. CMAJ, 178(1):42-8.

Rudall N, McKenzie C, Landa J et al. (2017) PROTECTED-UK - Clinical pharmacist interventions in the UK critical care unit: exploration of relationship between intervention, service characteristics and experience level. J Pharm Pract, 25(4):311-9.

Shulman R, McKenzie CA, Landa J et al.; PROTECTED-UK group. Pharmacist's review and outcomes: Treatment-enhancing contributions tallied, evaluated, and documented (PROTECTED-UK). J Crit Care, 30(4):808-13.

Shulman R, Singer M, Goldstone J et al. (2005) Medication errors: a prospective cohort study of hand-written and computerised physician order entry in the intensive care unit. Crit Care, 9(5):R516-21.

Tissot E, Cornette C, Demoly P et al. (1999) Medication errors at the administration stage in an intensive care unit. Intensive Care Med, 25(4):353-9.

Valentin A (2009) Errors in administration of parenteral drugs in intensive care units: multinational prospective study. British Medical Journal, 338:b814.

van den Bemt PM, Fijn R, van der Voort PH et al. (2002) Frequency and determinants of drug administration errors in the intensive care unit. Crit Care Med, 30(4):846-50.

Wheeler DW, Degnan BA, Sehmi JS et al. (2008) Variability in the concentrations of intravenous drug infusions prepared in a critical care unit. Intensive Care Med, 34(8):1441-7.

Zorrilla-Vaca A, Arevalo JJ, Escandón-Vargas K et al. (2016) Infectious disease risk associated with contaminated propofol anesthesia, 1989-2014(1). Emerg Infect Dis, 22(6):981-92.

What a difference a drug makes?

Asking why the patient needs to be sedated is as important as the choice of drug for sedation.

Jean-Daniel Chiche
Professor of Critical Care Medicine
Paris Descartes University
Medical Intensive Care Unit
Cochin University Hospital
Research Director
Cochin Institute (INSERM U1016)
Paris, France

jean-daniel.chiche@aphp.fr

@jdchiche

Why use sedation?

Intensivists should ask why they use sedation every time they order it. Sedation is used to reduce the burden and stress of critical illness. Sedative agents mixed with analgesic agents reduce pain and keep the patient calm, especially at night. Intensivists need to look for the cause of agitation and use an algorithm to eliminate the most common causes of agitation e.g. urinary retention, pain.

How much and what sedation?

Less is better in sedation. Side effects of sedation include prolonged mechanical ventilation, increased risk of infection, longer hospital and ICU length of stay and risk of mortality.

The ideal ICU sedation drug has a good ability to provide analgesia, is rapid onset and easy to titrate. Drugs for sedation should allow the possibility to communicate haemodynamic instability and not be associated with delirium.

The concept of titrating the drug to its effect is good. Intensivists should define the target of sedation so that the more drug used the closer to the target is achieved. Sedation is very time-sensitive. Sedating the patient with shock and high agitation so that they can be intubated is essential and they need a high dose for some hours.

The 2018 guidelines for management of pain, agitation/sedation, delirium and immobility and sleep disruption recommend propofol or dexmedetomidine over benzodiazepines for sedation in critically ill, mechanically ventilated adults who are not undergoing cardiac surgery [conditional recommendation, low quality of evidence] (Devlin et al. 2018). A 2013 meta-analysis of benzodiazepine vs non-benzodiazepine-based sedation for mechanically ventilated critically ill patients found that benzodiazepine-based regimens were associated with more ICU days and longer duration of mechanical ventilation, and probably more delirium (Fraser et al. 2013). Lonardo et al. (2014) compared midazolam and lorazepam in adult ICU patients in a retrospective, multicentre study for single ICU admissions with a single ventilation event (>48h) who were treated with continuously infused sedation. There were 2,250 propofol-midazolam and 1,054 propofol-lorazepam matched patients. Patients treated with propofol had a reduced risk of mortality, increased likelihood of earlier ICU discharge and earlier discontinuation of mechanical ventilation.

