Lorazepam in the Treatment of Refractory Neonatal Seizures

A Pilot Study

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• Seven neonatal patients with severe seizures unresponsive to conventional anticonvulsant therapy were treated with lorazepam. Immediate cessation of seizure activity occurred in all patients within five minutes. Although seizures recurred in two infants eight hours later, frequency and severity diminished. There were no apparent significant side effects attributed to the medication.

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Refractory seizures are often a difficult management problem in the neonatal patient. Seizure activity requires appropriate treatment to minimize mortality and to reduce neurologic sequelae.[1] The successful management of refractory neonatal seizures depends on the use of drugs with rapid onset of action, long duration, and minimal side effects. Therefore, phenobarbital sodium and phenytoin sodium are usually the drugs of first choice.[1] Diazepam, a benzodiazepine, has also been used in neonatal patients for many years for the treatment of seizures. Its use, however, is limited by its short duration of action and occasional reports of cardiovascular and/or respiratory complications.[2] Recent literature suggests that lorazepam, a new longer-acting benzodiazepine, is both effective and safe in the management of status epilepticus in adults and older children.[3-5] To our knowledge, comparative data documenting the safety and efficacy in neonates are unavailable to date. We con-

ducted a pilot study of seven critically ill infants with refractory seizures to investigate the safety and potential efficacy of lorazepam. The study was approved by the Institutional Review Board of the hospital.

METHODS

Seven infants with severe refractory seizures were studied (Table). The group consisted of two male and five female infants, varying in gestational age from 30 to 43 weeks. Birth weights ranged from 1540 to 4224 g. Five infants were full-term and two were preterm.

The seizures in all of these infants were a result of severe perinatal asphyxia and hypoxic-ischemic encephalopathy; one infant also incurred an intraventricular hemorrhage. Infants with seizures secondary to hypoglycemia or electrolyte disturbances were excluded, as were infants with congenital malformations of the brain. Infants were selected for the study only if they experienced severe asphyxia neonatorum. None of these infants had a five-minute Apgar score exceeding 5 (Table). All infants were evaluated and treated for presumptive sepsis; all cultures of blood and cerebrospinal fluid were subsequently negative for bacterial growth. The age of onset of seizures ranged from less than 1 to 72 hours. All patients had clinically documented seizures of the multifocal clonic and subtle types.

Initial treatment consisted of appropriate intravenous loading doses of phenobarbital and phenytoin sodium, each at 15 mg/kg per dose, within the range (15 to 20 mg/kg) previously recommended.[6] Some authorities have subsequently recommended a loading dose of 20 mg/kg for each.[2] Therapeutic levels of phenobarbital (20 to 30 mg/L) were documented in all seven infants. Therapeutic levels of phenytoin sodium (10 to 20 mg/L) were documented in five of the seven infants. In the

other two infants, the phenytoin levels were subtherapeutic when lorazepam was administered. Infants were enrolled in the study if seizures persisted after loading doses of these drugs.

After obtaining informed consent from the parent(s), infants received lorazepam in a dose of 0.05 mg/kg per dose given intravenously over two to five minutes. This dose was based on an extrapolation of the standard adult dose of 4 mg. In three of seven infants, electroencephalogram (EEG) monitoring was done before, during, and after lorazepam injection. In all infants, EEG monitoring was done within 24 hours after lorazepam administration. Lorazepam was considered to be effective on the basis of immediate cessation of clinical seizure activity and suppression of seizure activity in EEG, when available.

The clinical and laboratory data that were collected and monitored included the following: (1) vital signs, including blood pressure, up to 24 hours after lorazepam administration; (2) serial observations and descriptions of seizure activity; (3) baseline laboratory data, including a complete blood cell count, platelets, and 20-factor automated blood chemistry analysis profile, and phenobarbital and phenytoin levels. These data were obtained serially for 72 hours following lorazepam administration. Blood gases were monitored as dictated by the clinical condition. No infant received a second dose of lorazepam. Maintenance doses of phenobarbital and phenytoin, however, were begun 12 hours after loading doses of these drugs.

