CE 3.0 HOURS Continuing Education

Use of Benzodiazepines as Anxiolytics in Neonates

Are We There Yet?

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ABSTRACT
Few controlled trials exist to demonstrate the efficacy and the risks of pharmacologic agents used in treating pediatric, and more specifically neonatal patients. It is not different for the central nervous system altering class of drugs, benzodiazepines (BZDs). Little information is known about the long-term effects of BZDs use in neonates as anxiolytics and sedatives causing trepidation with their use in the clinical setting. Insufficient data related to the use of BZDs result in a lack of clear recommendations to guide caregivers at the bedside on the safest administration patterns to avoid long-term adverse effects. However, caring for ill neonates, in particular surgical patients and infants requiring prolonged hospitalizations, necessitates the use of these agents. A literature search within the electronic database, PubMed, of English language, full-text articles published between 2007 and 2012 was undertaken to determine the state of the science regarding the use of BZDs in neonates. These medications cause unwanted effects in neonates with immature hepatic function (primary site of metabolism) and during a developmental period of tremendous neuroplasticity. It benefits caregivers to recognize the need for improved monitoring of stress experienced by infants in the NICU and understand the impact of prolonged agitation and subacute pain on infant development.
Key Words: agitation, anxiolytics, benzodiazepines, chronic pain, cortisol, lorazepam, midazolam, N-PASS, stress

Advances in the field of neonatal intensive care have led to improved care and survival of infants born prematurely or those with congenital malformations that typically were not survivable. Although overcoming these conditions in the acute interim is an important feat of modern medicine, survival of these conditions introduces additional problems, such as long-term hospitalization with exposure to painful procedures, examinations, surgical procedures, and chronic disease. In reality, infants not only experience painful procedures with care in the neonatal intensive care unit (NICU) but also endure stressors related to the nonpainful stimuli present in an acute care setting.[1] Sedation is necessary in treating agitation in hospitalized children and protecting against the accidental removal of endotracheal (ET) tubes, chest tubes, gastric tubes, and central venous, arterial, and urinary bladder catheters. Commonly, caregivers turn to the drug class, benzodiazepine (BZD), for the sedative, anxiolytic, muscle relaxation, amnesiac, and anticonvulsant effects on the central nervous system (CNS), despite minimal analgesic effects.[2,3] The goal of sedation is to dampen the neonate's stress and increase comfort to enhance tolerance to the burden of excessive stimuli.[4] Although BZD medications have been in clinical use for the last 40 years, their use in neonates has been limited. Harmful effects suspected with their use include potential disruption in neurocognitive function, altered responses to pain, as well as other behavioral changes.[5]

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At the bedside, the use of BZDs as anxiolytics could be avoided in neonatal patients altogether until more information is known. However, the stress invoked by repeated painful procedures, prolonged assisted ventilation, and decreased bonding with parents requires that we do a better job addressing agitation and subacute pain in these infants. Caregivers of neonatal hospitalized patients are faced with tremendous uncertainty when it comes to prescribing and the administration of anxiolytics. Providers lack clear guidelines directing the use of BZDs in neonates.

The following case helps illustrate the lack of familiarity with BZD use in the NICU: A former 29-week twin, female, extremely low-birth-weight infant with chronic lung disease, patent foramen ovale, patent ductus arteriosus, cytomegaloviral infection, and tracheoesophageal fistula with esophageal atresia. The infant remained hospitalized postterm with a gastrostomy tube, suctioning sump tube to the esophageal pouch, and intermittent intubations for increased work of breathing, and deterioration of blood gases. The infant tolerated full enteral feedings, yet remained hospitalized for months until sufficient growth was reached for secondary repair and anastomosis of the esophagus. The infant would become agitated with hands-on care and have copious tracheal secretions requiring and leading to frequent ET tube suctioning, which represents a source for subacute neonatal pain.[6] The cycle was repeated daily. As a result of excessive secretions and difficulty positioning the infant, she had frequent, brief oxygen desaturations and limited periods of rest. As the child matured, she was able to grab the ET tube and suctioning sump tube leading to inadvertent tube removal followed by respiratory decompensation and the discomfort of having these tubes replaced. To reduce the infant's agitation and discomfort the BZD, midazolam, was initiated and provided on a pro re nata basis. However, there was a quite a bit of trepidation among caregivers regarding the frequency of administration or whether pharmacologic means should be used compared with conservative nonpharmacologic approaches. Nursing caregivers concerned about the agitation, discomfort, and limited sleep this infant experienced recommended giving routine, scheduled doses such that the infant could experience periods of rest and growth. Resident physicians expressed apprehension with giving repeated doses of a BZD to the infant. Beyond infancy, the effects of BZDs on long-term neurological development are unknown. Moreover, chronic agitation and heightened stress responses exhibited in response to prolonged mechanical ventilation and procedural care in the NICU have impacts on growth and development, as evidenced by altered cortisol levels in children born extremely premature.[7] A more complete understanding of the pharmacologic effects of BZDs used for infant sedation is essential to provide practical guidance in developing strategies that best meet the needs of chronically hospitalized infants, especially those awaiting growth for surgery.