How to use sedation?

A recent paper outlines assessment tools and advice on sedation (Mehta et al. 2018).

Daily sedation stops

Daily interruption of sedations was shown in a randomised controlled trial (RCT) to reduce duration of mechanical ventilation, facilitate weaning and shorten duration of ICU stay (Kress et al. 2000).

Paired sedation and weaning protocols

Sedation stops can be combined with spontaneous breathing trials (SBT); Girard et al. (2008) showed this reduced duration of mechanical ventilation, ICU stay and mortality. Computerised provider order entry (CPOE) systems can place sedation stops and SBT on the nurses' task list.

Tailor the drug to the patient status

The Sedation Practice in Intensive Care Evaluation (SPICE) study compared deeply sedated with lightly sedated (RASS score [-2 to +1]) patients. Patients who had light sedation within the first 4 hours had reduced time to extubation and improved probability of survival (Shehabi et al. 2012). Other studies demonstrated the same results with shorter time to extubation and better survival in patients with light sedation during the first hours (Shehabi et al. 2013; 2018); the probability of 180-day survival increased with how efficiently sedation was decreased (Shehabi et al. 2018). Importantly, the results did not depend on the drug used but did depend on how they used the drugs.

WHAT' S NEW IN INTENSIVE CARE

Ten tips for ICU sedation

1. **Prioritize pain assessment & management**
2. **Target an awake, interactive patient shortly after intubation**
3. **Multimodality symptom-based management**
4. **When deep sedation is indicated, de-escalate ASAP**
5. **For patients receiving opioids/sedatives, use validated tools and explicit targets**
6. **Use non-pharmacologic interventions for patient comfort & engagement**
7. **Avoid benzodiazepines, particularly infusions**
8. **Identify iatrogenic benzodiazepine & opioid withdrawal**
9. **Remove catheters (all) as soon as possible, and avoid physical restraint**
10. **Be attentive about night-time sedation**

Source: Mehta, Sangeeta, Spies, Claudia, Shehabi, Yahya (2018) Ten tips for ICU sedation. Intensive Care Med. 44: 1141-1143.
Reprinted by permission from Springer Nature: Springer Nature

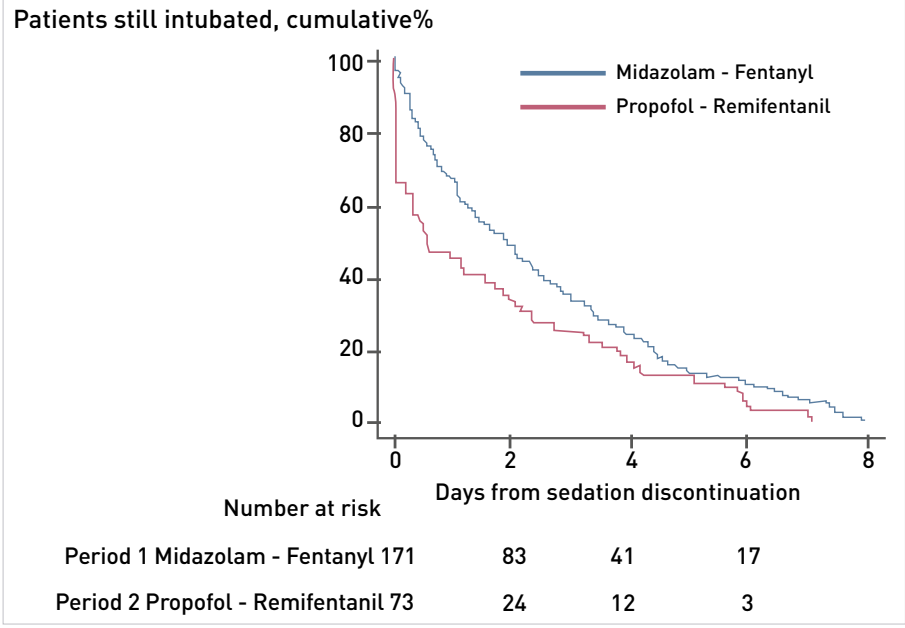

Figure 1. Time from discontinuation of sedation to weaning of mechanical ventilation in survivors

