Palliative Care Rounds

The Use of Propofol in Palliative Medicine

John Moyle, MB, BS, FRCA
The Hospice of Our Lady and St. John, Willen Village, Milton Keynes, United Kingdom

Abstract
Occasionally, terminally ill patients with severe agitated dilirium are extremely difficult to sedate, either becoming too deeply sedated when undisturbed or severely agitated when disturbed. This situation occurs even with the short-acting benzodiazepines such as midazolam. This paper discribes the use of a low-dose infusion of the anesthetic agent propofol (Diprivan, Zenica), which has a very short length of action and allows the depth of sedation to be easily controlled from minute to minute. J Pain Symptom Manage *1995;10:643–646.*

Key Words
Distress, agitation, propofol

Introduction

It is occasionally necessary to sedate terminally ill patients who are uncontrollably distressed or agitated. Although sedation in these situations can sometimes be achieved by the parenteral equivalent of the previously orally administered drug, this approach may not be feasible or may involve the use of drugs with long half-lives. The time required for the long half-life drug to reach steady state after a dose change can complicate efforts to titrate and monitor the drug. Various alternative drugs (opioid, benzodiazepine, barbiturate, or neuroleptic) have been used to accomplish sedation at the end of life. A new anesthetic agent, propofol, may be another option, as described in the following cases.

Case Report 1

A 71-year-old man was admitted to the Hospice in great distress and pain. He had far advanced carcinoma of the prostate. He had a supra-pubic urinary catheter, which was draining blood-stained urine and debris. He was complaining of severe pelvic pain and tenesmus. Over the previous week, the diamorphine he was receiving by subcutaneous infusion had been increased steadily. The dose was 2 g/24 hr on admission. He was also receiving midazolam 60 mg/24 hr by subcutaneous infusion. Because the pain was not responding to the opioid, an alternative approach, subcutaneous ketamine, was initiated. Control of the pain was obtained by ketamine 500 mg/24 hr by subcutaneous infusion. It was then possible to reduce the diamorphine to 600 mg/24 hr and the midazolam to 30 mg/24 hr.

By day 5, the pain and tenesmus had increased again despite escalation in the ketamine to 1000 mg/24 hr. The patient had become very agitated, especially when disturbed, and there was concern that the drugs may be contributing to his mental distress.

It was decided to use an epidural infusion of diamorphine and bupivicaine to treat the pain and tenesmus, and to use intravenous propofol as a sedating agent. An epidural catheter was placed at L3-L4, and an infusion of

Address reprint requests to: John Moyle, MB, BS, FRCA, The Hospice of Our Lady and St. John, Willen Village, Milton Keynes, MK15 9AB, United Kingdom.

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diamorphine 50 mg dissolved in 20 mL of 0.5% bupivicaine was infused. Sedation was obtained with a variable infusion rate of intravenous propofol (1%). The level of sedation followed changes in the dose rate within 5–10 min. The propofol infusion rate was between 10 mg/hr (1 mL/hr) and 50 mg/hr (5 mL/hr) during the first 24 hr.

After 12 hr, it was apparent that the epidural infusion was controlling the pelvic pain but not the tenesmus. He was also passing blood and tumor debris per rectum. The epidural infusion was therefore changed to 5 mL 0.5% bupivicaine with 5 mg diamorphine per hr, with good relief of both symptoms.

It was necessary to increase the propofol infusion daily by a small amount due to tachphylaxis. By day 9, the dose rate was 200 mg/hour (20 mL/hr). He died peacefully on day 9 with very grateful relatives and satisfied staff.

Case Report 2

A 73-year-old man in the terminal stage of disseminated carcinoma of the colon was admitted to the Hospice having suffered several gastrointestinal hemorrhages. He was a bachelor who lived alone and had no surviving relatives. He had a long-term anxiety disorder that was made worse following the hemorrhages. His pain was normally well controlled by oral slow-release morphine 20 mg twice daily; the anxiety state was initially controlled with lorazepam 1 mg twice daily. A decision was made not to transfuse blood with the agreement of the patient. Over the course of a week, he became much weaker, semi-conscious but still suffering from panic attacks. Diamorphine and midazolam administered by subcutaneous infusion replaced the oral medication. His fluctuating level of consciousness was found difficult to control; he became severely agitated when turned or other nursing procedures were carried out, but became deeply unconscious when left undisturbed. The midazolam infusion was therefore replaced by propofol by intravenous infusion. The infusion was started at 10 mL/hr (100 mg/hr). The sedation was then much more easily controlled by the nursing staff using a continuous infusion of between 10 mL/hr (100 mg/hr) and 40 mL/hr (400 mg/hr), with small boluses (3–5 mL) before procedures. The patient died peacefully 4 days later.

Discussion

Propofol (2,6-diisopropylphenol) is a short-acting general anesthetic agent with a rapid onset of action (approximately 30 sec). It was developed as an intravenous anesthetic agent for induction by bolus and maintenance of anesthesia by infusion. It is also commonly used in the intensive care unit for sedation of patients.

