SHORT REPORT

Low dose oral methotrexate treatment of multiple sclerosis: a pilot study

Robert D Currier, Armin F Haerer, Edward F Meydrech

Abstract

An 18-month double-blind treatment of multiple sclerosis with low dose oral methotrexate showed it to be well tolerated and suggested effectiveness in exacerbating-remitting MS but not in the exacerbating progressive and chronic progressive stages.

(J Neurol Neurosurg Psychiatry 1993;56:1217–1218)

Multiple sclerosis (MS) has been treated with immunological altering methods and drugs for the past two decades. Some appear to be beneficial but problems with administration, cost, side effects, the need for laboratory studies, delayed effectiveness, poor patient acceptance and compliance and the possibility of remote cancer, have limited their use.

Methotrexate in low dose format has been used to treat psoriasis and rheumatoid arthritis for four decades. It may be the most effective and least harmful treatment for progressive rheumatoid arthritis. 1 A trial of low dose methotrexate for MS seemed reasonable. Oral methotrexate was previously evaluated by Neumann and Ziegler2 who gave 15 patients 2.5 mg of oral methotrexate daily alternating with 6-mercaptopurine in three-month time periods over 10 to 24 months. When compared with a placebo group no obvious difference was noted.

One of us (AFH) acted as the 'blind' evaluator and the other (RDC) as the treating physician who might if necessary break the 'blind', a need that occurred twice. The patients were randomised as they entered the study.

The medication was given as one tablet (2.5 mg methotrexate or placebo) every 12 hours for three consecutive doses, once a week (7.5 mg/week); the usual treatment regime for rheumatoid arthritis. Complete blood counts, complete blood chemical analyses and chest radiographs were carried out at the beginning and end of the study. Blood counts and liver function studies were done every two months. Neurological examinations were done at entry, every four months and at the end, and graded on the Kurtzke3 scale. Additional treatments such as corticosteroids were allowed and were given for exacerbations during the study.

Forty-five patients were enrolled for a period of a year. One took a single pill and dropped out. The remaining 44 were included in the analysis. The time in the study of the six who stopped the medication before the 12 month point was included. At the end of the study the 'blinded' physician categorised the patients into subtypes of MS and tabulated the number and timing of exacerbations and worsening by one point or more on the Kurtzke scale. An exacerbation

Method

Approval for the trial was given by the University Human Investigation Committee. Requirements for inclusion were the presence of definite MS, a worsening in function or an exacerbation in the previous year, understanding and willingness to cooperate and no history or evidence of renal or hepatic disease, gross obesity or diabetes. All types of MS were accepted in an attempt to obtain 50 participants in the one year enrolment period. The initial 12 months active treatment period was changed to 18 months during the study on advice of the National Multiple Sclerosis Society. Three participants were unwilling to extend their time in the active phase of the study from 12 to 18 months and six dropped from the treatment phase of the study before 12 months, usually because of inadequate understanding.

Figure. Exacerbations and worsenings of multiple sclerosis of one Kurtzke grade or more in the exacerbating-remitting methotrexate group (nine patients) and the placebo group (11 patients). *If a patient had both an exacerbation and a Kurtzke worsening in the same month, it was counted as a single event.
lasting at least two weeks followed by incomplete or complete recovery and so judged by an experienced neurologist.

Fisher's Exact Test was used to look for an association between the placebo and methotrexate treatments and the proportion of subjects having exacerbations. The two-sample t test was used to compare the mean difference in the number of exacerbations between the treatment and placebo groups and to compare the mean difference in the number of exacerbations plus Kurtzke worsenings greater than one between the methotrexate and placebo portions of the exacerbating-remitting group.

Results
When considered as a single group there was no difference in outcome of the 22 methotrexate and 22 placebo patients. Eight on methotrexate and nine on placebo had exacerbations. Of the 44, 20 had exacerbating-remitting MS and 24 chronic MS including 18 exacerbating progressive, three chronic progressive and three spinal patients. In the exacerbating-remitting group of 20 (11 placebo, nine methotrexate) there were 14 females and six males, median age 39·5 years. In the 12 months before the study there were 12 exacerbations in the 11 placebo patients and nine in the nine methotrexate patients. During treatment a total of three exacerbations occurred in two of the nine exacerbating-remitting methotrexate patients over a period of 150 treatment months, for a mean of one exacerbation per 50 months. Seven of the 11 placebo patients had 12 exacerbations during 169 total group treatment months, a mean of one per 14 months. The difference in proportions of patients having exacerbations is not significant (p = 0·09) while the difference in the mean number of exacerbations just reaches significance with p = 0·05. Three of the nine methotrexate patients and five of 11 placebo patients worsened by one or more points on the Kurtzke scale.

