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[Intervention Review]

Treatment of seizures in multiple sclerosis

Marcus W Koch[1], Susanne KL Polman[1], Maarten Uyttenboogaart[1], Jacques De Keyser[2]

[1]Department of Neurology, University Medical Center Groningen, Groningen, Netherlands. [2]Department of Neurology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

Contact address: Marcus W Koch, Department of Neurology, University Medical Center Groningen, Postbus 30.001, Groningen, 9700RB, Netherlands. m.w.koch@neuro.umcg.nl.

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ABSTRACT

Background

Epileptic seizures occur in only a minority of patients with multiple sclerosis (MS), but can have serious consequences. The available literature suggests an association of seizures in MS with cortical and subcortical demyelinating lesions, which suggest that seizures in MS are probably most often symptomatic rather that idiopathic. It is currently unknown whether patients with MS should be treated differently from other patients with epileptic seizures.

Objectives

To evaluate the efficacy and safety of antiepileptic treatments in patients with MS.

Search methods

We searched for double-blind, single-blind or unblinded randomised controlled trials on antiepileptic treatment in patients with MS through electronic searches of The Cochrane Multiple Sclerosis Group's and Cochrane Epilepsy Group's Trials Registers, Cochrane Central Register of Controlled Trials (The Cochrane Library 2008, Issue 1), MEDLINE (From 1966 - Jan 2008) and EMBASE (From 1974 - Jan 2008).

Selection criteria

Double-blind, single-blind or unblinded randomised controlled trials on antiepileptic treatment in patients with MS.

Data collection and analysis

Searches yielded a total of 379 citations (CENTRAL: 20, MEDLINE: 264, EMBASE: 95). We perused titles and abstracts for relevance and independently excluded all 379 citations as clearly not meeting the inclusion criteria.

Main results

We found no studies meeting our inclusion criteria.

Authors' conclusions

Well-designed randomised controlled trials are needed to guide clinical practice. Such trials should preferably contain a head-to-head comparison of antiepileptic drugs in patients with MS.

PLAIN LANGUAGE SUMMARY

Treatment of seizures for patients with multiple sclerosis

Epileptic seizures occur in a relatively small number of patients with multiple sclerosis, but can have serious consequences. Because the cause of epileptic seizures in patients in MS may be different from that in other forms of epilepsy, it is uncertain whether patients with MS should be treated differently. We searched for studies on the treatment of epileptic seizures in patients with MS, but found none. Well designed studies that address this issue are needed.

BACKGROUND

The prevalence of epileptic seizures in patients with MS is about 3% (Poser 2003; Koch 2008) which is considerably higher than in the general population, in which it varies between 0.5 and 1% (Sander 2003; Forsgren 2005). Seizures are no common complaint in MS, but can have serious consequences. The available literature on seizures in MS suggests an association of cortical or subcortical demyelinating lesions with the occurrence of epileptic seizures (Koch 2008), which would make seizures in MS a form of secondary epilepsy comparable to seizures occurring in the context of stroke or traumatic brain injury.

In view of this probable pathophysiological difference between seizures that occur in patients with MS and those in patients with the idiopathic epilepsy, it is uncertain whether patients with MS should be treated differently from other patients with idiopathic epilepsy. A systematic review of randomised controlled trials of antiepileptic treatment in patients with MS is the best way to resolve this uncertainty.

OBJECTIVES

To evaluate the efficacy and safety of antiepileptic treatment in patients with multiple sclerosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials on antiepileptic treatment in patients with MS. Double-blind, single-blind or unblinded trials are included. Adequately randomised and quasi randomised trials are included, non-randomised trials are excluded. Individual patient data are included if available.

Types of participants

Children and adults with a diagnosis of definite MS according to the Poser (Poser 1983) or McDonald (McDonald 2001) diagnostic criteria, who suffer from any form of recurrent epileptic seizure including status epilepticus.

Types of interventions

Experimental intervention: pharmacologic and non-pharmacologic interventions for the treatment of epileptic seizures without restrictions regarding type of intervention, dose, manner of administration, frequency, or duration. Control intervention: placebo treatment or no treatment.

Types of outcome measures

Primary outcomes

- Time from randomisation to withdrawal of allocated treatment due to poor seizure control or side effects (retention time). This is a combined outcome measure which encompasses efficacy as well as tolerability (ILAE 1998).

Secondary outcomes

- Time to 12-month remission from seizures
- Time to first seizure post-randomisation
- Reduction in number of seizures until the end of follow-up
- Adverse effect rate: any adverse effect attributed to the treatment in question

Search methods for identification of studies

A systematic search without language restrictions was conducted to identify all relevant published and unpublished randomised controlled trials.

