Patients, methods, and results

Six patients, aged from 16 to 56 with various types of glomerulonephritis and deteriorating renal function underwent a total of four to six 2½-litre plasma exchanges using the Haemonelects-30 intermittent flow separator at 4-7 day intervals. The replacement fluid consisted of 2 litres of either plasma protein fraction or polygeline with 500 ml of normal saline containing 5000 units of heparin as anticoagulant. A loading dose of 2000-5000 units of heparin was given before exchange.

Samples were taken for full blood count, and to measure blood concentrations of urea, electrolytes, proteins, immunoglobulins, complement, and coagulation factors before and at one and 15 hours after completion of exchange. Creatinine clearances were measured between exchanges. Blood pressure was monitored throughout the exchange and for 24 hours after its completion.

In each case plasma protein fraction was used for one exchange and polygeline for all subsequent exchanges. Concurrent immunosuppression using a combination of prednisolone, azathioprine, and cyclophosphamide was given to all patients. In all patients blood pressure and pulse remained stable throughout the procedure and for 24 hours afterwards. Renal function between plasma exchanges, as measured by serum urea and creatinine concentrations together with serial 24-hour urine creatinine clearance measurements, did not deteriorate. Plasma treatment combined with immunosuppression either stabilised or improved renal function in our patients.

The effect on serum protein concentrations is shown in the table. After

Mean serum protein concentrations using plasma protein fraction or polygeline as sole replacement fluid in plasma exchange. Concentrations are expressed in g/l and ranges given in parentheses

	Polygeline (20 exchanges)			Plasma protein fraction (6 exchanges)		
	Total protein	Albumin	Globulin	Total protein	Albumin	Globulin
Before exchange	57 (71-43)	31 (41-20)	26 (30-19)	58 (65-40)	32 (38-18)	26 (29-22)
One hour after exchange	43 (55-30)	17 (28-8)	26 (35-21)	46 (57-35)	36 (42-36)	10 (15-6)
15 hours after exchange	47 (60-33)	21 (32-14)	26 (33-16)	49 (58-33)	33 (38-21)	16 (24-12)
4-7 days after exchange	55 (65-42)	30 (36-18)	25 (29-19)	54 (58-49)	31 (38-17)	23 (32-19)

plasma exchange the total protein concentration remained stable in both groups but the albumin concentration fell appreciably in the group given polygeline. This had recovered almost completely at 4-7 days. Haemoglobin concentration, white cell count, and platelet count remained stable in the two groups during plasma treatment, but coagulation factors, fibrinogen concentrations, and C3 and C4 concentrations fell equally with both solutions with complete recovery at 4-7 days. Serum immunoglobulin concentrations appeared to be reduced equally with both solutions but concurrent immunosuppression prevented a quantitative comparison and affected their concentrations.

Comment

Polygeline is a gelatin product of molecular weight 35 000 and a half life in the circulation of 5-10 hours. Using this material as sole replacement fluid 2½-litre plasma exchanges were performed successfully at intervals of 4-7 days. No evidence of hypoalbuminaemic hypovolaemia or postural hypotension occurred even though the serum albumin concentration in one patient fell as low as 8 g/l with no ill effects. Low albumin concentrations may be a problem if plasma exchange is contemplated at very short intervals, but an infusion of 1-2 units of plasma protein fraction at the end of the procedure may circumvent this problem (unpublished observations).⁴ Our results suggest that patients on weekly plasma exchanges do not need infusion of plasma protein fraction.

The serial reduction in immunoglobulin concentrations with repeated plasma exchange and immunosuppression, and the fall in complement, coagulation factors, and fibrinogen concentrations with each exchange are similar to those found by other workers.^{2,3} Polygeline has been reported to cause allergic skin reactions and, rarely, bronchospasm but only when the solution is infused rapidly. An urticarial reaction occurred in one of our patients on two separate occasions but was completely controlled and reversed by slowing the infusion rate.

Ideal protocols for the use of plasma exchange in various diseases have not yet been worked out. One factor limiting evaluation of plasma exchange is the high cost and limited availability of suitable replacement solutions. Polygeline is readily available and currently costs about £3.00 per 500 ml. In selected patients it seems to be

a safe substitute for plasma protein fraction and deserves further evaluation.

¹ Anonymous. Plasma exchange. *Lancet* 1980;ii:241-2.

² Keller AJ, Urbaniak SJ. Intensive plasma exchange on the cell separator: effects on serum immunoglobulins and complement components. *Br J Haematol* 1978;38:531-40.

³ Bayer WL, Farrates FB, Summers T, Belcher C. Coagulation studies after plasma exchange with plasma protein fraction and lactated Ringer's solution. In: Goldman JN, Lowenthal RM, eds. *Leucocytes: separation, collection and transfusion*. New York: Academic Press, 1975: 551-60.

⁴ Ibister JP. Fluid replacement during plasmapheresis. In: Biggs JC, chairman. *Clinical application of blood, plasma and plasma substitutes*. Macquarie University, Australia: Hoechst, 1977.

