SHORT REPORT

Double blind placebo controlled multicentre study of ginkgolide B in treatment of acute exacerbations of multiple sclerosis

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Abstract

After an open labelled pilot study of ginkgolide B, a potent inhibitor of platelet activating factor, in the treatment of acute exacerbations of multiple sclerosis, a randomised double blind placebo controlled study was undertaken. One hundred and four patients were enrolled in the study: for seven days 43 received placebo, 29 received 240 mg/day ginkgolide B and 32 received 360 mg/day ginkgolide B. There was no statistical difference between the three groups for changes in Rankin, Kurtzke expanded disability status scale (EDSS), and Hauser ambulation index (AI) scores. Although there was a trend in favour of groups treated with ginkgolide for a change of Rankin and AI scores, it is concluded that ginkgolide B is not an effective treatment of exacerbations of multiple sclerosis.

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Acute exacerbations of multiple sclerosis are associated with inflammation, white cell passage into the CNS, and damage to the blood-brain barrier.¹ This damage is shown consistently by CT and MRI with contrast enhancement.² Steroids are supposed to repair the blood brain barrier.³ Platelet activating factor is an important mediator of inflammation and has a pivotal role in the vascular stage of the inflammatory process.⁴ Experimental studies have shown that BN52021 (ginkgolide B), a compound known to be a potent inhibitor of platelet activating factor,⁵ can prevent and treat experimental allergic encephalomyelitis, a widely used model of acute inflammatory demyelination that mimics acute exacerbations of multiple sclerosis.⁵ In an open labelled pilot study it was shown that this compound was well tolerated in patients with acute exacerbations of multiple sclerosis and seemed to be associated with some degree of improvement.⁶ A placebo controlled multicentre study was therefore designed to assess the therapeutic efficacy of BN52021 in acute relapses in multiple sclerosis.

Material and methods

PATIENTS

One hundred and four patients with definite multiple sclerosis according to the criteria of Poser *et al*⁷ were entered into the study in 17 centres. The sample size was determined from the results of an open study,⁶ which showed an improvement of 1.1 (SD 0.5) on the Rankin scale. With a power of 0.80 (β risk = 20%) and α risk = 0.05, the sample sizes necessary to show an improvement of one point on the Rankin scale were 24, 24, and 36.⁸ Randomisation was made by centre, by blocks of six patients. The study was approved by the Comité de Protection des Personnes of the University of Bordeaux and all patients gave written informed consent. Inclusion criteria stated that all patients had to be aged between 18 and 55, all with a relapsing-remitting form of multiple sclerosis. They had to be in an acute exacerbation of more than 48 hours and less than 10 days, and to have a Kurtzke expanded disability status scale⁹ of seven or less. An exacerbation was defined as the appearance of a new symptom or the worsening of an old symptom attributable to multiple sclerosis accompanied by an appropriate new neurological abnormality. Patients with isolated optic neuritis were not included. No patient had received another treatment (for example, steroids) for the ongoing relapse.

STUDY MEDICATION

BN52021 was supplied by Institut Henri Beaufour, Paris, France. Patients received intravenously either 120 mg of BN52021 twice daily for seven days, 180 mg of BN52021 twice daily, or placebo under the same conditions. Each lyophilised vial of BN52021 also contained mannitol (20 mg), sodium hydroxide (2.5 mg), and HCl (pH 8.75). Each placebo vial contained mannitol (20 mg). The same solvent (isotonic saline) was used for placebo and BN52021. Vials had the same presentation. The treatment dose was established from toxicity studies and from the results of a pilot study⁶ performed with 240 mg/day of BN52021 given for five days. This study suggested that a longer treatment and a higher dose would be better.