Electronic searches

(a) The Cochrane Multiple Sclerosis Group's and Cochrane Epilepsy Group's Trials Registers
(b) Cochrane Central Register of Controlled Trials (CENTRAL) "The Cochrane Library" 2008 Issue 1" (Appendix 1)
(c) MEDLINE (From 1966 - Jan 2008) (Appendix 2)
(d) EMBASE (From 1974 - Jan 2008) (Appendix 3)

Searching other resources

(1) Checking reference tables of identified studies.
(2) Handsearching of published abstracts of conference proceedings.
(3) Personal communication with authors of identified studies and other researchers in the field.
Strategy (3) will be used to identify unpublished or ongoing studies.

Data collection and analysis

As no studies met inclusion criteria, all methods planned in the protocol and archived for future updates can be found in additional Table 1.

Table 1. Table of methods archived for use in future updates

Issue	Method
Selection of studies	The titles and abstracts of publications identified by the above search strategy are assessed independently for inclusion by two teams (MK/JDK and SP/MU), the full text is selected for further assessment if the abstract suggests relevance. Papers that do not meet the inclusion criteria are listed with the reason for omission. Disagreements are solved by discussion
Data extraction and management	Information about study population, type of intervention, outcome measures, and study design are extracted independently from the selected studies by two teams (MK/SP MU/JDK) on a data extraction form. Results are extracted as raw numbers. If additional outcome data are needed, the investigators of the studies are contacted. Disagreements are discussed, and solved by consensus
Assessment of risk of bias in included studies	The methodological quality of the studies are evaluated independently by two teams of reviewers (MK/JDK and SP/MU) according to the guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). The criteria used in the assessment of methodological quality are (1) allocation concealment, (2) method of randomisation, (3) blinding, (4) information on loss to follow-up, and (5) blinding of outcome assessment. Studies with a high risk of bias are included and discussed in the text of the review, but they will be excluded from all meta-analyses. Disagreements on the methodological quality of the identified studies among the teams of reviewers are discussed, and solved by consensus
Measures of treatment effect	For time-to-event data, treatment effects are expressed as the hazard ratio. For continuous outcome measures, treatment effects are either expressed as the weighted mean difference, or the outcome measures are dichotomised, depending on the outcome measure used (in the event of dichotomisation, treatment effects are expressed as odds ratios)
Assessment of heterogeneity	Statistical heterogeneity among the identified studies is tested for with the chi-squared test. Significant heterogeneity among the studies is addressed by either refraining from performing a meta-analysis altogether (in the case of serious heterogeneity), or by excluding one or a small minority of heterogenous studies. Heterogeneity is explored by investigating the influence of subgroups (men vs. women, adults vs. children, progressive

(*Continued*)

	vs. non-progressive MS, blinded vs. unblinded trials, and by type of seizure)
Data synthesis	The studies are summarised by meta-analysis using a fixed-effect model. Studies with time-to-event outcomes are summarised using a modified Peto fixed-effect model, and the hazard ratio is used as summary statistic. Studies with continuous outcomes are summarised with the inverse variance method and the weighted mean difference is given as summary statistic. If dichotomised outcomes are used, the studies are summarised with the Mantel-Haenszel fixed-effect model and the odds ratio is given as summary statistic Publication bias is assessed with Funnel plots as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006)

RESULTS

Description of studies

Results of the search

The search strategy yielded a total of 379 citations (CENTRAL: 20, MEDLINE: 264, EMBASE: 95). Two teams of reviewers (MK/JDK and SP/MU) perused titles and abstracts for relevance and independently excluded all 379 citations as clearly not meeting the inclusion criteria. There were no disagreements regarding study inclusion or exclusion between the two teams or between individual team members.

Included studies

There were no included studies.

Risk of bias in included studies

No randomised controlled trials were found that fulfilled the inclusion criteria.

Effects of interventions

No randomised controlled trials were found that fulfilled the inclusion criteria.

DISCUSSION

Although seizures in patients with MS occur in only a relatively small number of patients, they can have serious consequences. There is currently no evidence from clinical trials to guide the clinical management of patients with seizures. The association of seizures in MS with cortical and subcortical lesions suggests that they are a form of secondary epilepsy and it is uncertain whether patients should be treated according to guidelines designed for patients with idiopathic epilepsies. Furthermore, it is uncertain whether the tolerability of commonly used antiepileptic drugs is the same for patients with MS and patients with idiopathic epilepsy.

