ELSEVIER

Journal of the Neurological Sciences 258 (2007) 128–131

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Thalidomide inhibits pentylenetetrazole-induced seizures

Guadalupe Palencia, Alejandra Calderon, Julio Sotelo *

Neuroimmunology Unit, National Institute of Neurology and Neurosurgery, Insurgentes Sur 3877, 14269 Mexico City, Mexico

Received 20 October 2006; received in revised form 15 February 2007; accepted 15 March 2007
Available online 23 April 2007

Abstract

Thalidomide was originally synthesized and tested as a sedative, hypnotic and antiemetic; however, after its teratogenicity was noted its use for treatment of neurological and psychiatric disorders was abandoned. We studied the potential anticonvulsant effect of thalidomide: Different doses of thalidomide were tested against seizures induced by 50 mg/kg or 70 mg/kg of pentylenetetrazole (PTZ); the anticonvulsant effect of thalidomide was also compared with that of valproic acid. Seizures and latency time were individually recorded. Thalidomide in low doses (5–10 mg/kg) prevented seizures in all animals treated with 50 mg/kg PTZ; also, in a dose-dependent manner thalidomide inhibited seizures in rats exposed to a high dose of PTZ (70 mg/kg); thalidomide exhibited an anticonvulsant activity similar to that of valproic acid. Thalidomide is an effective anticonvulsant, and further studies on this potential antiepileptic substance seem warranted.

Keywords: Seizures; Epilepsy therapy; Thalidomide; Pentylenetetrazole; Hypnotic drugs

1. Introduction

Initial studies on thalidomide in the 1950s suggested that it had many properties as an ideal hypnotic drug [1–3]. It was developed and commercialized based on its effects on the central nervous system, mostly as sedative. Interestingly, after its sudden withdrawal from the market, due to severe congenital abnormalities in babies delivered by women who took thalidomide [3,4], other remarkable properties of this drug were discovered, with novel indications in infectious, autoimmune and neoplastic disorders [5,6]. It is ironic that a drug originally prescribed as sedative is now used for a variety of diseases and sedation is considered its main side effect [3]. From all its current applications for the therapy of several disorders [5,7], none is suggested for the treatment of primary neurological or psychiatric diseases. In recent decades, no neurophysiological research has been reported on the effects of thalidomide in the brain, despite early studies that defined a unique brain mechanism for its sedative effects in comparison with barbiturates and benzodiazepines [1,2].

Epilepsy is a disorder where most substances with sedative effects have been tested; however, to our knowledge no such studies have been conducted with thalidomide. We found only two case-reports of thalidomide use in refractory seizures secondary to Rasmussen encephalitis. The authors reported improvement of seizures after the administration of thalidomide, although they attributed the therapeutic effect mostly to the immunomodulatory properties of thalidomide, rather than to its direct effect on the central nervous system [8,9]. Of note, an increased incidence of epilepsy has been described in subjects who suffered thalidomide embryopathy [10,11].

In our laboratory, we have tested the effects of thalidomide on various inflammatory and neoplastic disorders [12]. In this work, we studied the potential effects of thalidomide in rats exposed to the convulsant substance pentylenetetrazole (PTZ).

2. Methods

The median dose of PTZ necessary to induce generalized seizures in rats was defined as follows: 40 adult, male Wistar rats were separated in four groups of 10 rats each; they received a single intraperitoneal injection of PTZ in dose of either 30, 40, 50 or 70 mg/kg dissolved in saline solution. The development

* Corresponding author. Tel.: +52 55 5135 0785; fax: +52 55 5135 2229.
E-mail address: jsotelo@servidor.unam.mx (J. Sotelo).

0022-510X/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2007.03.010

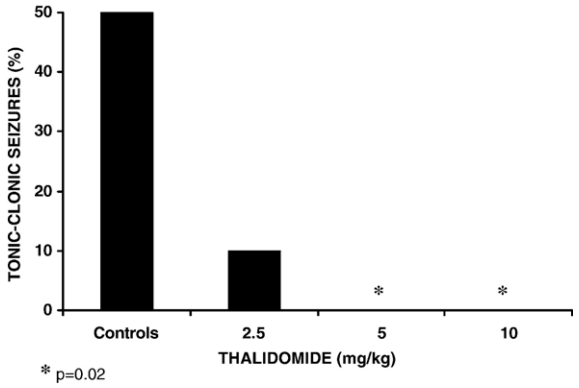

Fig. 1. Effect of various doses of thalidomide on the development of generalized seizures in rats with PTZ (50 mg/kg). Seizures were prevented in all animals that received thalidomide either 5 or 10 mg/kg and in most that received 2.5 mg.

of tonic–clonic generalized seizures was recorded, 50% of animals that received 50 mg/kg of PTZ developed a generalized seizure whereas 90% of animals that received 70 mg of PTZ had a generalized seizure; these two doses were selected for the experiments with thalidomide.

