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MIDAZOLAM FOR TREATMENT OF REFRACTORY NEONATAL SEIZURES

A CASE REPORT

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SUMMARY - Midazolam is a short-acting water soluble benzodiazepine that has been used with an increasing frequency in the last years. Although there are reports on its use in status epilepticus, there is none in the neonatal period. A pre-term (35 w) AGA newborn infant with a severe hypoxic-ischemic encephalopathy secondary to grade III hyaline membrane disease developed status epilepticus in the first 6 hours of life and was successfully treated with midazolam after phenobarbital and phenytoin failed to achieve seizure control. Dosage schedule was 0.2 mg/kg IV, followed by continuous infusion of 0.025 mg/kg/h. Midazolam is an effective drug for neonatal status epilepticus and more experience should accumulate before it can be routinely employed in the neonatal period. This case shows that it is a possible option before using more dangerous drugs, such as thionembutal.

KEY WORDS: status epilepticus, neonatal seizure, high risk newborn infant, neonatal hypoxic-ischemic encephalopathy.

Midazolam no tratamento de convulsões neonatais refratárias: relato de caso

RESUMO - Midazolam é benzodiazepínico hidrossolúvel que tem sido utilizado com frequência cada vez maior nos últimos anos. Apesar de existirem relatos de seu uso no status epilepticus, não há referências durante o período neonatal, o que nos levou a registrar o presente caso. Trata-se de um recém-nascido pré-termo, de 35 semanas, adequado para a idade gestacional, que desenvolveu estado de mal convulsivo nas primeiras 6 horas de vida, consequente a encefalopatia hipóxico-isquêmica por membrana hialina grau III. Após receber fenobarbital sódico e fenitoína em doses adequadas, sem sucesso, as crises foram controladas com midazolam EV, na dose de ataque de 0,2 mg/kg e de manutenção de 0,025 mg/kg/h EV, por infusão contínua, com controle eletroencefalográfico concomitante. Concluimos que o midazolam é eficaz para o tratamento de convulsões neonatais refratárias ao tratamento convencional e que é uma opção antes que drogas como o tionembutal sejam empregadas para o controle das crises. Entretanto, maior experiência clínica é desejável para que seu uso possa ser feito rotineiramente.

PALAVRAS-CHAVE: status epilepticus, convulsão neonatal, recém-nascido de alto risco, encefalopatia neonatal hipóxico-isquêmica.

Midazolam is an imidazobenzodiazepine with unique properties when compared with other benzodiazepines. It is water soluble in its acid formulation but is highly lipid soluble *in vivo*. Midazolam also has a relatively rapid onset of action and high metabolic clearance (half-life ranging from 1 to 4 hours) when compared with other benzodiazepines. Its anticonvulsant effects were demonstrated in experimental animals, possibly through an enhanced action of GABA on motor circuits in the brain[5]. Its use for treatment of status epilepticus, dates from 1981 when Elgi and Albani[1] described 8 cases successfully treated with midazolam administered by intramuscular

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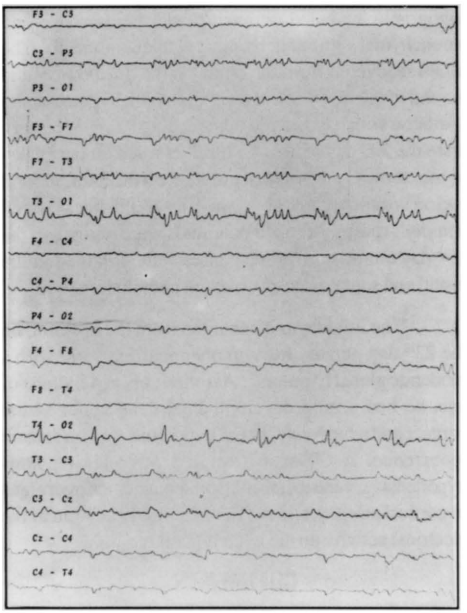

Fig 1. Patient VCCR/nb.: EEG showing seizure activity on both temporal regions just before midazolam attack dose.

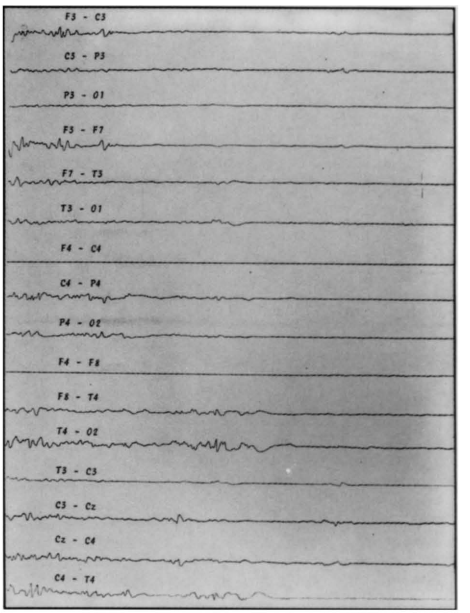

Fig 2. EEG 5 minutes after midazolam injection.

route. This was followed by other reports showing the drug's efficacy for status epilepticus treatment in adults and children[2,4]. The younger infant successfully treated with midazolam was a one month old infant that developed a status epilepticus following a closed cerebral trauma secondary to a "shake injury"[3].

