Case report

Epileptic seizures induced by dexmedetomidine in a neonate

Tetsuo Kubota a,⇑, Tatsuya Fukasawa a, Erina Kitamura a, Miyuki Magota a, Yuichi Kato a, Jun Natsume b, Akihisa Okumura c

a Department of Pediatrics, Anjo Kosei Hospital, Anjo, Japan
b Department of Pediatrics, Nagoya University School of Medicine, Nagoya, Japan
c Department of Pediatrics, Juntendo University Faculty of Medicine, Tokyo, Japan

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Abstract

Background: Dexmedetomidine hydrochloride, a highly selective 2-adrenoceptoragonist, is used in combination with local anesthetics for sedation and analgesia. It is known to be efficacious in adult patients and is enthusiastically expected to be successful for sedation in neonates. Patient: The present case report details a term infant who was sedated by dexmedetomidine during artificial ventilation. He underwent electroencephalograms that confirmed epileptic seizures and non-epileptic abnormal movements. Twelve hours after the discontinuation of dexmedetomidine, both symptoms gradually disappeared without the use of any antiepileptic medication. After then, he had achieved normal development, with no obvious neurological abnormalities. Conclusion: Dexmedetomidine acts throughout the central nervous system and leads to a reduction in the anticonvulsant activity of the locus coeruleus. This case suggests potential adverse effects of dexmedetomidine in terms of inducing both epileptic seizures and non-epileptic movements in neonates.

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Keywords: Dexmedetomidine; Neonatal seizure; Abnormal movements; Amplitude-integrated EEG

1. Introduction

Dexmedetomidine hydrochloride (DEX) is a selective alpha-2 adrenergic agonist and possesses sedative, analgesic, opioid-sparing, and anxiolytic properties. DEX is known to be efficacious for sedation in adult patients; however, its effectiveness in infants and children has been unclear. The efficacy of DEX in adults has prompted great enthusiasm for its application for sedation in neonates [1,2].

Antiepileptic medications can exacerbate symptoms of epilepsy by aggravating preexisting seizures or triggering different types of seizure activity [3]. Moreover, benzodiazepines such as midazolam have been shown to induce paroxysmal automatic movements that mimic neonatal seizures of cortical origin [4,5]. The present patient report details a neonate who experienced DEX-induced epileptic seizures and non-epileptic abnormal movements.

2. Patient report

The patient was a Brazilian male infant who had a birth weight of 3274 g. He was born after 41 weeks of uneventful gestation. He did not have a family history of seizure disorders, and he was delivered by scheduled repeated cesarean section. His Apgar score was 9 at both 1 and 5 min. He displayed signs of respiratory distress and was transferred to the neonatal intensive care unit (NICU) in Anjo Kosei Hospital. Surfactant

⇑ Corresponding author. Address: Department of Pediatrics, Anjo Kosei Hospital, 28 Higashihirokute, Anjo-cho, Anjo, Aichi 446-8602, Japan. Tel.: +81 566 75 2111; fax: +81 566 76 4335.
E-mail address: t-kubota@kosei.anjo.aichi.jp (T. Kubota).
supplementation and artificial ventilation were performed for severe transient tachypnea of the newborn. On admission, his cardiovascular and neurological status was normal. DEX was administered intravenously to sedate the infant because he had difficulty adapting to artificial ventilation. The dose of DEX was increased to 0.625 μg/kg/h. The infant did not display systemic side effects such as hypotension or hypothermia. A single dose (0.2 mg/kg) of midazolam was added because the infant was not sufficiently adapted to artificial ventilation. Neither catecholamines nor nitroglycerin was administered to the infant.

On postnatal day 5, about 80 h after DEX was infused, the infant showed abnormal pedaling-like movements every few hours. These abnormal movements were associated with elevated blood pressure and desaturation. DEX was gradually discontinued, and the patient was successfully extubated on postnatal day 6. DEX was infused continuously 84 h.

An amplitude-integrated electroencephalogram (aEEG) combined with simultaneous VTR-conventional EEG was used to determine whether his abnormal movements were epileptic after postnatal day 6 using Neurofax EEG1200 (Nihon Koden, Tokyo, Japan), with a bipolar configuration and eight surface electrodes (AF3, AF4, C3, C4, O1, O2, T3 and T4) placed according to the 10–20 international method. aEEG was displayed at 6 cm/h. The impedance was constantly <10 kΩ during the recordings. EEG recordings were performed until postnatal day 8. aEEG showed repetitive ictal changes, with transient elevation of the lower border. These aEEG epochs corresponded to ictal changes on conventional EEG showing stereotyped, semi-rhythmic, repetitive, and sequential delta/theta activity arising from multiple regions (Fig. 1). However, ictal changes were not related to the abnormal pedaling-like movements. Instead, ictal VTR-EEG revealed eye-opening and tonic posturing in his extremities just before the abnormal pedaling-like movements. Twelve hours after the discontinuation of DEX, both the epileptic seizures and non-epileptic movements gradually ceased without the use of any anti-epileptic medication. The background activities of conventional EEG after stopping of epileptic seizures were normal. MRI on postnatal day 14 did not reveal any abnormal findings. Blood examinations, including TORCH and metabolic screening, gave normal findings. At 8 months of age, he had achieved normal development, with no obvious neurological abnormalities.

