

A comparative evaluation of anticonvulsant activity of Magnesium Sulfate with Phenytoin and Valproate in experimentally induced seizures in albino rats

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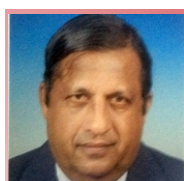
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Abstract: Background: Epilepsy is a global health problem. Many studies have suggested that N-methyl-D-aspartate (NMDA) receptors may play a role in the development and expression of seizures. Therefore the present study was designed to explore the potential of magnesium sulfate (MgSO₄), which is a NMDA receptor antagonist, as an anticonvulsant drug.

Methods: A randomized, prospective, active placebo controlled study was conducted on eighteen Swiss albino rats. In this study MgSO₄ was compared with phenytoin in maximal electroshock seizure (MES) model, with valproate in pentylenetetrazole (PTZ) induced convulsions model and with both in aminophylline induced convulsions model.

Results: The results in MES model, showed that MgSO₄ when compared with phenytoin was significantly effective ($p < 0.0001$). The combination of MgSO₄ and Phenytoin was more effective than either of the drugs used singly. In the PTZ model, valproate was able to control the parameters observed. MgSO₄ was not able to control any of the parameters when compared with valproate. In the aminophylline model MgSO₄, valproate and phenytoin were not able to control any of the parameters.

Conclusion: MgSO₄ appears to be effective in MES model but not in the PTZ and aminophylline models.

Keywords: Epilepsy, NMDA receptor antagonists, MgSO₄, MES model.

THESIS SUMMARY

Introduction

Epilepsy is a group of disorders characterized by chronic, recurrent, paroxysmal changes in neurologic function caused by abnormalities in the electrical activity of brain. Using the definition of epilepsy as two or more unprovoked seizures, the incidence of epilepsy is approximately 0.3 to 0.5% in different populations throughout the world, and the prevalence of epilepsy has been estimated at 5 to 10 persons per 1000. The ideal antiseizure drug would suppress all seizures without causing any unwanted effects. Unfortunately the drugs used currently have low therapeutic index, they not only fail to control seizure activity in some patients, but frequently cause unwanted effects that range in severity from minimal impairment of central nervous system to death, from aplastic anemia or hepatic failure. As a general rule, complete control of seizures can be achieved in up to 50% of patients, while another 25% can be improved

significantly. Thus a need for a new antiepileptic drug with minimal side effects & equal efficacy to existing drugs is perpetual. Many studies have suggested that N-methyl-D-aspartate (NMDA) receptors may play a role in the development and expression of seizures. There is considerable evidence from in vivo and in vitro studies that NMDA antagonists can suppress epileptiform activity. Early investigations found that these antagonists had anticonvulsant action in several chemical models of epilepsy and maximal electroshock seizures. NMDA and non NMDA mediated potentials may contribute to burst triggering and duration. NMDA receptor antagonists can slow the frequency of spontaneous bursts and can shorten the duration of each burst. Antagonists of the NMDA receptors decrease calcium influx through this receptor operated calcium channel. Magnesium sulfate (MgSO₄), an effective drug in eclamptic seizures, is an inorganic calcium antagonist and blocks

receptor operated calcium channels as well. Therefore the present study was designed to explore the potential of magnesium sulfate as an anticonvulsant drug.

Aims and Objectives

1. To study the anticonvulsant efficacy of MgSO₄ in comparison with phenytoin in maximal electroshock induced seizure (MES) in albino rats.

2. To study the anticonvulsant efficacy of MgSO₄ in comparison with valproate in pentylenetetrazole (PTZ) induced seizure in albino rats.

To study the anticonvulsant efficacy of MgSO₄ in comparison with phenytoin and valproate in aminophylline induced seizure in albino rats.

Methods

A randomized, prospective, active placebo controlled study was conducted on 18 Swiss albino rats in the Department of Pharmacology, Grant Medical College & Sir J.J. Group of hospitals, Mumbai, after approval from the institutional animal ethics committee. Study was done in 3 parts. Initially in Group 1 study, MgSO₄ was tested and compared with phenytoin by the Maximal Electroshock seizure (MES) method. A combination of MgSO₄ and phenytoin was also tested with the individual drugs. After that in Group 2 study, MgSO₄ was tested and compared with valproate by the Pentylenetetrazole (PTZ) induced convulsions method. A combination of MgSO₄ and valproate was also tested with the individual drugs. Finally in Group 3 study, MgSO₄ was tested and compared with phenytoin and valproate by the Aminophylline induced convulsions method. There were 6 rats in each sub-group of Group 1 & these rats were given a washout period of 10 days & were randomly reassigned for the Group 2 study, again a washout period of 10 days & they were randomly reassigned for the Group 3 study.