STUDY DESIGN

After inclusion and randomisation each

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Table 1 Demographic and baseline characteristics

Variable	Group 1 (placebo) (n = 43)	Group 2 (BN-240 mg) (n = 29)	Group 3 (BN-360 mg) (n = 32)
Sex (women/men)	37/6	23/6	18/14**
Age (medians and range)	34 (20–59)	35 (22–51)	36 (23–64)
Multiple sclerosis duration from diagnosis	5 (0.02–23)	6 (0.58–28)	7 (0.82–32)
Baseline EDSS score	4.0 (1.0–7.5)	4.0 (1.5–7.0)	5.5 (1.5–8.0)
Baseline Rankin score	3 (1–4)	2 (2–4)	3 (2–4)
Baseline AI score	2 (0–4)	3 (0–4)	3 (1–4)
Baseline pyramidal FSS	3 (0–8)	2 (0–7)	3 (1–7)*

Results are medians (95% CIs) unless otherwise stated.

* $p < 0.05$; ** $p < 0.01$ (group 3 v groups 1 and 2).

patient was admitted to one of the participating hospitals for seven days. Seventeen centres participated in the study. Patients and all personnel including investigators were blinded to treatment categories. Each patient was followed up and assessed by the same physician during the study. Patients were evaluated before the beginning of the treatment and at days 2, 4, 6, 8, 15, 30, and 60. Each assessment included a standardised neurological examination, Kurtzke EDSS,⁹ Kurtzke Functional system scales (FSS),⁹ Hauser AI,¹⁰ and a Rankin derived functional status scale.⁶ Clinical side effects were monitored daily for the first seven days and at each follow up visit. Laboratory monitoring was performed before the treatment and at days 8, 15, 30, and 60. If the clinical status of a patient required steroid treatment after day seven (for increasing disability), an intravenous methylprednisolone pulse (1 g/day for five days) was given and this was considered as a failure of treatment. Such patients were maintained in intent to treat analysis and the last score before steroid treatment was used for efficacy analysis.

EFFICACY CRITERIA

The primary end point was the change in Rankin modified score from baseline to day 15. Secondary endpoints included change in EDSS, FSS, and AI at day 15 from baseline and change of all scores at days 30 and 60. The number of patients receiving treatment with methylprednisolone in each treatment group was also analysed as a practical end-point.

Table 2 Primary and secondary outcome measures at day 15

Variables	Group 1- placebo (n = 42)	Group 2- BN 240 (n = 29)	Group 3- BN 360 (n = 32)	p Value
Rankin	-0.51 (0.83)	-0.69 (0.85)	-0.75 (0.84)	0.62
EDSS	-0.78 (1.3)	-0.76 (1.3)	-0.94 (1.17)	0.83
AI	-0.56 (1.75)	-0.76 (1.15)	-1.00 (1.16)	0.64
Pyramidal FSS	-0.42 (0.93)	-0.59 (0.68)	-0.84 (0.99)	0.19
Cerebellar FSS	-0.56 (0.85)	-0.24 (0.87)	-0.53 (1.08)	0.48
Brainstem FSS	-0.29 (0.86)	-0.41 (0.82)	-0.28 (0.81)	0.49

Results are change in score (SD) from baseline in intent to treat patients. The analysis concerned the last data before steroid treatment for patients receiving steroids during the study.

STATISTICAL METHODS

Patient characteristics at baseline were compared by χ^2 test. Fisher's exact test and analysis of variance for repeated measure were used to test changes in Rankin, EDSS, and FSS scores from baseline to day 15. The significance of decrease of Rankin score adjusted on EDSS score at day 0 was assessed with the Cochran-Mantel-Haenzel test.⁸ Statistical Analysis System software was used to perform this test.

Results

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Of the 104 patients entered 43 were in group 1 (placebo), 29 in group 2 (BN52021–240 mg/day), and 32 in group 3 (BN52021–360 mg/day). The three groups were comparable (table 1) except for sex: the proportion of men was significantly greater in group 3 (BN52021–360 mg; $p < 0.01$, χ^2 and Fisher tests). The differences for baseline Rankin, EDSS, and AI scores between group 3 and other groups were not statistically significant but pyramidal FSS was significantly more severe in group 3 than in the two other groups ($p < 0.05$). Exacerbation rates before the study were not significantly different between the groups.

