Plasma exchange in primary biliary cirrhosis

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Summary
The symptoms of patients with primary biliary cirrhosis are frequently intractable to traditional therapy. Three patients are reported of whom several symptoms were alleviated by plasma exchange, using a Hemonetics Model 30 cell separator.

Introduction
Primary biliary cirrhosis (chronic, destructive, non-suppurative cholangitis) is often accompanied by unpleasant complications such as pruritus, cutaneous lipid deposits, painful 'neuropathy', occlusive vascular disease and 'cholesterol arthritis' (Mills et al., 1978; Child, Mathews and Thompson, 1977), and all may be intractable to treatment. The pathogenesis of these clinical features is unclear but alterations of the plasma lipid profile are often present, while pruritus is often attributed to an increased bile acid pool size.

Reduction of the pools of lipid and bile acids by plasma exchange (plasmaphaeresis) might improve these symptoms, and since the apparatus for this is now more widely available, the results are now reported of its use in 3 patients with primary biliary cirrhosis.

Methods and case reports
An Hemonetics model 30 cell separator was used. Whole blood was removed from the patient, anticoagulated with acid citrate dextrose, and run into the centrifuge bowl until it was full of packed cells. The plasma that was separated was discarded and the cells re-transfused together with replacement plasma protein fraction. This cycle was repeated 4–6 times.

The plasma concentrations of fibrinogen and cholesterol were measured (in patients 1 and 3) before and after each session. Cholesterol concentration in the discard was also measured and the cholesterol removed calculated (see Table 1). Plasma fibrinogen and cholesterol concentrations were initially reduced by about 45% after each exchange. The concentrations of albumin and calcium (Buskard, Varghese and Wills, 1976; Thompson, 1976) remained constant. In spite of efforts to maintain the intravascular volume, syncope sometimes occurred.

Case 1
A 43-year-old female presented with a history of generalized pruritus and abdominal pain. Investigations revealed abnormal liver function tests and gall-bladder stones. Histological examination of a needle biopsy specimen of the liver confirmed the clinical diagnosis of primary biliary cirrhosis. Despite treatment with cholestyramine (12 g/day) and norethandrolone (10 mg daily), itching became intolerable. In addition she suffered from arthritis of the knees and shoulders, aspiration of which demonstrated cholesterol crystals. Unsightly lipid deposits developed on her hands, neck and face. She found it painful to grip objects and she developed angina.

Plasma exchange was therefore started at approximately 3-week intervals for 25 months while norethandrolone (10 mg/day) was continued. Symptomatic improvement was slow, but after 8 months itching was markedly decreased, angina was eliminated, some lipid deposits had disappeared, and she no longer had painful joints, or pain on gripping objects. The serum cholesterol concentration fell during each exchange, and the pre-exchange concentration fell gradually over the first 6 months. Then from a nadir of 10 μmol/l when symptoms were most improved, it rose to a peak of 20 μmol/l after 20 months. Finally it fell progressively until plasma exchange was stopped because of hypotension during exchanges. She died 5 months later.

Case 2
A 57-year-old female presented with a 7-month history of severe itching. Histological examination
of a needle liver biopsy specimen confirmed the diagnosis of primary biliary cirrhosis. The serum lipid profile was near normal: cholesterol 7.6 mmol/l (normal range 4.0–6.7) triglycerides 1.3 mmol/l (n.r. 0.6–1.5). Despite treatment with phenobarbitone (60 mg at night), and cholestyramine (4 g 4 times/day), or polidexide (3 g thrice/day) itching was uncontrolled. Norethandrolone (10 mg once/day) helped but the level of bilirubin, alkaline phosphatase and aspartate aminotransferase doubled and consequently the norethandrolone was stopped. Plasma exchange was therefore started while she continued on cholestyramine (4 g 4 times/day). Exchanges were performed every 3 months for one year, and each treatment produced complete freedom from itching for 3 weeks; the pruritus then rapidly returned and became intolerable. Unfortunately, because her estimated plasma volume was only 1.5 litre (body weight 44 kg) it proved difficult to prevent syncope and treatment was stopped. Serum bile acid concentrations were not measured.

