Dexmedetomidine: a real innovation or more of the same?

Sedation of critically ill patients is one of the commonest interventions in the intensive care unit (ICU). Historically, the purpose of sedation was to allow a patient’s ventilation to be controlled and, even today, sedation and ventilation remain inextricably linked. More recently, the comfort aspects of sedation have been emphasized, and we have become more aware of the safety issues involved. Morbidity and mortality have been reported with sedative agents, and even the way sedative agents are given may influence the patient’s outcome. Sedation scores and sedation-measuring devices are used in an attempt to reduce the risks of over-sedation, particularly excess drug administration and drug withdrawal reactions. Sedation has become safer and developments in ventilators and airway maintenance have made deep levels of sedation less necessary. In spite of this, problems related to sedation are common in the ICU and are often difficult to deal with.

One response to sedation-related problems has been to demand new and, hopefully, better sedative agents. Usually, when a new agent is introduced, there is initially enthusiasm for its use. When the first serious side-effects are reported, this enthusiasm wanes and may be replaced by cynicism. Finally, the agent finds its place in the armamentarium of each individual practitioner. Sedative agents have been introduced into the ICU and this pattern of response has happened. Our present range of sedative agents is limited but individual agents have found their place in the intensive care pharmacopoeia; nevertheless, the underlying problems of sedation remain. Now we have dexmedetomidine. This selective \( \alpha_2 \) adrenoreceptor agonist is already licensed in the USA for short-term postoperative sedation. It is the active ingredient of medetomidine, which has been used as a veterinary anaesthetic for some time [6].

\( \alpha_2 \) Adrenoreceptors are found in the central and peripheral nervous systems and in autonomic ganglia at both pre- and post-synaptic sites. Stimulation of pre-synaptic receptors in sympathetic nerve endings inhibits release of norepinephrine, while central post-synaptic receptor stimulation inhibits sympathetic activity; both effects result in a decrease in blood pressure and heart rate and an increase in sedation. Stimulation of \( \alpha_2 \) adrenoreceptors in the spinal cord produces analgesia. After administration, dexmedetomidine is distributed rapidly; it undergoes extensive metabolism in the liver and excretion in both urine and faeces [7].

The experience of dexmedetomidine suggests that it provides adequate short-term sedation for patients requiring intensive care. Although it reduces the stress response to surgery, it does not interfere with steroid formation in the way that etomidate does [8]. It provides analgesia and reduces opioid requirements, but does not affect respiratory rate or carbon dioxide clearance; in fact, it may improve oxygenation [9]. The major problem with dexmedetomidine may be its haemodynamic effects. Hypotension and bradycardia have been reported, particularly with more rapid infusion and in patients with pre-existing cardiac problems [7, 11]. The study reported by Venn and Grounds in this issue compares dexmedetomidine with propofol in patients requiring short-term post-operative sedation. The two agents provide comparable sedation acceptable to clinicians and patients, dexmedetomidine reducing analgesic requirement and heart rate.

One of the fascinating differences with dexmedetomidine is the quality of sedation it produces. Because it has a different mode of action, patients experience sedation in a different way [13]. Drugs acting on the GABA system, such as midazolam and propofol, produce a clouding of consciousness which is viewed as a part of the spectrum between consciousness and anaesthesia. Dexmedetomidine, acting on \( \alpha_2 \) adrenoreceptors, sedates patients by reducing sympathetic activity and the level of arousal. Thus, patients lie calmly in bed but are easily roused to full consciousness. Sedation with GABA-related agents can cause paradoxical agitation as well as tolerance, dependence and even addiction, which are probably related to changes in the receptors with long-term drug administration. These phenomena have not been described with dexmedetomidine, but its use has been confined to short-term sedation. It will be interesting to study the longer-term effects of dexmedetomidine administration.

What changes might dexmedetomidine bring to sedative practice? Should we use it in the same way as more conventional agents or can we use it differently? Continuous infusions and intermittent bolus doses given by nursing staff are the current methods of sedative administration. Is this a drug that can be given by a
patient-controlled system? Does this different type of sedation require a different monitor? Sedation scores have been devised in response to GABA-mediated drugs and opioids; sedation monitors have been developed to assess the depth of anaesthesia. Should we use the same criteria and methods that we currently use to monitor sedative level with dexmedetomidine? In the study by Venn and Grounds they used the conventional Ramsay scale and bispectral index and found no difference between propofol and dexmedetomidine. Does this do justice to the sedation produced by dexmedetomidine?

We have strategies and protocols for dealing with withdrawal from benzodiazepines and opioids when they occur in critically ill patients. Withdrawal from clonidine is associated with rebound hypertension. This has not yet been studied with dexmedetomidine. We now know a lot about the safety of individual sedative agents and a little about their safe use in the critically ill. We need to know a lot more about dexmedetomidine before we can use it with confidence.

Fundamentally, whether or not dexmedetomidine turns out to be just another sedative agent depends on how we use both the drug and the opportunity it provides. If we use this drug in the same way as our existing agents, it may well turn out to be just another sedative agent and we will become cynical as the side-effects are reported. However, if we use this different agent in a different way, we have the chance to reconsider what we want from sedation and possibly to take the sedation of critically ill patients to a new level. This is a real opportunity. An opportunity not only to try out another drug but also to re-evaluate sedation in the critically ill.

M. P. Shelly
Intensive Care Unit
Withington Hospital
Nell Lane
West Didsbury
Manchester M20 2LR
UK

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