Gangliosides and neurological diseases

EDITOR,—Albert Figueras and colleagues' recommendation that gangliosides should be withdrawn, which is based on their experience of 17 patients diagnosed as having the Guillain-Barré syndrome and other acute motor neuropathy, is inappropriate.[1] Firstly, they give no details from which the validity of the diagnosis can be judged. Retrospectively collected data are notoriously incomplete, and even if the diagnoses were "confirmed by a neurologist" it is not clear that acceptable diagnostic criteria were uniformly applied.[2] Moreover, in nine of their cases the use of gangliosides for prodromal symptoms of the disease allegedly caused by the ganglioside could not be excluded. In addition, in at least three cases an antecedent illness that often precedes the onset of polyneuropathy was known to have been present. Thus in 12 of the 17 cases the clinical basis for implicating gangliosides as a cause is uncertain at best.

If even five cases of acute motor polyneuropathy were caused by gangliosides the risk should be calculated. To do this requires knowledge of the size of the population exposed to ganglioside. Figueras and colleagues do not give this information, stating only that the 17 reports were among 18000 reports in their database. In a recent epidemiological study in Spain no association between use of gangliosides and polyneuropathy was found.[3] An epidemiological study in Italy reported that if a risk of polyneuropathy exists at all it is less than 1 in 10000 exposed.[4] Finally, evidence is accumulating, based on well controlled clinical trials, that GM1 ganglioside may be beneficial in several types of injury to the central nervous system.[5-8]

Colleagues and I recently completed a randomised double blind, multicentre clinical trial of 287 patients with acute stroke treated with 100 mg G_{m1} ganglioside intramuscularly or placebo daily for 28 days.[9] No cases of acute polyneuropathy occurred, nor was there any significant difference in deaths or adverse effects between the two groups of patients. We found consistent benefits favouring the group treated with G_{m1} when we measured the change from baseline values in the motor component of the Toronto stroke scale at day 28 ($p=0{\cdot}02$) and day 84 ($p=0{\cdot}06$). The Fugl Meyer scale, all 10 components of the Barthel index, and four of five tests in a neuropsychological battery also favoured the patients treated with G_{m1}.

To withdraw ganglioside treatment on the basis of the evidence presented by Figueras and colleagues would be a disservice to patients who suffer from conditions for which no other effective treatment exists.

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Advice to authors

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EDITOR,—Peter O Behan and B A G Haniffah suggest that the use of gangliosides in humans should be suspended.[1] Unfortunately, the information they present gives an inaccurate view of the state of research into gangliosides and the rationale for their therapeutic use.

Firstly, though the monosialoganglioside G_{m1} has been shown to be useful in reversing behavioural, and to a certain extent biochemical, alterations induced by damage to the nigrostriatal dopamine system, its effects may not simply be due to a neuroprotective mechanism. Whether protection against certain types of insults is provided by G_{m1} may depend on the type of insult. For example, G_{m1} may protect neurones against excitotoxicity induced by glutamate[2] but may not protect dopamine neurones in vivo[3] or in vitro[4] against damage by MPTP or MPP^+. G_{m1} does, however, apparently stimulate repair processes in damaged dopamine neurones and promote the survival of these injured neurones both in vivo and in vitro.[4,5]

Though Behan and Haniffah are correct in stating that gangliosides seem to be most effective when given shortly after injury, they are incorrect in stating that that explains their lack of efficacy in genetic disorders of the central nervous system. The evidence cited for this lack of effect is the negative results in patients with amyotrophic lateral sclerosis or Charcot-Marie-Tooth disease given low doses of ganglioside mixtures.[6] We recently showed in our laboratory, however, that treatment with G_{m1}, started shortly after birth can at least partially reverse striatal dopamine loss in homozygous Weaver mice, a genetic disorder of dopamine deficiency and incoordination (unpublished observation).

Albert Figueras and colleagues support the call to suspend human use of gangliosides,[7] but there are several problems with their short report. Though the total population from which their 17 patients with adverse effects are drawn is reported to be "over 18000," there is no estimate of how many patients may have been given ganglioside during 1989-92, when the 17 cases were reported.

It is difficult to compare recent data on pure G_{m1} ganglioside with past data obtained with ganglioside mixtures. Ganglioside mixtures (which contain only 17-25% G_{m1}) may be more immunogenic than pure G_{m1}, which is now used in most animal and human studies. The lack of immune response to pure G_{m1} is supported by results of determinations of G_{m1} antibody in serum from patients receiving G_{m1} long term for either stroke or acute spinal cord injury. To date, no antibody to G_{m1} has been detected in people treated solely with G_{m1} ganglioside.[8].

We agree that indiscriminate use of G_{m1} ganglioside should be stopped, but the call to suspend all use is too extreme. We suggest that human trials with G_{m1} ganglioside should proceed cautiously for scientifically indicated uses as animal studies continue to define the role of gangliosides in the function and repair of the nervous system.

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EDITOR,—On the basis of ample and convincing evidence obtained from experimental pathology[1] gangliosides derived from bovine brains are widely used to treat pathological conditions of the peripheral and central nervous system. Recent controlled trials conducted with the monosialoganglioside G_{m1} have indicated the efficacy of this treatment for stroke and spinal cord injury.[2,3] Concern for the safety of gangliosides, based on supposed immunogenicity causing autoimmune diseases, has been raised and the suspension of ganglioside treatment in humans has been suggested.[4] Immunogenicity of pure ganglioside derived from brains has not, however, been shown.

Gangliosides are normal constituents of the cell membrane. They are abundant in cells of the nervous system but are also present in all other tissues and body fluids. Expressed at the cell surface, they are steadily exposed to immune surveillance and recognised as self antigens. Injection of pure gangliosides does not result in antibody induction or T cell stimulation in experimental animals.[5] Immunisation with chemically modified gangliosides, in the presence of adjuvant, induces antibodies that do not crossreact with the natural gangliosides, thus indicating the mainten-