Naltrexone Therapy of Apnea in Children with Elevated Cerebrospinal Fluid β-Endorphin

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Previous studies have indicated increased immunoreactivity of the endogenous opioid peptide β-endorphin in the cerebrospinal fluid (CSF) of infants under 2 years of age with apnea. To assess the role of endogenous opioids in the pathogenesis of apnea in children, the effect of oral treatment with the opioid antagonist naltrexone was studied in apneic infants, as well as in older apneic children, with demonstrated increases in CSF immunoreactive β-endorphin (i-BE). In the 8 apneic infants with elevated i-BE in lumbar CSF (range, 55–155 pg/ml; normal, 17–52 pg/ml), no further apnea occurred during naltrexone therapy (1 mg/kg/day, by mouth). Five children (2–8 years old) with apnea of unknown cause had elevated CSF i-BE (range, 74–276 pg/ml) compared to 6 age-matched nonapneic children (range, 15–48 pg/ml). No apneic events occurred during naltrexone therapy, except in 1 child during stressful events, but apnea recurred in some patients after attempts to discontinue naltrexone treatment. Adverse effects of naltrexone included complaints of headaches in 2 children and symptoms of a narcotic withdrawal syndrome during the first 3 days of treatment in 1 child. Three children with Leigh's syndrome had elevated CSF i-BE (range, 104–291 pg/ml) and their apnea also responded to naltrexone. We conclude that elevated endogenous opioids contribute to the pathogenesis of apnea in children and may even result in physical dependence.

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Shortly after the discovery of endogenous opioid peptides in the central nervous system and the demonstration that the central administration of some of these peptides caused respiratory depression in animals (for reviews, see [1–3]), it was postulated that endogenous opioids might be involved in the sudden infant death syndrome (SIDS) or in clinical problems with apnea [4, 5]. The first clinical demonstration of this possibility was in a child with necrotizing encephalomyelopathy (Leigh's syndrome), who had prolonged apnea that responded to naloxone and who had markedly elevated cerebrospinal fluid (CSF) levels of endogenous opioid-like activity [6]. Subsequent clinical studies have demonstrated significantly elevated levels of immunoreactive β-endorphin (i-BE) in CSF from infants with apnea [7–9] and from infants who were siblings of SIDS victims [9]. A case of a marked postoperative elevation of met-enkephalin in CSF accompanied by profound respiratory depression in an adult has also been reported [10]. The likelihood that an elevation of endogenous opioids in CSF was contributing to, rather than simply resulting from, these respiratory problems was supported by the finding that the parenteral administration of the opioid antagonist naloxone resulted in improvement in respiratory status and apnea resolution [6, 7, 10].

Because of its relatively short duration of action and the necessity to administer it parenterally, naloxone would not be practical to use in the therapy of protracted apnea. Another opioid antagonist that circumvents the problems of oral bioavailability and short duration is naltrexone, which has been used in some drug-abuse treatment programs to block the euphoric effects of heroin [11]. Therefore, the present study was initiated to determine the effects of oral naltrexone treatment in infants with apnea, as well as in a group of older children who had recurrent episodes of apnea.

Methods

Subjects

Between 1985 and 1988, 14 children between 2 and 10 years old were evaluated in a prospective and controlled

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study to investigate a possible relationship between CSF levels of i-BE and the occurrence of apnea. This aspect of the study was conducted in a single-blind manner, such that the technical personnel analyzing the coded samples for i-BE in CSF were unaware of patient status. Five of the children with apnea (ages 2–8 years) had a history of repetitive, life-threatening apneic events of unknown cause, and 3 children (ages 2, 3, and 5 years) had a metabolic dysfunction (Leigh's syndrome) accompanied by apnea. Diagnoses of the 6 control children (ages 2–10 years), who did not have apnea, included Prader-Willi syndrome, tricyclic antidepressant drug overdose, otitis media, abnormal urea cycle, aseptic meningitis, and brain abscess. The 8 children with apnea, as well as 8 of the infants with apnea in a previous investigation [9], were also involved in a second aspect of this study, to determine the effects of oral naltrexone administration on the incidence of apnea.