1. Group 1 (MES seizure model):

On the previous day of testing the pre-determined strength and duration of current was given to each of the animals by ear clip electrodes. This was standardized 150 mA, 100 V for 0.2 sec. The ears were cleaned with spirit to remove any oil film due to sebaceous gland secretions in the skin of the ear and then with saline for electric contact. Only those rats which showed tonic clonic convulsion were selected. Next day rats received the test and standard drugs as per the study groups 30 mins before being subjected to an electric shock.

The parameters studied were:

- Duration of tonic extensor phase (in sec.)
- Duration of entire convulsion (in sec.)
- Duration of post-ictal phase (in sec.) i.e. time to resumption of normal activity following post-ictal stunning.

2. Group 2 (PTZ induced convulsion model):

On the previous day of testing Pentylenetetrazole was injected intraperitoneally at a dose of 50 mg/kg. Only those rats which showed clonic convulsions in the next 15 minutes were selected. Next day rats received the test and standard drugs as per the study groups 30 min before being subjected to PTZ treatment and the animals were observed for 30 mins.

The parameters studied were:

- Time of onset of first clonic convulsion (in sec.)
 - Duration of the clonic convulsion (in sec.)
 - Duration of post-ictal phase (in sec.) i.e. time to resumption of normal activity following post-ictal stunning.
3. Group 3 (Aminophylline induced convulsion model):

On the previous day of testing Aminophylline was injected intraperitoneally at a dose of 280 mg/kg. Only those rats which showed clonic convulsions in the next 15 minutes were selected. Next day rats received the test and standard drugs as per the study groups 30 min before being subjected to Aminophylline treatment and the animals were observed for 60 mins.

The parameters studied were:

- Time of onset of tonic clonic convulsion (in min.)
- Duration of convulsion (in sec.)
- Duration of postictal phase (in sec.) i.e. time to resumption of normal activity following post-ictal stunning.

All quantitative data is presented as mean & standard error of mean (SEM). Data of MES and PTZ induced seizure is analyzed by using student's unpaired 't' test. Data of aminophylline induced seizure is analyzed by one-way ANOVA. For all tests, a 'p' value of < 0.05 is considered as significant.

Result

Maximal electroshock seizure (MES) model:

a. Comparison of MgSO₄ with Phenytoin: MgSO₄ (270mg/kg), compared with phenytoin (20mg/kg), significantly reduced the duration of tonic extensor phase (p<0.0001), duration of convulsion (p<0.0001) as well as duration of postictal phase (p<0.0001).

b. Comparison of MgSO₄ with Combination of MgSO₄ and Phenytoin: The combination of MgSO₄ (135mg/kg) and phenytoin (10mg/kg) was more significant than MgSO₄ (270mg/kg) alone in reducing the duration of tonic extensor phase (p<0.0001), duration of convulsion (p<0.0001) as well as duration of postictal phase (p<0.0001).

c. Comparison of Phenytoin with combination of MgSO₄ and Phenytoin: The combination of MgSO₄ (135mg/kg) and phenytoin (10mg/kg) was more significant than Phenytoin (20mg/kg) alone in reducing the duration of tonic extensor phase (p<0.0001), duration of convulsion (p<0.0001) as well as duration of postictal phase (p<0.0001).

Pentylenetetrazole induced convulsion (PTZ) model:

a. Comparison of MgSO₄ with valproate: Valproate (200mg/kg) compared with MgSO₄ (270mg/kg), significantly increased the time of onset of clonic convulsion (p<0.0001), and significantly reduced the duration of clonic convulsion (p<0.0001) as well as duration of postictal phase (p<0.0001).

b. Comparison of MgSO₄ with combination of MgSO₄ and Valproate: The combination of MgSO₄ (135mg/kg) and Valproate (100mg/kg) compared with MgSO₄ (270mg/kg) alone significantly increased the time of onset of clonic convulsion (p<0.0001), and significantly reduced the duration of convulsion (p<0.0001) as well as duration of postictal phase (p<0.0001).

c. Comparison of Valproate with combination of MgSO₄ and Valproate: Valproate (200mg/kg) compared with combination of MgSO₄ (135mg/kg) and Valproate (100mg/kg), significantly increased the time of onset of clonic convulsion (p<0.0001), and

significantly reduced the duration of clonic convulsion ($p < 0.0001$) as well as duration of postictal phase ($p < 0.0001$).

Aminophylline induced convulsion model:

MgSO₄ (270mg/kg), valproate (200mg/kg) and phenytoin (20mg/kg) were not able to control any of the parameters.

Conclusion

MgSO₄ appears to be effective in maximal electroshock seizure (MES) model but not in the pentylenetetrazole induced convulsion (PTZ) model and Aminophylline induced convulsion model.

Clinical Message

MgSO₄ is an established drug for the treatment of eclampsia wherein the drug helps to control the convulsions. There is hope that MgSO₄ could be effective in patients who are refractory to presently available standard antiepileptic medication. MgSO₄ could be of value for acute treatment of status epilepticus, perhaps in conjunction with conventional agents.

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