(Accepted 1 December 1980)

Northern General Hospital, Sheffield S5 7AU

A J STELLON, BSC, MRCP, senior house officer in medicine

P J MOORHEAD, FRCP, consultant renal physician

Epidural morphine for ischaemic rest pain

Drowsiness and confusion often result when opiate analgesia is used to control severe rest pain in patients awaiting definitive treatment for ischaemia of the legs. To avoid these side effects we gave morphine by the epidural route, a procedure that is reportedly particularly effective in alleviating chronic pain.¹ The efficacy of this method of giving morphine is probably due to an action on specific receptors in the substantia gelatinosa.² Rapid penetration of the dura by morphine seems likely, as pain relief usually occurs within a few minutes of injection.¹ There is no loss of sensation or motor activity in the blocked segments.¹ A pin prick on the foot continues to feel sharp. This is a clear advantage over the effect of local anaesthetic agents given into the epidural space, which cause profound loss of sensation and power. Patients receiving epidural morphine analgesia may therefore go about their normal ambulant routine without risk of damaging an anaesthetised, chronically ischaemic limb. In addition, neither sympathetic blockade with risk of hypotension nor respiratory depression occurs with small doses. Cannulae have been left in situ without harm for up to 10 days.³

Changes in pain and duration of sleep at night produced by epidural morphine, showing mean values (and ranges)

	Pain score (cm)	Sleep at night (hours)
Before epidural analgesia started . .	8.28* (4-10)	3.25† (0-8)
After epidural analgesia started . .	0.94* (0-2)	6.93† (6-8)

Student's paired *t* test: **p* < 0.001; †*p* < 0.001.

Patients, methods, and results

We studied 16 patients with severe ischaemic rest pain that was poorly controlled by either dihydrocodeine or buprenorphine. An epidural cannula was inserted at the third to fourth lumbar interspace and connected to a bacterial filter at the shoulder. It was held in place by waterproof adhesive tape. Two millilitres of 1% plain lignocaine was injected down the catheter, followed several minutes later by 2 mg preservative-free morphine sulphate diluted in 10 ml isotonic saline. "Top-ups" were given when the patient felt the pain returning. While the cannula was in place patients were encouraged to walk about. Analgesia was continued during investigations before arterial grafting or amputation. Daytime pain relief was provided entirely by the epidural route. Occasionally, at night, oral analgesics were given if staff were not available to replenish the epidural. Immediately before operation the cannula was removed and the tip sent for bacteriological investigation. Pain was assessed using a 10 cm linear analogue scale⁴ once before and once after insertion of the epidural cannula. Changes in the number of hours' sleep at night and subjective changes in the temperature of the foot were also recorded.

Pain relief (table) was found to have reached its maximum within a few minutes. Before the planned end point nine cannulae had fallen out or become blocked or soiled. The mean time for which the cannula was retained was

2-6 days (range 1-5 days). The mean interval between top-ups was 12 hours (range 4-30 hours). Ten patients thought their symptomatic foot was warmer. Of the eight cannula tips sent for bacterial culture, all were sterile. Seven of the nine patients who received grafts experienced good pain relief as a result of surgery. Two patients with poor "run-off" and gangrene were unimproved and subsequently underwent major amputation.

Comment

Dramatic pain relief of rapid onset was achieved by giving epidural morphine. When the morphine was not preceded by local anaesthetic severe pain was momentarily felt in the limb. Patients were able to get a near-normal night's sleep and found that walking was much easier as weight could be borne on the more comfortable foot. This degree of analgesia was obtained without the side effects of systemic opiate analgesia. The time between top-ups was occasionally many hours. This has been reported by other workers.³ Possibly this was a placebo effect, but this seems unlikely as severe pain, present for many days, was often considerably alleviated. A sympathectomy effect from the lignocaine is unlikely to be responsible for pain relief as maximum symptomatic improvement cannot be expected so quickly in chronic ischaemia. In addition the dose given was probably

too small to cause sympathetic blockade or indeed analgesia. No untoward side effects were observed—in particular, no hypotension or respiratory depression occurred. We were disappointed that the cannulae could not be retained for longer periods, but this is difficult in ambulant patients. The increased preoperative activity and alertness may allow the patient to be better prepared for surgery.

¹ Behar M, Magora F, Olshwang D, Davidson JT. Epidural morphine in treatment of pain. *Lancet* 1979;ii:527-9.

² Snyder SH. Opiate receptors and internal opiates. *Sci Am* 1977;236:44-56.

³ Johnstone JR, McCaughey W. Epidural morphine. A method of management of multiple fractured ribs. *Anaesthesia* 1980;35:155-7.

⁴ Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976;2:175-84.

