Home Use of Intranasal Dexmedetomidine in a Child With An Intractable Sleep Disorder

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Sleep disturbance is a crucial issue in pediatric palliative care, with a dramatic impact on the quality of life of children and families. Dexmedetomidine (DEX) is a selective α -2 agonist, with anxiolytic, hypnotic, and analgesic properties, that could play a role in the management of refractory sleep disturbances. We describe the use of intranasal DEX as a sleep inductor in a 10-year-old female with dystrophic epidermolysis bullosa and a severe sleep disorder. After treatment with melatonin, benzodiazepines, and niaprazine had failed, she was admitted to the hospital where 3 mcg/kg/day of intranasal DEX was administered before bedtime. She received 0.7 mL of the IV formulation at a concentration of 100 mcg/mL with half the dose given in each nostril via a Mucosal Atomization Device. During this time, she was also monitored for potential side effects (e.g., bradycardia, blood pressure derangements). After 2 weeks of hospitalization, she was discharged with ready-to-use doses of DEX for home treatment. The child's heart rate and blood oxygen saturation were monitored at home. There was a definite improvement in sleep quality and duration, daytime alertness, pain control, and quality of life. No side effects were reported and the drug retained its effect over time (the patient is currently taking the drug). Intranasal DEX could be a safe and effective strategy to manage refractory sleep disturbances in children in pediatric palliative care.

ABBREVIATIONS CYP, cytochrome; DEX, dexmedetomidine; FDA, US Food and Drug Administration; IN, intranasal; IV, intravenous; MAD, Mucosal Atomization Device

KEYWORDS circadian rhythm; dexmedetomidine; intranasal dexmedetomidine; pediatric palliative care; sleep disturbance

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Introduction

Sleep disturbance is a significant issue in children with complex chronic conditions. Not only does it worsen pain perception and other distressing symptoms, but also it negatively affects the quality of life for children and caregivers.¹ Dexmedetomidine (DEX) is a selective α -2 agonist that provides sedative, anxiolytic, and, to a lesser extent, analgesic effects, without any interference on respiratory drive, airway patency, and tone. In this report, we describe a long-term home treatment with intranasal (IN) DEX as a sleep inductor for a 10-year-old female with dystrophic epidermolysis bullosa and a severe sleep disorder.

Case Report

The local pediatric palliative care team evaluated a 10-year-old female (23 kg) affected by Hallopeau-Siemens dystrophic epidermolysis bullosa for a severe sleep disorder. She had multiple skin and mucous ulcers that required medication under deep sedation with ketamine (maximum dose required 3.5 mg/kg/day) and propofol (maximum dose required 5 mg/kg/day) 3 times a week. Chronic skin infections from *Pseudomonas aeruginosa* and *Staphylococcus aureus* also required

monthly courses of IV antibiotics that were administered via a central venous catheter. Because of the recurrent esophageal stenosis, she underwent several endoscopic dilations and a percutaneous endoscopic gastrostomy placement for enteral nutrition. Her concurrent medications at the time of admission included metamizole (20 mg/kg/day), gabapentin (25 mg/kg/day), and tramadol (6 mg/kg/day) for the severe pain; cetirizine (1 mg/kg/day) and chlorphenamine (0.2 mg/kg/day) for refractory pruritus; and trazodone (1 mg/kg/day), aripiprazole (0.3 mg/kg/day), and alprazolam (0.01 mg/kg/day) for severe chronic anxiety, depressive disorder, and refractory sleep disturbances. A crucial issue was severe pain, for which she needed non-steroidal anti-inflammatory drugs (i.e., acetaminophen, ibuprofen). A weak opioid (i.e., tramadol) was used because other opioids caused unbearable itching.

