SOUNDING BOARD

BARBITURATES IN THE CARE OF THE TERMINALLY ILL

Barbiturates are well known for their capacity to cause death reliably and painlessly and for their efficacy in producing unconsciousness before the administration of other lethal drugs. Barbiturates are used in the execution of prisoners by lethal injection, are commonly employed by Dutch physicians in performing euthanasia, and have played a part in reported cases of assisted suicide in the United States. A recent best-selling book recommends barbiturates as a reliable method of suicide for the terminally ill.

Physicians also administer barbiturates to the terminally ill without intending that they be used to cause the death of the patient. Even in these circumstances, however, the unavoidable side effects of the drugs may hasten the patient’s death, and care givers may be uncertain about whether their actions will be viewed as killing or caring. In this article, we review situations in which the nonlethal use of barbiturates may be indicated and discuss situations in which their administration can be morally justified. We also provide practical advice for the use of these agents.

CASE REPORTS

Patient 1 was a 20-year-old woman with a retroperitoneal soft-tissue sarcoma that arose as a second cancer after she had been successfully treated for a rhabdomyosarcoma of the cervix and vagina at the age of 14. Despite surgical excision and chemotherapy, her second tumor spread locally, metastasized to her spine and lungs, and eventually invaded her spinal canal from T11 to L3. The intensity of her pain increased steadily. Maximal-dose radiation therapy had already been administered, and decompressive surgery was not feasible because of the size of the tumor. Trials of phenytoin and lorazepam were without benefit. A fentanyl infusion produced only partial relief.

A subarachnoid catheter was placed below the site of the tumor, and an infusion of bupivacaine diminished her leg spasms, but did not result in sensory analgesia in dermatomes above T11 because of a noncomplete spinal block at approximately L1. A subarachnoid injection of phenol at T7-T8 also failed to provide adequate pain relief.

Her pain became so severe that she relinquished most decision making to her mother. With understanding that she desired pain control even if it could only be achieved at the cost of sedation. She was then kept in a state of light sedation (with intermittent arousability to voice) with a fentanyl infusion (at a rate roughly corresponding to 5000 mg of morphine per hour), nitrous oxide (50 percent in oxygen) by face mask, and a methohexital infusion (loading dose 2 mg per kilogram of body weight; infusion, 4 to 5 mg per kilogram per hour) until she died of progressive hypoxemia two days later.

Patient 2 was a 19-year-old woman who for nine years had had an astrocytoma that now involved her brain stem and cervical spinal cord. As her tumor...
progressed, she became quadriplegic and dependent on a ventilator. Increasingly severe pain in her extremities prompted trials of systemic opioids, anticonvulsants, tricyclic antidepressants, and baclofen. Ultimately, a subarachnoid catheter was placed, and her pain was successfully managed for most of the next seven months with an infusion of bupivacaine, along with amitriptyline at bedtime. The details of her pain management have been described elsewhere. When refractory tolerance to these medications developed, at a time when the patient was lucid and comfortable, she chose to be disconnected from her ventilator and allowed to die.

She had discussed the discontinuance of mechanical ventilation with her family and care givers on many occasions. During her several years of dependence on the ventilator, an intense fear of being accidentally disconnected from the ventilator and dying of suffocation had developed. She had therefore repeatedly asked to be rendered unconscious before having the ventilator withdrawn. An anesthetic dose of the barbiturate thiopental was administered before withdrawal.

Patient 3 was a 20-year-old woman with widely metastatic Ewing’s sarcoma. She was admitted to the hospital for extreme exacerbation of ongoing hip, leg, and low back pain. She had multiple bony metastases, including numerous spinal lesions, for which she received ibuprofen and increasing doses of methadone and hydromorphone.

Dexamethasone was administered adjunctively, and she received palliative radiation therapy to her spine. Her pain escalated, and her hydromorphone infusion was increased to 100 mg per hour, along with bolus doses of methadone in excess of 300 mg every two to six hours. (Cumulatively, the methadone and hydromorphone were administered in doses roughly equivalent to 1500 mg of morphine per day.)

A lumbar intrathecal catheter was placed. A subarachnoid infusion of bupivacaine and hydromorphone produced good analgesia with markedly improved alertness. The systemic infusion of hydromorphone and methadone was discontinued. The next day, because of a miscommunication, she was without intrathecal infusion for approximately 20 minutes, which resulted in a rapid and profound recurrence of pain. In her agony she screamed that she wanted to be killed. She received ample doses of intravenous hydromorphone, but when this failed to relieve her pain immediately, she received a loading dose of pentobarbital (3.3 mg per kilogram) followed by an infusion (1 to 2 mg per kilogram per hour). This agent produced sleep, with good maintenance of respiration and stable hemodynamics. The spinal infusion of bupivacaine and hydromorphone was restarted shortly thereafter. The patient had relied heavily on her husband and her mother in earlier clinical decision making, and they were asked whether they believed she would want to be awakened from the barbiturate coma. They both believed that she would choose to remain sedated because of an overriding fear that severe pain would return. The pentobarbital infusion was continued until she died two days later.