Two randomised controlled trials that compared dexmedetomidine to midazolam (MIDEX) or propofol (PRODEX) for sedation in more than 1,000 patients during prolonged mechanical ventilation mandated SBT and RASS-targeted sedation (Jakob et al. 2012). The results showed very little change in duration of mechanical ventilation when comparing dexmedetomidine with midazolam; between dexmedetomidine and propofol there was no difference. Patients were more able to communicate and had similar duration of mechanical ventilation and outcomes when dexmedetomidine was used, compared to midazolam or propofol, in patients who did not require deep sedation (Jakob et al. 2012).

Delirium assessment

Some delirium is associated with sedation and is rapidly reversible so it is advised to coordinate delirium assessment with a daily sedation stop (Patel et al. 2014). Delirium is sometimes the result of inflammation and in patients with septic shock there is not significant benefit from dexmedetomidine (Kawazoe et al. 2017).

Does the choice of drug make no difference in all clinical contexts?

In a study of sedation in patients admitted after out-of-hospital cardiac arrest two periods were compared: propofol-remifentanil, period P2, vs midazolam-fentanyl, period P1 (Paul et al. 2018). Time to awakening and the proportion of comatose patients decreased with the propofol-remifentanil regimen. The propofol-remifentanil regimen was also associated with reduction in mechanical ventilation duration and reduction in incidence of delayed awakening (**Figure 1**).

How long to sedate?

Intensivists need to consider length of sedation. When strict protocols to target a specific RASS score are implemented, it is possible to reduce sedation, and the proportion of patients on sedation after five days goes down dramatically.

Conclusion

Always ask why the patient needs sedating. Protocols to target the level of sedation are extremely helpful and will reduce the proportion of patients who are sedated for a long period. The less sedation the better—for duration of mechanical ventilation and survival. ■

Key Points

- Prescribe sedation in response to pain, anxiety, agitation, sleeplessness
- Non-benzodiazepine-based sedation vs benzodiazepine is associated with less mortality, less ICU days and earlier discontinuation of mechanical ventilation
- Track compliance with protocols for stopping sedation
- The less sedation the better the likelihood of survival and the shorter the time to extubation

References

Devlin JW, Skrobik Y, Gélinas C et al. (2018) Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med, 46(9):e825-73.

Fraser GL, Devlin JW, Worby CP et al. (2013) Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Crit Care Med, 41(9 Suppl 1):S30-8.

Girard TD, Kress JP, Fuchs BD et al. (2008) Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet, 371(9607):126-34.

Jakob SM, Ruokonen E, Grounds RM et al.; Dexmedetomidine for Long-Term Sedation Investigators (2012) Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA, 307(11):1151-60.

Kawazoe Y, Miyamoto K, Morimoto T et al.; Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) Trial Investigators (2017) Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: a randomized clinical trial. JAMA, 317(13):1321-8.

Kress JP, Pohlman AS, O'Connor MF et al. (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med, 342(20): 1471-7.

Lonardo NW, Mone MC, Nirula R et al. (2014) Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. Am J Respir Crit Care Med, 189(11):1383-94.

Mehta S, Spies C, Shehabi Y (2018) Ten tips for ICU sedation. Intensive Care Med, 44(7):1141-3.

Patel SB, Poston JT, Pohlman A et al. (2014) Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. Am J Respir Crit Care Med, 189(6):658-65.

Paul M, Bougouin W, Dumas F et al. (2018) Comparison of two sedation regimens during targeted temperature management after cardiac arrest. Resuscitation, 128:204-210. Erratum in: Resuscitation, 2018 Oct;131:135.