Case 3

A 53-year-old female presented with jaundice, itching and hepatomegaly. The diagnosis of primary biliary cirrhosis was made from examination of a needle liver biopsy specimen. Generalized pruritus became intolerable 15 months later, but she was unable to take cholestyramine, and norethandrolone 10 or 20 mg on alternate days had no effect. In addition, generalized and painful eruptive xanthomata rapidly developed when the cholesterol level reached 25 mmol/l. Plasma exchange was therefore started. The painful lipid deposits became dramatically smaller and less painful after 2 treatments, but the severe pruritus was unaffected.

On each occasion plasmaphaeresis reduced serum cholesterol levels from 25 to 10 mmol/l, but these levels were not maintained between exchanges. She continued to deteriorate and exchanges were stopped. She died only 19 months after presentation.

Discussion

In 1972, Turnberg et al. reported 2 patients with primary biliary cirrhosis and painful 'xanthomatous neuropathy' whose symptoms improved after plasma exchange. In one patient, treatment (500 ml exchange) was given daily for 5 days, weekly for 14 weeks and then at varying intervals for one year. Pain and xanthomata began to improve after 4 weeks and, after 16 weeks, the pain had gone. In the second patient larger exchanges (1–2 litres) were possible and were performed at 2-week intervals for one month and then at monthly intervals for a further 6 months. Pain had resolved after 12 weeks (5 exchanges) and the xanthomata had also regressed. They used an intermittent method in the first and a continuous cell separator in the second case. In 1978, Geerdink et al. reported 2 patients with cholestasis in whom plasma exchange relieved severe itching after 3 weekly treatments (2–3 litres). Lauterberg et al. (1978) reported a similar case: itching resolved after 2 exchanges on successive days but had returned to its previous intensity at the end of the third week. Both groups used plasma perfusion to remove 'bile acids' and were therefore able to return the autologous plasma to the patient.

Intolerable generalized itching is frequently the presenting symptom of primary biliary cirrhosis. One explanation for this phenomenon is an increase in the size of the total bile acid pool leading to deposition of bile acids in the skin. However, measurement of the skin content of bile acids has not confirmed this (Ghent, Bloomer and Klatskin, 1977).

Another explanation has been that circulating immune complexes caused a skin vasculitis which produced the pruritus (Eriksson and Lindgren, 1980). Whichever is the correct answer, plasma exchange either by removing bile acids or immune complexes could decrease the itching.

Plasma exchange techniques have been used to treat hyperlipidaemia in order to reduce the angina of Type IIa familial hypercholesterolaemia (King, Breslow and Lees, 1980; Thompson, Lowenthal and Myant, 1975) and to decrease also the abdominal pain attributed to pancreatitis in diabetes mellitus (Betteridge et al., 1978).

It is suggested that the hypercholesterolaemia in the early stages of primary biliary cirrhosis is caused by a reduction of the elimination of cholesterol by the liver owing to cholestasis. Consequently, the cholesterol pool size is increased, the plasma concentration rises, and lipid deposits may appear in various tissues. However, as the disease progresses
the synthetic ability of the liver decreases and plasma concentrations begin to fall again. This was manifest in the first patient, but the terminal fall in serum cholesterol concentration occurred many months after the earlier improvement in symptoms associated with falling cholesterol that have been attributed to plasma exchange. Treatments in the third patient were given within 3 months of death and the highest cholesterol level was recorded 4 months earlier, so her level was already falling. But associated with the treatments, there was an impressive reduction in her pain and regression in the xanthomata and the serum cholesterol concentration did not fall spontaneously to post-exchange levels for a further 6 weeks. The pool sizes in these patients were not calculated.

Plasmapheresis is a specialized procedure. It may be trying for the patient and it is not cheap. It is, however, becoming more widely available because of interest in its use for haematological and immune complex diseases. Patients with primary biliary cirrhosis whose symptoms are not relieved by conventional treatment can benefit from it.

References


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