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Effect of Price Increase of Adrenocorticotrophic Hormone on Treatment Practices of Infantile Spasms

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Abstract

Intramuscular adrenocorticotrophic hormone putatively constitutes the most efficacious treatment for infantile spasms. Adrenocorticotrophic hormone in the United States is an “orphan drug,” made by a single manufacturer. The price of adrenocorticotrophic hormone increased almost 14-fold on August 27, 2007. We sought to evaluate the impact of this price increase on treatment practices at our institution, using a retrospective chart review of all children with infantile spasms treated during 2007–2009. We identified 97 patients whose spasms were treated using antiepileptic drugs, and we determined the length of stay for those hospitalized to initiate adrenocorticotrophic hormone. Patients before the price increase were more likely to have been treated with adrenocorticotrophic hormone as first medication, and were hospitalized 2.2 ± 0.5 S.D. days for initiation. Patients after the price increase were more likely to have been treated initially with oral antiepileptic drugs rather than adrenocorticotrophic hormone ($P < 0.002$). Those commencing adrenocorticotrophic hormone after the price increase were hospitalized significantly longer (5.1 ± 0.6 days S.D., $P < 0.001$). Treatment choices need to be evidence-based, but other factors often influence them.

Introduction

Infantile spasms constitute a unique, age-specific type of seizure that occurs during early infancy. They are often associated with developmental delay or regression, consistent with an epileptic encephalopathy. When accompanied by hypsarrhythmia on electroencephalogram, this triad is called West syndrome, which affects 1 in 2000 children [1].

The choice of drugs to treat infantile spasms is subject to wide global variability (Table 1). Before 2007, 88% of child neurologists in the United States used intramuscular adrenocorticotrophic hormone as initial therapy [2]. The American Academy of Neurology and the Child Neurology Society follow a practice parameter that supports this choice [3], despite the absence of a formal indication. At the end of 2009, vigabatrin, an oral antiepileptic drug, became the only approved medication for this disease in the United States. Previously vigabatrin was difficult to obtain, but was prescribed, especially in patients with tuberous sclerosis. Other oral antiepileptic drugs are used, although without strong evidence to support them [1]. Before publication of the United Kingdom Infantile

Spasm Study, vigabatrin was the first-choice drug in the United Kingdom [4]. The study indicated that hormonal treatments more often stopped spasms and improved outcomes than vigabatrin [5,6]. Since the study's publication, treatment practices may be shifting in favor of steroids [7]. Pyridoxine (vitamin B6) is some providers' drug of choice, in part because of its safety profile [8]. Phenobarbital is often used where cost concerns are paramount, even when adrenocorticotrophic hormone is the neurologists' first choice [9].

Providers in the United States who use adrenocorticotrophic hormone almost exclusively use the natural form, whereas the synthetic form is used elsewhere. Questcor, the sole manufacturer of natural adrenocorticotrophic hormone, increased the price of a bottle (5 mL of 80 units/mL) on August 27, 2007 from \$1650 to \$23,000 [23]. They based that decision on the reasoning that a typical treatment course with an orphan drug costs at least \$100,000, and an average patient needs slightly more than four bottles (according to Kevin Berents in personal communication with Don Bailey, CEO of Questcor). It is also not available through standard pharmacies (nor is vigabatrin). Pricing can affect which drug is chosen, either by physicians or payers. The timing of drug initiation is important, because prompt therapy may improve outcomes [1]. Some patients are hospitalized for the initiation of adrenocorticotrophic hormone. The indirect costs of this hospitalization include nosocomial infections because of immunosuppression. We sought to evaluate the impact of the price increase of adrenocorticotrophic hormone on treatment practices at the Children's Hospital (Denver, CO).

Patients and Methods

After approval by multiple institutional review boards in Colorado, we reviewed the charts of all children with infantile spasms treated during 2007-2009. We confirmed whether an underlying cause was found, and classified these causes in terms of their presumed timing and nature as "prenatal," including genetic problems and malformations of cortical development; "perinatal," including hypoxic-ischemic encephalopathy and stroke; and "postnatal," including environmental and metabolic causes. The drug initiated or increased after arriving at the diagnosis was declared the initial therapy. If children were hospitalized to initiate treatment with adrenocorticotrophic hormone, the length of stay was noted. We separated children into groups before and after the price increase, based on when they were discharged from the hospital. This grouping was uniformly dependent on the availability of adrenocorticotrophic hormone treatment on an outpatient basis.