Shehabi Y, Bellomo R, Kadiman S et al.; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group (2018) Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: a multinational prospective longitudinal cohort study. Crit Care Med, 46(6):850-9.

Shehabi Y, Bellomo R, Reade MC et al.; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators; ANZICS Clinical Trials Group (2012) Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med, 186(8):724-31.

Shehabi Y, Chan L, Kadiman S et al.; Sedation Practice in Intensive Care Evaluation (SPICE) Study Group investigators (2013) Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med, 39(5):910-8.

Good past—better future?

From massive sedation in the past, through current sedation practice relying on cooperation between patients and care providers, the future may further improve sedation in the ICU.

Marc Leone
Service d'Anesthésie et de Réanimation
Aix-Marseille University;
Assistance Publique Hôpitaux de Marseille
Marseille, France

marc.leone@ap-hm.fr

The concepts for good sedation include defining the range of sedation, the need for agents with rapid response that can be easily and rapidly varied in restless and confused patients, various modes of ventilation, continuous supervision and adequate monitoring.

The benzodiazepines era brought diazepam, lorazepam, midazolam, but they are associated with delirium, whatever the drug or dose (Ely et al. 2001; Pandharipande et al. 2007). Propofol has a better pharmacokinetic profile, but in most RCTs there was difference in time to extubation, and no difference in ICU discharge (Ely et al. 2001; Pandharipande et al. 2007). Propofol infusion syndrome limits the use of propofol as the main agent for sedation in the ICU for more than two days or at a dose of more than 4mg/kg/h (Bray 1998).

Current practice

Use boluses

When boluses are used sedation can be titrated. Kollef et al. compared continuous and intermittent intravenous (IV) sedation, and showed that intermittent boluses of IV sedatives can be titrated more easily and that duration of mechanical ventilation shortened when using an intermittent bolus (Kollef et al. 1998).

Build a sedation strategy

A sedation strategy should include:

- A daily sedation stop, which can reduce duration of mechanical ventilation (Kress et al. 2000).
- Choice of drug. An RCT published in 2006 showed there were more ventilator-free days when propofol was used with daily sedation interruption (Carson et al. 2006).
- Monitoring (De Jonghe et al. 2005).
- Progress towards no sedation. An example is from Strøm et al. (2010).

Reduce sedation by titration

De Jonghe et al. (2005) developed a management protocol based on an algorithm relying on monitoring by a nurse, and a target based on a score. The nurse is in charge of the flow of the sedation agent to keep the patient in a predefined target. Cooperation between the nurse and the patient is important (Reade et al. 2016; Flükiger et al. 2018).

Strategies are required for deep and light/comfort sedation (**Figure 1**). Deep sedation is required for patients with acute respiratory distress syndrome (ARDS) and who require intracranial pressure monitoring. Deep sedation targets a RASS score of -4 or -5. For light sedation a RASS score of 0 ensures that the patient is awake, not agitated and can cooperate with the nurses. There is no middle approach.

The future of sedation

Target-controlled infusion (TCI)

TCI rapidly loads plasmatic compartment up to the peak effect. This approach enables to reach the desired concentration effect very quickly. If continuous infusion is used, there is a long time to reach the target. Anyway, without a close titration, there is a risk of exceeding the target and of over-sedation (**Figure 2**).

TCI is based on predictive models (Struys et al. 2016). The target is set to also include patient features such as body mass index (BMI), gender and age. In future creatinine clearance or liver function could be included. The TCI system could have a pharmacokinetic parameter set in an infusion device and a user interface in a single smart pump. The concentration target can be set according to stimulation provided to the patient. For example, in the ICU, during nursing care, increase the target, when no nursing care is taking place, or at night, decrease the target.