ANALGESIA VERSUS ANXIOLYTICS

The lack of communication in preverbal children presents a significant challenge for meeting the needs and providing comfort to hospitalized infants. In particular, intubated infants who are unable to cry have limited means of communicating with caregivers. It is truly an art to distinguish patterns of crying to tease out symptoms of pain from those of agitation and anxiety. An assessment that differentiates between pain and agitation relies heavily on the subjective evaluation of caregivers.[8] Pain and irritability may be related and present simultaneously, but agitation is a behavior symptom that may be present in the absence of pain. Agitation or irritability can be the result of environmental overstimulation, respiratory insufficiency, a complication of neurologic pathology, or pain.[8] Although the goal is to prevent both pain and agitation from occurring initially, this is not realistic. It is imperative to (*a*) recognize the presence of pain with agitation and (*b*) be able to distinguish the 2 to adequately treat them both, whether it is through traditional comfort measures, pharmacologic therapy, or a combination of both. It is also important to distinguish pain from agitation so as to determine whether analgesia or sedatives will be used. For the purposes of this article, the discussion is limited to sedative therapy with the use of BZDs.

The goal of sedation is to induce "a calm tranquil state that allays anxiety and excitement."[9(p56)] The NICU environment with sonorous monitor and ventilator alarms, unnatural lighting, repeated painful stimuli, and multiple distinct caregivers contributes to overstimulation and disrupted sleep patterns for infant patients that may interfere with homeostasis and prolong recovery.[10] The setting and care provided often induce pain, irritability, and stress, especially with indwelling tubes, catheters, and maintenance of mechanical ventilation.

Lack of Sedation Studies and Scales Validated for Pediatric Use

In general, there is a lack of knowledge about appropriate sedation in the neonatal population and a need for valid, reliable, and clinically useful sedation assessment tools for preverbal infants.[11] Historically, research has focused on acute or procedural pain, such as the type caused by tissue injury related to surgery or heel puncture, overlooking the experience of prolonged pain.[6,12] The NEOPAIN study explored the use of the opioid, morphine, in the treatment of subacute pain in ventilated preterm

infants finding that morphine is a less effective analgesic agent for treating pain associated with mechanical ventilation and routine bedside care.[12] In spite of the discomfort that infants may experience in the hospitalized environment, whether it is from catheters, ET tubes, procedures, or prolonged mechanical ventilation, there is a significant gap in knowledge and consistency in evaluating the discomfort that results with care. A simple system to identify, assess, and evaluate treatments for persistent ongoing pain or distress related to mechanical ventilation and care provided in the NICU is lacking.[13] Infants, especially those who are intubated, are unable to communicate their pain experiences to caregivers. As a result, the Neonatal Pain, Agitation, and Sedation Scale (N-PASS) was developed as a tool for assessing ongoing pain, agitation, and sedation with mechanical ventilation and postoperative pain in neonatal patients (0-100 days of age).[8,9] Initial studies of the reliability and validity of N-PASS suggest that it is a clinically useful, reliable, and valid tool for the assessment of pain associated with agitation and sedation after surgery or with mechanically ventilated NICU patients.[9] N-PASS limitations include the inherent biases that result when interpreting behaviors in neonates, as well as the difficulty associated with determining the origin of behavioral responses. The tool has been studied in the clinical setting with a moderately sized sample. The validity is difficult to establish without a gold standard or comparable assessment tools.[9] Currently, the N-PASS appears to be the best available instrument in evaluating the need for sedation in neonates and the response to the provided treatments.

