SHORT REPORT

Immunoadsorption inferior to plasma exchange in a patient with chronic inflammatory demyelinating polyradiculoneuropathy

R D M Hadden, S Bensa, M P T Lunn, R A C Hughes

Staphylococcal protein A immunoadsorption and plasma exchange were compared for treating chronic inflammatory demyelinating polyradiculoneuropathy. In a single patient, plasma exchange had a more beneficial effect than immunoadsorption on clinical outcome measures. Serum IgM antibody activity to peripheral nerve fell significantly following plasma exchange. Serum IgM and IgA fell more and IgG less after plasma exchange than after immunoadsorption. The superior efficacy of plasma exchange to immunoadsorption in this case may have been the result of removal of an IgM antibody.

METHODS

Interventions
We compared immunoadsorption with plasma exchange in a crossover design. The patient received either plasma exchange or immunoadsorption every four weeks through the antecubital vein. It was planned that he should receive two to four months of each treatment (depending on response) and then change to the other treatment. Treatments were not randomised or blinded. The treatments actually received during the assessment period were four months of plasma exchange followed by four months of immunoadsorption, four months of plasma exchange, three months of immunoadsorption, and finally three months of plasma exchange. He continued to take prednisolone 10 mg on alternate days.

Plasma exchange was performed on two days every four weeks, separated by one day. Each exchange replaced three litres of plasma (about one plasma volume) with 2.5 litres of 4.5% human albumin and 0.5 litres of citrate, using a Cobe Spectra machine (Gambro, Sweden). Immunoadsorption used a Citem 10® machine (Excorim, Lund, Sweden) and two Immunosorb® protein A columns (Excorim). The first four immunoadsorption treatments filtered approximately 8 litres of plasma on one day every four weeks. Because of the poor response, this was then altered to two immunoadsorption treatments (of 6 litres and 8 litres, two days apart) every four weeks to maximise IgG removal.

CASE REPORT

A 39 year old 72 kg man had a 14 year history of definite CIDP supported by sural nerve biopsy. He was disabled by a severe sensory ataxia and action tremor and walked unsteadily with ankle supporting boots. Motor conduction velocities were reduced to 13 m/s in the ulnar nerve and 14 m/s in the median nerve, and sensory nerve potentials were absent. He had had a temporary response to oral prednisolone and failed to respond to azathioprine, cyclosporin, β interferon, and intravenous immunoglobulin. His symptoms had stabilised while receiving twice monthly plasma exchange and 10 mg prednisolone on alternate days for the past eight years. He usually noticed a symptomatic improvement five to 10 days after plasma exchange and a decline four to six days before his next treatment.

Table 1 Changes in clinical assessments over four weeks following each treatment

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Plasma exchange</th>
<th>Immunoadsorption</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task sum score</td>
<td>1 (−1 to 3)</td>
<td>−1 (−3 to 1)</td>
<td>0.02</td>
</tr>
<tr>
<td>10 m walk [s]</td>
<td>−0.8 (0.9)</td>
<td>1.4 [0.6]</td>
<td>0.07</td>
</tr>
<tr>
<td>Tremor: water remaining in cup [ml]</td>
<td>20 (12)</td>
<td>−12 (10)</td>
<td>0.05</td>
</tr>
<tr>
<td>Nine hole peg test [s]</td>
<td>4 (4)</td>
<td>5 (5)</td>
<td>0.2</td>
</tr>
<tr>
<td>MRC sum score</td>
<td>2 (2)</td>
<td>−2 (2)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values are mean (SEM) or median (range).
Clinical assessments were done immediately before and then weekly following each treatment. They included 10 metre walk time, nine hole peg test time, MRC sum score, a “task sum score” (four simple tasks, chosen by the patient, that initially he could not quite do, and five that he could do with difficulty; scoring 1 for each task done), and a “water spilling test” as a measure of tremor (millilitres of water remaining in an initially full 250 ml cup held in the right hand for 10 seconds). Serum IgG, IgM, and IgA concentrations were measured before and immediately after each treatment.

The effect of each treatment was defined as the change in each outcome measure over the following four weeks—that is, the difference in value from immediately before each course of treatment to immediately before the next course of treatment. For each outcome measure, the mean effect from all plasma exchange treatments was compared with the mean effect from all immunoadsorption treatments by unpaired t tests for parametric data and the Mann–Whitney U test for ordinal data.

Serum antibody activity
Antibodies to whole human peripheral myelin were measured by enzyme linked immunosorbent assay (ELISA). Peripheral myelin was prepared by standard methods from human cauda equina, obtained from a patient who had died of non-neurological causes. Microtitre plate wells were coated with 1 µg of human peripheral myelin protein in 50 µl of 1% methylglyoxal (pH 8) at 37°C and then blocked with 1% bovine serum albumin in phosphate buffered saline (BSA-PBS). Sera were diluted 1:200 in 1% BSA-PBS and incubated in wells overnight at 4°C. Immunoglobulin class and subclass activities were detected by the addition of specific secondary antibodies (mouse antihuman IgG1, IgG2, IgG3, or IgG4 (The Binding Site, Birmingham, UK) or rabbit antihuman IgM or IgA (Dako A/S, Glostrup, Denmark)) at 1:500. Optical densities were measured after alkaline phosphatase development. Normal sera were included as controls.