There are few publications on using TCI in the ICU for sedation. Sufentanil and ketamine, compared in a RCT using a TCI system, found the model was quite predictive for sufentanil but unpredictive for ketamine and midazolam (Bourgoin et al. 2005). The study showed that the increase in sufentanil or ketamine plasma concentrations using TCI was not associated with adverse effects on cerebral haemodynamics in patients with severe brain injury. A more recent paper used a TCI propofol Marsh model system for general anaesthesia and sedation in neurosurgical patients and found a bias of -34.7% and precision of 36% (Cortegiani et al. 2018). More data for specific pharmacokinetic models are needed for TCI to be used in ICU patients.

Closed-loop systems

A closed-loop system requires a relevant target

Deep sedation	Comfort sedation
Midazolam Propofol Sevoflurane + Opioids ± Muscle relaxants	**Dexmedetomidine** Propofol + **Non-opioid analgesics** ± Opioids (if VAS > 30)

Figure 1. Strategies for sedation

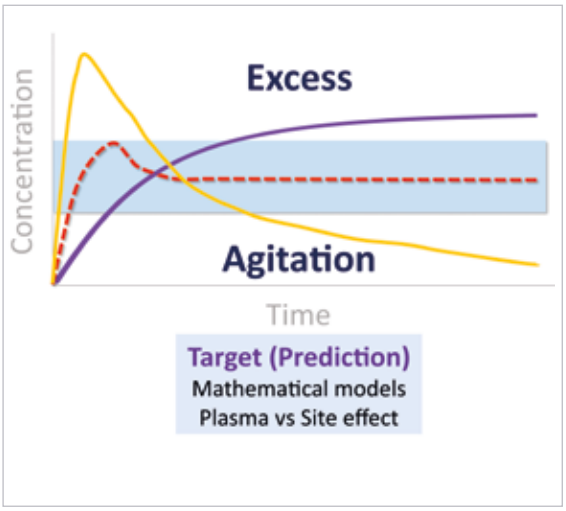

Figure 2. Target-controlled infusion in the operating room

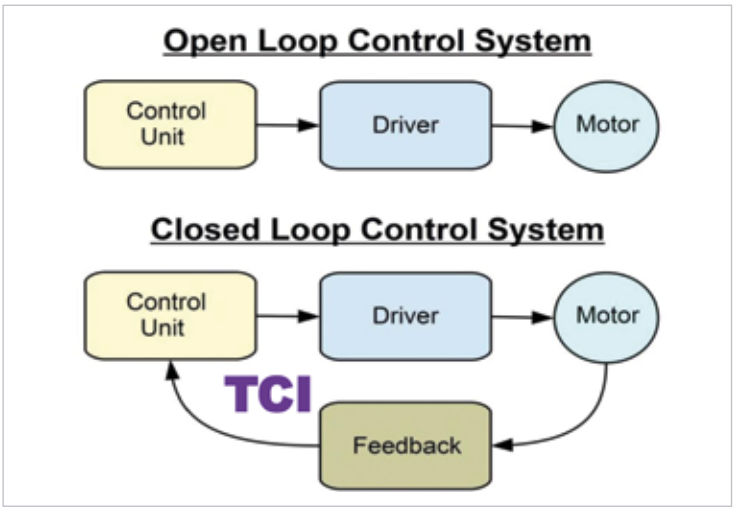

Figure 3. Closed-loop system

value (setpoint), strong monitoring that is not influenced by artefacts, a drug with a short delay and short half-life and an adaptive control algorithm with a dynamic learning strategy or fuzzy logic system (Le Guen et al. 2016). Closed-loop systems have been used in the operating room (**Figure 3**). A trial that compared dexmedetomidine to saline as a placebo using a bispectral index-guided closed-loop system found that dexmedetomidine significantly reduced propofol and remifentanil consumption during anaesthetic induction and reduced propofol use during maintenance of anaesthesia (Le Guen et al. 2014).