BENZODIAZEPINES: PHARMACOKINETIC PROPERTIES

Benzodiazepines are the most commonly used anxiolytic agents. As a class of drugs, they are generally therapeutic for short-term administration as sedatives, anxiolytics, anticonvulsants, muscle relaxants, and amnesic agents.[14] Both short- and medium-acting BZDs have been used for sedation in pediatric patients. The 2 most commonly used BZDs are midazolam and lorazepam. Diazepam is not routinely used in neonates because of its long half-life, decomposition into long-acting toxic metabolites, and the toxicity associated with its preservative benzyl alcohol. Diazepam also displaces bilirubin from albumin-binding sites contributing to hyperbilirubinemia in neonates.[15]

Benzodiazepine action relies on binding to neuronal γ-aminobutyric acid (GABA) receptors, where BZDs enhance activity of the neurotransmitter GABA, a major inhibitory neurotransmitter of the CNS.[16] Benzodiazepines are not GABA agonists but potentiate the function of endogenous GABA. There is a limit to the degree of CNS depression observed with BZD use based on the finite amount of GABA in the body.[17] Activation of the GABA receptors facilitates intracellular movement of chloride ions to the postsynaptic neuron causing hyperpolarization of that neuron. Hyperpolarization of the postsynaptic neuron prevents further neuronal excitation and widespread inhibition of nerve transmission.[16] The pharmacokinetic principles of BZDs are well studied in adults. However, these results are not directly applicable to children, infants, or neonates given variations in absorption, metabolism, distribution, and drug clearance.[8] The neonate contains significantly fewer GABA receptors compared with the adult, and these receptors have decreased affinity for binding with BZD.[18,19] The number of GABA receptors and ability to bind BZDs increases from 36 weeks postconception through adulthood.[19] The problem continues that the pharmacokinetics of most medications, including BZD, are difficult to identify from a limited number of pharmacologic studies in neonates.

Midazolam

Midazolam is considered a short-acting BZD with a rapid onset of action, and with intravenous, oral, intranasal, and sublingual administration routes.[20] It is used for sedation in neonates requiring long-term mechanical ventilation and is often coupled with opioids (for enhanced analgesia) for those undergoing invasive procedures.[8,21] The goals of midazolam use are anxiolysis, sedation, amnesia, and muscle relaxation. However, it does not have an effect on analgesia.[22] The primary mechanism of action relates to the binding of midazolam to GABA acid subtype A ($GABA_A$) receptors of the CNS resulting in enhanced GABA activity and greater neural inhibition.[18,23] Midazolam is metabolized by cytochrome P450 3A4 (CYP3A4) hepatic enzyme, which oxidizes midazolam into a less-active metabolite, hydroxylated midazolam (1-OH-midazolam). Subsequent transformation of midazolam occurs via glucuronidation for enhanced urinary excretion.[20] The enzymes responsible for glucuronidation are not mature at birth and mature at different rates.[18] Because of reduced CYP3A family activity in the ill or premature neonate, midazolam plasma clearance is delayed and can lead to drug accumulation, especially with repeated doses, prolonged infusions, or administration of multiple drugs utilizing the CYP3A metabolic pathway.[20,21,24] The duration of action ranges from 2 to 6 hours, with an elimination half-life in term neonates of 4 to 6 hours, and a highly variable elimination half-life in preterm infants, up to 22 hours (Table 1).[20] The increased elimination half-life and delayed plasma clearance of midazolam in premature infants compared with older infants, children, and adults have been demonstrated in

TABLE 1. Comparison of the Benzodiazepines: Midazolam and Lorazepam[a]

