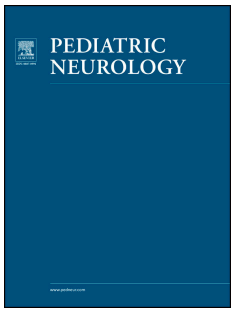

ACTH treatment of infantile spasms: Low-moderate vs. high dose, natural vs. synthetic ACTH. A retrospective cohort study

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ACTH treatment of infantile spasms: Low-moderate vs. high dose, natural vs. synthetic ACTH. A retrospective cohort study.

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Abstract

Background. High dosages of natural adrenocorticotropic hormone (ACTH) are used in many centers in the U.S. for the treatment of infantile spasms (IS). However, lower dosages of synthetic ACTH (tetracosactide) might be equally as efficient as high dosages.

Purpose. To shed light on the treatment options for IS, especially regarding the ACTH dosage and the formulation (natural versus synthetic), and to evaluate which options were more effective in a retrospective cohort from 1960-76.

Methods. We compared the short-term response rates of patients treated with high dosages of natural ACTH (120 IU/d) (N=31) (Group1) to those of patients treated with low-moderate dosages of natural ACTH (40 IU/d) (N=52) (Group2). We also compared the short-term response rates of patients treated with natural ACTH (N=83) to those of patients treated with synthetic ACTH, (N=23) (Group3). The responses were evaluated clinically and by EEG at 2-3 weeks after the onset of therapy.

Results. A response was seen in 24/31 children treated with high dosages and in 43/52 children treated with low-moderate dosages of natural ACTH (p=0.56). All children with an unknown etiology responded to both high and low-moderate dosages of natural ACTH. The proportion of children with a good early response to synthetic ACTH (16/23) did not differ from the proportion of children with a good early response treated with natural ACTH (67/83) (p=0.25).

Conclusions. High dosages of ACTH are not more effective than low-moderate dosages in the short term for treating IS. Synthetic ACTH is equally as effective as natural ACTH.

Keywords: infantile spasms; adrenocorticotropic hormone, 1-39 ACTH, 1-24 ACTH

1. Introduction

In children with infantile spasms (IS), hormonal treatment is the best single-use treatment for the cessation of spasms according to a Cochrane Review from 2013 [1]. Although best practice guidelines for the treatment of IS were developed by the American Academy of Neurology and the Child Neurology Society [2, 3], the treatment options for IS remain somewhat controversial with respect to the choice of drug (adrenocorticotropic hormone (ACTH) or prednisolone), the dosage of ACTH and the formulation of ACTH (natural or synthetic).

Some centers in the United States (U.S.) utilize prednisolone as the initial treatment for IS [4, 5], particularly because synthetic ACTH is not available in the U.S. for the treatment of IS and because natural ACTH is so expensive. There is some evidence that ACTH and prednisolone are equally effective [6, 7]. One of the long-standing controversies is whether a higher dosage of natural ACTH provides a better response than lower dosages of the drug. Another question is whether natural or synthetic ACTH should be used. Our data may shed light on these two questions.

Natural ACTH (or ACTH 1-39), a repository corticotropin injection, is a Food and Drug Administration (FDA)-approved treatment for IS in the U.S. It contains corticotropin, a naturally occurring hormone of the pituitary gland. It is not available for the treatment of IS in Europe. As previously stated, synthetic ACTH (synonyms ACTH 1-24 or tetracosactide) is not available in U.S. for the treatment of IS. Tetracosactide consists of the first 24 amino acids of the 39 that occur in the natural ACTH sequence and displays the full biological activity of natural ACTH [8, 9].

We retrospectively evaluated the treatment responses in a cohort of infants with IS at the Children's Hospital, University of Helsinki, Helsinki, Finland. Low-moderate dosages (40 IU/d) of natural ACTH were used during the first study period of 8 years (1960-1968), and high dosages (120 IU/d) were used during the following 8 years (1969-1976) in accordance with the treatment protocol at that time in this tertiary care center. Our dosage is called low-to-moderate because in Italy [10] and Japan [11], even lower dosages are in use, i.e., 10 IU/d and 0.1-1.0 IU/kg/d, respectively. The transition to synthetic ACTH was not based on any medical indications or applied at a certain date but was necessary because natural ACTH was sometimes unavailable in our country.