Results

Ninety-seven patients met our criteria (62 with new diagnoses). Of these, 30 were diagnosed at our institution before 2007 and then followed. Five patients were initially managed at other institutions, and were excluded from some analyses. Most patients ($n = 59$; 61%) were symptomatic, in a proportion similar to that reported in large published series [6,10,12,16]. Of these, most were prenatal (genetic, $n = 16$; malformations of cortical development, $n = 16$), followed by perinatal ($n = 19$) and postnatal (environmental, $n = 5$; metabolic, $n = 3$). Complete records were available for 41 patients initially treated before the price increase, and for 51 patients treated after the price increase.

The 25 patients treated with adrenocorticotrophic hormone before the price increase were hospitalized to initiate therapy for an average of 2.2 ± 0.5 days S.D. (range, 0-5 days). We hospitalized the 25 patients treated with adrenocorticotrophic hormone after the price increase for an average of 5.1 ± 0.6 days S.D. (range, 1-15, days; analysis of variance, $P < 0.001$, Fig 1). We found no effect of an underlying cause on length of stay. Adrenocorticotrophic

hormone was the initial therapy for the majority of our before the price increase, but was used significantly less often after the price increase (χ^2 test, $P < 0.002$, Fig 2).

Discussion

Infantile spasms in the United States are treated predominantly with an “orphan drug,” adrenocorticotrophic hormone, produced by a single manufacturer, because multiple studies suggest that it is the drug of choice [1,24]. After its price increased, more patients at our institution initially received drugs with lower documented efficacy. During the study period, all treatments of spasms were off-label. Many factors influence choice of therapy, including safety, ease of administration, and accessibility. The study period followed a burst of publications about topiramate, and these may have influenced practice patterns [1]. The end of the study period coincided with the approval of vigabatrin in the United States. It may be used more commonly in the future, but requires substantial monitoring for visual field defects and magnetic resonance imaging abnormalities. Treatment decisions need to be tailored to individual patients, and although adrenocorticotrophic hormone may be the most potent treatment available, it involves serious drawbacks.

At our institution, the length of hospitalization to initiate adrenocorticotrophic hormone therapy increased after its price increased. Some providers sought to circumvent this barrier to care by delaying admission until after approval, or else they initiated oral antiepileptic drugs, and then used adrenocorticotrophic hormone in nonresponders. These strategies may shorten hospitalization times, but may jeopardize the cessation of seizures and long-term neurodevelopmental outcomes.

Our study is retrospective and thus limited, because many factors affected the outcomes measured. Our department was enlarged considerably during the study period. Patients diagnosed more recently are often subject to “more sensitive investigative techniques that will lead with time to an increasing number of cases having identified diagnoses” [25]. Our treatment of patients is subject to many external influences. As cost control becomes a bigger issue, pricing decisions will continue to affect patient care. We need to continue to reexamine our practices to ensure that we provide our patients the best possible care.

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Figure 2. Use of adrenocorticotrophic hormone and other therapies as initial therapy before (left) and after (right) the price increase of adrenocorticotrophic hormone. ACTH = adrenocorticotrophic hormone.

Table 1
First drugs used to treat infantile spasms according to large published series from around the world

Location (Alphabetically, by Country)	Drug	Date	Study Type
Nova Scotia, Canada [10]	Adrenocorticotrophic hormone	2001	Center
Hong Kong, China [11]	Adrenocorticotrophic hormone or vigabatrin [*]	2001	Center
Finland [12]	Adrenocorticotrophic hormone	2001	National
Chandigarh, India [13]	Prednisolone	2005	Center
New Delhi, India [14]	Adrenocorticotrophic hormone + valproate	2001	Center
Tel Aviv, Israel [15]	Adrenocorticotrophic hormone	2005	Center
Japan [8]	Vitamin B6	2007	National
Korea [16]	Vigabatrin	2001	National
Klang, Malaysia [17]	Steroids [†]	2001	Center
Oman [18]	Vigabatrin	2001	National
Philippines [9]	Phenobarbital	2001	National
Singapore [19]	Vigabatrin	2001	National
Slovenia [20]	Steroids [‡]	2002	National
Taiwan [21]	Adrenocorticotrophic hormone	2001	National
Bangkok, Thailand [22]	Vigabatrin	2001	Center
United Kingdom [4]	Vigabatrin	1996	National
Oxford, United Kingdom [7]	Steroids [†]	2008	Center
United States [2]	Adrenocorticotrophic hormone	1994	National

^{*} Adrenocorticotrophic hormone before 1997, and vigabatrin afterward.

[†] Type not specified.

[‡] Combination of hydrocortisone and adrenocorticotrophic hormone.