PLASMA SEPARATION IN GOODPASTURE'S SYNDROME AND MULTIPLE MYELOMA

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Summary

1. Plasma separation using membranes is equally as effective as plasmapheresis using a cell separator.

2. In Goodpasture's syndrome pulmonary haemorrhage improves very quickly with plasma separation. In patients with multiple myeloma, hyperprotein-aemia is easy to correct.

3. Plasma separation is well tolerated, both subjectively by the patient and objectively by the circulation.

4. Since the membranes are permeable not only to IgG but also to IgM, circulating antigen-antibody-complement complexes must also be easy to remove using the plasma separation method.

Introduction

In 1975 Lockwood et al [1] described the first successful plasmapheresis treatment of Goodpasture's syndrome using a cell separator. Yamasaki and his co-workers [2] reported the separation of plasma using large-pore membranes in patients with hepatic coma. The separated plasma was passed over uncoated charcoal and then returned to the bloodstream. We have used these membranes instead of a cell centrifuge [3] for plasma separation to eliminate immune globulins in Goodpasture's syndrome and in multiple myeloma.

Methods

Cellulose di-acetate membranes with a pore size of 0.2μm and an upper limit molecular cut-off of 3 million daltons were used for the plasma separation. The hollow fibre module (Asahi Medical Ltd, Tokyo) had a membrane surface area
of 0.65 m². Using a microprocessor-controlled balance in the haemoprocessor (Fresenius, Germany), the separated plasma was substituted by a warmed isotonic-isoionic solution containing 20g of human albumin per litre (Figure 1). Dependent on the risk of bleeding 2000 to 5000 units of heparin were initially infused, and during the treatment from 600 to 6000 units/hr were continuously infused into the arterial bloodline, to keep the coagulation time to approximately 20 minutes. These high doses were required because a considerable part of the heparin was removed in the filtrate. During each treatment 5 litres of plasma were separated in approximately 80 minutes. At a blood flow of 350ml per minute the maximum filtrate flow rate was 90–100ml/min.

The technical details have already been published elsewhere [4,5].
Results

The results of treating rare diseases with new methods can only be 'anecdotal' communications.

Goodpasture's Syndrome

For comparison purposes a case of a 32-year old male patient with Goodpasture's syndrome treated with the cell separator will be described. The patient was referred to us in August 1976 with immunosuppressive treatment already in progress. On this treatment however the clearance and diuresis decreased further. Because of haemoptyses a plasmapheresis treatment was immediately commenced and a total of eight plasmapheresis treatments with 3–4 litre exchanges were carried out. The haemoptyses improved even after the first treatment and receded fully with the subsequent treatments. Because of a high serum urea and overhydration six additional dialysis treatments were needed. The anti-glomerular basement membrane antibodies (anti-GMB-ab), initially at 32%, fell with the treatment to below 3%. They were measured by specific precipitation in RIA [6].

After the first two plasmapheresis treatments the diuresis increased, and somewhat later the creatinine clearance. Six weeks after starting plasmapheresis, with the specific precipitation at less than 3% (within the normal range) and at an endogenous creatinine clearance of 60ml/min, a second biopsy of the kidney was carried out. There were linear deposits of IgG on the basement membranes of the glomeruli. Quantitative comparison with the first biopsy was not however possible. The patient is today free from symptoms and has normal kidney function. The immunosuppressive treatment was discontinued at the beginning of 1977.

A second, 18-year old, anuric male patient with Goodpasture's syndrome, diagnosed by immunofluorescence microscopy, was taken on for plasma separation in April 1978, using membranes and was immediately dialysed because of the high urea concentrations. On the following day, on account of haemoptyses and difficulty in breathing which made artificial respiration necessary, a plasma separation was carried out. In the first few days up to 500ml of blood was sucked out from the respiratory tract. On bronchoscopy carried out because of the massive bleeding, a lung biopsy via the bronchial tree showed that here too anti-basement membrane antibodies were present on the basal membrane of the lung alveoli. After the first plasma separation the haemoptyses improved. The specific precipitation, which was initially very high at 46%, rapidly fell to less than 3%, within the normal range, after three separations and simultaneous immunosuppressive treatment using Azathioprine and steroids. After three weeks, lung function improved with recession of the radiological lung changes and it was possible to carry out extubation (Figures 2a and 2b). A total of fourteen plasma separations were carried out, in three weeks. The treatment was continued until the specific precipitation figures were normal. In contrast to the lung changes, kidney function did not improve, so that the patient had to be taken onto a chronic dialysis programme. A pericardiectomy for persistent pericarditis was performed at the beginning of June. In the middle of July he experienced diarrhoea and convulsive abdominal pains. The immunosuppressive treatment was discontinued on 19th July after no anti-glomerular basement membrane antibodies were detectable in the serum. The diarrhoea and pains persisted.

Neither endoscopic nor X-ray examination explained the diarrhoea. An autopsy showed necrotising enterocolitis. Although the immunosuppressive treatment had already been discontinued for four weeks, we would attribute the enterocolitis to the immunosuppression.