The mechanism of action, like all general anesthetic agents, is poorly understood. Propofol has inhibitory actions at both spinal and supraspinal synapses, probably by its effect on GABA receptors. It inhibits GABA uptake and therefore potentiates GABA evoked potentials.[1] Propofol is extensively distributed in the body and rapidly cleared (total body clearance 1.5–2 liters/min). Clearance occurs by metabolic processes, mainly in the liver, to form inactive water-soluble glucuronide and sulphate conjugates of propofol and a small amount of the corresponding quinol, which are excreted in the urine. The quinol occasionally makes the urine green in color. Propofol is supplied as a white aqueous and isotonic emulsion for intravenous injection containing 1% (10 mg/mL) of propofol made water-soluble by a vehicle which contains glycerol, purified egg phosphatide, and sodium hydroxide.

The advantages of propofol over midazolam from a pharmokinetic point of view are clearly demonstrated in Table 1. The main advantages are that the level of sedation is more easily controlled[2] and recovery is more rapid if the infusion rate is reduced.[3,4]

The author's experience with this drug stems from his practice as an anesthetist/intensivist. In the intensive care situation, propofol is commonly used as a sedating agent by intravenous infusion. Its main advantage over other methods of sedation is the rapid way in which the level of sedation follows changes in the infusion rate. This is because of its rapid elimination and nonaccumulation. Although its use in the intensive care unit was originally intended to provide sufficient sedation to allow intermittent positive pressure ventilation, it is commonly used to provide lighter levels of sedation in the conscious patient breathing spontaneously. At these levels, full communication with the patient, by the staff and relatives, is possible.

Table 1
Comparison of the Pharmacokinetics of Propofol and Midazolam

	Midazolam	Propofol
Clearance	6.6 ± 1.8 mL/min/kg	1.3–2.2 mL/min/kg
Distribution half-life	0.3 ± 0.24 hr	2.5 min
Elimination half-life	1.9 ± 0.9 hr	54 min
Sedative plasma concentration	100 ng/mL	1 μg/mL
Therapeutic range	30–100 ng/mL	0.2–2.0 μg/mL
Duration of action	1–6 hr	5 min

Data from Park and Gempeler (reference no. 1).

A disadvantage of propofol in the palliative care setting is that it is necessary to administer the drug with a digitally controlled syringe driver or infusion pump. This is because it is impractical to use a syringe smaller than 50 mL, and it is necessary to be able to accurately adjust the rate of the infusion over a wide range with ease. Propofol is supplied at a concentration of 10 mg/mL in either 20 mL ampules or 100 mL bottles for administration with an infusion pump.

When an infusion of propofol is initiated, the infusion rate should be increased from 1 mL/hr (10 mg/hr) by 1 mL/hr increments every 15–20 min until a satisfactory level of sedation has been obtained. If the patient is oversedated, the infusion may be switched off for a few minutes and the started again at a lower infusion rate. If there is an urgent need to increase the sedation, boluses of between 2 mL (20 mg) and 5 mL (50 mg) may be administered by increasing the infusion rate to 60 mL/hr for 2–5 min as required before reducing the rate again to the continuous infusion level.

The author introduced the use of propofol for terminal sedation to manage patients who require sedation for psychological distress and anguish but who become oversedated when left undisturbed during sedation with longer-acting agents. It has advantages over anesthetic agents, such as thiopentone, as it is non-cumulative.

A draft protocol for the use of propofol at the Hospice of Our Lady and St. John at Willen is shown in the Appendix. This protocol has proved successful in allowing palliative care nurses with no experience of intensive care to feel confident in the safe administration of propofol.

References

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Appendix

Protocol for the Use of Propofol at Willen Hospital

Propofol is an ultra-fast-acting anesthetic agent normally used in bolus doses of 100–200 mg to induce general anaesthesia and in doses, 10–200 mg per hr to sedate patients in the intensive care unit. The sedation obtainable varies from that of a mild anxiolytic to unconsciousness suitable for full ventilatory support. It must be administered intravenously.

At Willen, we will be using propofol for sedation, especially in more difficult cases.

The dose range prescribed will be between 5 mg/hr and 70 mg/hr, although this range may be modified when we have gained more experience with its use in palliative care.

Please note:

1. Any change in the rate of administration will have an effect within 5 min.
2. If it is necessary to increase the sedation of a patient *quickly*, a small bolus may be

given, as prescribed by increasing the rate of the pump for 2–5 min until the bolus has been administered. *The nurse must remain with the patient while the bolus is being administered, observing the patient and the pump **ONLY**, while the pump is at the higher rate.* Immediately return the pump rate to the slower rate after the bolus has been infused.

3. If the patient is too "deep," the infusion may be switched off for a few minutes and then restarted at a lower rate when the patient "lightens."
4. When an infusion runs out, the patient will lighten very quickly. It is therefore necessary to have a fresh supply immediately available.
5. Midazolam will not be used in conjunction with propofol, as the latter is much faster, more controllable, and is metabolized more rapidly.