Sedation in intensive care: should we reach for dexmedetomidine sooner?

Maintaining adequate sedation for patient safety in intensive care is a priority in the management of agitation, but is also paramount for patient comfort and compliance with mechanical ventilation and invasive procedures.

Traditional agents (propofol and benzodiazepines) mainly target $GABA_A$ receptors. These may contribute to development of delirium, particularly with longer term use. Dexmedetomidine, a selective alpha-2 receptor agonist with anxiolytic, sedative and analgesic properties, may provide sedation with a lower risk of delirium.

Dexmedetomidine should be used as a primary sedative agent

Two non-inferiority sponsored randomized double-blinded trials compared midazolam and propofol against dexmedetomidine (Jakob et al, 2012). They were sponsored by Orion Pharma, but steps were taken to ensure independent analysis at each stage.

Use of dexmedetomidine significantly decreased the time to extubation (36 hours) *vs* propofol and decreased mechanical ventilation time by 41 hours *vs* midazolam. The incidence of neurocognitive adverse events (coma or delirium) was reduced, with 11% less time in these states with dexmedetomidine than propofol.

Importantly, patients had more time at target sedation and higher mean Richmond agitation-sedation scores (RASS) scores than with both midazolam and propofol. They were also significantly more rousable and more able to communicate pain to nursing staff.

Dr Christopher Cann, High Dependency Unit Fellow, Department of Anaesthetics, Whipps Cross Hospital, Barts Health Trust, London E11 1NR

Dr David Melia, Anaesthetics and Critical Care Specialist Registrar (ST7), Department of Anaesthetics, Whipps Cross Hospital, Barts Health Trust, London

Correspondence to: Dr C Cann (cjcann@doctors.org.uk)

In non-intubated patients, haloperidol is often the agent of choice for agitation or delirium. If repeated haloperidol boluses fail to produce an adequate response there is no clear recommendation as to what to try next.

A single centre, non-randomized controlled trial placed those who did not respond to repeated haloperidol boluses on a haloperidol and dexmedetomidine infusion, with haloperidol then tapered off. Those who did respond continued to receive haloperidol. Haloperidol-only patients had a failure rate of 43% with over-sedation in 11.6%. The dexmedetomidine arm showed a higher percentage of time at satisfactory sedation levels (92.7% *vs* 59.3%; P=0.0001) and a 0% failure rate (n=46) (Carrasco et al, 2016).

The cost of dexmedetomidine remains a barrier to its widespread adoption. However, the Scottish Medicines Consortium (2012) reported an overall saving of £1479 *vs* propofol and £2143 *vs* midazolam.

Use dexmedetomidine sparingly

The positives of the Prodex/Midex trials (Jakob et al, 2012) have been widely quoted, but the initial intent was to prove non-inferiority. Hypotension and bradycardia incidences were similar to those with propofol and significantly worse than midazolam (20.6%/11.6% *vs* 11.6%/5.2% respectively), raising questions of safety. The SEDCOM trial found no benefit compared to midazolam, but noted a 24.9% reduction in delirium, adding weight to use of dexmedetomidine in this setting (Riker et al, 2009).

In 2016 a multicentre randomized placebo-controlled trial assessed dexmedetomidine in patients in whom extubation was deemed unsafe as a result of agitation or delirium (Reade et al, 2016). The trial showed significant benefit in the time to extubation (21.9 hours *vs* 44.3 hours), and the time to resolution of delirium (23.3 hours *vs* 40 hours) compared to standard therapy alone.

Conclusions

Dexmedetomidine appears to reduce the rate of neurocognitive disorder compared to propofol, with no notable increase in clinically relevant adverse events. Sedation achieved with dexmedetomidine appears to be lighter and more stable, but the evidence is less convincing against midazolam. Lack of familiarity with the drug may be an issue, particularly as it has a higher rate of side effects than midazolam. In patients with established delirium in intensive care that is preventing extubation, addition of dexmedetomidine can be beneficial over standard therapy alone.

While the direct cost of the drug is higher, there is convincing evidence of a cost-benefit compared to alternatives. There is not yet the evidence to support widespread use as a primary sedative agent, but it should be strongly considered as an early adjunct in those with delirium. **BJHM**

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Anaesthetic and critical care dilemmas are coordinated by **Dr Rob Anker**, Anaesthetic Registrar (ST6), Royal Marsden Hospital, London and **Dr Prashanth Nandhabalan**, Specialist Registrar in Anaesthesia and Intensive Care, King's College Hospital NHS Foundation Trust, London