(Accepted 26 November 1980)

University Hospital, Queen's Medical Centre, Nottingham NG7 2UH

D J LAYFIELD, FFARCS, anaesthetic registrar

R J LEMBERGER, FRCS, surgical registrar

B R HOPKINSON, CHM, FRCS, consultant surgeon

G S MAKIN, CHM, FRCS, consultant surgeon

Depression of cellular immunity as an index of malnutrition in surgical patients

Increasing attention has been paid to nutritional support of surgical patients. The main problem is to identify malnourished patients. Association between protein-energy malnutrition and reduction in cellular immunity has been reported in catabolic patients.¹ Hence depression of cellular immunity has been suggested as one of the objective indices for selecting patients for nutritional treatment.² We investigated whether energy restriction and weight loss or surgery alone would affect cellular immunity.

Strikingly different results were obtained, however, from the surgical patients, of whom seven out of 10 converted from a positive response at 24 hours to a negative response at 48 hours when the operation came between these two readings.

Comment

This study showed that surgery depresses cellular immunity. This may be secondary to the increased secretion of stress hormones which occurs after trauma.⁴ Cortisol administration depresses cellular immunity within 24 hours in normal controls.⁵ We noted that energy restriction and weight loss did not depress cellular immunity. This study suggests that care should be taken in interpreting depression of skin response to recall antigens as evidence of malnutrition.

Delayed sensitivity reactions to four antigens in normal and obese subjects tested and retested after three weeks. Results expressed as mean ($\pm$ SD) area of induration in mm. Figures in parentheses are numbers of subjects giving positive response (area of induration over 5 mm)

	No of subjects	Streptokinase/streptodornase	Mumps	Candida	Purified protein derivative	Isotonic saline
<i>Normal controls</i>						
First test	5	28.6 $\pm$ 14.5 (5)	22.8 $\pm$ 7.7 (5)	19.4 $\pm$ 12.8 (4)	22.3 $\pm$ 13.6 (3)	0
Retest	5	30.4 $\pm$ 12.6 (5)	15.0 $\pm$ 7.2 (5)	20.3 $\pm$ 5.6 (4)	22.0 $\pm$ 10.1 (3)	0
<i>Obese patients</i>						
First test	10	25.6 $\pm$ 14.3 (10)	19.6 $\pm$ 6.9 (9)	21.8 $\pm$ 12.4 (8)	7.4 $\pm$ 2.4 (5)	0
Retest	10	33.8 $\pm$ 13.3 (10)	17.4 $\pm$ 8.2 (9)	20.5 $\pm$ 1.3 (8)	10.2 $\pm$ 5.3 (5)	0

Subjects, methods, and results

We studied five normal controls, 10 obese women, and 10 patients admitted for elective surgery. The protocol was approved by the Northwick Park Hospital ethical committee. The subjects were injected intradermally with 0.1 ml each of mumps skin test antigen USP, streptokinase-streptodornase (10 U and 2.5 U respectively) tuberculin purified protein derivative (10 U), and candida extract (0.33%). Isotonic saline (0.1 ml) was used as control. Response was assessed by measuring the induration at the site of injection by the ball-point technique.³

The table gives the results obtained by testing and retesting three weeks later five normal and 10 obese subjects. In every case subjects who had a positive response (more than 5 mm induration) on first test were also positive on retest. There was no significant difference in the area of induration on retesting, and the response was not affected by energy restriction and mean weight loss of 6.3 $\pm$ 1.6 kg in the obese patients.

To investigate the effect of surgery on cell-mediated immunity 10 surgical patients were tested the day before operation. The area of induration was read 24 hours after injection, immediately before operation, and again at 48 hours after injection, after the operation. Five normal controls were also tested and the reaction read at 24 and 48 hours. When a control subject gave a positive reaction at 24 hours to a particular antigen the reaction was still positive, usually with an increased area of induration, at 48 hours.

¹ Bistrian BR, Blackburn GL, Serimshaw NS, Flatt JP. Cellular immunity in semistarved states in hospitalized adults. *Am J Clin Nutr* 1975;28:1148-55.

² Blackburn GL, Kaminski MV. Nutritional assessment and intravenous support. In: Karran SJ, Alberti KGMM, eds. Practical nutritional support. Tunbridge Wells: Pitman Medical, 1980:166-89.

³ Sokal JE. Measurement of delayed skin-test responses. *N Engl J Med* 1975;293:501-2.

⁴ Woolfson AMJ. Metabolic considerations in nutritional support. In: Johnston IOA, Lee HA, eds. *Developments in clinical nutrition*. Tunbridge Wells: MCS Consultants, 1979:35-47.

⁵ Coburg AJ, Gray SH, Katz FH, Penn I, Halgrimson C, Starzl TE. Disappearance rates and immunosuppression of intermittent intravenously administered prednisolone in rabbits and human beings. *Surg Gynecol Obstet* 1970;131:933-42.

(Accepted 19 November 1980)

Clinical Research Centre, Harrow HA1 3UJ

K S NAIR, MRCP, KabiVitrum research fellow

J S GARROW, FRCP, consultant physician