The most commonly used target for ICU patients is bispectral index, and can include respiratory rate (RR) or blood pressure (BP) if it is important that the patient was not hypotensive (Haddad et al. 2009). Alternatively drug plasma concentration can be targeted directly. A future composite index might include cerebral activity, sedation score, RR, BP and blood plasma concentration.

Use fewer opioids

In the ICU up to 90% of patients receive opioids (Arroliga et al. 2005; Payen et al. 2007; Wøien et al. 2012), and these are associated with morbidity and mortality (Kamdar et al. 2017). Dexmedetomidine, ketamine, ketoprofen, paracetamol and lidocaine could be used as alternatives. It is important to monitor the patient first, and to consider other ways to provide analgesia apart from opioids.

Conclusion

In the past sedation patients received massive sedation. Now sedation relies on good cooperation between patients, nurses and intensivists. The future will bring target-controlled infusion in a closed-loop system, reduced use of opioids and a multimodal approach to sedation. ■

Key Points

- Include in the protocol a daily interruption of sedation
- Cooperation between patients, nurses and intensivists is vital in sedation
- In future, target-controlled infusions in a closed-loop system may be used in the ICU

References

Arroliga A, Frutos-Vivar F, Hall J et al. (2005) Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. Chest, 128(2):496-506.

Bourgoin A, Albanèse J, Leone M et al. (2005) Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients. Crit Care Med, 33(5):1109-13.

Bray RJ (1998) Propofol infusion syndrome in children. Paediatr Anaesth, 8(6):491-9.

Carson SS, Kress JP, Rodgers JE et al. (2006) A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med, 34(5):1326-32.

Cortegiani A, Pavan A, Azzeri F et al. (2018) Precision and bias of target-controlled prolonged propofol infusion for general anesthesia and sedation in neurosurgical patients. J Clin Pharmacol, 58(5):606-12.

De Jonghe B, Bastuji-Garin S, Fangio P et al. (2005) Sedation algorithm in critically ill patients without acute brain injury. Crit Care Med, 33(1):120-7.

Ely EW, Gautam S, Margolin R et al. (2001) The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med, 27(12):1892-900.

Flükiger J, Hollinger A, Speich B et al. (2018) Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. Ann Intensive Care, 8(1):92.

Haddad WM, Bailey JM (2009) Closed-loop control for intensive care unit sedation. Best Pract Res Clin Anaesthesiol, 23(1):95-114.

Kamdar NV, Hoftman N, Rahman S et al. (2017) Opioid-free analgesia in the era of enhanced recovery after surgery and the surgical home: implications for postoperative outcomes and population health. Anesth Analg, 125(4):1089-91.

Kollef MH, Levy NT, Ahrens TS et al. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. Chest, 114(2):541-8.

Kress JP, Pohlman AS, O'Connor MF et al. (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med, 342(20):1471-7.

Le Guen M, Liu N, Chazot T et al. (2016) Closed-loop anesthesia. Minerva Anestesiol, 82(5):573-81.

Le Guen M, Liu N, Tounou F et al. (2014) Dexmedetomidine reduces propofol and remifentanil requirements during bispectral index-guided closed-loop anesthesia: a double-blind, placebo-controlled trial. Anesth Analg, 118(5): 946-55.

Pandharipande PP, Pun BT, Herr DL et al. (2007) Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA, 298(22):2644-53.

Payen JF, Chanques G, Mantz J et al. (2007) Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. Anesthesiology, 106(4):687-95.

Reade MC, Eastwood GM, Bellomo R et al.; DahLIA Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group (2016) effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. JAMA, 315(14):1460-8. Erratum in: JAMA, 316(7):775.

Strøm T, Martinussen T, Toft P (2010) A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet, 375(9713):475-80.

Wøien H, Stubhaug A, Bjørk IT (2012) Analgesia and sedation of mechanically ventilated patients - a national survey of clinical practice. Acta Anaesthesiol Scand, 56(1):23-9.

EUCIS-DIPR-0119-0309