Dexmedetomidine at Home for Intractable Dystonia and Insomnia in Children With Special Needs: A Case Series

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Abstract

Background. We know that syndromic conditions and severe chronic diseases can be associated with symptoms that may interfere with sleep, significantly impacting the life quality of children and caregivers. Drugs commonly used in treating insomnia, such as melatonin, benzodiazepines, niaprazine, and antihistamines, are often either ineffective or associated with adverse effects, requiring new therapeutic perspectives. Dexmedetomidine is a selective alpha-2 agonist with hypnotic and anxiolytic effects, which, by stimulating alpha-2 adrenergic receptors in the locus coeruleus, induces sleep comparable to stages 2−3 of the non-REM phase without substantially affecting the respiratory drive during sedation. Its use has already been extensively described in pediatric intensive care or procedural sedation literature. In 2018, the Italian Medicines Agency (Agenzia Italiana Del Farmaco AIFA) authorized the off-label use of dexmedetomidine outside of intensive care in Children undergoing palliative treatment to control distressing symptoms related to pathology and refractory sleep disorders, and the literature reported cases of children who received dexmedetomidine at home.

Objective. Our study aims to describe the home use of dexmedetomidine in children with insomnia or intractable dystonic states.

Measures. We conducted a retrospective analysis through a questionnaire addressed to 12 Italian pediatric palliative care centers regarding the home use of dexmedetomidine in sleep disorders and intractable dystonic states.

Intervention. We collected a case series of 9 children treated with dexmedetomidine at home, 8 via intranasal and 1 via intravenous route. All children received the first drug administration in the hospital or hospice during a dedicated admission, under close monitoring of vital signs parameters for 72 hours (3 days, range 2−7 days). After discharge, the potential side effects of the drug were explained to the patient's families, and, once informed consent was obtained, the home administration of dexmedetomidine continued, with follow-up by the palliative care team. At home, dexmedetomidine was administered for 3000 days (minimum 1 month, maximum 36 months). The first patient was treated for 1095 days, from 2019 to 2021 (discontinued due to underlying condition-related death).

Outcomes. All patients observed a persistent benefit from the treatment on symptoms, and none of them discontinued dexmedetomidine administration due to drug-related adverse effects or perceived lack of therapeutic efficacy.

Conclusions. Therefore, its use at home may represent a promising therapeutic approach for intractable sleep disorders or dystonic states in pediatric palliative care children. Further studies are needed to confirm our results. J Pain Symptom Manage 2023;66:e653−e657.

Key Words

Home setting, intranasal dexmedetomidine, pediatric palliative care

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Introduction

Severe sleep disturbance is a possible feature of some syndromic illnesses and chronic conditions characterized by long-lasting pain, neuro-vegetative dysregulation, and dystonia.[1–3] Various conditions related to syndromic diseases, cerebral palsy, and epileptic encephalopathies may interfere with sleep, impacting its quality, such as obstructive sleep apnea, dystonia, pain from muscle contractures, tooth decay, osteopenia, and intestinal function disorders. Moreover, the most severe cases of dystonia may not only be hard to treat[4] but also interfere with sleep quality, representing an impressive burden of discomfort for patients and caregivers. While many of these causes may be addressed and treated, some patients still experience relevant sleep difficulties and require symptomatic relief treatment. The lack of sleep substantially impacts the patient's quality of life, conditioning the performance level during the day. From this point of view, we should consider that disabled children may have an even worse performance and quality of life.

Furthermore, the burden of sleepless nights on a caregiver's health, already challenged by multiple heavy tasks, should be regarded from a long-term perspective of a person's well-being.[5,6] Melatonin, benzodiazepines, niaprazine and other antihistamine are often used in therapy; however, their effectiveness may be limited or hampered by adverse effects such as sialorrhea, mouth dryness or constipation.[7,8] For all these reasons, there is a need for an effective and safe treatment for insomnia in more severe cases. The ideal drug should mimic a physiological mechanism, resulting in minimal adverse effects, a predictable onset of action, effortless intake, good quality of arousal and daytime performance, and should not induce tachyphylaxis. In the last decades, intranasal (IN) and intravenous (IV) Dexmedetomidine have demonstrated an impressive safety record in procedural sedation for infant diagnostic imaging, proved by hundreds of thousands of patients treated worldwide.[9–11]

