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What are the reasons for the strikingly different approaches to the use of ACTH in infants with West syndrome?

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Abstract

A large body of experience has been compiled in different countries, documenting the efficacy of adenocorticotrophic hormone (ACTH) for infantile spasms. This is important, because it may serve as a key for understanding this disorder, as well as for designing better medicines. However, significant discrepancies exist among studies originating in different countries regarding the relative efficacy of small or large ACTH doses.

These differences may be caused by a number of factors, including potential genetic or environmental-related differences in the biology of the disorder or associated genetic components that determine responsiveness to ACTH. In addition, striking differences in the preparations used around the world may be responsible. These include bio-availability and extent of blood brain barrier penetration, efficacy in activating the efficacy-mediating ‘ACTH receptors’, the presence in certain preparations of competing analogs, and others. These issues should not detract from the overall agreement that ACTH might be the most useful medication currently available to treat WS.

Keywords

Adenocorticotrophic hormone; West syndrome; Infantile spasms; ACTHARGEL; Clinical

1. Introduction

Around the world, clinicians use the adenocorticotrophic hormone (ACTH) to treat West syndrome (WS). However, marked discrepancies exist in several aspects of this treatment. These may involve:

1. A potential biological difference of WS in different countries.
2. Potential differences in the definition of efficacy, including duration of treatment.
3. The type of hormonal preparations.

These issues are discussed below.

2. WS is not a homogenous entity

Distinct properties of infants who have WS together with tuberous sclerosis (TS), including their exquisite responsiveness to vigabatrin have been recognized. If genetic factors contribute to WS – even if the actual seizures are triggered by superimposed insults – could it be that the biology of WS differs around the world? At a minimum, genetically based differential responsiveness to low doses of ACTH may well explain the apparent differences between response to very low doses of ACTH in Japan and in the US.

3. How do we define efficacy?

Because WS is such a difficult disorder, even relatively moderate responses are considered a success. For example, a number of landmark studies considered response rates of 40–50% highly significant, and indeed they are [e.g. 1,2]. Prednisone and related steroids demonstrate this type of efficacy, as does vigabatrin in non-TS patients (US data) and topiramate [3]. For other agents, several studies report on efficacy rates of 11% (for B6, [4]) or 23% [5]. In contrast, others considered the response of 85–90% of infants as ‘excellent efficacy’ [6,7]. Other difficulties in comparing efficacy are derived from often small numbers of patients (five per group, [8]) or from the occasional use of reduction in spasm numbers rather than their disappearance [3]. While these may explain some of the discrepancies, there are well designed and compelling studies with large number of patients which report very different results for either the use of low doses or of high doses (e.g. compare Ref. [9] with Ref. [6]). How do we reconcile these findings?

4. The hormonal preparations

Most US studies use a natural preparation of ACTH, whereas Japanese studies use a synthetic preparation [10,11]. The Americal preparation, ACTHARGEL is a mixture of many peptides and derivatives, and its potency is measured in units (U). It is generally considered that 0.025 mg is equivalent to 1 U. However, while this may be the case in terms of the ability to release steroids, it may not be the case for any effects on the brain.

Recently, it has been suggested that ACTH may work for WS not only by secretion of cortisol and other steroids, but also via direct effect on neurons, mediated by melanocortin receptors [12]. The affinity of different analogs, fragments and formulations of ACTH to these receptors is very different from the affinity to peripheral receptors, which are involved in steroid release. Thus, it is quite conceivable that the synthetic preparations or the preparations used in Japan contain ACTH forms, which are far more potent in activating these brain receptors. Thus, any comparison of doses in terms of ‘high’ and ‘low’ needs to be redefined. Indeed, the other peptides in the American preparation (ACTHARGEL) may actually compete with ACTH for the central brain receptors and interfere with its functions. In addition, the blood brain barrier penetration of each of the formulations may be entirely different (see discussion in Ref. [12]). Support for the fundamental importance of different ACTH preparations is provided also by the differing results using European preparations (e.g. [13]).

In summary, a large and impressive body of experience has been compiled in different countries, documenting the efficacy of ACTH for infantile spasms. This is important, because it may serve as a key to understanding this disorder, as well as to designing better medicines [14]. The large differences in the use of this hormone may derive from a number of factors, including the biology of the disorder or associated genetic components that determine responsiveness to ACTH. In addition, striking differences in the preparations used around the world may be responsible. These issues should not detract from the overall

agreement that ACTH might be the most useful medication currently available to treat WS. A suggested regimen for the use of ACTHARGEL is enclosed (Table 1).

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Table 1

Treatment regimen for infantile spasms (from Baram et al. [6])

A.	Two-week treatment schedule:
	ACTH: ACTHARGEL; 75 U/m ² twice a day, intramuscularly
	Monitoring: electrolytes, glucose at onset and end
	Glycosuria: all specimens
	Blood-pressure: twice a week
B.	Tapering schedule:
	For 3 days 30 U/m ² in the morning
	For 3 days 15 U/m ² in the morning
	For 3 days 10 U/m ² in the morning
	For 6 days 10 U/m ² every other morning
