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Gabapentin for Spasticity in Multiple Sclerosis – Absence of Efficacy in a Placebo Controlled Study

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Abstract

The use of Gabapentin for management of spasticity has become part of clinical guidelines despite a lack of objective scientific data. This is due to the problems associated with user dependent and insensitive to change clinical assessment tools. We sought to redress this using the Wartenberg's pendulum test. This is objective and sensitive to detect changes in spasticity. All patients had stable disease and did not have any changes to their medications within 30 days of the trial. If the patients were on muscle relaxants (namely Baclofen and tizanidine), these were stopped 10 days prior to the study. Patients were randomized to receive a single dose of either placebo (Ascorbic Acid), Gabapentin 300mg or Gabapentin 900mg, each at weekly intervals in a crossover manner. We found no evidence of any effect on spasticity at either dosage when compared with placebo. Our data does not support the use of Gabapentin for management of spasticity in patients with Multiple Sclerosis.

Introduction

Gabapentin is a GABA analogue and is an established antiepileptic agent [1]. It is currently licensed in the UK for resistant epilepsy as add on and for neuropathic pain. While its mechanism of action is unknown it is thought to target the α2δ subunit of the Ca^{++} channel [2]. In addition, despite rather modest efficacy data, it has been suggested through The National Institute for Health and Care Excellence (NICE) ,an independent public body that provides national guidance and advice to improve health and social care in England, for treatment of Multiple Sclerosis (MS) related spasticity. This is in addition to Baclofen it should be a first line treatment for spasticity and reflex spasms. The scientific data supporting this however is lacking. Clinical measurement of spasticity is difficult. Generally the Ashworth scale is used for this purpose. This has some limitations [3]. It is user dependent and insensitive to change. For that reason the Wartenberg's pendulum test was developed [4-6]. Previously we demonstrated a significant effect of Tizanidine on spasticity using Wartenberg's pendulum test [7]. If Gabapentin had a beneficial effect on spasticity and hence deserving of NICE guidance, there should be a reasonable effect using this test. We therefore quantitatively assessed spasticity in MS patients evaluating the effect of Gabapentin vs placebo.

Methods

Patients with a diagnosis of MS and spasticity in either or both lower limbs were recruited. This study was approved by the local ethical committee. All patients had stable disease and did not have any changes to their medications within 30 days of the trial. If the patients were on muscle relaxants (namely Baclofen and tizanidine), these were stopped 10 days prior to the study. Patients were randomised to receive a single dose of either placebo (Ascorbic Acid), Gabapentin 300 mg or Gabapentin 900 mg, each at weekly intervals in a crossover manner. Patients were admitted in the neurology ward.

The Wartenberg's pendulum test was performed with the patient lying in a propped up position at 45° with the lower limbs freely hanging at the knee joint. The angle of swing was measured by an electrogoniometer and was taken via a CED 1401 intelligent interface (Cambridge Electronic Design Ltd) into a PC compatible microcomputer. The measurement variables, R1 ratio-the amplitude of the first swing divided by the rebound angle and R2 ratio- amplitude of the first swing in degrees divided by the amplitude of the final position and maximum velocity were measured by computer software.

To take the measure the leg was elevated to the horizontal position and when the subject was completely relaxed it was released to swing freely about the knee. Six sets of measurements were taken at baseline and then every 15 minutes after the drug was administered until 180 minutes. Following this the subject was discharged home. This was repeated again at a week's intervals using the rest of the two study drugs. All the patients were blinded to the treatment drug. The study drug status and the results of the experiment were not available to the investigator until the end of the study. R2 index and maximum

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velocity were chosen as primary outcomes to assess treatment effect [4,5].

Result

Five patients (3 females and 2 males) with mean age of 43.6 years (range 31 to 55) were recruited. The pendulum test was carried out every 15 minutes after administration of the drug until 180 minutes. For each set a mean value was produced for R2 and a velocity. The data for the 7 groups (two patients had tests on both legs) was analysed using ANOVA. This is graphically represented in figure1 and figure 2.