To study the effect of thalidomide on the seizures induced by PTZ 40 Wistar rats were separated into 4 groups of 10 rats each; group I ($n=10$) was used as control, animals from group II ($n=10$) received 2.5 mg/kg of thalidomide mixed with corn oil and orally administered 30 min before the injection of PTZ; group III ($n=10$) received thalidomide 5 mg/kg, and group IV ($n=10$) received thalidomide 10 mg/kg. Afterwards, each animal was injected intraperitoneally with a single dose of PTZ 50 mg/kg of body weight. The number of rats that developed myoclonic jerks and tonic–clonic generalized seizures was recorded. Also, the time elapsed after PTZ injection for the initiation of the seizure (latency time) was individually measured.

To determine the anticonvulsant effectiveness of thalidomide on a high dose of PTZ (70 mg/kg) 166 Wistar rats were separated in nine groups; group I ($n=38$) was used as control; groups 2–9 ($n=16$ each) received thalidomide in doses of 5, 10, 25, 50, 100, 150, 200 or 300 mg/kg respectively, and the methods were identical to those used with the PTZ in dose of 50 mg/kg. The development of seizures and mortality were individually recorded.

To compare the anticonvulsant effect of thalidomide with that of valproic acid 48 rats were separated into 3 groups; group I ($n=18$) served as control; group II ($n=15$) received thalidomide 10 mg/kg 30 min before the injection of PTZ; group III ($n=15$) received orally valproic acid 160 mg/kg 30 min before the injection of PTZ. Afterwards, each animal received a single intraperitoneal injection of PTZ 50 mg/kg. The development of tonic–clonic seizures was recorded.

Experiments were carried out according to the institutional guidelines for protection and care of experimental animals.

Statistical analysis was made with the SPSS version for Windows; comparisons between groups were made by Fisher's exact test. Latency times were compared by ANOVA followed by Tukey post-hoc test.

3. Results

Administration of thalidomide prevented PTZ-induced (50 mg/kg) generalized seizures in all animals treated with doses as low as 5 or 10 mg/kg of thalidomide ($p=0.02$ as compared with controls) (Fig. 1); moreover, with the dose of 2.5 mg/kg of thalidomide seizures did not develop in 90% of animals ($p=0.07$ as compared to controls). In these experiments the administration of thalidomide did not prevent the development of myoclonic jerks (100% in the rats from all four groups) or modifications of the latency time of the jerks (between 45 and 52 s in animals from all groups).

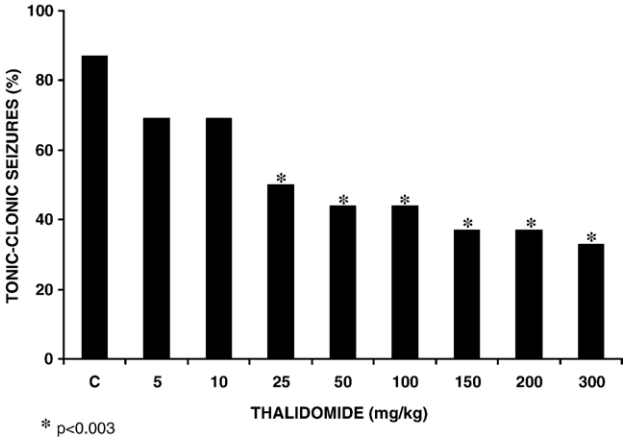

Fig. 2. Effect of various doses of thalidomide on the development of seizures induced by a high dose of PTZ (70 mg/kg). Seizures were prevented in a dose-dependant manner in a significant number of animals treated with thalidomide (from 25 mg/kg). All rats that developed seizures died as a consequence, no mortality was seen in animals that did not develop seizures.

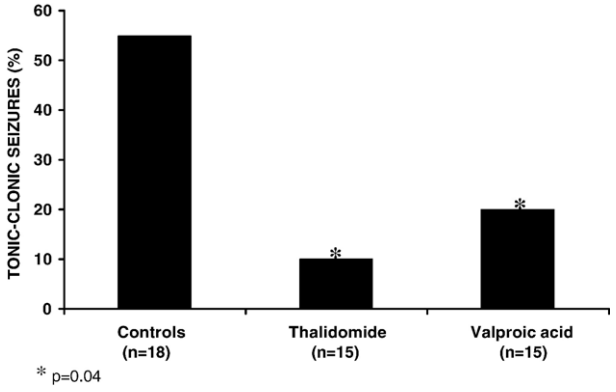

Fig. 3. Effect of thalidomide (10 mg/kg) or valproic acid (160 mg/kg) on PTZ-induced tonic–clonic seizures in rats. Thalidomide and valproic acid inhibited the development of seizures in 93% and 80% of animals, respectively.