The aim of this study was to compare the effects of high dosages of natural ACTH and low-moderate dosages of natural ACTH and to compare the effects of natural ACTH and synthetic ACTH on the treatment of IS. A short-term evaluation was carried out at 2-3 weeks when the ACTH dosage had reached the maximum level. Our hypothesis was that low and high dosages of natural ACTH have a similar efficacy and that synthetic ACTH is equally effective as natural ACTH, independent of the dosage.

2. Methods

The study cohort consisted of all children treated for IS in the Children's Hospital of the University of Helsinki, Finland during the study period 1960-76. The primary response of the patients to ACTH treatment was recorded at 2-3 weeks of therapy (N=106) by clinical observation (spasms) and electroencephalography (EEG) covering awake, awakening and asleep states over at least two hours. Children who had contraindications for treatment, such as severe heart disease, congenital or symptomatic acquired cytomegalovirus infection, or previous herpes infections, were excluded. All patients had clinical spasms and hypsarrhythmia or modified hypsarrhythmia before treatment. No patients had been given any hormonal therapy before ACTH. We did not exclude patients with tuberous sclerosis (N=2) or trisomy (N=1).

The data were collected from hospital records and analyzed retrospectively, and the patients were classified into three different treatment groups.

All patients were carefully examined for specific etiology by clinical and laboratory tests of associated disorders or for central nervous system infections before ACTH therapy was started. Ophthalmological examinations and neuroradiological investigations available at that time were performed in most cases. The previously reported etiological categorization [12] was changed to comply with the classification of the International League Against Epilepsy (ILAE) [13]. Unknown etiology was defined as prior normal development and a lack of known etiology. The proportion of these patients is important because this group is known to have the best response to ACTH treatment.

All patients were treated according to the standard protocol. ACTH was administered once a day in the morning intramuscularly. The duration of treatment was typically six weeks if there were no serious adverse effects. The ACTH treatment schedule was as follows. The low-moderate dosage was 40 IU/d for 3 weeks, 20 IU/d for 2 weeks, and then gradually tapering off for one week (the cumulative total dose being 1185 IU). The high dosage was 120 IU/d for 3 weeks, 80 IU/d for 2 weeks, and then gradually tapering off for one week (the cumulative total dose was 3545 IU). Natural and synthetic ACTH were administered similarly. The dosages of synthetic ACTH were low-moderate (40 IU/d) for 11 children, high (80 IU/d) for 7 children and higher (120 IU/d) for 5 children.

The patients were inpatients in isolation during the entire 6-week ACTH course to avoid infections and to allow the monitoring of the adverse effects of therapy and the occurrence of spasms. Spasms were monitored clinically several times daily for 5-10 min when the infant was waking up or falling

asleep. The numbers of spasms, seizures, and series of spasms were recorded by trained nurses or physicians (usually pediatric neurologists) by observation and using a seizure diary. The cessation of spasms was evaluated at 2-3 weeks after onset of therapy. The response to ACTH treatment was always confirmed by EEG at 2-3 weeks after the onset of therapy. At that time, the ACTH dosage was at the maximal level in all cases. Originally, the EEG of most patients was evaluated by a single experienced neurophysiologist throughout the study from 1960-76, who later re-evaluated all the EEGs retrospectively. The primary outcome was assessed electroclinically, and a good response was defined as the cessation of spasms between days 14 and 21 and the disappearance of hypsarrhythmia on the EEG.

Approval from the Ethics Committee of the Children's Hospital, University of Helsinki, was obtained for this retrospective data analysis.

Statistical analysis

Data are expressed as the number of cases (%), mean (SD) and median (minimum-maximum) as appropriate. The Kruskal-Wallis test was used to compare continuous data, and the chi-square test was used to compare the proportions of responders and other binary parameters. The treatment effect was considered significantly different if the p-value was less than 0.05 using a 2-sided test, and 95 % confidence intervals (95 % CI) were calculated for the differences between the proportions.