The patient also suffered from refractory pruritus, treated with antihistamine drugs (i.e., cetirizine and chlorphenamine), and had complaints of severe chronic refractory sleep disturbance. She denied any benefit from melatonin (0.05 mg/kg/day), experienced paradoxical arousal and agitation with diazepam 0.1 mg/kg/day, and could achieve only a few hours of sleep with niaprazine (1 mg/kg/day), without any relief from noc-

turnal awakenings. The sleep disturbance prevented the patient from going to school and participating in daily activities because of profound daytime tiredness, which then translated into her irritability and reduced quality of life.

The Italian Drug Agency AIFA (Agenzia Italiana del Farmaco) recently approved the off-label use of IN DEX at a dose of 1 to 4 mcg/kg/day for severe sleep disturbance and agitation in pediatric palliative care.² The pediatric palliative care team considered this issue and, once they obtained the authorization from the local Ethics Committee and parental written informed consent, they admitted the patient to hospital to start a trial with IN DEX at a dose of 3 mcg/kg/day (0.7 mL of the IV formulation at the concentration of 100 mcg/mL), with the dose divided in half and given in each nostril via a Mucosal Atomization Device (MAD) before bedtime. During her stay, the team monitored the patient's heart rate, blood pressure, and blood oxygen saturation for potential side effects. There was no evidence of adverse drug events during the 2 weeks of hospitalization.

The team provided ready-to-use doses of IN DEX for at-home administration via a MAD. A ready-to-use product minimized the risk of dosing errors, and use of an IN formulation avoided excessive central venous catheter manipulation. The team taught the parents how to correctly administer IN DEX and how to perform heart rate, blood pressure, and blood oxygen saturation measurements at home.

At the time of publication, the patient was receiving IN DEX at home, with no adverse effect, no need for dose escalation, and no evidence of loss of efficacy. The treatment increased sleep time from 2 to 3 consecutive hours to 6 to 8 consecutive hours. Both the patient and the parents reported improved sleep quality with better participation in daily activities and better pain control, which lowered the need for analgesic treatment both at home and during procedural sedation.

The team measured the patient's sleep quality before and after the treatment by using the Sleep Disturbance Scale in Children. This tool is a validated 26-item sleep rating scale that explores different aspects of sleep disturbances in children and adolescents through description of night behaviors and their frequency with a score system ranging from 1 (never) to 5 points (always). Covered issues include disorders in initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence, and sleep hyperhidrosis.³ The scale was administered to the parents before starting IN DEX, during in-hospital monitoring, and 1 month after DEX introduction. The team investigated parental satisfaction by a Likert scale and with open questions: they reported a significant improvement in the quality of sleep of the patient and the whole family, with a high degree of satisfaction.

Before the treatment, the patient had high scores

in disorders of initiating and maintaining sleep (mean score 29) and excessive daytime somnolence (mean score 20) with a total score suggestive of a severe sleep problem (mean total score 68). After introduction of IN DEX, initiating and maintaining sleep was easier (mean score 9), and daytime sleepiness was remarkably reduced (mean score 7), resulting in a less severe sleep disorder (mean total score 32).

Discussion

Sleep disturbance is a critical issue for children with complex chronic conditions and their families. Patients with chronic pain suffer from poor and interrupted sleep, which affects their level of pain, abilities, and interactions in their daily activities. Their parents often report a reduced sleep quality and a limited amount of sleep time due to night assistance, technology monitoring, or need for vigilance, resulting in decreased daytime functioning, depression, and anxiety.⁴

The pharmacologic treatment available with melatonin, benzodiazepines, and antihistamine drugs may be ineffective in severe cases. Melatonin may lose its effect over time. In some individuals there may be a slow metabolism due to a decreased activity of the cytochrome (CYP)1A2 enzyme, which may result in increased melatonin levels, with melatonin accumulation and loss of the circadian rhythm. This fact may explain the lack of efficacy of exogenous melatonin.⁵ Benzodiazepines may cause oversedation, excessive secretions, and paradoxical effect; moreover, there is no official approval for their use as hypnotics in children.⁶ Antihistamine drugs (e.g., niaprazine) may have severe anticholinergic side effects (e.g., fever, mydriasis, urinary retention, constipation, tachycardia, hypotension, dystonia, and sedation); there is neither approval from the FDA for the use of niaprazine, nor is there any similar approval in the 2019 edition of the British National Formulary for Children. Furthermore, tolerance develops to all of these drugs, which limits their usefulness as short-term treatment agents.⁵