In the setting of Pediatric Palliative Care in Italy, the National Drug Agency (AIFA—Agenzia Italiana del Farmaco) authorized the off-label use of 10 drugs, including Dexmedetomidine, for indication, age, modality of administration and formulation, under Law 648/96. Remarkably, the approval included home treatment so that off-label use was authorized by AIFA outside the Intensive Care Unit setting to control stressful symptoms or sleep disorders, which are refractory to the standard therapies, with an intranasal recommended dosage ranging from 1 to 4 μg/kg dose.[12] Dexmedetomidine is a selective alpha-2 agonist known for its sedative and anxiolytic action without substantially affecting the respiratory drive.[13] Dexmedetomidine decreases catecholamine release from adrenergic neurons in the locus coeruleus, inducing a sleep similar to the non-REM phase.[14] Children receiving Dexmedetomidine are, as a rule, arousable, retaining a responsive state for interaction.[14,15] Dexmedetomidine can cause dose and time-dependent effects on the cardiovascular system, particularly blood pressure and heart rate.[16] A biphasic effect on blood pressure is described, with initial hypertension secondary to systemic vasoconstriction because of the stimulation of peripheral α-2B receptors on the vascular smooth musculature. Eventually, hypotension may occur when the activation of the central α-2A receptors causes vasodilatation. Bradycardia results from decreased sympathetic tone, baroreceptor reflex and enhanced vagal activity.[15,16] Intranasal Dexmedetomidine produces a sedative effect on average within 30 minutes of administration.

Nasal administration does not cause local irritation, with a bioavailability of 84%, mainly exceeding the oral route (around 16%).[17] Due to its safety and benefits, the intranasal route is the most used extravascular route.[15] In the available literature, few single case reports describe the home use of Dexemedetomidine in pediatric palliative care in refractory sleep disorder, intractable dystonia, irritability and end-stage heart disease.[18–21]

Methods

We used a questionnaire to investigate dexmedetomidine's home use in Italy's pediatric palliative care. The study was approved by the Ethical Committee (Authorization no. 9/2014). All parents of children undergoing home dexmedetomidine treatment received complete drug information and signed written informed consent for drug use, data collection and disclosure. A questionnaire (Table 1) was sent to Italian Pediatric Palliative Services, followed by a phone call to all directors. All 12 centers contacted responded, recruiting 9 patients. Every subject was first administered dexmedetomidine in a hospital or hospice

Table 1
Questionnaire Sent to the Italian Pediatric Palliative Services

	Questionnaire
1	ID patient
2	Sex patient
3	Age patient
4	Diagnosis
5	Difficult symptom
6	Other drugs for symptom
7	Route of dexmedetomidine administration
8	Titration of dexmedetomidine (ug/Kg/dose)
9	Number of dexmedetomidine daily administration
10	Length of treatment
11	Vital signs monitored
12	Adverse effect
13	Efficacy

Table 2
Patients Receiving Dexmedetomidine

Sex	Age	Diagnosis	Challenging Symptom	Other Drugs for Symptom	ROA	ug/Kg/ Dose	N° Doses/ Die	ug/Kg/ Die	Time of Treatment	Adverse Effects	Efficacy	Reason for Treatment Suspension
F	8 y	EBD	Insomnia	Melatonine diazepam niaprazina	in	3	1	3	3 y	No	Yes	Death
M	17 y	SMA1	Insomnia	Melatonina niaprazina delorazepam	in	4	1	4	8 m still ongoing	No	Yes	
F	18 m	Lissencephaly Drug-resistant epilepsy	Refractory dystonia	Baclophene gabapentin lorazepam Tetrabenazine botulin toxin	in	3	1–2	6	3 m	No	Yes	Death
F	4 y	Metachromatic leukodystrophy	Refractory dystonia	Gabapentin lorazepam clonidine	in	3	3–4	12	9 m still ongoing	No	Yes	
M	7 m	Postasphyxia neonatal epilepsy	Refractory dystonia	Trihexyphenidyl hydrochloride, clonazepam sodium valproate	in	4	2	8	6 m still ongoing	No	Yes	
M	17 y	Spastic tretraparesis epilepsy	Refractory psychomotor agitation crisis	Gabapentin clonazepam amitryptiline cloni dine	in	3	4	12	5 m still ongoing	No	Yes	
F	4 y	Neurodegenerative encephalopathy	Refractory dystonia	Levetiracetam phenobarbital chlorpromazine midazolam clonidine	in	3,5	2	7	6 m	No	Yes	Death
F	8 y	Congenital dystonia	Refractory dystonia	clonidine	in	3	2	6	1 m	No	Yes	Death
F	10 y	Bilateral schizencephaly	Refractory dystonia	Trihexyphenidyl hydrochloride baclophene tetrabenazine benzodiazepine tizanidine gabapentin morphine	iv	0.98 ug/ Kh/h	24 h	23 ug/ Kg/die	6 m	No	Yes	