3. Discussion

The present patient had both epileptic seizures and non-epileptic abnormal movements during sedation by DEX. We differentiated non-epileptic movements from epileptic seizures based on ictal VTR-EEG. In our patient, epileptic seizures were observed before non-epileptic abnormal movements. Although aEEG revealed repetitive ictal changes with transient elevation of the lower border, it was difficult to clarify the detailed temporal relationship between the aEEG findings and motor phenomena using aEEG only. The combination of aEEG and simultaneous VTR-conventional EEG was useful for differentiation between epileptic seizures and non-epileptic movements. In our patient, epileptic seizures were always followed by non-epileptic movements. We considered that non-epileptic movements may be attributable to a brainstem releasing phenomenon due to suppression of cortical activities after epileptic seizures.

Fig. 1. EEG and aEEG findings. (A) At the beginning of the seizure, rhythmic activities are seen in the right frontal and left occipital regions. Ictal discharges propagated to the left front-cenral regions. The morphology of ictal discharges also changed into high-amplitude rhythmic spikes. (B) The aEEG (2–15 Hz, 6 cm/h) is displayed on a semi-logarithmic scale (0–100 μV) from one bipolar EEG channel (C3–C4). The aEEG shows repetitive ictal changes with transient elevation of the lower border. In the first half of each rise in the aEEG lower margin, ictal discharges were seen on conventional EEG.

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Although his epileptic seizures were first recognized after EEG monitoring had been started, we presume that they had occurred in combination with the non-epileptic pedaling-like movements. Therefore, his epileptic seizures are likely to have appeared after 80 h of continuous DEX infusion. Considering the general condition of our patient, a larger dose and longer duration of DEX were used compared with previous patients. This may be related to the occurrence of epileptic seizures in our patient. Benign idiopathic neonatal convulsions such as fifth day fits may be an alternative explanation for his seizures. However, his seizure followed the administration of DEX and stopped after discontinuing infusion, suggesting that DEX was highly associated with his seizures.

DEX acts throughout the central nervous system [6]. The sedative and anxiolytic effects of DEX are attributable primarily to its activity at noradrenergic receptors in the brain stem locus coeruleus (LC). Stimulation of alpha2-adrenergic receptors in the LC reduces central sympathetic output and increases the firing of inhibitory neurons. The LC is also involved in anti-seizure activity of the vagal nervous system, as the depletion of norepinephrine following the administration of 6-hydroxydopamine into the LC of rats resulted in the elimination of vagus nerve anti-seizure effects [7]. Moreover, DEX decreased the seizure threshold in an experimental rat model of generalized epilepsy [8]. The LC plays a role in DEX-induced modulation of mesolimbic dopamine pathways [9], suggesting that DEX-induced seizure activity is due to altered noradrenergic systems. Considering the relationship between the LC and DEX, we believe that the large dose and extended use of DEX led to a reduction in the anticonvulsant activity of the LC.

Midazolam has been shown to induce non-epileptic abnormal movements and a dystonic posture within seconds after administration and to induce choreoathetosis following prolonged intravenous administration [4,5]. We have also experienced these side effects in response to midazolam. However, midazolam was used 78 h before abnormal movements were first recognized. Thus, we consider that midazolam did not contribute to epileptic seizures or non-epileptic abnormal movements in our patient.

DEX has not been approved by the Food and Drug Administration for use in neonatal or pediatric populations. However, DEX has been used for the sedation of infants with congenital heart disease or during EEG and MRI testing [1,2,6,10,11]. DEX has also been used instead of midazolam for the sedation of neonates in some hospitals in Japan, although DEX has not been approved for use in this population. DEX is used in our hospital only after informed consent is obtained from the parents. Also in this case, we gained the grant of patient’s parent and approved by the ethics committee of Anjo Kosei Hospital.

DEX is one of the primary medications used for sedation, even in neonates [1]. Previous studies have reported that DEX has cardioprotective and neuroprotective effects [2]. To our knowledge, there are no details on the dosing requirements or pharmacokinetics of DEX in neonates. The use of DEX in the present case was based on previous adult and infant clinical data [6,12]. Future randomized controlled trials with a large sample size are necessary to ensure the safety of DEX in neonatal and pediatric patients. Moreover, long-term safety and efficacy data for commonly used sedatives should be collected in these populations.

References