Agent	Method of Action	Length of Action	Method of Administration	Sedation Dosages	Correlation With N-PASS Score
Midazolam (Versed)	Enhances neuronal effects of GABA (inhibitory neurotransmitter) Short-acting BZD Rapid onset of action because of high lipid solubility at neutral pH with rapid penetration of BBB	Onset: 1-2 min Duration: 30-60 min (half-life in term neonate is 4-6 h; and variable in the premature infant (up to 22 h)	Given as IV bolus slowly (**over at least 5 min to avoid apnea**) Dose repeated on the basis of response, typically every 2-4 h Also given as continuous IV infusion (though not currently recommended in premature infants), oral, intranasal, and sublingual routes	Single IV bolus dose: 0.05-0.15 mg/kg	Intervention and treatment considered with N-PASS scores > 3 Sedation marked by N-PASS ≤ -2
Lorazepam (Ativan)	Enhances neuronal effects of GABA (inhibitory neurotransmitter) Longer-acting BZD resulting in less frequent dosing Slower onset of action because of decreased BBB penetration Metabolites are inactive leading to fewer drug interactions	Onset: within 15 min; peak serum drug levels within 45 min Duration: 8–12 h (mean half-life in term neonate is 40 h)	Given as IV bolus slow-push Dose may be repeated dependent on clinical response Oral formulation also available	Single IV bolus dose: 0.05-0.1 mg/kg	

Note: Midazolam dosages are different for each of the other administration routes (eg, continuous, intranasal, sublingual, and oral routes), which all have different dosages. This table does not provide the dosing for continuous, intranasal, sublingual, or oral routes.

Abbreviations: BBB, blood-brain barrier; BZD, benzodiazepine; GABA, gamma-aminobutyric acid; IV, intravenous; N-PASS, Neonatal Pain, Agitation and Sedation Scale.

[a]Data from Anand and Hall,[2] Noerr,[4] Lieh-Lai and Sarnaik,[16] Lehne,[17] Young and Mangum[20] Hummel et al,[40] and Gomella et al.[41]

pharmacokinetic analyses and are associated with immature function of CYP3A4 activity.[21]

There are advantages to the use of midazolam in neonates attributed to its water solubility, relatively short half-life (compared with other BZD), and its less pharmacologically active metabolite. However, because of immature and variable pharmacokinetics, infants are at risk for drug accumulation and prolonged sedation with infusions or repetitive dosing over several days.[25] Given the lack of published controlled trials on midazolam used for ventilated prematvure infants, optimal dosing and dose ranges remain unknown.[25] The Cochrane Review of intravenous midazolam use as a sedative in neonates receiving intensive care concluded that there are insufficient data to promote the use of midazolam in neonates and the safety of midazolam use is questioned.[11] Hall et al make the following recommendations with respect to the intravenous use of midazolam for the sedation of ventilated neonates:

1. Doses should be individualized and titrated, and treatment should be limited to a few days;
2. Continuous infusions are preferred over bolus doses; the maximum dose for continuous infusion is 60 μg/kg per hour in term neonates, and should be decreased for lower gestational ages;
3. The maximum for individual bolus doses is 200 μg/kg, and should be infused over 1 hour;
4. Doses should be decreased by approximately 30% if treating concurrently with narcotics;
5. Do not use in infants who are hypotensive; and
6. Use with extreme caution in infants being treated with fluconazole or other medications (eg, erythromycin) that interferes with CYP 3A4 metabolism.[25(p294)]

Such recommendations provide adequate direction, express caution, and encourage conservative and tailored dosing regimens for administering BZD to treat the stress and agitation hospitalized infants may experience (Table 2).

Lorazepam

Lorazepam use is favored for sedation over midazolam because of its prolonged duration of action. It is also used as an anticonvulsant in neonates especially for seizures unresponsive to phenobarbital and phenytoin. As a medium-acting BZD, its duration of action is 8 to 12 hours reducing the need for repeated doses or a continuous infusion (Table 1).[2,25] Lorazepam is metabolized in the liver to an inactive glucuronide, for renal excretion. As is seen with midazolam, and many of the drugs used today, the immaturity of the liver enzymes in the neonatal period limits the degree of metabolism. In the neonate, there are fewer enzymes responsible for the glucuronidation of lorazepam compared with adults resulting in an increased half-life of the drug, delayed clearance, and decreased volume of distribution.[26] Lorazepam is highly lipid-soluble with a mean half-life in term neonates at 40 hours (Table 1).[20] The properties of lorazepam and the immature hepatic function of the neonate demonstrate that neonates metabolize lorazepam differently than adults and even older children (Table 3).