Evaluation

Evaluation of these subjects consisted of a complete clinical assessment and laboratory tests, including differential blood count, electrolytes and other blood chemistry, as well as lumbar puncture. Electroencephalograms (EEGs), pediatric pneumocardiograms (PPGs), or polysomnograms (PSGs) were obtained in patients with suspected apnea. Results of PPG and PSG were considered abnormal if any of the following were present during sleep studies: prolonged apnea (PA), longer than 15 seconds, with or without bradycardia; short apnea (SA), 10 to 15 seconds, accompanied by bradycardia; or excessive periodic breathing, greater than 5% of sleep time. Computed tomographic (CT) scans were performed when examination of a patient indicated hypotonia [12], but no abnormalities were noted in patients with apnea of unknown cause.

All of the apneic events were of central origin and occurred during sleep. Only PA required stimulation or cardiopulmonary resuscitation (CPR). These events were recognized by monitor alarms or observation, or both, of an apneic and limp infant who was pale or cyanotic. Abnormal breathing patterns were subsequently documented by PPG or PSG. None of the infants in this study had apnea of prematurity. All infants and children treated with naltrexone were on cardiac-respiratory monitors, which were continued for 2 to 3 months after discontinuation of naltrexone.

Parental informed consent was obtained before performing lumbar puncture. Institutional permission for conduct of human research was also obtained for this study.

Assay of CSF

The CSF obtained by lumbar puncture was divided into 1-ml aliquots and frozen immediately. All CSF samples were number coded without identification of diagnosis and stored at −70°C until a sufficient number of samples was obtained for analysis. The concentration of i-BE in CSF was determined as described previously [9], using a radioimmunoassay kit (Immunonuclear Corp, Stillwater, MN).

Statistics

For statistical evaluation, data were analyzed for significance with computer programs for analysis of variance and Student's t test for grouped data [13].

Results

Patient 1

One of the children in this study was a 6-year-old girl who was a sibling of a victim of SIDS. She was born at 28 weeks of gestation and her birth weight was 3 pounds, 6 ounces. Since infancy, she had documented recurrent apnea and bradycardia of unknown cause during sleep, which required CPR and repeated hospitalizations. In April 1984, she was seen at the University of Tennessee Hospital, where bradycardia was noted. At that time, however, her electrocardiogram, echocardiogram, CT scan, EEG, and audio evoked potential were normal. A sleep study showed an increase in tidal CO_2 with possible upper airway obstruction, and the patient underwent a tonsillectomy and adenoidectomy.

The patient did well until August 1985, when she was hospitalized after an apneic episode with cyanosis that lasted between 30 and 45 seconds. At this time she weighed 49 pounds (76th percentile), and physical and neurological examinations, including an EEG, revealed no abnormalities. The patient was placed on an apnea monitor at bedside, and apnea of central origin, which occurred frequently during sleep, was documented. Two of the apneic episodes were associated with bradycardia and 2 episodes of perioral cyanosis were also observed by hospital staff during 8 days of hospitalization. A lumbar puncture was performed in August 1985, and measurement of i-BE in her CSF indicated an extremely high concentration of 276 pg/ml (one of the highest observed in our study). The initiation of oral treatment in hospital with naltrexone (12.5 mg) resulted, within 90 minutes, in an opiate-withdrawal–like syndrome, which was witnessed by medical and nursing staff. This syndrome, characterized by restlessness, hyperactivity, sweating, abdominal cramps, nausea, and vomiting, lasted about 10 hours. The patient had minimal reaction to a second dose (12.5 mg) the next day and tolerated an increased dose (25 mg) well on the third day. No apnea was noted during the continuous treatment with naltrexone for one month. Discontinuation of naltrexone by her family after this time, however, was followed 4 days later by a prolonged apneic event, with cyanosis that required CPR. Naltrexone was reinitiated without further withdrawal-like symptoms, and no further apneic events occurred until June 1986, when monitor alarms, usually coinciding with deep sleep, indicated apnea and bradycardia. At this time, the patient was taking imipramine (25 mg) for hyperactivity and naltrexone (25 mg) at bedtime. A second determination of i-BE in CSF indicated a concentration of 177 pg/ml, which was still markedly above control values (see later). The imipramine was discontinued and naltrexone was increased to 50 mg/day. In February 1987, naltrexone was discontinued, and no further occurrence of apnea has been seen on subsequent follow-up study.