DBE = Dystrophic epidermiolysis bullosa; SMA1 = Spinal muscolar atrophy1; ROA = Route of administration; in = intranasa; iv = intravenous.

during an inpatient stay, for a preliminary observation of safety and effectiveness, under close monitoring for a few days (3 days, range 2−7). The patients were eventually followed at home by the Palliative Care Teams, and their parents received detailed instructions about possible adverse effects and a 24-hour phone availability for consultation in case of doubts or worries. No adjunctive monitoring was used at home unless already employed per each specific patient's need. Data about the patients receiving Dexmedetomidine are shown in Table 2.

Discussion

This preliminary report demonstrated the safety of the home use of IN or IV dexmedetomidine in selected children with refractory insomnia and dystonia, followed by PPC teams. Our study presented the first series concerning the home-based use of dexmedetomidine. In the literature, we found four case reports of single patients. One was a syndromic boy treated intranasally with refractory irritability,[20] another was a 19-year-old girl who received Dexmedetomidine intravenously with end-stage heart disease and cyclic vomiting,[21] and the other two were included in this series.[18,19] Treatment was reported as effective and safe in the two cases not included in this series. In the setting of complex patients with special needs, safety remained the primary concern in case of a new drug administration outside the hospital. The safety record of dexmedetomidine, both IN and IV, is substantial in PICU and hospital sedation,[12] while data on long-term home use were lacking. This report's results concerning nine patients did not allow any definite statement.

However, the preliminary evidence in this series dealt with an overall number of 3000 days of home treatment, closely monitored by PPC teams, without any reported adverse effect. The lack of a control group with a placebo or another cure did not permit any firm conclusion about effectiveness. However, all these therapies were started in patients with special needs who experienced the failure of previous pharmacological treatments in a population of highly selected and suffering subjects. All the patients started their treatment in a hospital setting to assess the safety and clinical improvement, eventually resulting in the indication to continue the treatment at home. Remarkably, in a home setting, all the caregivers reported a persistent benefit from treatment and an improvement in their perception of life quality, and no patient stopped the drug assumption due to the adverse effects or perception of ineffectiveness. This management was supported by the PPC teams, who offered a close home follow-up after the hospital/hospice setting where the therapy began, guaranteeing strict monitoring of safety, compliance, and possible action against adverse effects. The burden of severe insomnia and intractable dystonia in children with special needs can be relevant, with a poor response to the available treatments. A further safe and effective therapeutic option may significantly improve the quality of care for these patients and their families, especially in a home setting.

This study has some limits being a retrospective case series without a control group in a limited number of patients.

However, it has some points of strength. The in-hospital/hospice setting in which treatment started and the eventual close-home follow-up performed by PPC teams allowed strict monitoring of safety, compliance, and possible adverse effects.

Conclusion

In conclusion, home use of dexmedetomidine may be a safe approach to intractable insomnia and dystonia in children with special needs who did not benefit from other treatments, ensuring patient home management according to the goals of pediatric palliative care. More extensive studies data are needed to confirm these results.

Author Contributions

LDZ and EB discussed the writing project. SS and LDZ wrote the manuscript with significant support from EB, AD, and GM. EB supervised the final manuscript. All authors contributed to the article and approved the submitted version.

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