Antibodies to myelin proteins were measured by western immunoblotting. In brief, samples containing 40 µg total protein were fractionated by 10% SDS-PAGE and transferred to a polyvinylidene fluoride membrane by semi-dry transfer. Sera were diluted 1:500 and incubated with membranes overnight at 4°C. Alkaline phosphatase conjugated antihuman IgG or IgM antibodies were added at 1:2500 dilution and detected with CDP-Star chemiluminescence (NEN Inc, Boston, Massachusetts, USA).
Antibodies to gangliosides were sought by thin layer chromatography-immuno-overlay. Whole ganglioside extracts of human cauda equina or ovine brain were separated by high performance thin layer chromatography in chloroform-methanol-0.02% CaCl₂ (60:40:8). Sera were overlaid at 1:200 and detected with rabbit antihuman IgG or IgM secondary antibodies (1:250; Dako) and then 125I labelled donkey antirabbit IgG (1:250; Dako).

RESULTS
Immunoadsorption was significantly worse than plasma exchange on two objective outcome assessments—the task sum score and the water spilling test—and there was a tendency for immunoadsorption to be worse than plasma exchange on the other assessments (table 1, fig 1). The patient felt subjectively that all his symptoms gradually worsened following immunoadsorption and improved following plasma exchange.

Serum IgM concentrations were reduced more effectively by plasma exchange (by 71 (3%)) (mean (SEM)) than by immunoadsorption (by 54 (3%), p = 0.05). IgA concentrations were also reduced more effectively by plasma exchange (by 69 (2%)) than by immunoadsorption (by 42 (3%), p = 0.008). Conversely, IgG concentrations were reduced slightly less effectively by plasma exchange (by 71 (2%)) than by immunoadsorption (by 84 (3%), NS).

IgM antibody activity against whole human peripheral myelin by ELISA was greater in the patient’s serum before plasma exchange than in normal control sera. No significant antitrypsin activity was detected by ELISA in any IgG subclass or IgA. Western immunoblotting of pretreatment sera detected IgM and IgG antibodies against a 36 kDa myelin protein. No IgG, IgM, or IgA antibodies to gangliosides were detected. Two hours after plasma exchange, IgM antimyelin antibody activity by ELISA was reduced by 22% compared with pre-plasma exchange values (p = 0.05) but there was no significant change in IgG or IgA antineurite activity.

DISCUSSION
We report the first direct prospective comparison of plasma exchange and immunoadsorption in a patient with CIDP, and show that plasma exchange had a greater clinical effect. This difference was significant for measures of tremor and functional tasks. The worsening during immunoadsorption presumably reflected withdrawal of plasma exchange. A likely explanation was the greater reduction by plasma exchange than by immunoadsorption of total IgM concentration, with a reduction by plasma exchange of the activity of an IgM antibody to peripheral nerve myelin. These results argue for a pathogenic role for an IgM antibody in this patient, although the antibody detected to a 36 kDa peripheral myelin protein is only one of a number of possible candidates. Antibodies to a 36 kDa protein, probably related to P0, have been described in 5% of patients with CIDP and in 39% of patients with amyotrophic lateral sclerosis, as well as in some patients with other neuropathies. An alternative reason for the greater benefit from plasma exchange is that it might remove complement factors and proinflammatory cytokines more effectively than immunoadsorption, although concentrations of these would probably rise again within days.

As CIDP is a heterogeneous condition, other cases probably have a different pathogenesis. A small proportion of CIDP sera have IgG or IgM antibodies to various proteins and glycolipids in peripheral myelin (reviewed by Meléndez-Vásquez et al.). In a study of 12 patients with CIDP, four had an IgG antibody capable of inducing demyelination in rats. Two of these sera contained IgM which bound to sciatic nerve sections but were not pathogenic in rats. Previous reports of immunoadsorption in CIDP using various types of column have described beneficial responses in six patients, although none was randomised or controlled.

In the only report comparing immunoadsorption with plasma exchange in a single patient, the authors expressed the opinion that their patient responded better to immunoadsorption than to plasma exchange, but this conclusion was weakened by the retrospective nature of the study without a crossover design, by the lack of data on the response to plasma exchange, and by the simultaneous use of varying immunosuppressive agents. Another patient with CIDP did not respond to immunoadsorption. In the present study, IgG was removed more effectively by immunoadsorption than by plasma exchange, as expected from the characteristics of protein A. No IgG anti-peripheral nerve antibodies were detected by ELISA, but IgG did bind to the same 36 kDa protein to which IgM bound on western immunoblotting. IgG and IgM may differ in their recognition of the same antigen presented in different contexts. A previous study showed that plasma exchange reduced total IgG, IgM, and IgA concentrations and antibodies to gangliosides more effectively than tryptophan-immobilised immunoadsorption in Guillain-Barré syndrome and Miller Fisher syndrome, although staphylococcal protein A immunoadsorption was not tested.

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REFERENCES