Eight patients did not fulfil inclusion criteria: two were older than 55 (one in the placebo group and one in group 3), three had an EDSS score at baseline > 7 (one in the placebo group and two in group 3), and three had a baseline Rankin score = 1 (two in the placebo group and one in group 3). One patient of the placebo group experienced a rash and dropped out at day 3 and was excluded from the analysis. Three patients of the placebo group dropped out at days 4, 6, and 60 but were included in the intent to treat analysis (103 patients).

PRIMARY AND SECONDARY OUTCOME MEASURES

Fourteen patients of the placebo group (33%), eight (28%) treated with 240 mg (BN52021) and five (16%) treated with 360 mg (BN52021) received steroids. The difference was not significant but the ordered trend was in favour of a dose related efficacy of the treatment as conditional steroid treatment was considered as a failure of the trial treatment.

There was no statistical difference between the three groups for changes in Rankin, EDSS, and AI scores between day 15 and baseline. Medians and 95% CIs of Rankin scores were 2 (1–4) in the three groups. There was a trend in favour of both groups treated with BN52021 for the mean change of Rankin and AI scores (table 2). A similar trend was found for the change of EDSS score, as well as for FSS scores except for cerebellar functions, in favour of patients treated with 360 mg BN52021. This non-significant trend was more pronounced for pyramidal FSS but not brainstem FSS in patients treated with 360 mg BN52021.

Analysis of results at day 60 showed a similar trend for Rankin score and a more pronounced trend (in favour of both BN52021 groups) for EDSS, AI, and pyramidal FSS.

ADVERSE EVENTS

No serious adverse event occurred during the study. One patient dropped out because of a benign rash (placebo group). Seventeen patients in the placebo group, 11 in the low dose BN52021 group, and 18 in the high dose BN52021 group reported at least one adverse effect. Only hiccup was reported more often in patients treated with BN52021 (eight patients at the low dose and 14 patients at the high dose *v* one patient in the placebo group), but this was always mild or moderate, and transient. No adverse biological effects were found. Alkaline phosphatase concentrations were significantly greater in patients receiving high dose BN52021, although still in the normal range.

Discussion

Intravenous steroid courses are the only established effective treatment for acute exacerbations in multiple sclerosis.^{11–13} There is no evidence that usual doses of oral steroids are of benefit.¹¹ A recent study on optic neuritis even raised the possibility that they were noxious¹⁴; patients treated with oral steroids experienced more relapses than patients treated with placebo. Intravenous high dose methylprednisolone is superior to placebo in alleviating symptoms of exacerbations of multiple sclerosis and optic neuritis on a short term basis.^{12–14} High doses of methylprednisolone given intravenously were recently shown to reduce the rate of development of multiple sclerosis over a two year period in the optic neuritis trial but steroids given orally did not do this.¹⁵ The repeated use of steroids in patients with frequent exacerbations expose such patients to serious side effects. Therefore there is a need for new drugs to treat exacerbations in multiple sclerosis.

The present trial showed that BN52021 was not significantly superior to placebo in patients with exacerbations in the small sample studied. Patients treated with 360 mg BN52021 daily had a more severe neurological deficit at baseline as shown by a pyramidal FSS significantly greater than in other groups. This is not, however, likely to explain the failure of treatment as the difference was small. The negative results make it unlikely that the higher rate of hiccups in patients treated with BN52021 have compromised blindness.

A non-significant trend was found, however, in favour of BN52021, with a dose effect relation. Brain MRI was not used systematically in this study. A subgroup of patients were followed up, however, using serial MRI with gadolinium contrast injection and the results (not shown) suggest that BN52021 may have a beneficial but partial effect on lesion enhancement and therefore

on damage to the blood brain barrier. Although the clinical trend does not in itself justify another trial of this compound in multiple sclerosis, these results raise the possibility that a more potent inhibitor of platelet activating factor may be useful in the treatment of exacerbations of multiple sclerosis or to prevent relapses.

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