Patient 3 was an eight-year-old girl in whom multisystem organ failure developed after unsuccessful liver transplantation. Those caring for her eventually reached the conclusion that she could not survive and that it would be appropriate to withdraw ventilatory support. Her family would not assent to the withdrawal of her ventilator, however, despite their belief that her death was inevitable, they viewed the withdrawal as an active decision to end her life.

Rather than seek ways to force the termination of mechanical ventilation, those caring for the patient chose to focus on how to support her and her family within the limits of their requests. Pharmacologic paralysis was discontinued, allowing a better assessment of the child’s suffering. Paralysis had to be reinstated, however, in order to maintain respiratory stability. The patient responded to most routine nursing interventions with hypertension and tachycardia, and her care givers were concerned that she might be suffering. Escalating doses of opioids and benzodiazepines were prescribed, with some improvement in the hemodynamic response to nursing care. Nonetheless, some involved in her care believed that even if she were free of physical pain, she might still be suffering from an awareness of her condition, her paralysis, and her total dependence on life support. The question arose whether it would be more humane to begin an infusion of barbiturates in order to render her deeply sedated or unconscious. This possibility was rejected for fear of giving the impression that those caring for her were trying to kill her.

**Ethical Considerations**

Administering barbiturates to the terminally ill is potentially problematic from an ethical perspective because these agents generally hasten a patient’s death and have often been used to kill patients intentionally. Although clinicians generally acknowledge an overriding moral duty to relieve pain and suffering, most also believe that this duty is constrained by the prohibition against killing. Despite the increasingly popular view that euthanasia is morally permissible under some circumstances and the fact that several states are considering pro-euthanasia legislation, intentionally killing anyone is illegal at present. Can we identify relevant criteria for the permissible use of barbiturates that respect the prohibition against killing?

This question is closely analogous to one that arises in the administration of opioids to the terminally ill. Like barbiturates, opioids not only comfort patients, but may also hasten death through respiratory depression. The administration of opioids in this setting is often ethically justified on the basis of the principle of double effect. This principle draws a distinction between the intended effects of a person’s action and the
unintended although foreseen effects of that action. A nurse or physician who administers morphine to a terminally ill patient intends to relieve the patient’s pain; the possibility of respiratory depression and an earlier death is unintended but foreseen. In this setting, since the care giver’s first responsibility is to relieve pain and suffering, the potential for hastening death is tolerated as a necessary evil.

Can the administration of barbiturates be justified on the basis of double effect? Whereas providing analgesia is uncontroversially beneficial in virtually all instances, rendering a patient deeply sedated or unconscious is at most beneficial in only limited circumstances. We present three situations in which inducing deep sedation or unconsciousness with barbiturates may be viewed as beneficial: to relieve physical suffering when all reasonable alternatives have failed (as with Patient 1), to produce unconsciousness before terminal extubation (as with Patient 2), and to produce deep sedation and unconsciousness as a means of relieving nonphysical suffering (as with Patients 3 and 4).

The first category exemplifies the instrumental use of barbiturates to relieve physical pain. Barbiturates can be used for this purpose only after attempts to achieve adequate analgesia with opioids and other agents have failed, since barbiturates involve a much greater risk of potentially life-threatening side effects.

The proportion of terminally ill patients who require heavy sedation to control symptoms is controversial. A prospective study of 120 consecutive patients with cancer who were referred to a palliative care service found that more than half ultimately required sedation-induced coma to control unendurable physical symptoms. Others claim (and our experience leads us to agree) that the overwhelming majority of patients with cancer and other terminal illnesses associated with pain can be made comfortable by the titrated administration of opioid analgesics and still maintain an adequate clarity of sensorium and respiratory drive. Such treatment may require extraordinarily high doses of opioid, in some cases more than 1000 mg of morphine or its equivalent per hour. When these more traditional approaches to controlling physical suffering are inadequate, however, barbiturates should be considered an ethically appropriate approach for the relief of pain and suffering.

In regard to the second category, sedating patients before withdrawing mechanical ventilation is widely practiced and generally condoned. Experience has shown, however, that dyspnea can be an exceptionally difficult symptom to extirpate. Opioids are often effective, since they blunt the physiologic responsiveness to hypercarbia and hypoxia and diminish the anxiety associated with hunger for air and shortness of breath. These actions may be sufficient in many cases, but some patients clearly request more than these effects. Some patients want to be “asleep” when the ventilator is withdrawn. This request is similar to those of patients who prefer general anesthesia for procedures that could be performed under regional anesthesia. In both cases the impending event is so psychologically distressing to the patient that mere pain control is not enough. When an informed and competent patient (such as Patient 2) requests to be unconscious before the withdrawal of a ventilator (or when a surrogate makes the same request for a patient), we believe that care givers should accede.