Either computed tomography of the brain or cranial ultrasound was performed in six infants. The ultrasound of patient 3 revealed grade II intraventricular hemorrhage. Results of imaging studies in the remainder of the infants were normal.

RESULTS

Following the administration of lorazepam, temperature, blood pres-

| | | | Apgar Scores at 1, 5, and | Etiology of | Age at Onset of | | |
Patient	Birth Weight, g	Gestational Age, wk	10 min	Seizures*	Seizures, h	Response	Short-term Outcome
1	3580	42	2, 5†	HIE	4½	No recurrence of seizures for 24 h after lorazepam except occasional lipsmacking at 12 h	Discharged from hospital on 13th d of life on regimen of phenobarbital; neurologic examination results abnormal
2	2640	39	2, 4, 5	HIE	<1	No recurrence of seizures for 24 h after lorazepam except occasional lipsmacking	Discharged from hospital on regimen of phenobarbital on 46th d of life; neurologic examination results abnormal
3	1540	30	0, 2, 4	HIE IVH IVH	1	No seizures for 24 h after lorazepam	Discharged from hospital on regimen of phenobarbital on 78th d; neurologic examination results abnormal
4	4120	42-43	0, 0, 0 0, 3‡ 0, 3‡	HIE	1	Bicycling movements recurred 8 h after lorazepam	Life support discontinued 4 d after lorazepam administration; died within 5 min; postmortem examination revealed encephalomalacia
5	2807	36-37	2, 4, 7	HIE	72	Bicycling movements recurred 8 h after lorazepam	Died at 19 d of age following acute renal failure and multiple organ infarcts
6	2830	38-39	2, 4, 4	HIE	4	No recurrence of seizure activity for 24 h after lorazepam	Discharged from hospital on 16th d of life on regimen of phenobarbital; neurologic examination results abnormal
7	4224	40 +	0, 2, 5	HIE	4	Recurrence of multifocal clonic seizures 12 h after lorazepam	Discharged from hospital on 70th d on regimen of phenobarbital; neurologic examination results abnormal; prolonged stay necessitated by plastic surgery for extensive slough of buttocks

*HIE indicates hypoxic-ischemic encephalopathy; IVH, intraventricular hemorrhage.
†Ten-minute Apgar score not available.
‡Fifteen at 20 minutes.

sure, and pulse remained stable in all infants. In the three patients who required assisted ventilation before lorazepam administration, no deterioration of their respiratory status was observed, ie, they did not require increased respiratory support. In the remaining four infants who were not receiving mechanical ventilatory assistance, no respiratory or cardiovascular compromise was noted.

In five patients, a complete blood cell count and platelet count remained stable. Two infants required blood transfusions for conditions believed to be unrelated to lorazepam administration. One infant required a blood transfusion to replace blood drawn for frequent analysis of blood gases and other laboratory determinations. A second infant required a blood transfusion because of bleeding secondary to disseminated intravascular coagulation. No changes or deterioration was noted in the values of serum electrolytes, calcium, glucose, or protein or liver and renal functions during the 72-hour monitoring. In two infants who required umbilical artery catheterization, serial blood gas monitoring after lorazepam administration revealed no deterioration in acid-base balance or oxygenation.

The onset of action of lorazepam was rapid, with immediate cessation of seizure activity in five minutes. In one infant, bicycling movements recurred eight hours after lorazepam administration, but the severity diminished. In another infant, recurrence of subtle seizures with buccolingual activity recurred eight hours after lorazepam administration, but the frequency and duration decreased.

Electroencephalographic monitoring before lorazepam administration in patients 3, 5, and 6 demonstrated burst suppression patterns and electrographic seizures in the form of rhythmic theta and delta activity or multifocal sharp waves. Within minutes of the administration of lorazepam in patient 3, there was a marked generalized suppression of the background activity with cessation of electrographic seizures. A follow-up tracing three hours later in this patient continued to demonstrate marked background suppression.

In patient 1, an EEG was obtained before receiving lorazepam and a follow-up tracing was performed 24 hours later. The initial EEG showed burst suppression and ictal patterns in the form of multifocal high-voltage spikes and rhythmic delta activity. The next day the EEG was improved, with multifocal epileptogenic activity but no electrographic seizures. Two weeks later, this patient's tracing was normal for conceptual age.