3. Results

The clinical characteristics are shown in Table 1. Although the groups differed in size, the three groups were suitable for comparison because they were similar with respect to factors that can affect the prognosis. The mean age at onset of the spasms was 6 months (range 1-23), and the age at treatment onset was 8 months. The proportion of patients with an unknown etiology was similar (17-22 %).

The outcome results are shown in Table 2. An electroclinical response was seen in 24/31 (77 %) of the children treated with a high dosage of ACTH and in 43/52 (83 %) of the children treated with a low-moderate dosage. The difference was not significant (95 % confidence interval (CI) for

difference -23 % - 12 %) (p=0.56). In all children with an unknown etiology, the electroclinical response to ACTH was good for both high and low-moderate dosage groups.

There was no significant difference in the number of children with a good response to synthetic ACTH (16/23; 70 %) and the number of children with a good response to natural ACTH (67/83; 81 %); the difference was 11 % (95 % CI for difference -30 % - 8 %) (p=0.25).

The response was maintained during the 6-week treatment and hospital stay, plus an additional two weeks, except in 8 patients: two patients in Group 1 (one at the cessation of therapy, and one a week later), four patients in Group 2 (one immediately after the cessation of treatment, one a week later and two cases 2 weeks later), and two patients in Group 3 (one during the treatment, and one 10 days after the cessation). If there was no response to the first ACTH course, it was futile to repeat the course. However, when a relapse occurred after a good primary response, a new course was also effective in most cases (74 %) [14]. If the number of relapses was taken into account, the response rates were 22/31 (71 %) in Group 1, 39/52 (75 %) in Group 2 and 14/23 (61 %) in Group 3, (p=0.56) (Table 2).

Pronounced adverse effects (mainly infections and arterial hypertension) were seen in each treatment group: 9 out of 31 patients in Group 1, 13 out of 52 patients in Group 2, and 13 out 23 patients in Group 3 (p=0.024).

4. Discussion

The novelty of this retrospective, nonrandomized open-label study is that by data mining, we were able to provide some answers to the pending questions on the use of ACTH in IS. We compared the responses between different dosages of natural ACTH and between natural ACTH and synthetic ACTH to treat IS. Different dosages of ACTH have rarely been compared, and previous data are inconclusive (Table 3). To the best of our knowledge, at present (in 2020), there are no comparative studies of response rates to natural ACTH and synthetic ACTH (tetracosactide). This is an economically important issue, as natural ACTH is much more expensive than synthetic analogs. We think that the two groups, i.e., high dosage and low-moderate dosage, were suitable for comparison because of the large difference in the dosages.

The outcome is dependent on etiology. The group of patients with an unknown etiology always shows the best response, and their representation in a cohort may cause bias and affect the interpretation of the results. Although the etiological workup has greatly evolved since this retrospective cohort, including the introduction of magnetic resonance imaging and genetic

analyses, the proportion of an unknown etiology cases remained constant during the periods 1960-76 [14], 1977-91 [23] and 1994-99 [24] in the same hospital.

We focused on short-term outcomes. In IS patients, spasms ceased most often simultaneously with the disappearance of hypsarrhythmia in EEG. However, IS may remain unnoticed by the bare eye or may be very subtle. We think that an EEG examination is necessary to evaluate the effect of ACTH [25]. Long-term responses have been analyzed in other studies [26-33]. The early cessation of the spasms and the disappearance of hypsarrhythmia were associated with more favorable long-term outcomes both in IS children with known etiology and those with an unknown etiology [26].

4.1 Which is the optimal dosage?

Reported short-term response rates with different dosages of ACTH are shown in Table 3. Despite the guidelines by the American Academy of Neurology/Child Neurology Society that were updated in 2012 to describe the equal efficacy of low-dose ACTH [3] and high-dose ACTH, the practice of administering high dosages of natural ACTH (150 IU/m^2 divided in two daily injections) continues. This is based on a couple of studies in which the response rate was reported to be 90-97 % [16, 18]. Results with such a high response rate could, however, not be replicated in a prospective, large national study by Knupp et al.[20]. In a more recent report from Boston Children's Hospital, outcome data with once-daily high-dosage practice were reported [19]. Forty of 57 children (70 %) were spasm-free at day 14 after natural ACTH initiation. EEG showed the disappearance of hypsarrhythmia in all responders.