Patient 2

At the age of 2 months, this male infant was first seen with repeated events of prolonged apnea and bradycardia that required CPR. Examination revealed extreme hypotonia and gastroesophageal reflux. The latter was treated successfully, but life-threatening apneic events during sleep were witnessed by medical staff and were documented with PPG and PSG. At the age of 8 months, he had 5 and 8 episodes of PA

Table 1. Evaluation of Infants Under 2 Years Old with Elevated Immunoreactive β-Endorphin

Sex	Age	i-BE (pg/ml)	Initial Evaluation[a]	Length of Treatment	Results with Naltrexone	Subsequent Evaluation
M	3 wk	99	PA events on PPG[b]	3 mo	No alarms	PPG normal
M	15 mo	155	Multiple SA on PPG	4 mo	No alarms	PPG normal
F	3 wk	73	PPG abnormal[c]	3+ mo	No apnea	
F	1 mo	95	PPG abnormal[b]	2 mo	No alarms	PPG normal
M	3 mo	80	PPG and PSG normal[d]	3 mo	No alarms	PPG normal
F	6 wk	76	PPG normal; excess SA on PSG	2 wk[e]	No alarms	i-BE = 106
F	2 mo	55	PSG normal; PA events on monitor	2 mo	No alarms	i-BE = 23[f]
F	3 mo	89	PA events on PPG	3 wk[g]	No alarms	

[a]All patients were referred because of observed apnea, except the 1-month-old girl, who had an apparent life-threatening event.
[b]Sibling of victim of sudden infant death syndrome.
[c]Reported from other centers.
[d]Repeated stimulation required during apnea.
[e]Naltrexone discontinued because of mother's claim that it caused excessive salivation and sweating; apnea resumed on discontinuation and subsequent PPG was abnormal.
[f]Subsequent meningitis and failure to thrive continued.
[g]Vomited medication; apnea resumed on discontinuation of naltrexone.

i-BE = immunoreactive β-endorphin; PA = prolonged apnea; PPG = pneumocardiogram; PSG = polysomnogram; SA = short apnea.

Table 2. Evaluation of Children 2 to 8 Years Old with Elevated Immunoreactive β-Endorphin

Sex	Age (yr)	i-BE (pg/ml)	Initial Evaluation	Length of Treatment	Results with Naltrexone	Subsequent Evaluation
F	6	276	See Patient 1 (text)	18 mo	See Patient 1	See Patient 1
M	3	74[a]	See Patient 2 (text)	4+ yr	See Patient 2	See Patient 2
M	3	75	PPG abnormal[b,c]	18 mo	No apnea[d]	i-BE = 195, 66
M	8	188	Multiple PA on PPG	3+ yr	No apnea	PSG normal[e]
M	4	77	PSG normal; PPG abnormal[c]	2+ yr	Improved[f]	i-BE = 71

[a]Measured at age 18 mo.
[b]Repeated apnea that required resuscitation.
[c]Reported from other centers.
[d]Apnea did not recur when naltrexone was stopped.
[e]No apnea while on naltrexone, but apnea recurred on attempt to stop naltrexone.
[f]Occasional alarm, but none requiring cardiopulmonary resuscitation; partial complex seizures recognized during subsequent evaluation and treated with carbamazepine; naltrexone treatment continued.

i-BE = immunoreactive β-endorphin; PPG = pneumocardiogram; PA = prolonged apnea; PSG = polysomnogram.

with bradycardia during 2 recording periods. Attempted therapy with theophylline resulted in aggravation of reflux but did not affect central apneic events. Administration of naloxone resulted in dramatic cessation of apnea. Three months later, naltrexone was initiated. Subsequent apneic events during naltrexone administration occurred only when the infant was stressed, for example, during an infection and after an automobile accident in which he was not injured. The concentration of i-BE in his CSF, measured when he was 18 months old, was found to be elevated (74 pg/ml). At the age of 23 months, while not receiving naltrexone, he had a 42-second apneic episode without bradycardia and a 20-second episode with bradycardia. Treatment with naltrexone has been continued since attempts to remove the drug have resulted in resumption of apnea.