TABLE 2. Adverse Effects and Special Considerations With Midazolam Use[a]

Black box warning: respiratory depression (apnea) and respiratory arrest with rapid administration
Hypotension
Effects on respiration and blood pressure increase with concurrent use of other narcotic agents; risks are minimized with slower rates of administration
Seizures
Alterations in cerebral blood flow—with potential impact on development of periventricular leukomalacia
Drug interactions with other agents—because of hepatic microsomal oxidation metabolism pathway
In renal failure: decreased urinary excretion and subsequent accumulation of the active metabolite of midazolam
Dependence: significant adverse effects with abrupt withdrawal after long-term sedation (irritability, agitation, tremors, sleeplessness)
Monitor hepatic function with continued use

[a]Data from Anand and Hall,[2] Khurana et al,[15] Lieh-Lai and Sarnaik,[16] Young and Mangum[20] and Hall et al.[25]

ADVERSE EFFECTS OF TREATMENT

Use of sedation in the acute care setting requires further evaluation of the long-term outcomes of treatments provided during the early days of an infant's life. Adverse effects associated with the use of BZD are primarily limited to neurologic insults and this is anticipated because of the target site of action for BZD. The immediate harmful effects are respiratory depression with bradycardia and hypotension.[20,22] Other effects attributed to the use of BZDs include dependence, tolerance, myoclonic activity, seizures, increased incidence of intracranial hemorrhage, and subsequent development of periventricular leukomalacia.[2,15,25] In addition, constipation, nausea, urinary retention, and limited to no effect on pain are notable disadvantages to the use of BZDs.[25] It is important to consider that the method of administration may contribute to the harmful effects of

TABLE 3. Adverse Effects and Special Considerations With Lorazepam Use[a]

Respiratory depression, apnea.
Rhythmic myoclonic jerking observed with the use for sedation in premature neonates.
Lorazepam is a hyperosmolar agent, which may cause extravasation. Monitor intravenous site for swelling, erythema, and pain.
Several available products contain 2% benzyl alcohol and 18% polyethylene glycol 400. Consider diluting lorazepam dose with sterile water, normal saline, and D5W to reduce exposure to benzyl alcohol.

Note: D5W, 5% dextrose in water.
[a]Data from Noerr,[4] Lehne,[17] and Young and Mangum.[20]

midazolam treatment as alterations in cerebral blood flow and oxygenation have been observed with intermittent bolus doses[2,27] (Table 4).

The metabolism of BZDs via a glucuronidation step disrupts bilirubin metabolism, which also relies on hepatic glucuronidation for clearance. The inhibition of bilirubin metabolism can be particularly harmful in premature and asphyxiated infants.[25] The constipation and urinary retention that have been associated with BZD use may also contribute to delayed bilirubin excretion.[2]

Tolerance and Withdrawal

Similar to the properties of opioids, patients receiving BZDs develop tolerance and can experience dependence and withdrawal from these medications.[25] The incidence of BZD withdrawal in critically ill pediatric patients ranges from 17% to 35%, although this incidence may be lower in neonates.[28] Benzodiazepine withdrawal can result in an abstinence syndrome with the symptoms of anxiety, agitation, and sympathetic activation (hypertension and tachycardia) and can be observed with abrupt discontinuation of the BZD.[29] Ironically, the same symptoms we aim to treat with the initiation of BZD therapy are exacerbated with discontinuing BZDs.

Seizures

Seizures, myoclonus, hypertonia, hypotonia, and extrapyramidal movements are among the adverse neurologic effects related to BZD use in neonates.[30] Although the exact origins of these symptoms are not yet known, it is speculated that they are likely because of the immature neuroinhibitory pathways and paucity of GABA receptors in the cerebellum of the neonate compared with the adult's.[30] In addition, rat models demonstrate that $GABA_A$ is an excitatory neurotransmitter at birth and becomes inhibitory later in the newborn period.[31] Although it is not known when the $GABA_A$ receptors change to an inhibitory receptor in humans, these findings have significant implications for the neurodevelopment and contribute to understanding the role BZD may play as mediators of $GABA_A$ activity.