Well-designed randomised controlled trials are needed to guide clinical practice. Such trials should preferably contain a head-to-head comparison of antiepileptic drugs in patients with MS.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence to guide the treatment of epileptic seizures in MS

Implications for research

Well-designed randomised controlled trials are needed to evaluate efficacy and tolerability of antiepileptic treatments in patients with MS.

ACKNOWLEDGEMENTS

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ILAE 1998

ILAE Commission. ILAE Commission on antiepileptic drugs. Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. *Epilepsia* 1998;**39**(7):799–803.

Koch 2008

Koch M, Uyttenboogaart M, Polman S, De Keyser J. Seizures in Multiple Sclerosis. *Epilepsia* 2008;**49**(6):948–53.

McDonald 2001

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for MS: Guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology* 2001;**50**(1):121–7.

Poser 1983

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for Multiple Sclerosis: guidelines for research proposals. *Annals of Neurology* 1983;**13**:227–31.

Poser 2003

Poser CM, Brinar VV. Epilepsy and multiple sclerosis. *Epilepsy & Behaviour* 2003;**4**(1):6–12.

Sander 2003

Sander J. The epidemiology of epilepsy revisited. *Current Opinion in Neurology* 2003;**16**:165-70.

* *Indicates the major publication for the study*

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL (2008, Issue 1)

#1 ”multiple sclerosis“
#2 MeSH descriptor Multiple Sclerosis explode all trees
#3 ”Demyelinating disease*“
#4 MeSH descriptor Demyelinating Diseases, this term only
#5 ”transverse myelitis“
#6 MeSH descriptor Myelitis, Transverse, this term only
#7 ”neuromyelitis optica“
#8 ”optic neuritis“
#9 MeSH descriptor Optic Neuritis explode all trees
#10 MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only
#11 ”encephalomyelitis acute disseminated“
#12 ”devic“
#12 MeSH descriptor Epilepsy explode all trees
#13 MeSH descriptor Seizures explode all trees
#14 epilep*
#15 seizure*
#16 convulsion*
#17 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#18 (#12 OR #13 OR #14 OR #15 OR #16)
#20 (#17 AND #18)

Appendix 2. MEDLINE (PubMed) (1966 - Jan 2008)

((((”Multiple Sclerosis“[mh]) OR (”Myelitis, Transverse“[mh:noexp]) OR (”Demyelinating Diseases“[mh:noexp]) OR (”Encephalomyelitis, Acute Disseminated“[mh:noexp]) OR (”Optic Neuritis“[mh])) OR (((”multiple sclerosis“) OR (”neuromyelitis optica“) OR (”transverse myelitis“) OR (encephalomyelitis) OR (devic) OR (”optic neuritis“)) OR (”demyelinating disease*“) OR (”acute disseminated encephalomyelitis“))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh])))))) AND ((”Epilepsy“[Mesh]) OR (”Seizures“[Mesh]) OR (epilep*) OR (seizure*) OR (convulsion*))

Appendix 3. EMBASE (1974 - Jan 2008)

(((’encephalomyelitis’/exp) OR (’demyelinating disease’/exp) OR (’multiple sclerosis’/exp) OR (’myelooptic neuropathy’/exp) OR (’multiple sclerosis’:ti,ab) OR (’neuromyelitis optica’:ab,ti) OR (encephalomyelitis:ab,ti) OR (devic:ti,ab)) AND ((’crossover procedure’/exp) OR (’double blind procedure’/exp) OR (’single blind procedure’/exp) OR (’randomized controlled trial’/exp) OR (random*:ab,ti) OR (factorial*:ab,ti) OR (crossover:ab,ti) OR (cross:ab,ti AND over:ab,ti) OR (placebo:ab,ti) OR (’double blind’:ab,ti) OR (’single blind’:ab,ti) OR (assign*:ab,ti) OR (allocat*:ab,ti) OR (volunteer*:ab,ti))) AND (((’epilepsy’/exp OR ’epilepsy’)) OR ((’seizure’/exp OR ’seizure’)) OR (epilep*) OR (seizure*) OR (convulsion*)) AND [humans]/lim AND [embase]/lim

CONTRIBUTIONS OF AUTHORS

All authors cooperated in the literature search, data extraction, data analysis and in writing the review.

DECLARATIONS OF INTEREST

We declare we have no conflicts of interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Multiple Sclerosis [*complications]; Seizures [etiology; *therapy]

MeSH check words

Humans