Due to urgent clinical considerations, EEG monitoring could not be obtained during lorazepam administration in the other three patients. Tracings obtained within 24 hours were all abnormal due to background suppression, disorganization, and

focal or multifocal epileptogenic activity. In patient 4, the record was severely suppressed and the question of electrocerebral silence was raised. This patient's tracing reverted to a severe burst-suppression pattern three days later.

COMMENT

Adult human data indicate that lorazepam has a half-life of 13 to 15 hours, rapidly penetrates the central nervous system, and produces minimal cardiovascular and respiratory depression in normal subjects.[7,8] Our preliminary data indicate that lorazepam appears to be a safe and effective adjunct to traditional anticonvulsant medications in the management of refractory neonatal seizures. No cardiorespiratory embarrassment was noted in any neonate receiving lorazepam. Furthermore, there were no instances of anemia, neutropenia, or thrombocytopenia that could be attributed to lorazepam administration. In all patients, serum electrolyte, calcium, glucose, albumin, globulin, cholesterol, and triglyceride levels, and hepatic and renal functions remained unchanged or improved following lorazepam administration. (Improvements in biochemical values correlated with recovery from asphyxia.) In two instances following lorazepam administration, the serum phenobarbital level increased into the toxic range. Both of these levels returned to normal within 72 hours after withholding phenobarbital therapy. Such fluctuations are common in severely ill neonates with variable hepatic function. Additional controlled studies may clarify a possible relationship between elevated phenobarbital levels and lorazepam.

One milliliter of the lorazepam preparation used contains 2 mg of lorazepam, 0.18 mL of the drug solubilizer, polyethylene glycol 400 in propylene glycol, and the preservative, 2.0% benzyl alcohol. The former has caused hyperosmolality in infants receiving 10 mL of a multivitamin preparation containing 30% propylene glycol.[9] The largest dose of lorazepam used in this study, 0.20 mg, required 0.1 mL of the solution, containing 0.018 mL of the solubilizer, approximately 1/500 the volume in the above-mentioned report. Benzyl alcohol has caused a fatal toxic syndrome in preterm infants who received approximately 100 to 400 mg/kg/d of the substance.[10,11] Since the largest *total* dose received by any infant in this study was *2 mg*, the occurrence of this syndrome was considered unlikely.

Another concern relates to the potential for benzyl alcohol to displace bilirubin from albumin binding sites. Theoretically this could result in kernicterus at low serum bilirubin levels in asphyxiated and low-birth-weight infants who already have decreased bilirubin-binding capacity. Other than in vitro data, there is no documentation that benzoate enhances this risk in the human newborn.[12] Furthermore, the dose of benzyl alcohol was so small in our study (0.5 mg/kg) that the effect of bilirubin displacement was considered insignificant.

In all of our infants, lorazepam administration was followed rapidly by cessation of clinical seizure activity. Compared with diazepam, a primary advantage of the drug appears to be the duration of seizure control following administration.[5] Lorazepam prevented recurrence of seizure activity up to 24 hours after administration. The longer duration of seizure control obtained with lorazepam may be due to its slower tissue distribution.[13]

Electroencephalographic data confirmed the cessation of seizure activity accompanied by a generalized suppression of background activity. Such background suppression has also been observed after the administration of diazepam in neonates.[14] The duration of background suppression, however, may be longer after lorazepam administration. Caution must therefore be exercised in cases of suspected electrocerebral silence if the patient has recently received lorazepam.

CONCLUSION

In summary, based on preliminary data in seven patients, lorazepam appears to be a safe and probably effective agent for the treatment of refractory neonatal seizures. Its efficacy appears at least comparable with that of diazepam. Other advantages may include prolonged duration of action and absence of cardiorespiratory depression. We cannot recommend the routine use of lorazepam in the treatment of neonatal seizures. Its use, however, may be justifiable in severely ill neonates with seizures refractory to conventional therapy. A controlled study is needed, perhaps comparing diazepam with lorazepam in randomly assigned cases and including blood level determinations and pharmacokinetics.

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