TABLE 4. Adverse Effects of Benzodiazepines[a]

Respiratory depression with bradycardia and hypotension
Seizures, myoclonus, hypertonia, hypotonia, dependence, and extrapyramidal movements
Little to no effect on pain
Constipation, nausea, and urinary retention

[a]Data from Noerr,[4] Lieh-Lai and Sarnaik,[16] Young and Mangum,[20] Anand,[22] and Gomella et al.[41]

Although development differs across species, there are similarities in the patterns of basic developmental processes. Thus, the excitatory nature of $GABA_A$ receptors at birth is thought to explain the seizures in premature and term infants after BZD exposure.[31,32]

Long-term Effects on Neurologic Development

The long-term behavioral and cognitive effects of neonatal exposure to midazolam are unknown.[5] Publications discussing BZD use frequently comment on the lack of longitudinal studies that focus on neurodevelopmental impacts of BZD use in the infant and this remains the case today.[30] Previous studies measuring cerebral arterial blood flow in premature neonates given intravenous boluses of midazolam demonstrated a significant, transient decrease in the cerebral blood flow subsequent to administration of a single dose of midazolam.[11] The cerebral blood flow changes observed were also associated with increased incidence of intraventricular hemorrhage and periventricular leukomalacia, which have neurodevelopmental implications for the use of BZD in premature infants. Although a more recent animal study (mouse model) demonstrated that midazolam use early in life has no effect on learning and memory behavior in adult mice, the results should be scrutinized.[33] However, in vitro studies have identified altered patterns of neuronal development by interfering with dendritic branching, and other animal models demonstrate neuroapoptosis in the cerebral cortex and basal ganglia of newborn mice given a single dose of midazolam.[5] There have been no prospective studies in the NICU to uncover the effects of sedatives on infant brain development.[5]

EFFECTS OF PROLONGED HOSPITALIZATION

Prolonged hospitalization in the NICU and repeated exposures to the subacute and chronic pain induce stress and activation of the stress response and release of catecholamines.[34] The role of cortisol is essential to physiologic and metabolic function and at inappropriate levels is thought to play a role in altered neurodevelopment with effects on cognition, learning, and memory. During periods of prenatal and early development of brain "hard-wiring," it has been shown that alterations in cortisol levels and stimulation of the hypothalamic pituitary axis are linked to reduced hippocampal function and impaired cognitive ability.[35] Inappropriate glucocorticoid plasma levels are associated with other elements of adult disease such as atherosclerosis, immunosuppression, depression and cognitive impairment, hypercholesterolemia, and increased incidence of type II diabetes mellitus.[36]

Finally, recent studies have elucidated the effects of neonatal procedural pain on early postnatal body and head growth demonstrating that there is a delay in growth in preterm infants experiencing repeated procedural pain.[37] As is the case with the infant discussed previously, linear growth is critical to her progress and directly influences the time she will await surgery and length of hospitalization. In combination, the negative stimuli of the NICU setting and the associated pain contribute to infant stress and disrupt normal brain development as a result of excitatory cell death.[38]

APPROPRIATE ALTERNATIVES

Initial treatment for agitation in the neonate should focus on nonpharmacologic interventions as is recommended for adults with anxiety disorders. The use of behavioral techniques, relaxation exercises, and distraction would reduce the reliance on pharmacologic sedatives. In the NICU population, developmentally appropriate care that decreases environmental stimuli, optimizes positioning in neutral flexion, incorporates swaddling, provides opportunities for nonnutritive sucking, and minimizes handling can reduce stress and obviate the need for medications.[25] With few available data on the particular physiologic action of BZDs, researchers resort to modeling the pharmacokinetics of the drugs by piecing together known information. Models are able to assist with understanding midazolam pharmacokinetics and clearance. Anderson and Larsson[39] assert that such models be employed to avoid further direct practice and address gaps in knowledge about drug profiles commonly used in pediatric patients.

CONCLUSION

Despite advances in the field of neonatology, long hospitalizations exist wherein infants experience stress and subacute pain associated with care in the NICU and possibly prolonged periods of intubation and mechanical ventilation. There are gaps in knowledge related to recognizing and treating episodes of agitation. Although sedation is common in other patient populations, there is unfamiliarity with sedative use, particularly BZD, in neonatal patients. It remains unclear as to whether BZDs are effective and safe for use in the neonate, as the long-term effects of BZDs on neurodevelopment remain unknown. It is imperative for longitudinal studies to explore the impacts of these medications on the learning, cognition, and behavior and for additional research to identify other potential pharmacologic agents that better target neonatal metabolism and absorption. In the meantime, clinicians and caregivers should use these medications with caution and in combination with traditional nonpharmacologic measures to achieve comfort and sedation.

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