The decrease in the specific precipitation of anti-GMB-antibodies was approximately the same for both treatment methods. With 4 litres of plasma removed
Figure 2. Pulmonary findings in the 18-year old patient with Goodpasture's syndrome.
   a) before treatment; b) after 6 plasma separations
by the cell separator the value fell to 64% of the initial value, while with 5 litres of plasma separated with the membrane it fell to 67% of the initial value. The protein content in the filtrate was approximately two-thirds of the plasma protein. Correspondingly the proportions of IgG were 67%, IgA 62% and IgM 59%. During one plasma separation the concentration of IgG fell to 41%, of IgA to 47% and of IgM to 51% of the initial value in blood plasma. The albumin concentration remained almost constant during the substitution.

No significant decrease in the thrombocyte counts during the treatment was detected. The fibrinogen value fell during the separation to the same extent as the other plasma proteins.

Twenty-four hours later the fibrinogen concentration was once more within the normal range. The lowest thrombin times measured were 73%, on the day following the treatment. In contrast with the other enzymes the LDH often showed no decrease or a slight increase to a maximum of 80U/L which indicates slight haemolysis during the treatment.

Both subjectively and haemodynamically the plasma separation was well tolerated by the patients even at high exchange rates.

*Multiple Myeloma*

In two patients with multiple myeloma plasma separation was started for hyperproteinaemia and threatened hyperproteinaemic coma. In both cases renal insufficiency had developed within a few weeks. The first treatment reduced the total protein content from 14.0 to 7.8g/100ml in the one case and 12.0 to 8.7 in the other. The IgG fell from 7.9 to 5.1 and from 5.3 to 2.7g/100ml respectively. After two further plasma separations in the one case, and six in the other, with simultaneous treatment with melphalan and cyclophosphamide, no improvement in renal function resulted. After the IgG concentration had fallen to 1g/100ml, six weeks elapsed before it rose again to 3g/100ml. One patient finally succumbed to his basic illness; the other is presently on a chronic dialysis programme.

*Discussion*

Plasma separation using large-pore membranes and plasmapheresis using cell separators are of comparable effectiveness. The advantage of the plasma separation method is that it can be carried out using a hollow fibre module and commercially available haemofiltration equipment. The lower protein content in the filtrate during plasma separation is compensated by increasing the quantity of filtrate. Using plasma separation the initial decrease in plasma protein concentration occurs more slowly than in plasmapheresis, so that after a period the quantities of protein eliminated per time equalise out. Since separation is carried out by convection, there is only a small ‘sieve effect’ on proteins of high molecular weight. The IgM content in the filtrate is thus only slightly less than the IgG content. If IgM is well separated out by membranes, then it is likely that circulating immune complexes of molecular weight in the region of 1 million daltons can also be satisfactorily removed.

In Goodpasture’s syndrome the haemoptysis rapidly receded after plasma separation. Plasmapheresis or plasma separation with additional immunosuppres-
sive treatment appears to be the method of choice in these cases. The operative removal of both kidneys seems to be no longer justified [7]. An improvement in kidney function is only to be expected in patients who are not anuric. In one case the improvement of kidney function took place after the disappearance of the anti-GBM antibodies from the plasma; despite improved kidney function, the presence of linear deposits of immune globulins was still demonstrable by fluorescence microscopy. This could mean that damage occurs directly as the anti-basement membrane antibodies are deposited, and that their presence thereafter probably has no effect.

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References

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Open Discussion

SAMTLEBEN (Munich) I would like to mention another indication for plasma exchange with the plasma flow hollow-fibre filter, and that is myasthenia gravis. Despite anticholinesterase treatment, a 20-year old female patient developed a myasthenic crisis. She could not lift her arms against gravity and her vital capacity was only 1.3L. We performed three 2L plasma exchanges, and within six hours after the first treatment, her clinical state improved and the dosage of anti-cholinesterase treatment could be reduced gradually. Six days after the first treatment she was able to walk again. Therefore we think extensive plasma exchange is a highly effective method for emergency treatment in myasthenic crisis.

REES (London) I am very interested in the technique that you used. At Hammersmith Hospital now we have a large experience of treating anti-GBM antibody-mediated disease by plasma exchange, having treated some 32 patients. Broadly, our experience is that patients who have residual renal function improve with the institution of this treatment, and as you have shown, pulmonary haemorrhage rapidly subsides. The regimen that we use really is very intensive. We use 4L plasma exchanges daily from the day of admission, combined with cyto-
static therapy. Doing this we have also been able to dissociate the level of circulating anti-GBM antibody from other factors that influence the disease. One of these is fluid overload. Minor fluid overload can precipitate catastrophic pulmonary haemorrhage, and in this respect your technique may be very useful indeed, being very good for pulling off fluid — rather more effective for pulling off fluid than plasma exchange alone. Do you have any comments on this?

SIEBERTH Yes I agree that fluid overload is very dangerous for the patient. You can overload the patient with this technique when you use higher albumin concentrations as substitute. We used only 2 gram per 100 ml. When you have a higher level of albumin then you expand blood volume and you see more severe pulmonary haemorrhage due to hypervolaemia.