The figure shows the time of exacerbations and worsenings of one Kurtzke grade or more in the exacerbating-remitting methotrexate and placebo groups. The placebo group had 16 events which continued to occur to the end of the study (three placebo patients experienced an exacerbation and a Kurtzke grade worsening simultaneously which were considered as one event in each case) and the methotrexate group had six events, with no worsenings after 12 months. The difference in the mean number of exacerbations plus Kurtzke score worsenings of one or more is just significant with p = 0·05.

There were 24 patients (11 placebo, 13 methotrexate) in the chronic MS group, 19 female and five male, median age 46·8 years. The three early dropouts at four, five and eight months were all on placebo. Total treatment times were 156 months for placebo and 230 for methotrexate.

Two of 11 patients on placebo had a total of three exacerbations in 156 months of treatment, one per 52 months, and six of 13 methotrexate patients had a total of nine exacerbations in 230 months of treatment, or one every 25·5 months. Two of 13 methotrexate patients worsened by one or more points on the Kurtzke scale and none of the 11 placebo patients worsened by one point or more.

While none of the outcome variables nears statistical significance in the chronic MS group (p = 0·15 for the difference in proportions with exacerbations and p = 0·11 for the difference in the number of exacerbations), it may be important to notice that the direction of the differences is opposite to the exacerbating-remitting group.

The methotrexate was tolerated reasonably well. Two patients complained of headaches, both were on placebo. Nausea was helped by taking the medication with meals. One methotrexate patient had moderate hair thinning. Liver enzymes became mildly to moderately abnormal on more than one occasion in eight methotrexate and one placebo patients but were persistently abnormal in only one methotrexate patient. In that patient the medication was stopped, the enzymes returned to normal and the medication was restarted with the enzymes remaining normal.

Discussion
The effect of methotrexate on the liver has been a concern over the years. It is proving to be less toxic than originally thought, and the rheumatologists, the chief users of oral low dose therapy, are gradually using fewer tests of hepatic function. In a recent five year study of low dose methotrexate in the treatment of rheumatoid arthritis,4 44 of 124 patients stopped the treatment because of side effects including nausea, stomatitis, hair loss, rash, pulmonary reactions, elevated liver enzymes, haematological abnormalities and hepatic fibrosis. Although 93% of the total experienced at least one drug reaction the majority did not require permanent drug discontinuation. There is no evidence that low dose methotrexate causes cancer.

In the present study those with exacerbating-remitting MS apparently benefited and those with chronic MS worsened. Why did not the methotrexate benefit both types? The question of dosage is debatable.

This is a small trial and must be considered a preliminary study of low dose oral methotrexate in the treatment of multiple sclerosis. Methotrexate therapy is now under evaluation by others with larger and longer studies which should help determine the truth of the matter.

Lederle Pharmaceuticals kindly provided the methotrexate and placebo for this study and helped defray the cost of the laboratory work.


R D Currier, A F Haerer and E F Meydrech

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Updated information and services can be found at:
http://jnnp.bmj.com/content/56/11/1217

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Errata
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Notes

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There are also practical and concise chapters on operative positioning and peri-operative management, and on cranial nerve function monitoring.

The scope of the book is therefore very wide, but—no criticism intended—those sections on vascular lesions or intra-axial tumours should look elsewhere. The text is invariably practical and authoritative, and the illustrations uniformly good. I could not fault the index.

This book is probably a must for departmental libraries, and will be welcomed by all neurosurgeons undertaking surgery in the posterior fossa, and perhaps particularly by those preparing to sit specialty Fellowship.

AJ STRONG

Cerebral Small Artery Disease.
(Advances in Neurology, Vol 62). Edited by
P M PULLICINO, L R CAPLAN and M HOMMEL
(Pp 241, Illustrated; Price: $123.50). 1993
New York, Raven Press. ISBN 0-7817-
0051-5 (Order Code 2591)

In the Middle Ages a favoured topic for
debate among theologians concerned how
many angels could rest on the point of
a needle; latter-day neurologists debate with
equal vigour (but no more success) the
dynamics of the lacune. These perplexing
holes were first well described by French
pathologists as small cavities within the sub-
stance of the brain and thought by most to
be ischaemic in origin. Other pathological
conditions resembling but distinct from
lacunes were recognised and the term came
to be used to describe small circumscribed
deep-seated infarcts. Early attempts to
correlate individual lacunes with clinical
symptoms and signs were hampered by the
fact that there was no way of locating with
certainty the site of lesion during life and
when the patient eventually came to autops-
py the lacunes were usually multiple. Pierre
Marie however recognised the clinical cor-
relate of longstanding 
lacune as a
pseudobulbar palsy, spastic quadriparesis
and dementia.

In the 1960s Fisher using a classical
clinico-pathological approach defined a
group of clinical syndromes (pure motor
stroke, ataxic hemiparesis, dysarthria-
clumsy hand syndrome) caused by small
deep infarcts in specific locations. It soon
came clear that the same syndrome could
result from a lacune in a number of differ-
ent sites, that a clinical lacunar syndrome
did not always signify a small deep-seated
lesion and that pathological lacunes could
be found in the absence of any symptoms.