Finally, should barbiturates be used for the heavy sedation of patients who are not in unmanageable pain? Is there a role for barbiturates in the treatment of nonphysical suffering? Cassell has drawn attention to the fact that whereas physicians tend to conceptualize suffering in terms of physical pain, “patients and their friends and families do not make a distinction between physical and nonphysical sources of suffering in the same way that doctors do.” Defining the role of barbiturates and other sedatives in the care of terminally ill patients therefore requires recognition of the fact that “suffering can include physical pain but is by no means limited to it.” In this view, even if a patient is free of pain, there may be suffering associated with prolonged dependence on life-sustaining procedures such as mechanical ventilation and dialysis, confinement to bed, loss of control over bodily functions, and witnessing the deterioration of one’s own health. This may have been the case with Patient 1. Or, as with Patient 3, patients who are not currently in pain may suffer from the fear that the pain will return. Even though many religious and philosophical traditions hold that this suffering may be of great value, some patients reject this view and may prefer a state of deep sedation or unconsciousness. Some care givers may have moral objections to administering medications to make the patient unconscious. They may believe that this practice crosses the threshold between making the patient’s suffering tolerable and effectively terminating the patient’s conscious existence. Although these views deserve respect, those who hold them must nevertheless acknowledge the right of patients to make the choices for themselves and must attempt to find others who are willing to care for a patient in accord with the patient’s desires.

Justification based on the principle of double effect requires that the clinician intend only to relieve the patient’s suffering and not to cause death. When barbiturates or opioids are administered to the terminally ill, however, both effects are often seen as desirable. The hastening of death in these cases is sometimes referred to as “a blessing in disguise.” Justification by double effect may therefore function as a “fig leaf” for euthanasia. This was a central issue in a recently reported case involving the administration of barbiturates to a newborn with a serious congenital malformation. The same ambiguity arises when one chooses the means of sedation for terminally ill patients who are receiving mechanical ventilation. Since virtually no amount of opioid will hasten death in these patients, barbiturates may be chosen precisely...
because they will hasten death through myocardial depression. Since the true intent in this case would be the death of the patient, this practice would not be permissible under the traditional ethic.

**Practical Aspects**

As a class, barbiturates are not analgesic and may even be hyperalgesic at low doses. For this reason, we believe that barbiturates should be used in sufficient doses to maintain effective sedation and should only be used when the goal is to produce deep sedation or unconsciousness. Other agents, such as benzodiazepines, opioids, and phenothiazines, may be preferable for achieving mild-to-moderate sedation and analgesia. Although it was reported in one clinical series that opioid analgesics were not necessary after barbiturate sedation had begun in patients with terminal cancer, we strongly recommend maintaining opioid infusions along with barbiturates for patients in severe pain.

All barbiturates are capable of producing deep sedation and unconsciousness. When this effect is needed for only a brief period, as with Patient 2, thiopental is an ideal choice. In healthy patients, 5 to 7 mg of thiopental per kilogram reliably produces unconsciousness. Terminally ill patients may be cross-tolerant because of other sedatives, however, and the dose may need to be increased accordingly.

When long-term deep sedation or unconsciousness is desired, either thiopental or one of the longer-acting barbiturates may be used. Thiopental infusions for up to 1+ days have been reported in patients receiving mechanical ventilation, with minimal alterations in hemodynamic measures. Mean rates of infusion ranged from 70 to 180 mg per hour, but not all the patients maintained spontaneous ventilation at these doses.

Pentobarbital is a longer-acting barbiturate with a half-life of 15 to 48 hours. It has been used extensively for short-term sedation and to control intracranial hypertension and status epilepticus. It is commonly used for one to three days in patients with cancer who have intolerable nausea with chemotherapy. These patients remain sedated but arousable to stimulation, and they have adequate depth of respiration and maintenance of protective airway reflexes. We recommend beginning with an intravenous dose of 1 to 3 mg per kilogram, administered slowly to minimize adverse hemodynamic effects, with additional doses then given to achieve the desired effect. Since tolerance may develop rapidly, we have found it helpful to administer pentobarbital by continuous infusion (beginning at 1 mg per kilogram per hour), escalating the dose as often as necessary to maintain the desired level of sedation.

**Conclusion**

The failure of the medical profession adequately to address pain control in the terminally ill is allegedly responsible for much of the public's recent interest in euthanasia and assisted suicide. Barbiturates present an interesting paradox, since they may provide both effective relief from suffering and a means of intentionally killing. The symbolic association of barbiturates with killing has probably contributed to the reluctance of physicians to use them to relieve symptoms in the terminally ill.

Euthanasia is arguably becoming more acceptable among the public and the medical profession. Proponents of euthanasia and assisted suicide will find it necessary to justify the administration of barbiturates by appealing to the distinction between intended and unintended effects. They justify their views on other grounds, such as the right of autonomous persons to choose for themselves. Even if euthanasia becomes legal, however, many care givers will continue to believe that their commitment to providing relief from suffering is constrained by a prohibition against the intentional killing of patients. For these care givers, barbiturates may nevertheless remain an important therapeutic option.

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**REFERENCES**