In contrast, low-dosage ACTH administration is supported by data from the blinded, randomized prospective study by Hrachovy et al. [17]. In our study, after three weeks of treatment, the disappearance of hypsarrhythmia was observed in 85 % of patients treated with low-moderate dosages, which is consistent with two other ACTH studies where low-moderate dosages were used; those studies reported the disappearance of hypsarrhythmia in 86 and 80 % of patients [6, 12]. In Japan, the dosages have been substantially lower, and the response rates have been similar to those of others countries [13, 22]. The fact that all patients also received pyridoxine for one week before ACTH therapy may affect the results.

A recent meta-analysis and two retrospective studies compared the efficacies of low-dosage and high-dosage synthetic ACTH and did not observe any difference between the two dosages [34]. This meta-analysis included 184 children and 6 trials and included both synthetic and natural ACTH preparations.

In summary, the present and previous studies (Table 3) support the hypothesis that no significant differences between high-dosage and low-moderate dosage treatments exist. Even dosages lower than those used in Finland seem to be effective, but whether this is due to ethnic differences (Japanese versus American children) is not known.

4.2 Is natural ACTH or synthetic ACTH more efficient?

A comparison of studies on natural ACTH versus synthetic ACTH and the heterogeneity of methods are shown in Table 3. When comparing natural and synthetic ACTH, it must be considered that the duration of stimulation of the adrenals (analyzed by serial plasma and urinary 11-hydroxysteroid measurements) by subcutaneous depot tetracosactide was twice as long as that induced by corticotropin gel [35, 36]. Consequently, the effective dosage of 40 IU/d of synthetic ACTH might be somewhat higher than the dosage of natural ACTH. Most therapeutic effects of ACTH are probably mediated by glucocorticoids. Maximal adrenal stimulation can be achieved with small dosages [37]. In addition, ACTH also has direct, less understood effects on various organs, including the central nervous system, possibly through the inhibition of corticotropin-releasing hormone [38, 39] or through the promotion of brain maturation and growth [40, 41].

A pharmacokinetic comparison of the two types of ACTH has only been reported in a small number of patients and needs to be studied further, along with the optimal time intervals for ACTH administration.

4.3 Strengths and limitations of our study

A strength of our study is that it is a single-center study with standardized treatment protocols and data collection. There was no heterogeneity due to multicenter trials and multiple interpreters of the outcomes.

This study is a retrospective observational cohort study and was not randomized or blinded. However, we think that the two groups, i.e., the high and low-moderate dosage groups, are suitable for comparison because of the large difference in dosages. A major limitation is the lack of power to show differences between groups due to the small sample size, a common problem in studies of IS. In rare epilepsy syndromes, it is difficult to conduct large, double-blind, randomized studies. A prospective randomized trial requires enrolling at least 250 - 1000 infants. Other limitations include the lack of modern imaging, genetic testing, and video monitoring to verify the cessation of spasms

during the study period. The results from a single center may not be generalizable to a broader population.

An alternative to ACTH is prednisolone, and it has several advantages, including its price, route of administration and equal efficacy to ACTH [4, 7]. Our current protocol is a combination of the two: the first 6 doses of synthetic ACTH injections have 2- to 3-day intervals (usually Monday-Wednesday-Friday) followed by peroral prednisolone for 2 weeks [6, 42].

The treatment of IS is a major challenge due to the severity of the disease for the majority of infants. ACTH remains the treatment of choice, especially in cases with an unknown etiology. We show that low-moderate dosages of ACTH and the use of synthetic ACTH are effective.

5. Conclusions

Despite efforts to cure IS efficiently, the response rates have not truly changed over time. In fact, arguments about the same medications, including ACTH, and their dosages and optimal administration methods have been ongoing for decades. For rare epilepsy syndromes, such as IS, it is difficult to conduct large, double-blind, randomized studies that could help to establish best practice guidelines for IS treatment. This retrospective study shows that the short-term efficacy of low-moderate dosages and high dosages of natural ACTH were similar for the treatment of IS. The data also indicate that synthetic ACTH and natural ACTH were equally effective, independent of the dosage. In the absence of novel therapy options, the optimization of and guidelines for ACTH are needed.