Evaluation of Naltrexone Therapy

The initial evaluations, the levels of i-BE in CSF, and the results of treatment with naltrexone in individual patients are summarized in Tables 1 to 3. Apart from hypotonia and occasional gastroesophageal reflux, none of the patients presented in Tables 1 and 2 had a demonstrable cause for their central apnea after full investigation. Presence or absence of PA, SA, SA with bradycardia, and excessive periodic breathing were confirmed by PPG or PSG, or both, as indicated in the tables. Correction of PA during treatment was estimated by monitor alarms and documentation by caretakers or PSG or PPG where indicated in the tables. After initiation of naltrexone (1 mg/kg, by

Table 3. Evaluation of Children with Leigh's Syndrome

Sex	i-BE (pg/ml)	Initial Evaluation	Results with Naltrexone
F	104	Cytochrome oxidase deficiency; apnea	Apnea improved
F	96	Elevated pyruvate and lactate; apnea, hypotonia; ataxia	Apnea controlled for 2+ yr; subsequent i-BE = 100, 57, 120
F	283, 291	Elevated pyruvate and lactate; apnea	Apnea improved, but patient subsequently died; no autopsy

i-BE = immunoreactive β-endorphin.

Table 4. Comparison of Immunoreactive β-Endorphin in Cerebrospinal Fluid Among Infants with Apnea, Older Children with Apnea of Unknown Cause or Metabolic Dysfunction, and Control Subjects in the Same Age Ranges

Subjects (n)	Age Range	Mean ± SEM (pg/ml)	Range (pg/ml)
Control infants (20)[a]	0.5–15 mo	32 ± 3	17–52
Apneic infants (8)[b]	0.5–18 mo	90 ± 11[c]	55–155
Control children (6)	2–10 yr	30 ± 5	15–48
Apneic children (5)	2–8 yr	162 ± 39[d]	74–276
Leigh's syndrome (3)	2–5 yr	162 ± 62[e]	104–291

[a]From Myer et al [9].
[b]Subjects from Myer et al [9] who were treated with naltrexone.
[c]$p < 0.001$, compared to control infants.
[d]$p < 0.01$, compared to control children.
[e]$p < 0.05$, compared to control children.

mouth) in a single daily dose, no further apneic events were noted in the subjects with apnea of unknown cause (Tables 1 and 2), except in Patient 1 (see Table 2), who required an increase in the dosage of naltrexone to approximately 2 mg/kg/day, and in the infant who experienced stressful events (Patient 2, see Table 2). Attempts to discontinue naltrexone after a period of successful treatment resulted in the recurrence of apnea in some of these patients (see Table 2). All 3 children with Leigh's syndrome showed respiratory improvement with naltrexone treatment (1 mg/kg/day, by mouth), although 1 subsequently died (see Table 3). That patient had an extremely high concentration of i-BE in her CSF. The only adverse effects of naltrexone treatment noted in this study were the complaint of headaches and other occasional pains in 2 of the children and the apparent withdrawal syndrome described in Patient 1.

Comparison of CSF i-BE in Apnea with That in Control Subjects

Comparisons of i-BE in CSF from infants with apnea and control infants and in CSF from older apneic children and control children in the same age range are indicated in Table 4. No age-related changes in CSF levels of i-BE were noted, and no significant difference was seen between the mean concentrations in the two control age groups. In both age groups, however, significant increases of i-BE were observed in children with either a recent or a protracted history of apnea.