We found no significant effect of Gabapentin at a dose of 300 mg or at 900 mg over placebo at any of the time points after administration. There was no effect in either the R2 ratio or velocity.

Discussion

Spasticity occurs in many non-progressive as well as progressive neurological conditions and is a cause of significant disability [8]. There have been limited numbers of studies for oral antispasmodic agents [9,10]. Currently Gabapentin is licensed for use in partial or secondarily generalised epilepsy and neuropathic pain in the UK. It is also in the NICE guidelines for MS as a first line treatment for spasticity and reflex spasms. Its mechanism of action is unknown though; its action is GABAergic in the central nervous system. There have been few trials previously that studied gabapentin for spasticity [11-14]. These, though seemed promising, also used clinical methods such as hyper-reflexia, clonus, Ashworth scale and patient generated scales- spasm frequency, for assessing spasticity. Spasm frequency is not a measure of spasticity or hypertonia. These scales lack reproducibility, validity and have interpersonal variability. We used the Wartenberg's pendulum test to overcome this problem. The pendulum test was initially devised to measure increased tone in patients with Parkinson's disease. Subsequent studies have shown its equal usefulness in assessing spasticity objectively as a research tool. Wartenberg's pendulum test is objective and sensitive to detect changes in spasticity [4,6,15]. In our study we did not find any significant change in spasticity in subjects given 300mg or 900mg of Gabapentin as compared to placebo. The strengths of this study are that it was double blind placebo controlled trial and we used objective and valid test for assessing the spasticity. The maximum serum concentration of Gabapentin (C-max) irrespective of dose or preparation is achieved at 3 Hrs and the half-life of Gabapentin is between 5 to 7 Hrs. We would therefore have expected to observe an effect, as we did with Tizanidine, if there was a benefit in spasticity.

We therefore feel that there is limited data to suggest Gabapentin is useful in spasticity. Moreover the current study demonstrates no effect over placebo.

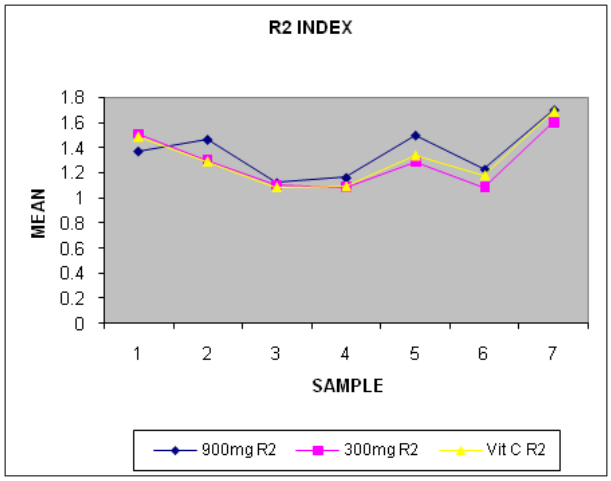

Figure 1: Graph representing mean R2 values in each ample for the three study drugs

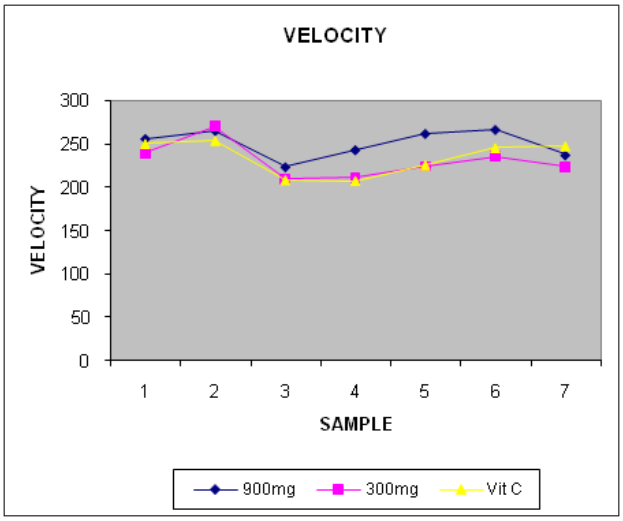

Figure 2: Graph representing mean velocity in each sample for the three study drugs

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