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Declaration of interests

Raili Riikonen has received a speakers' honorarium from Questcor Pharmaceuticals 2010 (New York) and from Amzell B.V. Pharmaceuticals, 2017 (New York). Hannu Kokki has nothing to disclose. Jaana Lähdetie has received training and travel grants from PTC Pharma and Biogen.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Patient characteristics (N=106). Data are median (minimum, maximum) or number of cases

Parameter	Natural ACTH		Synthetic ACTH	p-value
	Group 1 High dosage N = 31	Group 2 Low-moderate dosage N =52	Group 3 N =23	
Age at onset of Infantile Spasms, months	6 (0.3-13)	6 (0.4-24)	6 (2-20)	0.342
Age at treatment, months	6 (1-24)	7 (0.5-24)	7 (2-24)	0.557
Treatment lag, months	1 (0-7)	1 (0-8)	1 (0-7)	0.958
Prior seizures: yes/no	8/23	5/47	3/20	
Etiology:				known vs. unknown 0.884
-structural	11	21	12	
-metabolic	2	13	2	
-genetic	8	5	1	
-infectious-immunological	3	3	4	
-unknown	7	10	4	

ACTH = adrenocorticotropic hormone

Table 2. Outcome at 2-3 weeks of ACTH treatment, electroclinical response rate including and excluding early relapses. Data are number of cases (%)

Parameter	Natural ACTH		Synthetic ACTH	p-value
	Group 1 High dosage N = 31	Group 2 Low-moderate dosage N = 52	Group 3 N = 23	
Responders	24 (77 %)	43 (83 %)	16 (70 %)	0.441
Relapse within 2 weeks after end of treatment	2 (6 %)	4 (8 %)	2 (9 %)	0.952
Responders, cases with early relapses excluded	22 (70 %)	39 (75 %)	14 (60 %)	0.463

ACTH = adrenocorticotropic hormone

Table 3. Previous studies of ACTH use to treat infantile spasms and short-term response rates using different dosages of ACTH and either natural or synthetic ACTH.

Class of evidence*	Number of patients	ACTH-dose	Duration of full dose, weeks	Treatment response		Reference
				Spasms stopped	EEG resolution	
HIGH DOSAGE STUDIES, natural ACTH						
III	54	80-120 IU/d	3	54 %	68 %	Riikonen 1982 [14]
III	73	110 IU/m^2/d	3	49 %	39 %	Lombrosco 1983 [15]
III	15	80-150 IU/m^2/d	2	93 %	93 %	Snead et al. 1989 [16]
I	26	150 IU/m^2/d	3	54 %	23 %	Hrachovy et al. 1994 [17]
I	15	150 IU/m^2/d	2	87 %	87 %	Baram et al. 1996 [18]
III	57	150 IU/m^2/d	2	70 %	70 %	Hodgeman 2016 [19]
II	97	150 IU/m^2/d	2	55 %	55 %	Knupp et al. 2016 [20]
LOW-MODERATE DOSAGE STUDIES, natural ACTH						
NA	112	40-60 IU/d	3-4	68 %	86 %	Jeavons 1964 [21]
III	97	20-40 IU/d	3	64 %	77 %	Riikonen 1982 [14]
I	26	20 IU/d	3	58 %	21 %	Hrachovy et al. 1994 [17]
I	49	40-60 IU/d	2	37 %	18 %	Wanigasinghe et al. 2017 [7]
SYNTHETIC ACTH STUDIES						
III	25	10 IU/d	3-3.5	74 %	78 %	Vigevano, Cilio 1997 [10]
III	12	0.2 IU/kg/d	2-4	75 %	75 %	Yanagaki et al. 1999 [22]
III	13	1.0 IU/kg/d	4-6	84 %	75 %	Yanagaki et al. 1999 [22]
III	25	0.5 mg/kg on alternate days	3	76 %	69 %	Lux et al. 2004 [6]
III	72	0.2 mg/kg/d	2	88 %	88 %	Hamano et al. 2008 [11]
III	63	0.015 mg/kg/d	2	85 %	75 %	Hamano et al. 2008 [11]
III	50	0.0125 mg/kg/d	2	78 %	78 %	Hamano et al. 2008 [11]