DEX is a selective α -2 agonist with peculiar sedative and anxiolytic properties: it acts by reducing firing from adrenergic neurons in the locus coeruleus, mimicking the onset of physiologic recovery sleep. It improves sleep efficiency and subjective sleep quality by increasing stage 2 and decreasing stage 1 sleep, as demonstrated in studies concerning critically ill patients.⁷⁻¹⁰ Moreover, its mild analgesic effect may slightly reduce pain, which indirectly may enhance sleep quality. For all these reasons, DEX could be more effective and safer than either benzodiazepines or niaprazine. It may lead to increased sedative, anesthetic, and cardiorespiratory effects when coadministered with other anesthetics, hypnotics, or opioids; therefore, dosage reductions may be necessary owing to pharmacodynamics interactions.^{10,11} The patient in this case report required smaller propofol doses for sedation during

dressings changes after DEX initiation. Moreover, there is *in vitro* evidence that DEX induces CYP2B6, which may lead to interactions between DEX and drugs that are substrates for CYP2B6 metabolism (e.g., bupropion, pethidine, methadone).¹⁰ Increasing evidence exists in the pediatric palliative care setting on DEX use as an adjuvant, opioid-sparing, and *per se* analgesic medication to treat chronic pain, as well as a sedative during withdrawal of support¹²; however, there is no evidence regarding its use in inducing sleep.

Furthermore, there is still little experience on the use of DEX for prolonged periods. There is a single case report of the use of a continuous IV infusion of DEX for more than 2 years, without significant side effects (bradycardia, hypertension, or hypotension), in a 14-year-old with chronic heart failure and cyclic vomiting syndrome.¹³

There is conflicting evidence about the potential for tolerance or withdrawal symptoms associated with DEX: Walker et al¹⁴ reported on the use of IV DEX for an average of 11 days (range, 2–50 days) in pediatric burn patients in the intensive care unit. Their patients did not require any dose escalation, suggesting no development of tachyphylaxis to the drug. Furthermore, there was no evidence of rebound 12 to 24 hours after DEX was discontinued. However, there are some case reports that point out the development of withdrawal symptoms (e.g., agitation, tachycardia, and even tonic-clonic seizures) after abrupt discontinuation of IV DEX.¹⁵

The AIFA recommended an IN dose of 1 to 4 mcg/kg/day2. A recent pharmacokinetic study by Miller et al¹⁶ reported that 1 mcg/kg/day of IN DEX produced an average peak plasma concentration of 199 pg/mL within 46 minutes, which is the low end of the concentration range for sedation. By doubling the dose to 2 mcg/kg the plasma concentration was reached within 10 minutes, achieving almost twice the peak concentration.¹⁶

Conclusion

The IN route is safe, effective, and widely used in patients with dystrophic epidermolysis bullosa, since it is not invasive and may be used at home, even by non-specialized caregivers. The IN formulation of DEX is not irritating, so that it can be used even on fragile mucosa; it avoids first-pass hepatic metabolism; moreover, when compared to IV treatment, serum concentration and plasma peak are lower, thus reducing the risk of side effects.¹⁷

To our knowledge, this is the first case report of long-term out-of-hospital use of IN DEX as a sleep inductor for children in the pediatric palliative care setting. The use of a validated scale before and during the treatment, both in an inpatient and outpatient setting, may result in reliable measures; however, the therapeutic success in our patient is anecdotal, and more evidence is needed. Although further research is needed to validate our preliminary finding, this experience could

provide a new perspective on the management of severe refractory sleep disturbance in pediatric palliative care, which would result in a significant improvement in the quality of life for both children and their families.

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