The following is the first case described in a newborn infant.

CASE REPORT

VCCR/nb, a pre-term (35w.) male newborn infant, born through a C-section because of fetal distress (heart rate variation), with Apgar scores of 7 and 9. Two hours after birth, the infant developed respiratory distress, cyanosis, cardiac arrhythmia. Mechanical ventilation was started, and 6 hours later the infant was transferred to our Service. He arrived with generalized cyanosis, bradicardia, hypothermia, hypotonia, arterial hypotension, apnea and the pupils were medium sized and not reactive to light. Adequate ventilatory support improved the cyanosis and a chest film revealed a grade III hyaline membrane disease. He received sodium bicarbonate, dopamine and dolbutamine with stabilization of the arterial pressure. Cranial sonography at 12 hours of life was normal. The infant received phenobarbital (up to 35 mg/kg IV) and phenytoin (15 mg/kg IV) because of repeated hypertonic episodes that were interpreted as seizures, with adequate serum levels (PB 34 ug/ml; DPH 18 ug/ml). A neurological examination at 24 hours of life disclosed a hypotonic and comatose infant, reacting with flexion of arms and legs to painful stimuli; absent myotatic and primitive reflexes, with preserved brain stem reflexes. The anterior fontanel was tense with a slight disjunction of the sagittal suture. During the examination the infant had a partial tonic seizure, lasting 30 seconds, that recurred frequently. An electroencephalogram (EEG) showed electrographic seizure activity in both temporal regions and a multifocal abnormal electrical activity (Fig 1).

Midazolam was then started, with a loading dose of 0.2 mg/kg IV, under EEG control, with cessation of the seizure activity after 5 minutes (Fig 2). Continuous infusion of 0.025 mg/kg/h IV was maintained for the next 24 hours, under electrographic continuous recording with Neurotrack®. A continuous burst-suppression electrical activity was observed with this dosage. No clinical seizure activity was observed during this period. After 24 hours without midazolam, EEG revealed an electrical activity with no major abnormalities, compatible with that of a newborn with 35 weeks gestational age (Fig 3). The infant was mechanically ventilated during the whole period of midazolam administration and there was no need to change the vasoactive drugs dosage during this period. Serial cranial

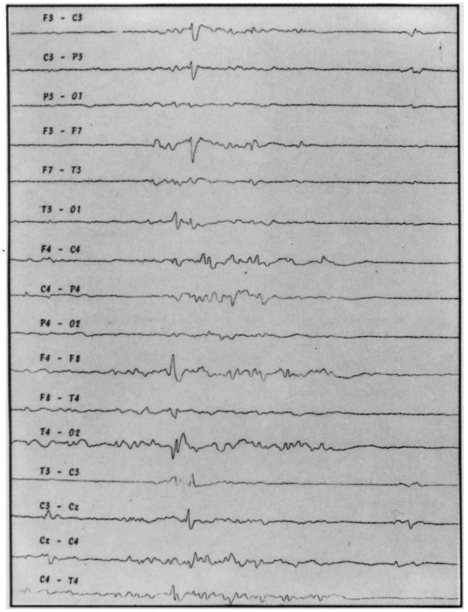

Fig 3. EEG obtained 24 hours after midazolam withdrawal.

sonography revealed intraventricular hemorrhage and parenchymal signs of periventricular leukomalacia. The infant recovered from the coma on the third day, but at the end of the first week of life, he was still hypotonic and apathetic with nasogastric tube feeding being necessary up to the 20th day of life. An EEG repeated on the 8th day of life, showed electrical depression on the left temporal region without major abnormalities in the background activity. Auditory evoked potentials were normal on the 15th day but no cortical responses were obtained in the visual and somato-sensory evoked potentials.

The infant was discharged from the hospital, on the 23rd day, seizure free, on phenobarbital, and with a moderate global hypotonia. At follow-up, at 4 months of age, he had a mild developmental delay, poor visual contact and a moderate global hypotonia, and no seizure recurrence. A CT-scan revealed a moderate, non-hypertensive, ventricular enlargement with indirect signs of cortical atrophy, and the EEG a mild depression of the electrical activity on the left temporal region.

COMMENTS

This case shows that midazolam can be effective for treatment of status epilepticus in the newborn period. The loading dosage of 0.2 mg/kg used in our case is similar to those reported in other childhood cases[3,4]. The latency of effect of 5 minutes for seizure control observed in our case is in agreement with that seen in the study of Lahat et al[4] in which 85% of the cases had their control clinically observed within 1 to 5 minutes after IM midazolam administration, and differed from the study of Kumar and Bleck[3], that had seizures controlled within 0.8 to 1.4 minutes after IV administration.

We were not able to judge whether midazolam determined respiratory depression or arterial hypotension, because the infant was on mechanical ventilation and was already receiving vaso-active drugs before midazolam administration was started. Mild hypotension was reported in an infant 5 hours after midazolam continuous IV infusion, promptly corrected with dopamine[3]. It was also impossible for us to detect the sedative effect, as the neurological status of the infant was most probably due to the hypoxic-ischemic encephalopathy.

Despite the limitations that a single case report can have on the more widespread use of a drug in a situation so delicate and complex as neonatal status epilepticus, we believe that midazolam is a drug that may turn out to be of value in the treatment of status epilepticus in the newborn infant.

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