* Class of evidence based on the American Academy of Neurology (AAN) evidence classification scheme [2, 3, 45,]

Online supplemental material

ACTH formulas and preparations

ACTH belongs to a group of melanocortin peptides. Melanocortin peptides derive from the common precursor protein pro-opiomelanocortin by cleavage and processing. Most actions of ACTH are probably mediated by glucocorticoids. In addition, ACTH also has direct, less understood effects on various organs, including the central nervous system. It is thought that ACTH acts directly on amygdala neurons to downregulate corticotropin-releasing hormone gene expression [38, 39]. The extra-adrenal effects that natural ACTH and synthetic ACTH have in common include increased melanotropic activity and increased growth hormone secretion [8, 9].

Natural ACTH

In the U.S., the FDA-approved therapy for IS is repository corticotropin injection (H.P. Achtar Gel^{R} 80 units/mL, Mallinckrodt Specialty Pharmaceuticals, Ireland Limited, Dublin, Ireland), a highly purified sterile formulation of ACTH in 16 % gelatin that provides a prolonged release of the hormone obtained from porcine pituitaries [43]. The pharmacokinetics of Achtar Gel^{R} have not been well characterized. This ACTH formulation is currently used in the U.S.

Acton prolongatum^{R}, carboxymethyl-cellulose corticotrophin, Ferring, Malmö, Sweden was used in this and earlier studies by Riikonen [14, 23, 26, 27]. Acton prolongatum^{R} was recently shown to be more effective than Achtar Gel^{R} (Mallinckrodt) in a rodent model [44]. Wanigasinghe et al. [7] used Acton prolongatum, carboxymethyl-cellulose corticotrophin, Himachal Pradesh, India in his study.

Synthetic ACTH

Tetracosactide, cosyntropin, consists of the first 24 amino acids (SYSMEHFRWGKPVGKKRRPVKVYP) of the natural ACTH polypeptide. It is a product given parenterally with pharmacokinetics showing prolonged absorption compared to corticotropin. Therapeutically, it is used in the form of a depot preparation formulated for the adsorption of the active N-terminal amino acids 1-24 of ACTH onto zinc phosphate. Therefore, therapy may be maintained with less frequent administration compared to natural ACTH. In contrast to natural ACTH preparations obtained by extraction, the composition of tetracosactide is not subject to variation, so that dosage can be expressed in terms of weight.

Tetracosactide exhibits the full range of activities of natural ACTH. It has been shown that 0.25 mg of tetracosactide will stimulate the adrenal cortex maximally and to the same extent as 25 international units (IU) of natural ACTH in adults [36].

The long-acting depot formulation of synthetic ACTH is not available for the treatment of IS in the U.S. The immediate-release formulation is approved only for diagnostic testing of adrenal function. In Europe, the formulation Synachten Depot^{R}, a long-acting synthetic 24-amino-acid polypeptide and zinc complex, is in use. In Japan, where natural ACTH is neither available, the most widely used synthetic analog is Cortosyn-Z^{R}, a zinc hydroxide suspension of a 24-amino-acid polypeptide similar to Synachten Depot^{R}.

Synachten Depot^{R}, Mallinckrodt Specialty Pharmaceuticals Ireland Limited, Dublin, Ireland, and S-Cortrophin Depot^{R}, ADVANZ Pharma, London were used in the present study.

Cortrosyn Z, (N.V. Organon, Oss, Netherlands) and Cortsosyn Z (Daiichi Sankyo Co., Tokyo, Japan) were used in Japanese studies [13, 22]. One milligram of the preparation used corresponds to 40 IU ACTH in Japan. Synthetic ACTH marketed in Europe is twice as strong as in Japan: 1 mg corresponds to 80 IU natural ACTH [36].