Discussion

The results of the present study indicate that oral naltrexone is effective for the treatment of PA, excessive periodic breathing, and SA with bradycardia in infants, as well as for recurrent apnea in older children. In contrast, neither the apnea of prematurity in infants [14] nor the recovery of asphyxiated newborn infants during resuscitation [15] was significantly improved by opioid antagonist administration. It is not known whether infants with apnea of prematurity have elevated levels of β-endorphin or other endogenous opioid peptides in their CSF, although elevated levels of i-BE were found in the plasma from such infants [14]. However, in a previous study of the infant apnea syndrome, we found elevated i-BE in CSF, without a concomitant increase in plasma [9]. Therefore, measurement of plasma levels of i-BE probably does not provide a reliable index of excessive endorphinergic activity within the central nervous system.

All of the infants and children with apnea in the present study had demonstrated elevations of i-BE in their lumbar CSF. Because i-BE has not been detected in the human spinal cord [16], it is likely that its appearance in lumbar CSF is mainly due to its release from supraspinal sites that are enriched in i-BE, such as the arcuate nucleus of the hypothalamus, periaqueductal gray matter, and pituitary [17, 18]. Studies in animals have also identified a group of β-endorphin–containing neurons in the nucleus tractus solitarius, as well as dense i-BE in the nucleus parabrachialis

medialis (for review, see [19]). In addition to the anterior hypothalamus, the solitary tract and parabrachial areas are sensitive to opioid-induced respiratory depression, as demonstrated by direct local application of the drugs [20–22]. The elevated i-BE observed in the present study may have originated from these areas, as excessive endorphinergic activity in other areas of the brain could lead to other symptoms of neurological dysfunction that were not exhibited by the subjects with idiopathic apnea [23]. The cause of the elevated i-BE is unknown. The synthesis and release of β-endorphin appear to be regulated by several different mechanisms [24], but a recent study failed to show a significant effect of hypoxia on i-BE in CSF [25].

The respiratory depression produced in animals by the central administration of β-endorphin has been reported to be antagonized by naloxone [26–28]. Unlike naloxone, naltrexone has good oral bioavailability and a much longer duration of action. Although the pharmacokinetics of naltrexone have not been studied in children, studies in adult males have indicated mean plasma half-lives of 8.0 to 10.3 hours after acute oral doses of 50 to 100 mg [29, 30]. A mean plasma half-life of 9.7 hours was found after chronic oral doses of 100 mg/day, indicating no induction of its own metabolism with chronic administration [30]. Plasma concentrations of the major unconjugated metabolite of naltrexone, 6β-naltrexol, were higher than plasma concentrations of naltrexone, and this metabolite had a mean half-life of 8.9 to 12.7 hours [29, 30]. Studies in animals have indicated that 6β-naltrexol also possesses opioid antagonistic activity but is considerably less potent than naltrexone (for review, see [31]). Therefore, the extent to which this metabolite contributes to the therapeutic efficacy of naltrexone against apnea is unknown.

The role of 6β-naltrexol in the appearance of side effects is also unknown. A review of phase II clinical testing of naltrexone in over 1,000 detoxified (postaddict) adults indicated a low, but significantly increased, incidence of nausea, abdominal pain, skin rash, and headaches, when compared to control subjects who received placebo treatment [11]. Two of our subjects complained of headaches, but the most striking adverse effect of naltrexone treatment was the precipitation of a withdrawal-like syndrome in one child with a high level of i-BE in CSF. To our knowledge, this is the first suggested demonstration of physical dependence on endogenous opioids, although the development of physical dependence in rats during chronic central administration of either met-enkephalin or β-endorphin has been reported [32].

Although opioid peptides other than β-endorphin were not measured in the present study, it is possible that an elevation of met-enkephalin or other endogenous opioids could contribute to the cause of apnea in some of our patients. Brandt and co-workers [6] reported a marked elevation of met-enkephalin in a brain from a child with Leigh's syndrome who died during an apneic attack. The fact that all of our subjects with apnea had both elevated i-BE in CSF and a positive response to naltrexone indicates the possibility that the measurement of i-BE in CSF from children with apnea may be a good marker for predicting a favorable response to naltrexone and also indicates that the apnea is likely due to excessive endorphinergic activity in the areas of the brain that regulate respiration.

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