In recent years modern imaging has
opened up the possibility of clarifying
pathological correlation during life. How-
ever radiological changes may be decep-
tive—not all regions of signal change are
infarcts, the lesions are often multiple and
the size of the lesion on imaging (an impor-
tant diagnostic criterion) may differ
greatly from its pathological size.

We end up with three definitions of
lacunes—pathologists mean a small deep
infarct in certain sites, clinicians mean one
of a number of neurological syndromes and
radiologists mean a region of signal
change of a specified size and location.
The possibilities for argument and mis-
understanding are endless.

As if this were not enough, the disagree-
ment about the nature of a lacune has
developed into a further argument about its
cause. Modern views on this have again
been much influenced by Fisher who
regarded a lacune as a small deep infarct ex-
clusively in the territory of a penetrating
artery. In most cases the penetrating
artery is occluded by fibrinolyisis, a conse-
quence of chronic hypertension, but in
a few occlusion results from atheroma or
embolism. Furthermore the artery is not
always completely blocked and it now
appears that small deeply placed infarcts in
distal field territories can be caused by
haemodynamic events such as systemic
hypotension in patients with occlusions of
large extracranial arteries.

This well-produced book deals extensive-
ly with these controversies and leaves the
reader (like FE Smith's judge) possibly
none of the wiser but certainly better
informed. There are excellent reviews of
cerebrovascular anatomy, microvascular
territories, arterial pathology, radiology and
clinical syndromes and much speculation
on pathogenesis, notably a well-balanced
and informative chapter from Dr Pullicino,
one of the editors. The illustrations are also
unusually good and the chapters are fully
referenced. All in all this is a book to be
recommended to all those interested in
clinical vascular disease and one which
shines some welcome light into dark places
and small holes.

R ROSS RUSSELL

The Biology of the Autistic
Syndromes/2nd Edition. By C GILLBERG
and M COLEMAN. (Pp 317, Illustrated; Price

This is a remarkable book. No one who
deals with autism will ever be the same after
reading this book which is a fresh edition of
the original 1985 work by Gillberg and Gilber-
ghas been published by Praeger New York in
1985. In scope and detail it is as rich as an old-
fashioned Christmas cake, not to mention
the hidden charms which may cause injury if
not noticed. One of the strengths of the book
is aimed not only at psychiatrists and neurolo-
ysts but also at psychologists special educators
and even parents of children with autism,
it is inevitable that which components are
indigestible will vary from one readership
group to another.

Originally there was Kanner's infantile
autism but that has not been a helpful
concept nor has the idea of "pervasive
developmental disorder": autism is a
specific neurological symptom complex not
nearly as pervasive as in less politically
correct times was called mental deficiency
or mental retardation. Having teased that
out the authors review the clinical,
epidemiological, genetic, biochemical,
endocrine, immunological, electrophysio-
logical, brain imaging, neuropathological
and neuropsychological literature with
extensive references.

I have concerns that child psychiatrists
who read this book may do the recom-
meded neurological examination and the
recommended investigations without the
intermediary of a paediatric neurologist, a
difficulty being that the authors are not
neurologists themselves. My substitution
for the second part of table 25.1 (neuro-
psychiatric assessment check list for autism)
would be first to get a first quality paediatric
neurologist to conduct the examination (for
example one doesn't just look for Lasch
nodules as confirmation of type I
Neurofibromatosis—one arranges for a slit-
lamp by the ophthalmologist). You may
investigate using the philosophy of testing
outlined in Handbook of Neurological
Investigations in Children. This table ends
with a novel invented definition of the milk-
maid sign.

There are lucky charms in this book as
for example in the section on epilepsy.
There one finds for example a fine reference
to "autism convulsii" to emphasise that
not only do epilepsy and autism go together
but that autism might be a symptom of the
epileptic process, the manifestation of
one type of minor epileptic status. This
is an autism treatable by anti-epileptic
medication. There is uncontrolled evidence
that vigabatrin when it abolishes infantile
spasms may reduce subsequent autism
liability.

J B P STEPHENSON

SHORT NOTICES

Electrical and Magnetic Stimulation
of the Brain and Spinal Cord (Advances
in Neurology, Vol. 63). Edited by
O DEVINSKY, A BERIC AND
MICHAEL DOGALI.
(Pp 323; Price: $139.00) 1993.
New York, Raven Press. ISBN 0-7817-
0066-3.

Anatomic Localization for Needle
Electromyography. By STEVE R
REININGER.
Philadelphia, Hanley & Belfus Inc. ISBN
1-56053-068-5.

CORRECTION

Currier RD, Haerer AF, Meydrech,
EF. Long-term corticosteroid treat-
ment of multiple sclerosis: a pilot
study. J Neurol Neurosurg Psychiatry
1993;56:1217–18. The final sentence on
p.1217 should read "An exacerbation was
defined as a focal neurological worsening
lasting at least two weeks followed by
incomplete or complete recovery and so
judged by an experienced neurologist."