

Short report

Trial of ganglioside GM1 in acute stroke

B I HOFFBRAND, P J BINGLEY, S M OPPENHEIMER, C D SHELDON

From the Department of Medicine, Whittington Hospital, London, UK

SUMMARY Ganglioside GM1 (100 mg) was given daily by intramuscular injection for 28 days in a double-blind placebo controlled trial of acute stroke. No significant difference was detected in a 6 month follow-up period between well matched control and active groups. Although the number of patients studied was small the findings are believed to indicate that GM1 is unlikely to be of value in the treatment of acute stroke in the dose and route of administration used.

Brain gangliosides are natural components of neuronal membranes and play a role in neuronal development, differentiation and regeneration probably by acting synergistically with endogenous nerve growth factors.¹ Two studies^{2,3} have shown evidence that GM1, a component of the ganglioside series, may have a beneficial effect on recovery from stroke. In both trials the final evaluation was at only 6 weeks and was by neurological, electrophysiological and computed tomographic (CT) assessment. We have conducted a double-blind placebo controlled single centre study in acute stroke using a larger dose of GM1, earlier treatment and final assessment at 6 months.

Methods

All patients aged 35 to 85 years presenting within 72 hours of the onset of a cerebral hemisphere stroke with limb weakness were assessed. Patients were excluded if they were premenopausal, in poor general health, had a history of previous stroke, or a condition, neurological or otherwise, that would interfere with clinical assessment and rehabilitation. After stratification based on initial examination there was random double blind allocation of patients to treatment with GM1 100 mg intramuscularly or matching saline placebo daily for 28 days. Standard rehabilitation and physiotherapy was conducted by staff unassociated with the trial

and all other medication was continued and altered as indicated by the physicians concerned. Neurological and functional assessment by the Barthel index⁴ was made by PB, SO or CS at entry, and one week, one, 3 and 6 months after entry. Haematological and biochemical examinations were made at entry to the study and repeated at the end of treatment. CT of the head was done as soon as possible and generally 5–6 days after stroke onset. Between-group comparisons were made using unpaired *t* tests or Mann-Whitney tests, on both raw data and within group changes from baseline. Confidence intervals 95% for the difference between the group means were calculated for the Barthel index scores which appeared normally distributed. The trial was conducted under terms of permission granted by the Committee on Safety of Medicines and was approved by the Islington Health District Ethical Committee. Patients or their relatives gave informed consent.

Results

The table shows that the GM1 and placebo groups were very similar in clinical state, underlying pathology and risk factors for stroke. Only one in five of those assessed (54 out of 257) proved eligible for entry, the major exclusions being due to coma, poor general health, previous neurological disease and aged over 85 years. There was one secondary exclusion due to tumour. The GM1 withdrawals were due to epilepsy 5 months after entry, and neurosurgery for a haematoma. The placebo withdrawals were due to a second stroke and lost records. There were no significant differences between the two groups at any assessment time in deaths, clinical neurology scores (not shown) or Barthel index scores (table). The 95%

Address for reprint requests: Dr B I Hoffbrand, The Whittington Hospital, Archway Wing, Highgate Hill, London N19 5NF, UK.

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Table Clinical and laboratory data on 53 patients with acute stroke treated with GM1 or placebo

	GM1	Placebo
No	27	26
Age (years)	66.9* (9.4)	67.4 (10.6)
M/F	16/11	15/11
CT single infarct	11	9
multiple infarcts (recent and old)	7	9
haemorrhage/haemorrhagic infarct	6	4
normal	0	1
not done	3	3
Hypertension	10	12
Glycosylated haemoglobin (%)	6.7* (2.0)	6.5 (1.0)
Haemoglobin (g/l)	14.5* (1.5)	14.0 (1.7)
Deaths	5	9
Withdrawals	2	2
Barthel index—baseline	32.7* (28.3)	28.0 (28.9)
one month	70.2* (29.8) n = 22	72.3 (29.9) n = 15
six months	88.2* (16.2) n = 19	80.0 (28.0) n = 14

* Mean (SD)

confidence intervals of the difference between the means (GM1—placebo) were +16.8 to -21.0 and +23.2 to -7.4 at 1 and 6 months respectively. There were no adverse reactions or significant change in laboratory investigations in either group.

Discussion

A major problem in the assessment of the new treatments in acute stroke is the beta error inherent in trials with relatively small numbers of cases. Trials of adequate statistical power generally require multicentre studies which introduce their own problems and are extremely costly. Confidence intervals analysis provides a method of more precise evaluation of results obtained.⁵

Although there was a lower mortality rate in the patients receiving GM1, our findings make it evident that only a larger study with either higher doses and/or a different route of administration (intravenous) may show a worthwhile clinical effect. From the sample we studied, we could not detect differences in responses between haemorrhagic and ischaemic stroke patients so that it is difficult to predict whether selecting cerebral infarction alone would be more effective. Results from on-going multicentre international studies on administration of GM1 in the

early stages of stroke (D Massari, personal communication) are awaited with interest.

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References

- 1 Gorio A, Janigro D, Zanoni R. Neuritogenesis and regeneration in the nervous system: an overview on the problem and on the promoting action of gangliosides. In: Ledeen RW, Yu RK, Rapport MM, Suzuki K, eds. *Ganglioside Structure, Function and Biochemical Potential*. New York: Plenum Press, 1984:465-74.
- 2 Bassi S, Albizzati MG, Sbacchi M, et al. Double blind evaluation of monosialoganglioside (GM) therapy in stroke. *J Neurosci Res* 1984;12:493-8.
- 3 Battistin I, Cesari A, Galligioni F, et al. Effects of GM1 ganglioside in cerebrovascular disease: a double blind trial in 40 cases. *Eur Neurol* 1985;24:343-51.
- 4 Orgogozo JM, Capildeo R, Anagnostou CN, et al. Mise au point d'un score neurologique pour l'évaluation clinique des infarctus sylvien. *Presse Med* 1983;12:3039-44.
- 5 Detsky AS, Sackett DI. When was a "negative" clinical trial big enough? How many patients you needed depends on what you found. *Arch Intern Med* 1985;145:709-12.